

BIOCHEMICAL (PROSTATE SPECIFIC ANTIGEN) RECURRENCE PROBABILITY FOLLOWING RADICAL PROSTATECTOMY FOR CLINICALLY LOCALIZED PROSTATE CANCER

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ABSTRACT

Purpose: We retrospectively reviewed the clinical followup for a large series of men with clinically localized prostate cancer who underwent radical retropubic prostatectomy to identify clinical and/or pathological indicators of biochemical (prostate specific antigen [PSA]) recurrence. We then used those indicators to develop multivariate models for determination of recurrence probability following radical retropubic prostatectomy.

Materials and Methods: From 1982 to 1999, 2,091 consecutive men underwent radical retropubic prostatectomy and pelvic lymphadenectomy for clinically localized adenocarcinoma of the prostate (clinical stage T1c or T2 disease with Gleason score 5 or greater). Actuarial analysis was performed comparing freedom from biochemical recurrence after radical retropubic prostatectomy (PSA 0.2 ng/ml. or greater.) using the Kaplan-Meier method. Event time distributions for the time to recurrence were compared using the log rank statistic or the Cox proportional hazards regression model. The first model was developed using preoperative variables only and the second model using all available variables. Observed and predicted recurrence-free survival curves for different models were compared to select a model for calculation of predicted recurrence-free probabilities and confidence intervals.

Results: With a median followup of 5.9 years (range 1 to 17) 360 men (17%) had biochemical recurrence. Overall actuarial 5, 10 and 15-year biochemical recurrence-free survival rates were 84%, 72% and 61%, respectively. The relative risk of biochemical recurrence following surgery decreased with time, even after adjusted for other perioperative parameters. Variables identified for the preoperative model were biopsy Gleason score, clinical TNM stage and PSA. Variables identified for the postoperative model were prostatectomy Gleason score, PSA and pathological organ confinement status. Nomograms were generated and corrected for the decreasing relative risk of biochemical recurrence over time.

Conclusions: Using 3 preoperative or postoperative parameters, these nomograms can easily be used to determine the 3, 5, 7 and 10-year biochemical recurrence-free survival probabilities among men who undergo radical retropubic prostatectomy for clinically localized prostate cancer in the modern era.

KEY WORDS: prostatectomy, recurrence, prognosis, neoplasms

Cancer recurrence is a concern for men undergoing definitive treatment with curative intent for localized prostate cancer. Especially for those men who decide to undergo radical prostatectomy for clinically localized prostate cancer, nearly 30% are reported to experience an isolated increase in serum prostate specific antigen (PSA) with long-term followup.^{1–8} Therefore, patients and treating physicians want to know the probability of recurrence following surgery based on preoperative and/or postoperative parameters, such as tumor stage, grade and PSA when making treatment decisions.

Many clinical and pathological variables, individually or in combination, have been shown to indicate the probability of recurrence following radical prostatectomy.^{2–8} However, it is unclear which variable or combination of variables accurately indicates tumor recurrence for the individual patient. In addition, there has been a significant downward stage migration of prostate cancer with an increasing proportion of

men presenting with organ confined disease during the last 2 decades.⁹ An ideal statistical model should easily and reliably indicate long-term biochemical recurrence following radical retropubic prostatectomy with adjusted risk factors because of a downward stage migration of prostate cancer in the modern era. We retrospectively reviewed a large series of men who underwent radical retropubic prostatectomy to identify clinical and pathological indicators of biochemical recurrence of disease. We then used those indicators to develop multivariate models, adjusted for the change in relative risk of biochemical recurrence over time, for the determination of biochemical recurrence-free survival probability following radical retropubic prostatectomy in the modern era.

