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Prognostic Implications of an Undetectable Ultrasensitive Prostate-Specific Antigen Level after Radical Prostatectomy

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Abstract

Background—The prognostic meaning of an undetectable ultrasensitive prostate-specific antigen (USPSA) level after prostatectomy remains unclear.

Objective—To determine whether an undetectable USPSA level obtained after surgery is a predictor of biochemical recurrence (BCR)–free survival.

Design, setting, and participants—From the Urologic Oncology Database at the University of California San Francisco, 525 men were identified who had a USPSA measurement 1–3 mo postoperatively with at least 2 yr of follow-up. All preoperative and pathologic criteria were recorded.

Measurements—Patients were stratified based on their initial USPSA level. We defined an undetectable USPSA level at ≤ 0.05 ng/ml. Recurrence was defined as two consecutive prostate-specific antigen (PSA) levels ≥ 0.2 ng/ml or secondary treatment.

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Author contributions: Michael Eisenberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Carroll, Eisenberg, Davies

Acquisition of data: Eisenberg, Davies, Carroll

Analysis and interpretation of data: Eisenberg, Davies, Cooperberg, Cowan, Carroll

Drafting of the manuscript: Eisenberg, Davies, Carroll, Cowan

Critical revision of the manuscript for important intellectual content: Eisenberg, Davies, Cooperberg, Carroll, Cowan

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Take-home message

An undetectable ultrasensitive prostate-specific antigen level obtained 1–3 mo after radical prostatectomy is a useful prognostic indicator of biochemical recurrence–free survival that may aid in postoperative risk stratification.

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Results and limitations—We found that 456 patients (87%) had undetectable USPSA and 69 patients (13%) had detectable USPSA immediately postprostatectomy. A 5-yr recurrence-free rate of 86% was found in the undetectable USPSA group compared with 67% in the detectable USPSA group ($p < 0.01$). For patients with pT3 disease, men with an undetectable USPSA had a 5-yr BCR-free survival rate of 78% compared with 40% for men with a detectable USPSA ($p < 0.01$). A multivariable analysis confirmed that patients with an undetectable USPSA were 67% less likely to recur (hazard ratio: 0.33; 95% confidence interval: 0.20–0.55). As the detection level of PSA is lowered, the false-positive rate of BCR necessarily increases. A limitation of the study is its retrospective nature.

Conclusions—An undetectable USPSA after radical prostatectomy is a prognostic indicator of BCR-free survival at 5 yr and may aid in predicting outcome in higher risk patients.

1. Introduction

Prostate-specific antigen (PSA) was introduced as a screening tool for prostate cancer in the late 1980s, and was recognized shortly thereafter as a surrogate biomarker for residual or recurrent disease [1–4]. Assays that measure PSA to levels <0.1 ng/ml are denoted *ultrasensitive PSA* (USPSA) tests and are now widely available to clinicians. The utility of USPSA testing postprostatectomy has been the focus of some controversy in the urologic literature. Some authors claim that USPSA nadir values postprostatectomy are helpful in identifying cases of early biochemical relapse [5–7]. Others believe that USPSA offers minimal advantages and often causes an increase in anxiety in patients who are destined to have only clinically meaningless rises of USPSA [8].

Studies centered on the prognostic utility of an undetectable PSA postprostatectomy have not been widely reported. Our study hypothesizes that an undetectable USPSA as the initial test after radical prostatectomy (RP) will be a robust predictor of biochemical recurrence (BCR)–free survival regardless of clinical risk stratification or pathologic findings. As such, it may aid clinicians in determining who may either benefit by or forgo adjuvant therapy.

2. Patients and methods

2.1. Urologic Oncology Database

The Urologic Oncology Database (UODB) is a clinical and research resource in the Department of Urology at the University of California San Francisco (UCSF). The UODB contains diagnostic, surgical, pathologic, and clinical outcomes data on men treated for prostate cancer in the Urology Department at UCSF. Age, PSA history, biopsy findings, imaging and lab test results, surgical procedure and pathology details, BCR, secondary treatment, and mortality data are collected on patients who undergo RP or who are followed on active surveillance. Patients included in the UODB have signed consent forms that are approved and monitored by the Institutional Review Board of UCSF.

