A BIOCHEMICAL DEFINITION OF CURE AFTER BRACHYTHERAPY FOR PROSTATE CANCER

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Abstract

Background and Purpose: To identify a PSA threshold value at an intermediate follow-up time after low dose rate (LDR) prostate brachytherapy associated with cure, defined as long-term (10 to 15 year) freedom from prostate cancer.

Materials and Methods: Data from 7 institutions for 14,220 patients with localized prostate cancer treated with LDR brachytherapy, either alone (8,552) or with external beam radiotherapy (n=1,175), androgen deprivation (n=3,165), or both (n=1,328), were analyzed. Risk distribution was 42.4% favorable, 49.2% intermediate, and 8.4% high-risk. Patients with clinical failure before 3.5 years were excluded. Kaplan-Meier analysis was used with clinical failure (local, distant, regional or biochemical triggering salvage) as an endpoint for each of four PSA categories: PSA ≤ 0.2, >0.2 to ≤ 0.5, >0.5 to ≤ 1.0, and >1.0 ng/mL. PSA levels at 4 years (±6 months) in 8,746 patients without clinical failure were correlated with disease status at 10–15 years.

Results: For the 77.1% of patients with 4-year PSA ≤ 0.2, the freedom-from-recurrence (FFR) rates were 98.7% (95% CI 98.3–99.0) at 10 years and 96.1% (95% CI 94.8–97.2) at 15 years. Three independent validation cohorts confirmed 97%–99% 10-year FFR rates with 4-year PSA ≤ 0.2. Successive PSA categories were associated with diminished disease-free rates at 10 and 15 years. PSA category was strongly associated with treatment success ($p<0.0005$).

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Conclusions: Since 98.7% of patients with PSA 0.2 ng/mL at 4 years after LDR prostate brachytherapy were disease-free beyond 10 years, we suggest adopting this biochemical definition of cure for patients with 4 years' follow-up after LDR brachytherapy.

Keywords

adenocarcinoma of prostate; brachytherapy; low dose rate brachytherapy; prostate specific antigen; PSA definition of cure

INTRODUCTION

Since post-treatment PSA values were first introduced into clinical practice in the 1980s, clinicians have grappled with interpretation of these values. Two consensus conferences, ASTRO in 1996 (1) and Phoenix in 2005 (2), defined biochemical failure after external beam radiotherapy (EBRT), but neither included data from patients treated with androgen deprivation therapy (ADT) or brachytherapy (3). Neither consensus conference attempted to define cure and neither definition is readily comparable to a surgical definition of failure.

Having observed over the past two decades that the incorporation of brachytherapy into the radiation management of prostate cancer is associated with extremely low and stable PSA values, we extracted, combined, and analyzed mature, prospectively collected brachytherapy data sets from 7 institutions to identify a PSA threshold value associated with cure, as defined by long-term (10–15 year) freedom from prostate cancer.

MATERIALS AND METHODS

A total of 14,220 patients with localized prostate cancer from 7 participating international institutions (Table 1) were treated with low-dose-rate (LDR) brachytherapy, either alone (n=8,552) or combined with ADT (n=3,165), EBRT (n=1,175), or both (n=1,328). Clinical failures and dates of failure were defined by the institutions and were considered to be local, nodal, distant or biochemical failure triggering salvage ADT. All analyses were approved by the Institutional Review Board at University of Texas MD Anderson Cancer Center in compliance with each participating institution's policies, and consents were waived given the retrospective nature of the data.

After either 3.5 or 4.5 years of failure-free follow-up, a particular PSA value was used to predict long-term success or failure as follows. For patients with at least 3.5 years of follow-up, the "4-year" PSA measurement was selected that was closest to, but still less than 4.5 years and grouped into one of four categories: PSA 0.2 ng/mL, >0.2 to 0.5 ng/mL, >0.5 to 1.0 ng/mL, and >1.0 ng/mL. The most favorable of these categories (0.2 ng/mL) is comparable to a surgical PSA threshold of 0.2 ng/mL, and the least favorable (PSA >1.0 ng/ml) still encompasses 5% of the readings. Similarly, for patients with at least 4.5 years' follow-up, the PSA measurement that was closest to, but still less than 5.5 years was selected as the "5-year PSA."

Patients with insufficient PSA follow-up data, within 3.5 years after treatment, were excluded (n=3,929), as were patients without a PSA value in the interval of interest

(n=1,473) and those with clinical failure before 3.5 years (n=72), leaving 8,746 patients for analysis based on a 4-year PSA level. By a similar exclusion process, 7,615 patients were analysed based on a 5-year PSA. The analyses were performed using the last-measured (most recent) PSA during the interval of interest and then repeated using the first-measured PSA value in the interval to determine if there was obvious time dependency.

