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Comparison of Observed Biochemical Recurrence Free Survival in Patients with Low PSA Values Undergoing Radical Prostatectomy to the Predictions of a Preoperative Nomogram

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Abstract

Objectives—A preoperative nomogram is an effective tool for assessing the risk of disease progression following radical prostatectomy for localized prostate cancer. To better understand the performance of nomograms for patients with a low PSA, we examined whether patients with PSA < 2.5 had different outcomes versus that predicted by a validated preoperative nomogram.

Methods—A cohort of 6130 patients from two referral centers was analyzed. Kaplan-Meier methods were used to estimate the recurrence-free probabilities based on PSA grouping (< 2.5 vs ≥ 2.5 ng/mL). Cox proportional hazards regression was used to evaluate whether PSA grouping was associated with biochemical recurrence controlling for preoperative nomogram probability.

Results—A total of 399/6130 (6.5%) patients had PSA < 2.5. Patients with PSA ≤ 0.5 had a high rate of non-organ confined disease (33% vs. 15% for PSA 0.6 – 2.5). The median follow-up for recurrence-free patients was 2.4 years, and 10 patients with PSA < 2.5 and 597 patients with PSA > 2.5 recurred (total 607/6130). With adjustment for the preoperative nomogram probability, there was no significant difference in recurrence by PSA grouping (hazard ratio 0.78 for PSA <2.5 vs ≥2.5; 95% C.I. 0.42, 1.48; p=0.5).

Conclusions—Patients with a low PSA comprise a small proportion of those treated, and the majority have palpable disease. Patients with especially low PSA values (≤ 0.5) have a high rate of non-organ confined disease. We saw no evidence that patients with low PSA have worse outcomes, after stage and grade were taken into account.

Keywords

prostate cancer; PSA; nomogram

Prostate cancer is the second leading cause of cancer death among men in the US, and it is expected to account for 27,050 deaths in 2007. But with an incidence-to-mortality ratio of roughly 8 to 1, most patients diagnosed with prostate cancer will die of other causes.1 Most men in a screening population (≥ 50 years old) have a low serum PSA value of < 4 ng/ml, but a significant proportion of these men, about 15%, have detectable prostate cancer if biopsied. 2 It is estimated that roughly 40% of detectable prostate cancers occur in men with low PSA values, so the clinical significance of cancers in patients with low PSA values is in question.

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3 What is apparent is that treating prostate cancer does improve disease specific and overall survival, and patients with long enough life expectancies (> 15 years) have an increasing likelihood of dying of prostate cancer the longer that they have a diagnosis of untreated prostate cancer.4–7

The AUA Best Practice Guidelines from 2000 recommend a prostate biopsy threshold for biopsy of 4.0 ng/ml, but more contemporary screening recommendations suggest the use of a set point of PSA > 2.5 ng/ml to trigger a prostate biopsy based on the observation that using this set point increased the likelihood of diagnosing organ confined cancers to 88%.[8] Most patients that are biopsied with a PSA < 2.5 ng/ml have other significant prostate cancer risk factors, including suspicious findings on DRE, a strong family history, or an increasing PSA velocity. These additional risk factors contribute to the observation that a higher than expected number of patients diagnosed with cancer at these low PSA values have aggressive features at biopsy.[9]

A validated preoperative prostate cancer nomogram using some of these risk factors is an effective tool for assessing the risk of recurrence of prostate cancer after treatment.[10,11] One criticism of using a nomogram in the setting of patients with low PSA values is that nomograms are less accurate in making predictions when evaluating extreme values, such as a low PSA.[12,13] In this study, we examined whether patients with a PSA < 2.5 ng/ml have different outcomes compared to the predictions of a preoperative nomogram in a large cohort of patients treated with RP at three referral centers.

Materials and Methods

An Institutional Review Board approved retrospective study was conducted on consecutive patients undergoing radical prostatectomy from Baylor and Memorial-Sloan Kettering treated from 1987 to 2006 (6225 patients) and from Cleveland Clinic from 1991 to 2007 (4213 patients). Exclusion criteria included patients undergoing salvage or perineal RP, patients with missing data for predictors in the nomogram, and patients who received neoadjuvant hormonal therapy. In all, 6130 patients between both groups were evaluated, with 3762 from Baylor and MSKCC and 2368 from Cleveland Clinic. Demographic and clinical data were compared.