2.2. Patient population

There were 2825 patients who consented and were enrolled in the UODB database as of July 2008; of those, 2251 underwent laparoscopic or open RP. Year of surgery was restricted to 1996–2006 ($n = 1674$) to ensure that ultrasensitive testing was available. Men who received neoadjuvant androgen deprivation therapy (ADT) or radiation treatments (9%) were excluded to ensure consistent treatment across patients. Patients with positive lymph nodes at pathology were also excluded. All patients had ultrasensitive PSA values 1–3 mo after surgery, at least two postsurgery PSA tests to determine BCR, and at least 2 yr of follow-up.

2.3. Definition of undetectable ultrasensitive prostate-specific antigen

The definition of undetectable USPSA for this analysis was ≤ 0.05 ng/ml. PSA data in the UODB come from multiple laboratories that define undetectable PSA levels at either ≤ 0.02 ng/ml or ≤ 0.05 ng/ml. We used the higher cut-off when identifying undetectable PSA to minimize measurement bias.

2.4. Treatment failure

PSA recurrence was defined as two consecutive rises in PSA of ≥ 0.2 ng/ml at least 8 wk after surgery. This definition has been used widely and has been proposed as a national standard [9]. We also report the patient having a recurrence if the patient underwent secondary therapy (ADT or radiation therapy), regardless of whether the PSA failure definition was met, to capture patients who were deemed primary treatment failures by urologists but who did not meet PSA criteria.

2.5. Statistical analysis

Characteristics of the patients with detectable versus undetectable USPSA were compared using chi-square tests for categorical variables and analysis of variance for continuous variables. TNM staging adhered to the American Joint Committee on Cancer (AJCC) 2002 guidelines. Clinical risk groups were based on a modification of categories defined by D'Amico et al [10]. Patients were considered low risk if they had PSA ≤ 10 ng/ml, Gleason sum < 7 with no primary or secondary Gleason of 4 or 5, and clinical stage T1–T2a. They were considered intermediate risk if they had PSA 10.1–20 ng/ml, Gleason secondary pattern 4 or 5, or clinical stage T2b–2c. High-risk patients were those who had PSA > 20 ng/ml, Gleason sum > 7 or Gleason primary 4 or 5, or cT3a. Life table product-limit estimates and Kaplan-Meier curves, stratified by USPSA cohort, were used to examine time to BCR > 5 yr after RP. In multivariate Cox proportional hazards regression models, we examined whether USPSA cohort predicted BCR, adjusting for pretreatment age, diagnostic PSA, biopsy Gleason total, clinical stage, pathologic Gleason total, pathologic stage, and surgical margins. Significance was set at $p < 0.05$. All analyses were performed using SAS v.9.1 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline patient characteristics

Of 1674 patients who underwent RP in 1996–2006, 1323 received no neoadjuvant or adjuvant treatments and had pN0. Of those, 525 patients had at least 2 yr of postsurgery follow-up data, including ultrasensitive PSA values measured 1–3 mo after surgery.

The median follow-up was 4.7 yr (range: 2.1–14.5 yr). There were 456 patients (87%) who had undetectable USPSA and 69 patients (13%) who had detectable USPSA immediately postprostatectomy. Most undetectable PSA values ($n = 349$) were ≤ 0.02 ng/ml. Table 1 describes the baseline characteristics of both the detectable and the undetectable cohorts.

In bivariable analysis, a higher proportion of patients with an undetectable USPSA had lower percentages of biopsy cores that were positive than those with detectable USPSA ($p < 0.05$). Age, race, PSA, clinical T stage, Gleason grade, and risk category were not significantly different between the two cohorts.