Statistics

Kaplan-Meier (KM) analysis was carried out for each interval (to 10 or 15 years) using clinical failure (local, distant, regional or biochemical triggering ADT) as the endpoint for each of the four PSA categories. The starting date for the KM analysis was the date of the brachytherapy implant, and the final date was that of the clinical failure or the last PSA measurement. Equality of failure rates was tested using the log-rank test (which assumes proportional hazards across the PSA categories) and checked by using the Wilcoxon-Breslow-Gehan test (which does not assume proportional hazards). The KM results are presented as percentage of patients in each PSA category who were free of disease at 10 and 15 years after treatment.

Results were validated by analyses of three independent, prospectively collected data sets. The first was prospectively collected LDR brachytherapy data from Melbourne Australia (n=377) for patients with favorable- (75%) or intermediate-risk (25%) prostate cancer with >10 years of follow-up (6). This cohort was treated largely with monotherapy, although short-term ADT for prostate downsizing was used in 12.6% of patients and 2% had supplemental EBRT. The second validation cohort was from a 300-patient prospective phase II study of LDR brachytherapy alone for intermediate-risk prostate cancer conducted at the University of Texas MD Anderson Cancer Center (4) with a median follow-up time of 6 years. The final validation cohort was the brachytherapy arm of the Canadian 398-patient phase III randomized trial (Ascende-RT) comparing 12 months of ADT combined with either dose-escalated EBRT or EBRT plus an LDR brachytherapy prostate boost (5) for patients with high-risk (70%) or upper-tier intermediate-risk (30%) prostate cancer with >10 years follow up.

RESULTS

The clinical characteristics of the patients and tumors are shown in Table 2. In the index cohort the distribution by risk category was 42.4% favorable, 49.2% intermediate, and 8.4% high-risk. Median follow-up time was 8.0 years (range 3.5–21.3), with more than 2800 patients followed beyond 10 years and more than 400 beyond 15 years. The median number of PSA readings per patient was 13. Clinical failures occurred in 660 patients, 245 before 3.5 years (patients excluded from analysis) and 351 afterward.

Nearly 80% of patients were in PSA category 1 (Table 3) with a PSA 0.2 ng/mL at 3.5–4.5 years. For those patients, the probability of being free of clinical failure at 10 years was 98.7% and at 15 years, 96.1%. Analysis was repeated in a similar fashion using the 5-year PSA level, at which time 85.4% of patients had a PSA of 0.2 ng/mL associated with a 99.1% chance of being disease-free at 10 years and 96.6% at 15 years. The results of KM analysis with the log-rank test (with 95% confidence intervals) for the four PSA categories

are shown in Table 3. The association of treatment success with PSA range was highly significant (*p*<0.0005); results were also significant with the Wilcoxon-Breslow-Gehan test (*p*<0.01).

For patients in PSA category 2 (4-year PSA >0.2 ng/mL but ≤ 0.5 ng/mL), the probability of being disease-free at 10 and 15 years decreased but remained high at 93.5% at 10 years and 86.8% at 15 years. PSA categories 3 and 4 did less well, but many patients still had not experienced failure by 15 years. Based on 4,864 PSA readings between 9.5 and 10.5 years; the median 10-year PSA level was 0.01 (interquartile range [IQR] 0–0.05 ng/mL). At 15 years, based on 1,137 readings between 14.5 and 15.5 years, the median PSA level was 0.0 (IQR 0.0–0.02 ng/mL).

Because no statistically significant difference was found in disease-free survival (data not shown) when the analyses were repeated using either the first PSA in the 3.5–4.5-year interval for all patients, or the last PSA in the interval, the results presented are for the first PSA in the interval.

Table 4 shows the distribution of PSA categories within each risk group. A significantly higher portion of high-risk patients had a 4-year PSA level in category 1 (≤ 0.2 ng/mL) compared with favorable-risk (82% vs. 75%, *p*<0.00001: 2-sided binomial test), but also a significantly higher proportion in the >1.0 ng/ml category (8% vs. 4%, *p*<0.00001). However, these risk groups were originally defined for patients receiving EBRT and may differ for those treated with brachytherapy.

Validation cohorts

Characteristics of the validation cohorts are shown in Table 2. For the three validation sets, largely favorable-risk, intermediate-risk, and higher-risk, a PSA level of ≤ 0.2 ng/mL at 4 years was associated with 10-year freedom from failure rates of 99.0%, 99.4%, and 96.7%, respectively (Table 3).