MATERIALS AND METHODS

Patient population and inclusion criteria. Between April 1982 and February 1999, 2,494 men with clinically localized adenocarcinoma of the prostate (clinical T1, T2 and T3a) underwent staging pelvic lymphadenectomy and radical retropubic prostatectomy. Of these men 2,091 (83.8%) were in-

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cluded in the current analysis. We excluded 90 men (3.6%) from the analysis due to insufficient followup (15), clinical stage D0/D2 disease (9), preoperative radiation therapy (3), immediate postoperative adjuvant radiation therapy based on poor pathological features (30), neoadjuvant hormonal therapy (17), immediate postoperative adjuvant hormonal therapy (15) and immediate postoperative mortality (1). We also excluded 233 men from the study for T1a/b (177) or T3a (56) disease since the proportion of men with those stages of disease decreased significantly in a contemporary radical retropubic prostatectomy series.⁹ A total of 80 men were excluded from the study for Gleason score less than 5 (biopsy 64 and radical prostatectomy specimen 16) since typically radical retropubic prostatectomy is performed on patients with Gleason score 5 or greater 5 disease.⁹

The average age of the 2,091 men at the time of surgery was 58.1 ± 6.6 years (range 33 to 76). A total of 845 (40%) and 1,246 (60%) had T1c and T2 disease, respectively. Of the 1,872 men with available preoperative serum PSA level 452 (24%) had a PSA of less than 4 ng./ml. while 1,021 (55%) had PSA ranging from 4.1 to 10 ng./ml. The remaining 399 men (21%) had PSA greater than 10 ng./ml. Table 1 summarizes the disease characteristics of the 2,091 men according to clinical stage, preoperative PSA, postoperative Gleason score and final pathological stage.

Preoperative and postoperative evaluation and pathological characteristics. Cases were staged according to the 1992 American Joint Committee on Cancer staging guidelines with digital rectal examination by a single surgeon and routine serum PSA assays (Hybritech Tandem-R and E, Beckman Coulter, San Diego, California, and TOSOH, Tosoh Medics, S. San Francisco, California).¹⁰ Also a serum enzymatic acid phosphatase level was measured (Roy assay), and a nuclear bone scan was performed on all patients until the last 5 years when bone scans were mandated only on men with PSA greater than 10 ng./ml. Pathological diagnosis of adenocarcinoma of the pros-

tate was based on examination of prostate tissue from digitally or transrectal ultrasound guided prostate biopsy. The Gleason scoring system was used for histological grading of the needle biopsy and prostatectomy specimens. Surgical specimens were examined as previously described.^{2, 11, 12}

Postoperative followup consisted of digital rectal examination and serum PSA measurements at quarterly intervals for the first year, semiannually for the second year and yearly thereafter. Bone scans were performed at the time of initial biochemical recurrence and on a yearly basis thereafter, unless performed earlier for symptoms suggestive of distant metastatic disease. No patients included in this analysis received neoadjuvant chemotherapy or hormonal therapy. No patients received immediate adjuvant hormonal or radiation therapy based on pathological features. Therefore, adjuvant hormonal therapy or chemotherapy had no impact on the time to biochemical progression in this analysis. Minimum followup was 1 year.

Statistical methods to build biochemical recurrence prediction models. Available preoperative parameters for multivariate analysis were age, clinical TNM stage (categorical, table 1), Gleason score from biopsy specimen (categorical), PSA (categorically divided into 4.0 or less, 4.1 to 10.0, 10.1 to 20.0 and greater than 20.0 ng./ml.) and acid phosphatase level. Available postoperative variables were organ confinement, focal extraprostatic extension, extensive extraprostatic extension, lymph node involvement, seminal vesicle invasion, surgical margin status and Gleason score from surgical specimen (categorical, table 1).

Actuarial analysis was performed comparing freedom from biochemical recurrence after radical retropubic prostatectomy (PSA 0.2 ng./ml. or greater). Patients were censored if they were lost to followup or there was no recurrence. Event time distributions for the time to recurrence end point were estimated with the Kaplan-Meier method and compared using the log rank statistic or the proportional hazards regression model.^{13, 14} The simultaneous effect of 2 or more factors was studied using the multivariate proportional hazards model. Covariates and interactions marginally significant ($p < 0.19$) in univariate analyses were entered into the multivariate regression model and insignificant effects were removed in a stepwise fashion. The first model was developed using preoperative variables only and the second model using all available variables.