3.2. Biochemical recurrence-free rates between cohorts

Overall, the 5-yr failure-free recurrence rate was 86% in the undetectable USPSA group versus 67% among detectable patients (log-rank $p < 0.01$, Fig. 1). Median time to recurrence was 3.5

yr (range: 0.2–12.2) in the detectable group and 4.1 yr (range: 0.4–11.4) in the undetectable group.

In the undetectable cohort, the 5-yr BCR-free rates stratified by risk category are outlined in Table 2. The 5-yr BCR-free survival rates of low-, intermediate-, and high-risk patients (based on preoperative clinical risk stratification) with undetectable USPSA were 91%, 89%, and 71%, respectively. The 5-yr recurrence-free rates for patients with low, intermediate, or high risk with detectable USPSA were 89%, 52%, and 59%.

Moreover, 5-yr recurrence-free survival rates were also significantly different between detectable and undetectable postoperative PSA levels for the PSA cut-off points 0.02, 0.1, and 0.2 ng/ml. Treatment failure rates were highest for patients with postoperative PSA levels >0.2 ng/ml and lowest for patients whose postoperative levels were <0.02 ng/ml (Table 3).

3.3. Undetectable ultrasensitive prostate-specific antigen and positive surgical margins

We examined treatment failure rate stratified by surgical margins status at pathology in a subanalysis of patients with undetectable USPSA. Overall, 91 of 525 (17%) patients had positive margins at final pathology, with 79 of 456 (17%) in the undetectable group. Margin status was not associated with postoperative detection of USPSA ($p = 0.99$). The 5-yr BCR-free survival rates of patients with negative and positive margins were 86% and 69%, respectively (log-rank $p < 0.01$). For patients with positive margins, 5-yr failure-free survival was 72% for patients with an undetectable USPSA and 50% for men with a detectable USPSA (log-rank $p = 0.07$; Fig. 2).

3.4. Ultrasensitive prostate-specific antigen and pathologic T3 disease

We examined BCR rate for men with pathologic T3 disease. In all, 151 of 525 (29%) patients had pT3 disease (pT3a: $n = 102$; pT3b: $n = 49$). Of those men, 135 of 151 (89%) had an undetectable USPSA postoperatively. The 5-yr BCR-free survival was 78% for undetectable USPSA and 40% for detectable USPSA in pT3 patients (log-rank $p < 0.01$; Fig. 3). Median time to biochemical relapse was 1.7 yr (range: 0.2–8.5) in the detectable group and 3.9 yr (range: 0.6–10.3) in the undetectable group.

3.5. Multivariate analysis of time to biochemical recurrence

We performed a Cox proportional hazards regression of time to treatment failure with covariates of age at diagnosis, diagnostic PSA, biopsy Gleason score, clinical stage, postoperative USPSA at 6 wk, pathologic Gleason score, pathologic stage, and surgical margin status. Table 3 shows the significant variables established in our model. Patients with undetectable USPSA were 67% less likely to experience a recurrence (hazard ratio: 0.33; 95% confidence interval: 0.20–0.55) than those with detectable USPSA after controlling for other established risk factors. Lower PSA, pathologic Gleason total, tumor stage, and negative surgical margins were also associated with lower risk of treatment failure (Table 4).

4. Discussion

USPSA detection following RP has been shown to provide earlier detection of BCR than standard PSA measurements [5]. However, the prognostic ability of an undetectable USPSA has not been thoroughly evaluated. This study found that an undetectable USPSA 1–3 mo postoperatively was associated with a significant treatment failure advantage compared with men who have a detectable postoperative USPSA regardless of surgical margin status or pathologic stage.

The favorable prognosis of an undetectable USPSA has been noted in other surgical series. Doherty et al noted that in their series of 200 men, only 2 men who had undetectable USPSA later had BCR [6], although the follow-up was limited to 2 yr. Similarly, Shen et al also evaluated patients with undetectable USPSA values. At New York University (NYU), men with USPSA levels <0.01 ($n = 423$) had a recurrence rate of 4% with a mean follow-up time of 3 yr [5]. Shen et al excluded USPSA values from outside laboratories, using only a solitary assay to assess USPSA. The current study uses the USPSA results from several laboratories throughout the country, establishing greater external validity of the current findings. Additionally, our report uses the initial postoperative USPSA rather than nadir, establishing earlier efficacy of the test.