In the multi-institutional international cohort, 77.1% patients had a 4 year PSA ≤ 0.2 ng/mL. In the high-risk Ascende-RT validation cohort, this was achieved in 85.7%, and in the intermediate-risk MD Anderson cohort, 73.5%. In the largely favorable-risk Australian cohort, only 54.6% had a 4-year PSA level of ≤ 0.2 ng/mL; however, by 5 years this had increased to 72%.

DISCUSSION

In more than 3 decades of clinical use, no serum marker has caused more controversy than PSA, a serum protease produced in the prostate. PSA elevation is associated with many conditions, diminishing its utility in prostate cancer screening. However, as a marker of response to treatment, PSA is much more reliable. The absence of circulating PSA is an indicator of success after radical prostatectomy and a PSA level of >0.2 ng/mL is an accepted definition for biochemical failure (7) (8). After radiation therapy for prostate cancer, the PSA level cannot be expected to be zero, but the actual target level associated with cure has been much debated.

The 1996 ASTRO Consensus Panel (1) considered clinical outcomes for men treated with EBRT without ADT from several institutions in an effort to standardize an approach to PSA monitoring and reporting after radiation treatment. Although PSA nadir was recognized as a strong prognostic factor, no threshold nadir to determine successful treatment was identified. Three consecutive rises, at a minimum of 3- to 4-month intervals, was chosen as an appropriate definition of biochemical failure for reporting of results; but importantly this was not to be mistaken as a surrogate for clinical progression or survival, or to be a justification for salvage intervention. Further, the definition was not derived from patients whose treatment included either ADT or brachytherapy, both of which subsequently came into more frequent clinical use.

A second consensus conference took place in Phoenix, Arizona (2) in 2005. It was recognized that the definition of biochemical cure is very different from that for biochemical failure. Because biochemical failure correlates with clinical endpoints of local failure, distant metastasis, and cause-specific mortality, it often triggers intervention intended to prevent or delay these consequences. Clearly, specificity in the definition is a priority, and the false-positive rate with the Phoenix "nadir+2" definition ranges from <3% to 5%. However, many patients who do not meet this definition of failure are not cured. A definition of successful treatment and cure remains to be determined. If the absence of failure is considered to be cure, then a highly specific definition of failure will overestimate cure. Similarly, a rigorous definition of cure would risk misidentifying patients who have not met the strict definition of cure as therefore having experienced failure. There must be widespread acceptance that depending on the dose and method of delivery of radiation, there will always be a proportion of patients who cannot be declared as "cured" or as "failed." Such patients need continued follow-up and PSA monitoring.

Brachytherapy has long been recognized to result in lower post-treatment PSA nadirs, with a PSA level of 0.2 ng/mL at 3–5 years predicting sustained disease-free status (9) (10) (11), with some even suggesting that monitoring for such patients can be ceased (11). Lo et al demonstrated that a PSA of < 0.2 at 4 years after brachytherapy predicted for long-term biochemical control with no biochemical failures at 8 years (9). Tetreault-Laflamme et al. reported on more than 2,000 patients treated with LDR brachytherapy (12). At a median follow-up time of 7 years, 86% demonstrated very low and stable PSA levels, with the median PSA nadir being 0.03 ng/mL and the 5-year PSA level 0.04 ng/mL.

Morris et al. (13) suggested using the surgical definition of biochemical failure (PSA >0.2 ng/mL) for the 398 patients with intermediate- or high-risk prostate cancer treated in the Ascende-RT randomized trial (12 months ADT, 46 Gy in 23 fractions of pelvic EBRT followed by either a further 32 Gy EBRT prostate boost or LDR brachytherapy). When a failure definition of PSA >0.2 ng/mL was applied, relapse-free survival rates in the 78-Gy arm decreased from 76% (nadir+2 definition) to 38%, whereas in the BT arm, 85% of patients maintained a PSA 0.2 ng/mL at 7 years.

In the current analysis of more than 14,000 patients treated with brachytherapy, either alone or combination with EBRT, ADT, or both, we chose a relatively early but intermediate time point as being potentially predictive of long-term clinical outcome. To avoid PSA

perturbations from the benign PSA bounce phenomenon (14) (15) (16), we chose 3.5–4.5 years as the earliest suitable time point to assess the predictive capacity of the post-brachytherapy PSA value. We found that a 4-year PSA level of 0.2 ng/mL was associated with a 98.7% chance of freedom from prostate cancer at 10 years and a 96.3% chance at 15 years. Almost 80% of the patients in this analysis achieved this PSA threshold at 4 years, and 85.4% had done so by 5 years. Further, the median PSA at 10 and 15 years was maintained at 0.01 ng/mL.

The definition of 'cure' seems to be equally valid across risk groups, as shown by the three validation cohorts. Clearly the percentage of patients in any risk group achieving a PSA level of 0.2 ng/mL will depend on the intensity of treatment. Nadir is known to be dose-dependent (17) (18), but one weakness of our study is that we have not yet assessed the correlation of nadir with implant quality in our cohort. In addition, PSA testing was not standardized among the contributing centers.