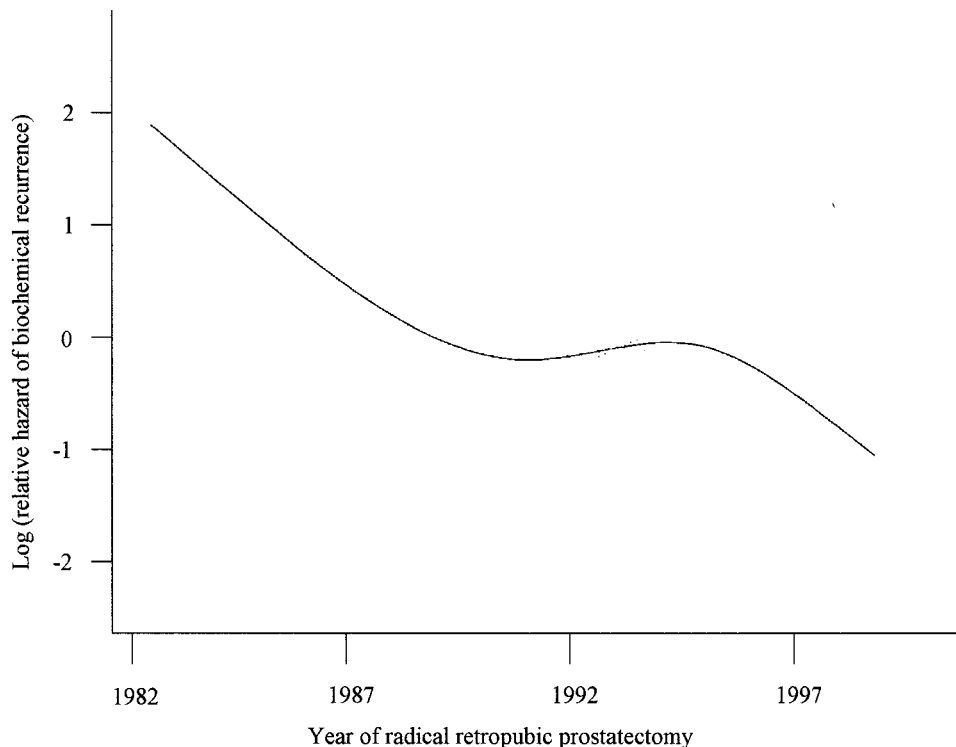
Early detection programs encouraged in the later years of this study produced significant shifts towards early stage disease over time.⁹ Interactions of PSA, Gleason score and TNM stage with calendar time were tested to determine if the risks attributable to these variables were also functions of time. For all analyses PSA, Gleason score and TNM stage were categorized into discrete levels and entered in regression models in unfactored form. When calendar year of surgery was entered into the proportional hazards model, a restricted cubic spline transformation was used to allow non-linearity.

In addition to the shift toward early stage disease, the relative risk of biochemical recurrence following surgery decreased significantly over time.⁹ Most importantly, when the relative risk of biochemical recurrence was adjusted for clinical TNM stage, preoperative PSA and Gleason score, there was still a significant decrease in relative risk of biochemical recurrence over time. For example, the figure demonstrates the decreasing relative risk of biochemical recurrence over time for the most common group of men who underwent radical retropubic prostatectomy at our hospital, namely those with clinical stage T1c, Gleason score 6 disease and preoperative PSA between 4 and 10 ng./ml.

Observed and predicted recurrence-free survival curves for 2 proportional hazards models (1 stratified for year of surgery and 1 including year of surgery as predictor) and 3 parametric survival models (Weibull, log-normal and

TABLE 1. Clinical stage, preoperative PSA, Gleason score and pathological stage in 2,091 men who underwent anatomic radical retropubic prostatectomy for T1c or T2 disease with Gleason score 5 or greater

	No. Men (%)
TNM stage:	
T1c	845 (40)
T2a	771 (37)
T2b/c	475 (23)
Total	2,091 (100)
Serum PSA (ng./ml.):	
0-4	452 (24)
4.1-10	1,021 (55)
10.1-20	319 (17)
Greater than 20	80 (4)
Total	1,872 (100)
Gleason score:	
5	241 (12)
6	1,020 (49)
7	693 (33)
8-10	137 (6)
Total	2,091 (100)
Pathological stage:	
Organ confined	1,050 (50)
Extraprostatic extension, Gleason score less than 7, neg. surgical margins	310 (15)
Extraprostatic extension, Gleason score less than 7, pos. surgical margins	96 (5)
Extraprostatic extension, Gleason score 7 or greater, neg. surgical margins	306 (15)
Extraprostatic extension, Gleason score 7 or greater, pos. surgical margins	119 (6)
Seminal vesicle involvement, neg. lymph nodes	98 (4)
Micrometastases to pelvic lymph nodes	112 (5)
Total	2,091 (100)