We confirmed the prognostic ability of USPSA in a multivariate model. Not surprisingly, other well-established risk factors, pathologic stage and Gleason score, were also significantly associated with BCR.

An analysis by patient preoperative risk stratification provides evidence of the prognostic utility of an undetectable USPSA. Estimates of biochemical disease-free survival in most large, contemporary series of high-risk patients using the D'Amico et al criteria [10] (PSA >20 , Gleason sum 8–10, AJCC stage T2c) are in the range of 40–60% [10,11]. Our high-risk cohort with undetectable USPSA had a 5-yr BCR-free rate of 71%. It should be noted, however, that there is wide variability among the D'Amico et al high-risk group, and this group may be substratified using a multivariable instrument such as the Cancer of the Prostate Risk Assessment (CAPRA) score [12]. While preoperative low-risk patients had similar low failure rates regardless of USPSA level (90.9% undetectable vs 88.9% detectable), intermediate-risk patients showed marked stratification by USPSA level (88.7% undetectable vs 51.9% detectable). This finding suggests that a detectable USPSA 1–3 mo after RP was predictive of BCR for higher risk patients, a fact that was confirmed by our multivariate analysis. It is important to note, however, that our number of men with a detectable USPSA ($n = 69$) was small, which did limit our analysis somewhat.

The effect of positive surgical margins after RP is controversial. Several groups have shown positive margins to be an independent predictor of BCR [11,13–15], while others have not found this association [16,17]. Our model did find a worse outcome with a positive surgical margin. It is interesting to note that the presence of a positive surgical margin did not predict a detectable USPSA. This suggests that USPSA may be able to predict micrometastatic disease at the time of surgery and the need for secondary therapy rather than acting solely as a surrogate marker for the adequacy of surgical extirpation. While immediate adjuvant therapy is a consideration for patients with adverse pathologic features [18–20], an undetectable USPSA, in light of the current data, would not favor such treatment. Additionally, as earlier salvage therapy with its inherent morbidities is discussed in the literature [21–23], the identification of patients who are most at risk of disease recurrence is crucial. With the use of USPSA, pT3 patients may be stratified into different risk categories. Men with an undetectable postoperative USPSA are at significantly decreased risk of biochemical failure compared with men with a detectable USPSA, and the benefit of adjuvant therapy in this group warrants further investigation. While adding prognostic value, a detectable postoperative USPSA does not perfectly predict ultimate BCR. Indeed, at a cut-off level of 0.05 ng/ml, 66.8% of men with detectable USPSA remained free of biochemical disease at 5 yr. This detection rate was similar to that for a PSA cut-off of 0.1 ng/ml. Nevertheless, a detectable USPSA does place the patient at higher risk for recurrence compared to those with undetectable levels. Not surprisingly, the risk of future BCR after a detectable postoperative PSA rises as the PSA cut-off increases (Table 3). Conversely, lowering the PSA cut-off will lessen the risk of recurrence with a detectable PSA level. Stated another way, a lower USPSA threshold increases the risk of detecting a clinically meaningless PSA rise. While the increased information provided by

USPSA could increase patient anxiety in some patients with detectable USPSA levels, other men with undetectable USPSA levels but poor pathologic features may feel reassured. Additionally, it is important to note that as the lower limit of the serum PSA test falls, the coefficient of variation (CV) of the test itself will rise. The increased CV implies a decline in the reliability of the test at lower PSA values—a fact that should be considered by patients and practitioners.