Although some controversy remains over which PSA level best predicts subsequent failure-free survival, we recommend using the 0.2 ng/mL threshold at 4 years after brachytherapy to define cure. This threshold applies to almost 80% of patients who have received LDR brachytherapy, either alone or in combination with EBRT, ADT, or both. It has high specificity, and facilitates direct comparisons with surgical series. This threshold can be adopted as an intermediate biochemical endpoint in future clinical trials involving brachytherapy. Notably, however, failure to achieve this strict threshold does not imply failure and should not trigger investigation or intervention. The established nadir + 2ng/ml definition of failure should still be followed and remains unchallenged. Those patients who do not achieve a PSA 0.2 ng/ml by 4 or 5 years should continue to be monitored. Although many will remain free of clinical recurrence, advanced imaging or biopsy can be considered, especially for those in PSA category 4, with a PSA level of >1.0 ng/mL, for whom more than 50% are destined to experience clinical recurrence.

Validation from the three independent prospective cohorts in our analysis supports the value of 4-year PSA 0.2 ng/mL as the biochemical definition of cure after LDR brachytherapy across all risk groups, with predicted rates of freedom from prostate recurrence of 97% to 99% at 10–15 years. However, the significance of reaching this PSA threshold still requires validation for patients treated with other types of radiation, specifically EBRT or stereotactic body radiotherapy (19).

Use of this definition of cure for comparison with surgical series may seem to put brachytherapy outcomes at a disadvantage because not all of the patients who do not meet this threshold will ultimately fail; however, the same is true of surgical patients with a PSA level of >0.2 ng/mL. Not all will experience clinical failure or require salvage therapy. Although most patients who have a PSA level of >0.1 ng/mL after radical prostatectomy will progress to >0.2 ng/mL (7), only about 50% will develop metastases by 10 years (20). Factors such as PSA doubling time can help to define the risk of clinical progression (21).

Over 20 years ago Critz et al called for the adoption of a post-treatment PSA 0.2 ng/ml to define disease freedom after radiotherapy for prostate cancer based on patients treated with

combined transperineal implant and external radiotherapy(22). He sought a universal PSA nadir goal, equally applicable after prostatectomy or radiotherapy. It's time we followed his lead.

Conclusion:

By 4 years after LDR brachytherapy, most patients will achieve a PSA level of 0.2 ng/mL. Regardless of risk group, this is associated with rates of freedom from prostate cancer recurrence of 97% to 99% at 10 years. Adoption of PSA 0.2 ng/mL as a common definition of cure should facilitate comparison with outcomes from surgical series. Many patients who do not achieve a PSA 0.2 ng/ml may also remain free of prostate cancer recurrence, but the risk of recurrence is sufficient that they require continued monitoring.

Funding:

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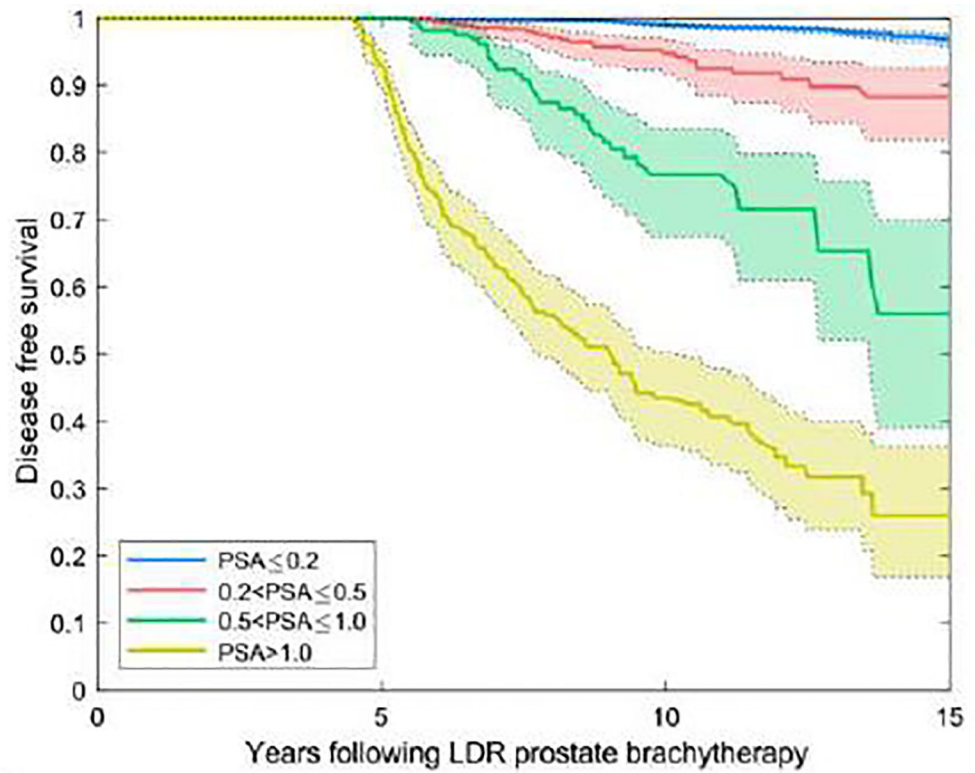
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Highlights