Shape of year predictor (year of radical retropubic prostatectomy) on log hazard of biochemical recurrence (PSA 0.2 ng./ml. or greater) following radical retropubic prostatectomy (adjusted for men with clinical stage T1c, PSA between 4.1 and 10 ng./ml., and Gleason score 6 disease).

gamma) were compared to select a model for calculation of predicted recurrence-free probabilities and confidence intervals. For each model coefficients from the multivariate regression were used to generate a prognostic factor score for each individual. This score is the weighted average of prognostic factor values with weights determined by the estimated coefficients from the model. The proportional hazards regression model is the patient's hazard relative to a patient with the most favorable level of all prognostic factors. These scores were then ranked and categorized to form 4 risk groups. Plots of the observed survival, Kaplan-Meier curves, for these risk groups were then compared to the model of predicted recurrence-free survival for each risk group (data not shown). From the chosen model (proportional hazards), the nomograms were constructed from biochemical recurrence-free survival probability with corresponding 95% confidence intervals at 3, 5, 7 and 10 years following radical retropubic prostatectomy, adjusting for the latest year in which surgical data were available (1999). All p values are 2-sided. All statistical analyses were performed using the Intercooled Stata 6.0 statistics and graphics data management system (Stata Corporation, College Station, Texas), SAS system (SAS Institute, Inc., Cary, North Carolina), EGRET (Cytel Statistical Software, Cambridge, Massachusetts) or the S-plus Design package (Mathsoft Data Analysis Products Division, Seattle, Washington).

RESULTS

Overall progression. At a median followup of 5.9 ± 4.1 years (range 1 to 17) recurrence was noted in 360 men (17%), including 203 with isolated detectable PSA (0.2 ng./ml. or greater), 36 with local recurrence and 121 with distant metastases. No one had local or distant recurrence without an increase in PSA at the time of progression. Overall actuarial 5, 10 and 15-year biochemical recurrence-free survival rates were 84%, 72% and 61%, respectively. Overall actuarial 5, 10 and 15-year metastasis-free survival rates were 96%, 89%

and 81%, respectively. Overall actuarial cancer specific survival rates at 5, 10 and 15 years were 99%, 96% and 89%, respectively.

Recurrence-free survival prediction models. Variables chosen for the preoperative model were biopsy Gleason score, preoperative PSA and clinical TNM stage. Variables chosen for the postoperative model were Gleason score from surgical specimen, preoperative PSA and organ confinement status. Biochemical recurrence-free probability and 95% confidence interval are summarized in tables 2 to 4 (preoperative model), and tables 5 and 6 (postoperative model). The numbers within each cell of the nomogram represent the percentage of likelihood of biochemical recurrence-free survival at a given postoperative year based on the regression of all 3 variables combined. For example, a man with a preoperative serum PSA of 4.5 ng./ml., a biopsy Gleason score of 6 and nonpalpable (stage T1c) disease has 98%, 97%, 96% and 95% probability of biochemical recurrence-free survival at 3, 5, 7 and 10 years, respectively, following surgery in the modern era according to table 2. A man with a PSA of 5.7 ng./ml., a prostatectomy specimen demonstrating Gleason score of $3 + 4 = 7$ and organ confined disease has 96%, 94%, 91% and 89% probability of biochemical recurrence-free survival at 3, 5, 7 and 10 years, respectively, following radical retropubic prostatectomy in the modern era according to table 5.