Our studied end point of BCR itself remains controversial [24,25]. While some studies show few differences in overall mortality between patients with and without BCR [26], other studies show progression to metastatic disease and prostate cancer death [27,28]. Indeed, long-term studies have shown that between 18–34% of patients ultimately progress to metastatic disease, with some patients progressing in as short a time as 1 yr [27,29]. With more younger patients with few comorbidities presenting with prostate cancer than in the past, the risk of prostate cancer mortality may be increased [24,30]. In such cases, earlier information on PSA kinetics may allow for earlier intervention or secondary therapy when there may be an improved chance of altering the disease course [18]. Such suggestions warrant further investigation in prospective studies.

There are limitations to our study beyond the standard problems inherent to retrospective analysis. As a tertiary referral center, many patients are cared for by their local urologist after surgical treatment and are unavailable for follow-up at UCSF. As such, only 39.7% (525 of 1323) of patients who met our surgical inclusion criteria also had adequate 2-yr follow-up for analyses. Separate analyses comparing patients lost to follow-up with those retained for analysis revealed no differences in preoperative or pathologic variables. Thus, we assume this loss to follow-up represents uninformative censoring and should not meaningfully affect our results.

Additionally, the number of patients with a detectable USPSA is relatively small. We used the higher cut-off of ≤ 0.05 ng/ml when identifying undetectable PSA values reported by various laboratories. This selection bias made distinctions between detectable and undetectable patients less robust, thus favoring the null hypothesis. Despite this limitation, we saw significant differences in patient outcomes based on the initial postprostatectomy USPSA level, and the minimum of 2 yr of postsurgery follow-up data strengthened our findings.

5. Conclusions

An undetectable USPSA after RP is a useful prognostic indicator of BCR-free survival at 5 yr that may aid in postoperative risk stratification and yield an earlier assessment of postoperative PSA kinetics. While an undetectable postoperative USPSA can reassure patients with unfavorable pathology, a detectable USPSA may cause unnecessary anxiety in patients who never suffer formal BCR.

Acknowledgments

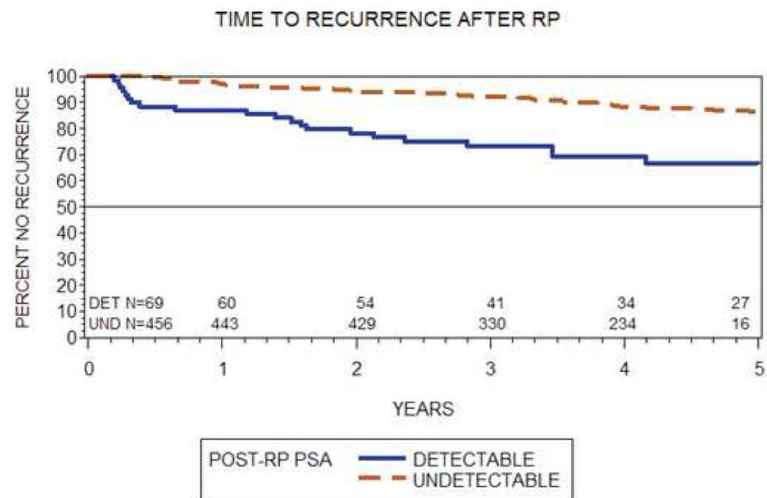
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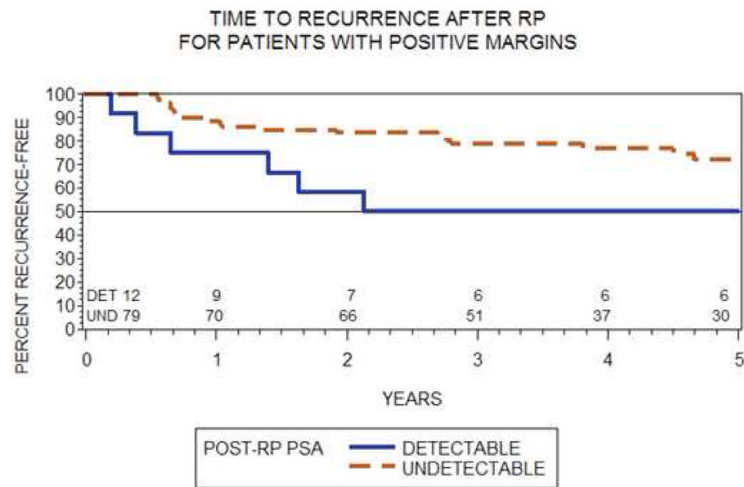
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PSA 1-3MO POST-RP	TOTAL N	RECUR RED WITHIN 5YRS N	FREE OF RECURRENCE 1YR %	2YRS %	3YRS %	4YRS %	5YRS %
DETECTABLE	69	21	87.0	78.3	73.3	69.2	66.8
UNDETECTABLE	456	51	97.1	94.1	92.0	88.3	85.9