- Close to 80% of men 4 –5 years after LDR prostate brachytherapy will achieve a PSA of 0.2 ng/ml or less.

- PSA   0.2 ng/ml is associated with 97–99% freedom from prostate cancer recurrence at 10–15 years

- This applies across all risk groups and to LDR brachytherapy alone or combined with ADT and/or EBRT
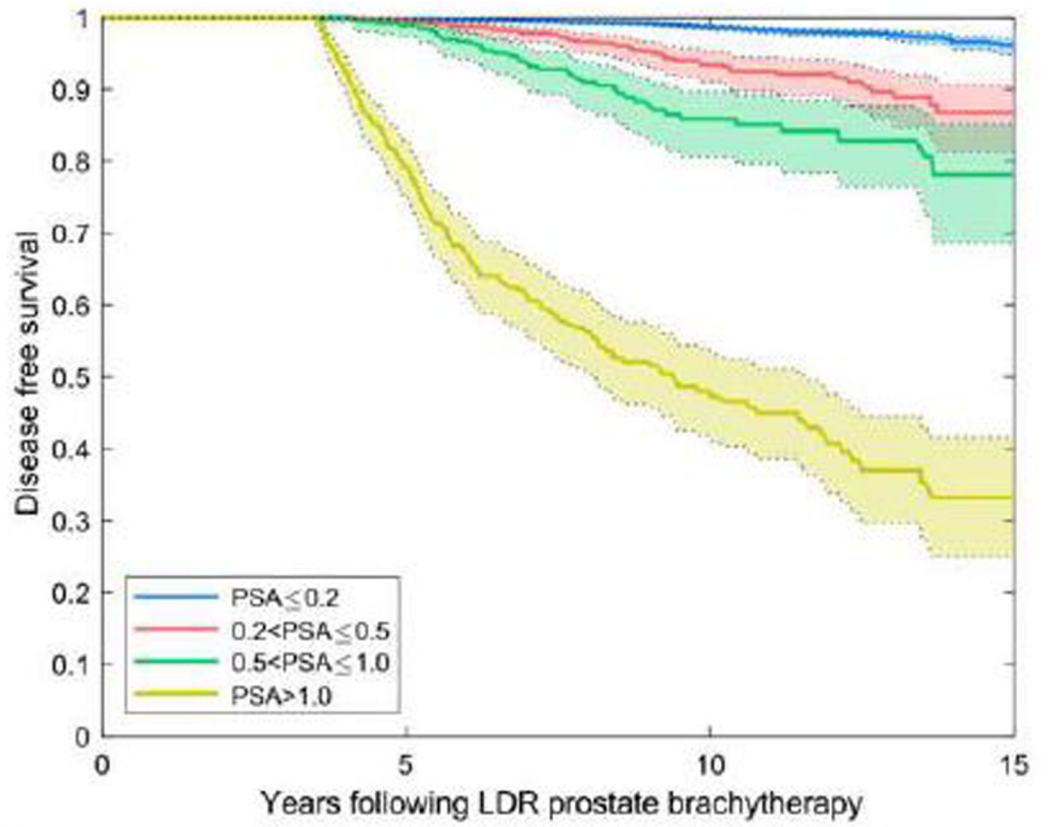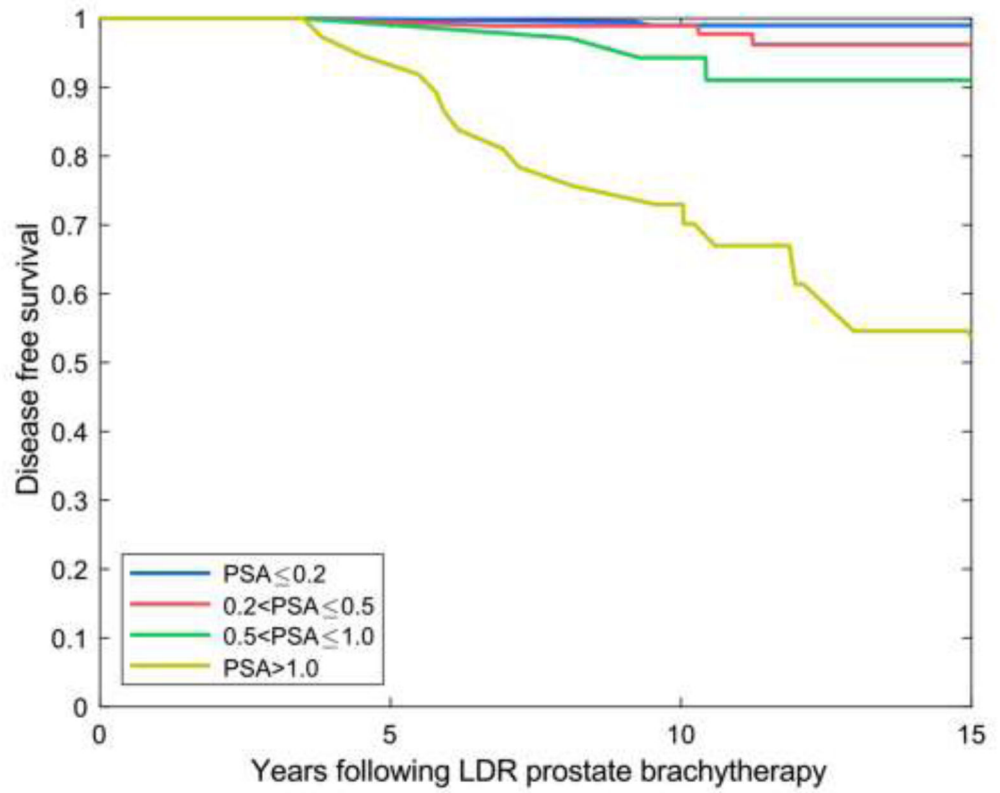