DISCUSSION

During the last 2 decades several important anatomic discoveries were introduced that have allowed surgeons to perform anatomical dissection of the prostate and reduce perioperative morbidity.^{15,16} As a result anatomic radical retropubic prostatectomy has demonstrated improved cancer control and has become the most widely performed definitive treatment for clinically localized prostate cancer.¹⁷ However, a significant proportion of men (30% to 40%) who undergo radical retropubic prostatectomy present with isolated biochemical evidence of cancer recurrence at long-term fol-

TABLE 2. Biochemical recurrence-free (PSA less than 0.2 ng./ml.) survival probability following radical retropubic prostatectomy for clinical stage T1c disease

Postop. Yr.	Probability (95% CI)			
	PSA 0-4	PSA 4.1-10	PSA 10.1-20	PSA Greater Than 20
Biopsy Gleason score 5:				
3	1.00 (0.99 1.00)	0.99 (0.97 1.00)	0.98 (0.93 0.99)	0.96 (0.85 0.99)
5	0.99 (0.98 1.00)	0.99 (0.95 1.00)	0.97 (0.89 0.99)	0.93 (0.76 0.98)
7	0.99 (0.97 1.00)	0.98 (0.93 0.99)	0.95 (0.84 0.99)	0.90 (0.67 0.97)
10	0.99 (0.95 1.00)	0.97 (0.91 0.99)	0.94 (0.80 0.98)	0.87 (0.59 0.96)
Biopsy Gleason score 6:				
3	0.99 (0.97 1.00)	0.98 (0.94 0.99)	0.97 (0.89 0.99)	0.93 (0.79 0.98)
5	0.99 (0.95 1.00)	0.97 (0.91 0.99)	0.95 (0.82 0.98)	0.89 (0.67 0.97)
7	0.98 (0.93 0.99)	0.96 (0.87 0.99)	0.92 (0.76 0.98)	0.85 (0.56 0.96)
10	0.97 (0.91 0.99)	0.95 (0.83 0.98)	0.90 (0.69 0.97)	0.81 (0.47 0.94)
Biopsy Gleason score 3 + 4:				
3	0.98 (0.94 0.99)	0.97 (0.90 0.99)	0.94 (0.83 0.98)	0.90 (0.70 0.97)
5	0.97 (0.90 0.99)	0.95 (0.84 0.98)	0.91 (0.73 0.97)	0.85 (0.55 0.95)
7	0.96 (0.87 0.99)	0.93 (0.77 0.98)	0.87 (0.63 0.96)	0.79 (0.43 0.93)
10	0.95 (0.83 0.98)	0.91 (0.72 0.97)	0.84 (0.54 0.95)	0.73 (0.33 0.91)
Biopsy Gleason score 4 + 3:				
3	0.96 (0.88 0.99)	0.94 (0.82 0.98)	0.91 (0.73 0.97)	0.86 (0.58 0.96)
5	0.94 (0.81 0.98)	0.91 (0.72 0.97)	0.86 (0.58 0.96)	0.78 (0.40 0.93)
7	0.92 (0.73 0.98)	0.87 (0.62 0.96)	0.80 (0.46 0.94)	0.70 (0.27 0.91)
10	0.89 (0.67 0.97)	0.83 (0.53 0.95)	0.74 (0.36 0.92)	0.62 (0.18 0.88)
Biopsy Gleason score 8-10:				
3	0.93 (0.75 0.98)	0.90 (0.68 0.97)	0.85 (0.58 0.96)	0.80 (0.42 0.94)
5	0.88 (0.62 0.97)	0.83 (0.53 0.95)	0.77 (0.40 0.93)	0.69 (0.24 0.91)
7	0.83 (0.50 0.95)	0.77 (0.40 0.93)	0.69 (0.27 0.90)	0.59 (0.12 0.87)
10	0.79 (0.40 0.94)	0.71 (0.30 0.91)	0.61 (0.18 0.87)	0.50 (0.06 0.84)

TABLE 3. Biochemical recurrence-free (PSA less than 0.2 ng./ml.) survival probability following radical retropubic prostatectomy for clinical stage T2a disease