For an initial descriptive analysis, patients were grouped according to PSA range, including 0 – 0.5 ng/ml, 0.6 – 1.0 ng/ml, 1.1 – 2.0 ng/ml, 2.1 – 3.0 ng/ml, and > 3.0 ng/ml, which are the same groupings as evaluated in the Prostate Cancer Prevention Trial. .[2] Pathologic features and Kaplan-Meier 5-year recurrence free probability at the time of RP were summarized. Recurrence was defined as either biochemical or clinical. A biochemical recurrence included patients with a follow up PSA value ≥ 0.2 ng/ml with a confirmatory level. Clinical recurrence included evidence of local and/or metastatic progression of disease diagnosed at follow up and/or the initiation of salvage therapy (e.g. radiation or hormonal therapy). The groups were further subdivided according to whether the patient had non-palpable (AJCC 1992 clinical stage T1) or palpable (AJCC 1992 clinical stage T2 or greater) disease, and pathologic features and Kaplan-Meier 5-year recurrence free probability was summarized in these groups as well.

Patients were then grouped according to low versus elevated PSA values based on current screening recommendations (< 2.5 ng/ml versus ≥ 2.5 ng/ml). Cox proportional hazards regression was used to evaluate whether PSA grouping was associated with biochemical recurrence following surgery, controlling for the predictions for those patients made by the Stephenson et al 2006 updated preoperative nomogram.[11] By controlling for the preoperative nomogram, the estimate and p-value for the indicator of low versus elevated PSA tell us whether these patients have different outcomes compared to what would be expected using standard prognostic tools. This was done in the entire cohort and according to Gleason score

(≤ 6, 7, or ≥ 8). All statistical analyses were conducted using Stata 9.0 (Stata Corp., College Station, TX).

Results

In all, 399/6130 (6.5%; 95% C.I. 5.9%, 7.1%) patients had a PSA < 2.5 ng/ml. Patient demographic and clinical data in the two groups are shown in Table 1. Patients in the low PSA group were a median 2 years younger and had more cases with palpable disease (57% versus 32%). Patients in the elevated PSA group, though, had a higher biopsy Gleason score (Gleason ≥ 7 in 37% versus 22%) and a higher pathologic Gleason score (Gleason ≥ 7 in 64% versus 44%). The rate of non-organ confined disease at RP was also much higher in the elevated PSA group (30% versus 16%).

The pathologic features stratified by PSA groupings are demonstrated in Table 2. In Table 2a, we observe that, among patients with low PSA, the majority have PSA value greater than 0.5 ng/ml (568/593 or 96%). These patients had lower rates of Gleason score ≥ 7 and non-organ confined disease compared to patients in the > 3.0 ng/ml group. The 25 patients with PSA 0 – 0.5 ng/ml, however, had the highest rate of non-organ confined disease (32%). Table 2b evaluates patients with non-palpable disease by PSA grouping. The low PSA patients across all groups have lower Gleason scores and pathologic stage than the PSA > 3.0 ng/ml patients, although 50% (4/8) of patients in the PSA 0 – 0.5 group had ECE. Similarly, among patients with palpable disease (Table 2c), all low PSA groupings have a lower rate of high grade and stage disease. In general, patients with PSA > 3 ng/ml had a lower 5-year recurrence-free probability compared to patients with PSA ≤ 3; however, patients with PSA 0 – 0.5 ng/ml also tended to have unfavorable recurrence-free probabilities, likely due to advanced stage.