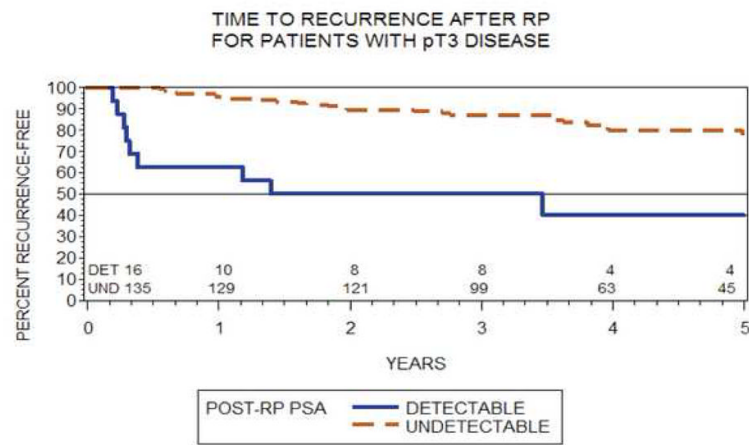
Fig. 1. Kaplan-Meier curves for detectable ultrasensitive prostate-specific antigen (USPSA) and undetectable USPSA to failure-free survival (log-rank $p < 0.01$)

RP = radical prostatectomy; Det = detectable; Und = undetectable; PSA = prostate-specific antigen.



PSA 1-3MO POST-RP	TOTAL N	RECUR RED WITHIN 5YRS N	FREE OF RECURRENCE 1YR %	2YRS %	3YRS %	4YRS %	5YRS %
DETECTABLE	12	6	75.0	58.3	50.0	50.0	50.0
UNDETECTABLE	79	19	88.6	83.5	78.9	76.8	72.2

Fig. 2. Kaplan-Meier curves of failure-free survival in patients with positive surgical margins stratified by ultrasensitive prostate-specific antigen level (log-rank $p = 0.07$)
RP = radical prostatectomy; Det = detectable; Und = undetectable; PSA = prostate-specific antigen.



PSA 1-3MO POST-RP	TOTAL N	RECUR RED WITHIN 5YRS N	FREE OF RECURRENCE 1YR %	2YRS %	3YRS %	4YRS %	5YRS %
DETECTABLE	16	9	62.5	50.0	50.0	40.0	40.0
UNDETECTABLE	135	24	95.6	89.6	87.0	79.9	78.2

Fig. 3. Kaplan-Meier curves of failure-free survival in patients with pT3 disease stratified by ultrasensitive prostate-specific antigen level (log-rank $p \leq 0.01$)
RP = radical prostatectomy; Det = detectable; Und = undetectable; PSA = prostate-specific antigen.