Postop. Yr.	Probability (95% CI)			
	PSA 0-4	PSA 4.1-10	PSA 10.1-20	PSA Greater Than 20
Biopsy Gleason score 5:				
3	0.99 (0.98 1.00)	0.99 (0.96 1.00)	0.97 (0.91 0.99)	0.94 (0.80 0.98)
5	0.99 (0.97 1.00)	0.98 (0.93 0.99)	0.96 (0.85 0.99)	0.90 (0.69 0.97)
7	0.99 (0.95 1.00)	0.97 (0.90 0.99)	0.94 (0.80 0.98)	0.86 (0.59 0.96)
10	0.98 (0.94 1.00)	0.96 (0.88 0.99)	0.92 (0.74 0.98)	0.83 (0.50 0.95)
Biopsy Gleason score 6:				
3	0.99 (0.96 1.00)	0.98 (0.93 0.99)	0.96 (0.86 0.99)	0.91 (0.73 0.97)
5	0.98 (0.94 0.99)	0.96 (0.88 0.99)	0.93 (0.77 0.98)	0.86 (0.59 0.96)
7	0.97 (0.91 0.99)	0.95 (0.83 0.98)	0.90 (0.69 0.97)	0.81 (0.46 0.94)
10	0.97 (0.89 0.99)	0.93 (0.79 0.98)	0.87 (0.61 0.96)	0.75 (0.37 0.92)
Biopsy Gleason score 3 + 4:				
3	0.98 (0.92 0.99)	0.96 (0.87 0.99)	0.93 (0.77 0.98)	0.87 (0.62 0.96)
5	0.96 (0.88 0.99)	0.93 (0.79 0.98)	0.88 (0.65 0.96)	0.80 (0.45 0.94)
7	0.94 (0.83 0.98)	0.90 (0.71 0.97)	0.83 (0.54 0.95)	0.72 (0.32 0.91)
10	0.93 (0.78 0.98)	0.88 (0.64 0.96)	0.79 (0.44 0.93)	0.65 (0.22 0.89)
Biopsy Gleason score 4 + 3:				
3	0.95 (0.84 0.99)	0.92 (0.77 0.98)	0.88 (0.65 0.96)	0.82 (0.49 0.94)
5	0.92 (0.75 0.98)	0.88 (0.64 0.96)	0.81 (0.49 0.94)	0.71 (0.30 0.91)
7	0.89 (0.66 0.97)	0.83 (0.53 0.95)	0.74 (0.35 0.92)	0.62 (0.17 0.88)
10	0.86 (0.58 0.96)	0.78 (0.43 0.93)	0.67 (0.26 0.89)	0.53 (0.10 0.84)
Biopsy Gleason score 8-10:				
3	0.90 (0.68 0.97)	0.86 (0.60 0.96)	0.86 (0.60 0.96)	0.74 (0.32 0.92)
5	0.84 (0.53 0.96)	0.78 (0.43 0.93)	0.78 (0.43 0.93)	0.61 (0.15 0.88)
7	0.78 (0.40 0.94)	0.70 (0.30 0.90)	0.70 (0.30 0.90)	0.49 (0.06 0.83)
10	0.72 (0.30 0.92)	0.63 (0.20 0.88)	0.63 (0.20 0.88)	0.39 (0.03 0.78)

lowup.¹⁻⁸ Knowing the probability of recurrence following surgery would help patients rationally choose appropriate treatment options, either primary and/or adjuvant therapy, for prostate cancer.

Many previous studies have attempted to determine recurrence following radical prostatectomy using proportional hazards modeling. Some developed models to select men at high risk for disease progression for adjuvant therapy trials following radical prostatectomy.^{11, 18} They identified serum PSA, surgical Gleason score and margin status, and capsular penetration as independent indicators of biochemical recurrence.^{11, 18}

Recently Kattan et al developed nomograms for disease progression probability using a cohort of more than 900 men who underwent radical retropubic prostatectomy.^{19, 20} The

nomograms used multiple perioperative variables to predict either 5 or 7-year probability of recurrence-free survival (PSA less than 0.4 ng./ml.) following surgery. Their models offered biochemical recurrence-free survival probability rather than relative risk of disease progression. However, the risk of cancer recurrence persists beyond 5 or 7 years following surgery.²¹ In addition, their models failed to address improved therapeutic outcome and changes in patient demographics as early detection became available in the PSA era.