There were 607 recurrences overall, with 10 among the patients with PSA < 2.5 ng/ml and 597 among patients with PSA ≥ 2.5 ng/ml. The median follow up for recurrence free patients was 2.4 years. The 5-year Kaplan-Meier recurrence-free probability was 85% (95% CI 84%, 86%) for patients with PSA ≥ 2.5 ng/ml and 94% (95% CI 88%, 97%) for patients with PSA < 2.5 ng/m; the respective 5-year progression-free probability from the preoperative nomogram was 90% and 97%. With Cox regression analysis, we found no evidence that patients with PSA < 2.5 ng/ml had different outcomes from those expected from the preoperative nomogram (hazard ratio 0.78 for low vs elevated PSA; 95% C.I. 0.42, 1.48; p = 0.5) (Table 3). Similarly, we found no significant association between PSA < 2.5 ng/ml and recurrence, with adjustment for the preoperative nomogram, within the subsets of pathologic Gleason score. In the subset with Gleason score ≤ 6, the adjusted hazard ratio for low vs elevated PSA was 0.77 (95% C.I. 0.18, 3.30); for Gleason score 7 and Gleason score ≥ 8, the corresponding figures were, respectively, 0.37 (95% C.I. 0.12, 1.18) and 0.95 (95% C.I. 0.38, 2.36).

We performed a sensitivity analysis excluding patients treated at Baylor or Memorial-Sloan Kettering prior to 2003; these patients were included in the cohort that created the preoperative nomogram, and therefore the performance of the preoperative nomogram could be overoptimistic in these patients. The remaining 4020 patients (all 2368 patients treated at Cleveland Clinic and 1652 patients treated at Memorial-Sloan Kettering from 2003 – 2006) comprised an independent group of patients from those used to build the nomogram. There was no important difference in results: on multivariable analysis, the hazard ratio for normal vs elevated PSA was 0.70 (95% C.I. 0.29, 1.72; p=0.4). We additionally performed a sensitivity analysis restricting the data set to those 2368 patients treated at Cleveland Clinic; the results were again very similar to our main analysis (hazard ratio 0.75; 95% C.I. 0.27, 2.04; p=0.6). We can therefore be confident that our results are robust to inclusion of patients used to build the preoperative nomogram.

Comment

Frequent screening for prostate cancer in the United States with DRE and PSA has lead to stage migration, improved survival rates, and a widening incidence to mortality ratio.[14,15] Treatment with surgery provides a survival advantage in patients with intermediate or high risk disease undergoing RP compared to delayed therapy at the time of symptomatic progression, but the effect is small and limited to younger men.[4] Many patients with low-risk tumor characteristics are currently being treated, and these usually have favorable features at pathologic evaluation.[16] Given the negative effects that RP can have on health related quality of life,[17] care must be taken when determining what patients need to undergo prostate biopsy and ultimately treatment.

Currently, a widely used PSA threshold to trigger a biopsy is a PSA value of 2.6 ng/ml or greater. This is based on the observation that detection of small, OC tumors increased to 88% at a value of 2.6 ng/ml versus 63% using a value of 4.0 ng/ml, while clinically insignificant tumors (OC, volume <0.5 cm^3, Gleason score ≤6) were not overdetected.[8] Therefore, a higher proportion of prostate cancers currently diagnosed at a PSA value ≤2.5 are detected through an abnormal DRE (clinical stage T2a or higher) or increasing PSA velocity.[9,16,18]

In our series, low-PSA patients were more likely to have clinical stage T2a or greater disease (57% versus 32%) as this was often the trigger for biopsy, but were less likely to have unfavorable tumor characteristics at biopsy (Gleason score ≥7 in 22% versus 37%). Although we have previously shown that DRE has a poor predictive value for cancer detection at low PSA values, in our study the majority of low-PSA cases were detected on DRE, and we have shown that location of a lesion on DRE usually corresponds to location of the tumor on biopsy.[19] A Dutch study underscores the low-yield of the DRE in detecting cancers in patients with a PSA <3 ng/ml, where 289 DRE are performed for every clinically significant cancer detected.[20] Not surprisingly, patients with a PSA ≤2.5 ng/ml accounted for only 6.5% of all of our cases.