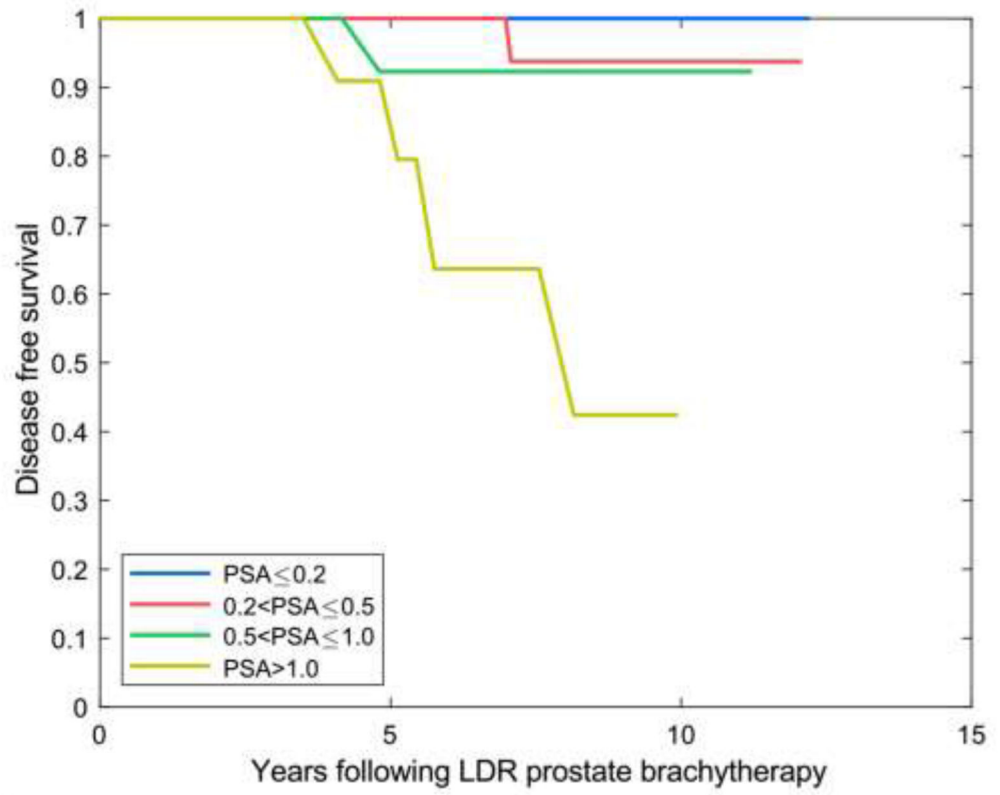| Number at risk				
PSA≤0.2	6746	5540	2292	341
0.2<PSA≤0.5	1100	877	321	34
0.5<PSA≤1.0	444	366	121	16
PSA>1.0	456	282	70	11

Fig. 1 —.
Disease-free survival rates by prostate-specific antigen (PSA) category at 4 years (A) and 5 years (B). PSA measurements before the interval of interest were excluded.