Our models are based on the followup information from a large group of men who underwent radical retropubic prostatectomy. All 5 variables integrated in the final model are commonly used and readily reproducible for men who are considering or have already undergone radical retropubic prostatectomy. We excluded from analysis men with clinical

TABLE 4. Biochemical recurrence-free (PSA less than 0.2 ng./ml.) survival probability following radical retropubic prostatectomy for clinical stage T2b/c disease

Postop. Yr.	Probability (95% CI)			
	PSA 0-4	PSA 4.1-10	PSA 10.1-20	PSA Greater Than 20
Biopsy Gleason score 5:				
3	0.99 (0.97 1.00)	0.98 (0.94 1.00)	0.96 (0.88 0.99)	0.92 (0.74 0.98)
5	0.99 (0.96 1.00)	0.97 (0.91 0.99)	0.94 (0.80 0.98)	0.87 (0.60 0.96)
7	0.98 (0.94 1.00)	0.96 (0.87 0.99)	0.92 (0.73 0.98)	0.82 (0.48 0.95)
10	0.98 (0.92 0.99)	0.95 (0.83 0.99)	0.89 (0.66 0.97)	0.77 (0.38 0.93)
Biopsy Gleason score 6:				
3	0.99 (0.95 1.00)	0.97 (0.90 0.99)	0.94 (0.81 0.98)	0.88 (0.65 0.97)
5	0.98 (0.91 0.99)	0.95 (0.84 0.99)	0.90 (0.70 0.97)	0.82 (0.48 0.95)
7	0.96 (0.88 0.99)	0.93 (0.78 0.98)	0.86 (0.60 0.96)	0.75 (0.35 0.92)
10	0.95 (0.85 0.99)	0.91 (0.72 0.97)	0.83 (0.51 0.95)	0.68 (0.25 0.90)
Biopsy Gleason score 3 + 4:				
3	0.97 (0.90 0.99)	0.94 (0.82 0.98)	0.90 (0.70 0.97)	0.83 (0.52 0.95)
5	0.95 (0.83 0.98)	0.91 (0.72 0.97)	0.84 (0.56 0.95)	0.74 (0.34 0.92)
7	0.93 (0.77 0.98)	0.87 (0.63 0.96)	0.78 (0.43 0.93)	0.65 (0.21 0.89)
10	0.90 (0.71 0.97)	0.84 (0.54 0.95)	0.73 (0.33 0.91)	0.57 (0.13 0.85)
Biopsy Gleason score 4 + 3:				
3	0.94 (0.79 0.98)	0.90 (0.70 0.97)	0.84 (0.56 0.95)	0.76 (0.37 0.93)
5	0.90 (0.68 0.97)	0.84 (0.54 0.95)	0.75 (0.37 0.92)	0.64 (0.19 0.88)
7	0.85 (0.57 0.96)	0.78 (0.42 0.93)	0.67 (0.24 0.89)	0.52 (0.09 0.84)
10	0.81 (0.48 0.94)	0.72 (0.32 0.91)	0.59 (0.15 0.86)	0.43 (0.04 0.80)
Biopsy Gleason score 8-10:				
3	0.87 (0.59 0.96)	0.82 (0.50 0.94)	0.75 (0.37 0.92)	0.67 (0.21 0.90)
5	0.80 (0.42 0.94)	0.72 (0.32 0.91)	0.63 (0.19 0.88)	0.51 (0.07 0.84)
7	0.72 (0.28 0.92)	0.62 (0.19 0.87)	0.51 (0.09 0.83)	0.38 (0.02 0.78)
10	0.65 (0.19 0.89)	0.54 (0.11 0.84)	0.41 (0.04 0.78)	0.28 (0.01 0.72)

TABLE 5. Biochemical recurrence-free (PSA less than 0.2 ng./ml.) survival probability following radical retropubic prostatectomy for men with organ confined disease