Table 1

Baseline characteristics of detectable and undetectable patients

	Detectable		Undetectable		p-value
	n	%	n	%	
Age at diagnosis	12	17	101	22	0.38
	39	57	266	58	
	18	26	89	20	
Race	59	87	391	91	0.23
	9	13	37	9	
Relationship	51	75	377	86	0.02
	17	25	61	14	
PSA (ng/ml) at diagnosis	27	39	228	50	0.09
	42	61	228	50	
	27	39	158	35	
cT stage	42	61	298	65	0.47
	40	58	265	58	
Biopsy Gleason	29	42	191	42	0.98
	18	35	177	54	
Percent biopsy cores positive	25	48	107	33	0.03
	9	17	45	14	
	27	39	164	36	
D'Amico et al clinical risk group	25	36	206	45	0.32
	17	25	86	19	
	24	49	172	52	
CAPRA clinical risk group	19	39	136	41	0.38
	6	12	22	7	
	21	33	158	36	
Gleason at pathology	43	67	279	64	0.60
	57	83	377	83	
Positive margins	12	17	79	17	0.99

PSA = prostate-specific antigen; CAPRA = Cancer of the Prostate Risk Assessment.

Table 2

Failure-free survival stratified by D'Amico et al [10] clinical risk stratification and ultrasensitive prostate-specific antigen (USPSA) level

USPSA	Preoperative risk category	Total n	Recurred within 5 yr, n	Free of failure [*] , %				
				1 yr	2 yr	3 yr	4 yr	5 yr
Undetectable	Low	164	10	98.2	97.6	96.8	92.6	90.9
	Intermediate	206	19	96.6	94.7	92.4	90.9	88.7
	High	86	22	96.5	86.0	82.2	74.7	70.7
Detectable	Low	27	3	92.6	88.9	88.9	88.9	88.9
	Intermediate	25	11	92.0	80.0	67.3	57.7	51.9
	High	17	7	70.6	58.8	58.8	58.8	58.8

PSA = prostate-specific antigen.

* Failure defined as two consecutive PSA values ≥ 0.2 ng/ml or secondary treatment.

Table 3

Five-year biochemical recurrence-free survival (BFS) rates for detectable versus undetectable prostate-specific antigen (PSA) cut-off levels of 0.2, 0.1, 0.05, and 0.02 ng/ml taken 1–3 mo postprostatectomy

PSA level*	n at risk(total)	n at risk at 5 yr	BFS at 5 yr, %	CI for BFS at 5 yr, %	Log-rank p-value
≥0.02	169	73	73	64–81	<0.01
<0.02	356	113	88	81–93	
≥0.05	69	27	67	50–79	<0.01
<0.05	456	160	86	80–90	
≥0.1	60	26	68	51–80	<0.01
<0.1	465	161	85	79–90	
≥0.2	17	6	50	21–74	<0.01
<0.2	508	175	85	79–89	

CI = 95% confidence interval.

* Total number of men (out of 525 total) with detectable and undetectable PSA levels at each PSA cut-off level listed at baseline and at 5 yr.

Table 4

Multivariate proportional hazards regression predicting treatment failure*

		<i>p</i> -value	Hazard ratio	95% confidence interval
Age at diagnosis	Trend	0.14	–	–
	55–64 vs ≥65	0.22	0.73	0.45–1.21
	<55 vs ≥65	0.05	0.49	0.24–1.01
PSA at diagnosis	Trend	0.01	–	–
	4.1–6 vs ≥10.1	0.001	0.38	0.21–0.68
	6.1–10 vs ≥10.1	0.03	0.56	0.32–0.95
	<4 vs ≥10.1	0.20	0.57	0.24–1.35
Biopsy Gleason total	<7 vs ≥7	0.07	0.63	0.38–1.04
T-stage at diagnosis	cT1 vs cT2/3	0.91	0.97	0.61–1.56
Surgical margins	Negative vs positive	0.001	0.46	0.29–0.74
	USPSA 4–12 wk post-RP	Undetectable vs detectable	<0.0001	0.33–0.20
Pathologic Gleason total	<7 vs ≥7	0.01	0.39	0.20–0.79
	T-stage at pathology	pT2 vs pT3	0.001	0.48–0.30

PSA = prostate-specific antigen; USPSA = ultrasensitive prostate-specific antigen; RP = radical prostatectomy.

* Failure defined as two consecutive PSA values ≥0.2 ng/ml or secondary treatment.