Cancer detection based on lower-limits of absolute PSA values can miss a significant amount of disease, as reflected in the PCPT. At the termination of that study in patients with a normal DRE, 17% of patients with a PSA of 1–2 ng/ml and 23.9% of patients with a PSA of 2–3 ng/ml had biopsy proven prostate cancer.2 No set-point for PSA value in triggering a biopsy in that study provided an equally sensitive and specific value from which to make a biopsy recommendation.[21] After biopsy, a preoperative nomogram provides excellent performance characteristics when compared to other currently available prediction tools, although nomograms often perform poorly at extremes (for example in very low-risk or very high-risk disease).[10,12,13]

The preoperative nomogram functioned as a robust model in our study with no statistically significant difference in biochemical recurrence free survival for patients with extreme values on the low end of PSA. In our series, patients with PSA < 2.5 ng/ml accounted for only a small portion of all cases treated (6.5%), and the majority of these cases were detected due to an abnormal DRE (57%). The unusual cases of patients with very low PSA values (0 – 0.5 ng/ml) had a high rate of non-organ confined disease (32%), but the small number of cases limited any conclusions that could be made about the unfavorable 5-year recurrence free probability in this group (76%; 95% C.I. 24%, 95%). Although some unusual types of prostate cancer can be of high-risk at a low PSA value, such as that found in some hypogonadal men and in rare recurrences after radiation treatment and surgery, these types of disease are usually clinically suspected prior to intervention because of high-risk features on their biopsy specimens.[22–24] In our series, additional risk factors in our low PSA patients such as higher Gleason score

and clinical stage were factored in to the predictions of the nomogram, leading to its robustness in patients with low PSA.

The limitations of this study include its retrospective nature and its reliance on patients referred to tertiary centers.

Conclusions

Patients with a low PSA comprise a small proportion of those treated, and the majority have palpable disease. Patients with especially low PSA values (≤ 0.5) have a high rate of non-organ confined disease. We saw no evidence that patients with low PSA had worse outcomes, after stage and grade were taken into account.

Abbreviations and Acronyms

AJCC	American Joint Committee on Cancer
DRE	digital rectal exam
ECE	extracapsular extension
PCPT	Prostate Cancer Prevention Trial
PSA	prostate specific antigen
RP	radical prostatectomy

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Table 1

Patient Characteristics for all patients. Data are represented as median (interquartile range) or frequency (percentage).

	PSA < 2.5ng/ml N=399	PSA ≥ 2.5ng/ml N=5731
Age at surgery (years)	58 (53, 63)	60 (55, 65)
Preoperative PSA (ng/ml)	1.65 (1.07, 2.18)	5.90 (4.55, 8.20)
Preoperative 5-year recurrence-free probability (%)	97 (96, 98)	94 (88, 96)
Clinical stage ≥ T2	228 (57%)	1820 (32%)
Biopsy Gleason grade		
≤ 6	311 (78%)	3602 (63%)
7	72 (18%)	1765 (31%)
≥ 8	16 (4%)	364 (6%)
Pathology Gleason grade (n=6062)		
≤ 6	213 (53%)	1985 (35%)
7	160 (40%)	3266 (57%)
≥ 8	17 (4%)	421 (7%)
Extracapsular extension (n=6070)	59 (15%)	1629 (29%)
Seminal vesicle invasion (n=6093)	10 (3%)	382 (7%)
Positive surgical margins (n=6095)	43 (11%)	1339 (23%)
Lymph node involvement*	8 (2%)	192 (3%)
Non-organ confined** (n=6056)	62 (16%)	1711 (30%)

* Patients without a lymph node dissection (n=1797) were considered as having negative lymph nodes.

** Presence of extracapsular extension, seminal vesicle invasion, or lymph node involvement

Table 2

Table 2a. Pathologic features and Kaplan-Meier 5-year recurrence-free probabilities by PSA group. Data are represented as frequency (proportion) unless otherwise noted.