Number at risk

PSA≤0.2	164	119	7	0
0.2<PSA≤0.5	33	25	5	0
0.5<PSA≤1.0	14	9	1	0
PSA>1.0	12	8	0	0
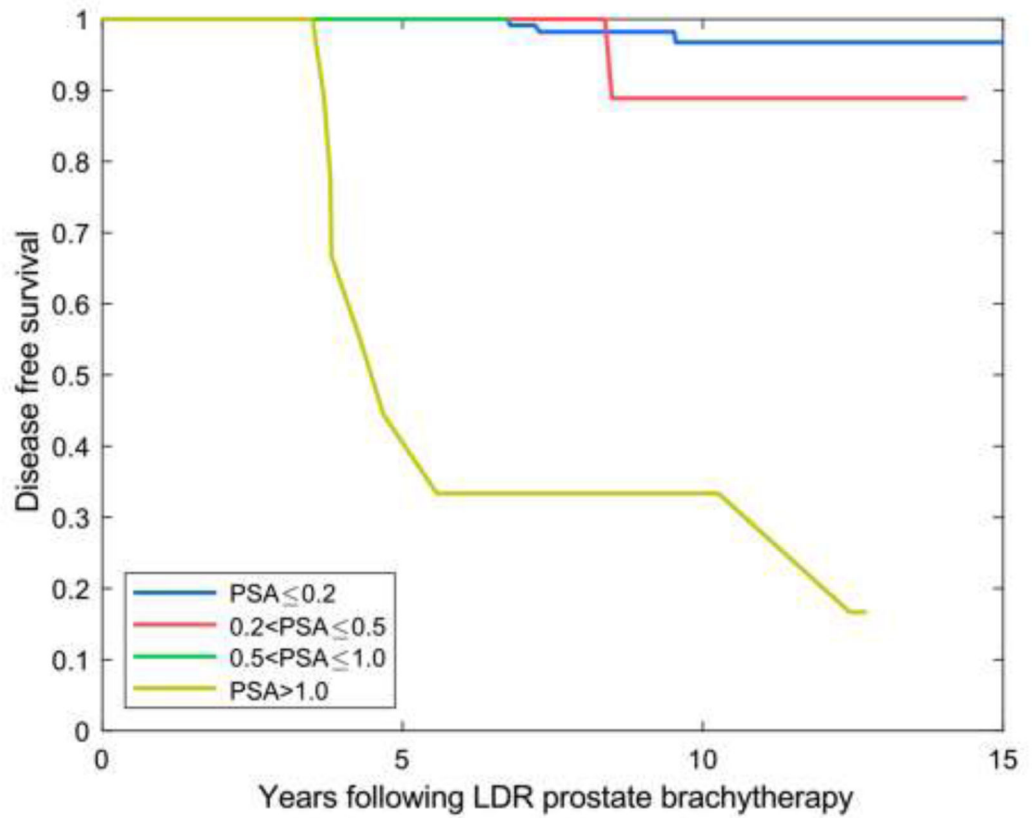
Fig 2 —.
Disease-free survival by prostate-specific antigen (PSA) category at 4 years for the 3 validation cohorts. (A) Favorable risk (Australia: 75% favourable risk and 25% intermediate risk). (B) Intermediate risk (MD Anderson). (c) High risk (Ascende RT: 70% high risk and 30% upper tier intermediate risk).

Table 1 —

Contribution of each institution and reasons for exclusion from 3.5–4 .5 year interval follow-up.

Institution	Total No. of Patients	Excluded 1st for lack of PSA follow-up	Excluded 2nd for no PSA value at 3.5–4.5 years	Excluded 3rd for failure <3.5 years	Total remaining
BC Cancer	3,656	771	328	43	2,514
Cleveland	4,094	1,968	249	2	1,875
Galway	380	262	16	1	101
MD Anderson	717	294	80	3	340
Mt Sinai NY	1,842	100	437	16	1,289
Toronto	604	50	54	2	498
Wheeling	2,927	484	309	5	2,129
Total	**14,220**	**3,929**	**1,473**	**72**	**8,746**

Table 2 —

Patient and tumor characteristics.