Pathologic Features	Pretreatment PSA (ng/ml)				
	0–0.5	**0.6–1.0**	**1.1–2.0**	**2.0–3.0**	**>3.0**
	N=25	**N=66**	**N=176**	**N=326**	**N=5537**
Pathologic Gleason					
<=6	11 (44%)	50 (76%)	98 (56%)	158 (48%)	1881 (34%)
7	9 (36%)	14 (21%)	67 (38%)	154 (47%)	3182 (57%)
>=8	3 (12%)	2 (3%)	6 (3%)	11 (3%)	416 (8%)
Unknown	2 (8%)	0 (0%)	5 (3%)	3 (1%)	58 (1%)
Extracapsular Extension					
No	16 (64%)	59 (89%)	153 (87%)	258 (79%)	3896 (70%)
Yes	8 (32%)	7 (11%)	20 (11%)	60 (18%)	1593 (29%)
Unknown	1 (4%)	0 (0%)	3 (2%)	8 (2%)	48 (1%)
Seminal Vesicle Invasion					
No	22 (88%)	65 (98%)	171 (97%)	313 (96%)	5130 (93%)
Yes	2 (8%)	1 (2%)	3 (2%)	9 (3%)	377 (7%)
Unknown	1 (4%)	0 (0%)	2 (1%)	4 (1%)	30 (1%)
Lymph Node Involvement					
No	24 (96%)	64 (97%)	173 (98%)	323 (99%)	5346 (97%)
Yes	1 (4%)	2 (3%)	3 (2%)	3 (1%)	191 (3%)
Non-Organ Confined					
No	16 (64%)	58 (88%)	153 (87%)	255 (78%)	3801 (69%)
Yes	8 (32%)	8 (12%)	20 (11%)	62 (19%)	1675 (30%)
Unknown	1 (4%)	0 (0%)	3 (2%)	9 (3%)	61 (1%)

Table 2a. Pathologic features and Kaplan-Meier 5-year recurrence-free probabilities by PSA group. Data are represented as frequency (proportion) unless otherwise noted.

Pathologic Features	Pretreatment PSA (ng/ml)				
	0–0.5	**0.6–1.0**	**1.1–2.0**	**2.0–3.0**	**>3.0**
	N=25	**N=66**	**N=176**	**N=326**	**N=5537**
5-Year Recurrence-free Probability (95% C.I.)	76% (24%, 95%)	100%	92% (82%, 96%)	97% (93%, 99%)	85% (83%, 86%)

Table 2b. Patients with low clinical stage (T1). Pathologic features and Kaplan-Meier 5-year recurrence-free probabilities by PSA group. Data are represented as frequency (proportion) unless otherwise noted.

Pathologic Features	Pretreatment PSA (ng/ml)				
	0–0.5	**0.6–1.0**	**1.1–2.0**	**2.0–3.0**	**>3.0**
	N=8	**N=26**	**N=65**	**N=183**	**N=3800**
Pathologic Gleason					
<=6	4 (50%)	21 (81%)	41 (63%)	103 (56%)	1467 (39%)
7	4 (50%)	5 (19%)	18 (28%)	75 (41%)	2114 (56%)
>=8	0 (0%)	0 (0%)	3 (5%)	3 (2%)	191 (5%)
Unknown	0 (0%)	0 (0%)	3 (5%)	2 (1%)	28 (1%)
Extracapsular Extension					
No	4 (50%)	26 (100%)	57 (88%)	158 (86%)	2923 (77%)
Yes	4 (50%)	0 (0%)	6 (9%)	19 (10%)	845 (22%)
Unknown	0 (0%)	0 (0%)	2 (3%)	6 (3%)	32 (1%)
Seminal Vesicle Invasion					
No	8 (100%)	26 (100%)	63 (97%)	178 (97%)	3615 (95%)
Yes	0 (0%)	0 (0%)	1 (2%)	3 (2%)	165 (4%)
Unknown	0 (0%)	0 (0%)	1 (2%)	2 (1%)	20 (1%)
Lymph Node Involvement					
No	8 (100%)	25 (96%)	64 (98%)	182 (99%)	3740 (98%)
Yes	0 (0%)	1 (4%)	1 (2%)	1 (1%)	60 (2%)
Non-Organ Confined					

Table 2b. Patients with low clinical stage (T1). Pathologic features and Kaplan-Meier 5-year recurrence-free probabilities by PSA group. Data are represented as frequency (proportion) unless otherwise noted.