Characteristic	Cohort Patients (%)	Validation Grp 1 (Australia)	Validation Grp 2 (MD Anderson)	Validation Grp 3 (Ascende-RT)
No. of Patients	8,746	366	221	160
Baseline PSA Level, ng/mL, median	6.2	5.5	5.1	10.0
<4	1184 (13.5)	76 (20.8)	56 (25.4)	7 (4.4)
4–<10	6154 (70.4)	279 (76.2)	157 (71.0)	68 (42.5)
10–<20	1202 (13.7)	11 (3.0)	8 (3.6)	60 (37.5)
20–<30	119 (1.4)	0 (0.0)	0 (0.0)	17 (10.6)
30	87 (1.0)	0 (0.0)	0 (0.0)	8 (5.0)
Not reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gleason Score				
6	4739 (54.2)	314 (85.8)	10 (4.5)	10 (6.3)
7	3379 (38.6)	52 (14.2)	211 (95.5)	81 (50.6)
8	362 (4.1)	0 (0.0)	0 (0.0)	37 (23.1)
9 or 10	232 (2.7)	0 (0.0)	0 (0.0)	32 (20.0)
Not reported	34 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
T Category				
T1a-T2a	7376 (84.3)	325 (88.8)	217 (98.2)	67 (41.9)
T2b-T2c	1093 (12.5)	41 (11.2)	4 (1.8)	49 (30.6)
T3a-T3b	61 (0.7)	0 (0.0)	0 (0.0)	44 (27.5)
Not reported	216 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Age, years, median	66.0	61.0	64.9	67
<50	156 (1.8)	5 (1.4)	9 (4.1)	0 (0.0)
50–<60	1803 (20.6)	136 (37.1)	48 (21.7)	21 (13.1)
60–<70	4162 (47.6)	176 (48.1)	114 (51.6)	64 (40.0)
70	2624 (30.0)	49 (13.4)	50 (22.6)	75 (46.9)
Not reported	1 (0.0)	0 (0.0)	0 (0)	0 (0.0)
No. of PSA measurements				
<10	2443 (27.9)	0 (0.0)	42 (19.0)	4 (2.5)
10–<20	4777 (54.6)	254 (69.4)	172 (77.8)	105 (65.6)
20	1526 (17.5)	112 (30.6)	7 (3.2)	51 (31.9)
PSA follow-up, years, median, maximum	7.8 (19.7)	12.1 (18.9)	6.0 (12.2)	9.7 (15.5)

Table 3 —

Kaplan-Meier estimated free-of-clinical failure rates by PSA category at 3.5–4.5 years for combined cohort and for validation cohorts.

PSA category	% in category (no.)	Combined Cohort PSA @ 4 years		Validation Cohort 1 (Australia) 75% low-risk/25% intermediate-risk			Validation Cohort 2 (MD Anderson) intermediate-risk			Validation Cohort 3 (Ascende-RT) 70% high-risk/30% upper-tier intermediate-risk		
		% NED 10 years	% NED 15 years	% pts in category (no.)	% NED 10 years	% NED 15 years	% in category (no.)	% NED 10 years	% NED 15 years	% pts in category (no.)	% NED 10 years	% NED 15 years
0.2	77.1% (6746)	98.7 (98.3–99.0)	96.1 (94.8–97.2)	54.6% (200)	99.0 (96.1–99.8)	99.0 (96.1–99.8)	73.5% (164)	99.4 (95.8–99.9)	------	85.7% (137)	96.7 (89.9–99.0)	96.7 (89.9–99.0)
>0.2 to 0.5	12.6% (1100)	93.5 (91.0–95.3)	86.8 (81.4–90.7)	25.7% (94)	98.9 (92.7–99.9)	96.2 (88.4–98.8)	14.8% (33)	92.7 (53.9–98.8)	------	8.1% (13)	88.9 (43.3–98.4)	------
>0.5 to 1.0	4.1% (444)	85.9 (80.6–89.8)	78.2 (68.6–85.2)	9.6 (35)	94.3 (79.0–98.5)	91.0 (74.6–97.0)	6.3% (14)	90.9 (50.8–98.7)	------	0.6% (1)	------	------
> 1.0	5.1% (456)	48.0 (41.8–53.8)	33.2 (24.9–41.6)	10.1 (37)	73.0 (55.6–84.4)	54.6 (32.9–71.9)	5.4% (12)	------	------	5.6% (9)	33.3 (7.8–62.3)	------

%: percentage of patients with readings in that category

NED 10 years / 15 years: % of patients with no evidence of recurrence at 10 years or 15 years (followed by 95% confidence intervals)

Table 4 —

Distribution of 4-year PSA levels in primary cohort according to risk grouping.

PSA Level, ng/mL	Favorable Risk	Intermediate Risk	High Risk	*P* Value
0.2	2738 (75%)	3383 (77%)	578 (82%)	<0.00001
>0.2 – 0.5	573 (16%)	516 (12%)	39 (6%)	<0.00001
>0.5 – 1.0	194 (5%)	232 (5%)	29 (4%)	0.000126
>1.0	156 (4%)	248 (6%)	60 (9%)	<0.00001