Pathologic Features	Pretreatment PSA (ng/ml)				
	0–0.5	**0.6–1.0**	**1.1–2.0**	**2.0–3.0**	**>3.0**
	N=8	**N=26**	**N=65**	**N=183**	**N=3800**
No	4 (50%)	25 (96%)	57 (88%)	157 (86%)	2877 (76%)
Yes	4 (50%)	1 (4%)	6 (9%)	20 (11%)	882 (23%)
Unknown	0 (0%)	0 (0%)	2 (3%)	6 (3%)	41 (1%)
5-Year Recurrence-Free Probability (95% C.I.)	100%	100%	86% (61%, 96%)	97% (89%, 99%)	89% (88%, 91%)

Table 2c. Patients with high clinical stage (T2 or higher). Pathologic features and Kaplan-Meier 5-year recurrence-free probabilities by PSA group. Data are represented as frequency (proportion) unless otherwise noted.

Pathologic features	Pretreatment PSA (ng/ml)				
	0–0.5	**0.6–1.0**	**1.1–2.0**	**2.0–3.0**	**>3.0**
	N=17	**N=40**	**N=111**	**N=143**	**N=1737**
Pathologic Gleason					
<=6	7 (41%)	29 (73%)	57 (51%)	55 (38%)	414 (24%)
7	5 (29%)	9 (23%)	49 (44%)	79 (55%)	1068 (61%)
>=8	3 (18%)	2 (5%)	3 (3%)	8 (6%)	225 (13%)
Unknown	2 (12%)	0 (0%)	2 (2%)	1 (1%)	30 (2%)
Extracapsular Extension					
No	12 (71%)	33 (83%)	96 (86%)	100 (70%)	973 (56%)
Yes	4 (24%)	7 (18%)	14 (13%)	41 (29%)	748 (43%)
Unknown	1 (6%)	0 (0%)	1 (1%)	2 (1%)	16 (1%)
Seminal Vesicle Invasion					
No	14 (82%)	39 (98%)	108 (97%)	135 (94%)	1515 (87%)
Yes	2 (12%)	1 (3%)	2 (2%)	6 (4%)	212 (12%)
Unknown	1 (6%)	0 (0%)	1 (1%)	2 (1%)	10 (1%)
Lymph Node Involvement					

Table 2c. Patients with high clinical stage (T2 or higher). Pathologic features and Kaplan-Meier 5-year recurrence-free probabilities by PSA group. Data are represented as frequency (proportion) unless otherwise noted.

Pathologic features	Pretreatment PSA (ng/ml)				
	0–0.5	**0.6–1.0**	**1.1–2.0**	**2.0–3.0**	**>3.0**
	N=17	**N=40**	**N=111**	**N=143**	**N=1737**
No	16 (94%)	39 (98%)	109 (98%)	141 (99%)	1606 (92%)
Yes	1 (6%)	1 (3%)	2 (2%)	2 (1%)	131 (8%)
Non-Organ Confined					
No	12 (71%)	33 (83%)	96 (86%)	98 (69%)	924 (53%)
Yes	4 (24%)	7 (18%)	14 (13%)	42 (29%)	793 (46%)
Unknown	1 (6%)	0 (0%)	1 (1%)	3 (2%)	20 (1%)
5-Year Recurrence-Free Probability (95% C.I.)	75% (13%, 96%)	100%	94% (81%, 98%)	97% (92%, 99%)	77% (74%, 79%)

Table 3

Cox proportional hazards regression. Hazard ratios and p-values presented are for normal vs elevated PSA, controlling for the preoperative nomogram.

	Number of patients	Hazard ratio (95% C.I.)	P value
All patients	6130		
PSA < 2.5	399	0.78 (0.42, 1.48)	0.5
PSA ≥ 2.5	5731	Reference	
Pathologic Gleason ≤ 6	2198		
PSA < 2.5	213	0.77 (0.18, 3.30)	0.7
PSA ≥ 2.5	1985	Reference	
Pathologic Gleason 7	3426		
PSA < 2.5	160	0.37 (0.12, 1.18)	0.10
PSA ≥ 2.5	3266	Reference	
Pathologic Gleason ≥ 8	438		
PSA < 2.5	17	0.95 (0.38, 2.36)	0.9
PSA ≥ 2.5	421	Reference	