Postop. Yr.	Probability (95% CI)			
	PSA 0-4	PSA 4.1-10	PSA 10.1-20	PSA Greater Than 20
Surgery Gleason score 5:				
3	1.00 (0.99 1.00)	0.99 (0.98 1.00)	0.98 (0.95 0.99)	0.97 (0.90 0.99)
5	0.99 (0.98 1.00)	0.99 (0.96 1.00)	0.97 (0.92 0.99)	0.95 (0.84 0.98)
7	0.99 (0.97 1.00)	0.98 (0.94 0.99)	0.96 (0.89 0.99)	0.92 (0.77 0.98)
10	0.99 (0.96 1.00)	0.97 (0.93 0.99)	0.95 (0.86 0.98)	0.90 (0.71 0.97)
Surgery Gleason score 6:				
3	0.99 (0.97 1.00)	0.98 (0.95 0.99)	0.97 (0.91 0.99)	0.95 (0.85 0.98)
5	0.98 (0.95 0.99)	0.97 (0.92 0.99)	0.95 (0.86 0.98)	0.91 (0.76 0.97)
7	0.98 (0.93 0.99)	0.96 (0.88 0.98)	0.93 (0.80 0.97)	0.88 (0.66 0.96)
10	0.97 (0.91 0.99)	0.94 (0.85 0.98)	0.91 (0.75 0.97)	0.84 (0.59 0.95)
Surgery Gleason score 3 + 4:				
3	0.98 (0.93 0.99)	0.96 (0.90 0.99)	0.94 (0.84 0.98)	0.91 (0.76 0.97)
5	0.96 (0.89 0.99)	0.94 (0.83 0.98)	0.91 (0.75 0.97)	0.86 (0.64 0.95)
7	0.94 (0.84 0.98)	0.91 (0.76 0.97)	0.87 (0.66 0.95)	0.80 (0.52 0.93)
10	0.92 (0.79 0.97)	0.89 (0.71 0.96)	0.83 (0.58 0.94)	0.75 (0.42 0.91)
Surgery Gleason score 4 + 3:				
3	0.94 (0.84 0.98)	0.92 (0.79 0.97)	0.89 (0.72 0.96)	0.86 (0.64 0.95)
5	0.90 (0.75 0.97)	0.87 (0.67 0.95)	0.83 (0.58 0.94)	0.78 (0.47 0.92)
7	0.86 (0.65 0.95)	0.82 (0.56 0.93)	0.76 (0.45 0.91)	0.70 (0.33 0.89)
10	0.82 (0.57 0.94)	0.77 (0.47 0.91)	0.70 (0.36 0.89)	0.62 (0.24 0.86)
Surgery Gleason score 8-10:				
3	0.86 (0.64 0.95)	0.84 (0.59 0.94)	0.81 (0.53 0.93)	0.78 (0.46 0.92)
5	0.78 (0.48 0.92)	0.75 (0.42 0.91)	0.71 (0.35 0.89)	0.66 (0.27 0.88)
7	0.70 (0.33 0.89)	0.65 (0.28 0.87)	0.60 (0.22 0.84)	0.55 (0.15 0.83)
10	0.63 (0.24 0.86)	0.57 (0.19 0.83)	0.52 (0.14 0.80)	0.46 (0.08 0.78)

stage T1a/b or T3a disease or Gleason score less than 5 since the percentage of men with those diseases has decreased significantly in the contemporary patient population.⁹ Our nomograms provide biochemical recurrence-free survival probability, which is easier to explain to patients.

The most important distinction of our models is that we integrated a significant downward stage migration and an improved surgical outcome over time into the models. We have previously demonstrated the decreasing relative risk of biochemical recurrence following surgery in the modern era.⁹ That change may reflect the benefits of early detection, better preoperative selection of patients for surgery as well as lead time bias.⁹ In the current study we attempted to delineate whether downward stage migration alone could account for the improved therapeutic outcome over time. When the rel-

ative risk of biochemical recurrence was adjusted for clinical TNM stage, preoperative PSA and Gleason score, there was still a significant decrease in relative risk of biochemical recurrence over time (see figure). Since patients have a decreasing relative risk of biochemical recurrence over time, our nomograms were generated for men who underwent radical retropubic prostatectomy at the latest year of followup (1999). Therefore, these nomograms can be applied to men with clinically localized prostate cancer who underwent or plan to undergo surgery in the modern era.

Our models suggest that the surgical outcome in terms of biochemical recurrence-free survival for men with higher grade disease (Gleason grade 8 to 10) from biopsy is better than conventionally thought. Disease demographics are changing for the patient population with fewer men being

TABLE 6. Biochemical recurrence-free (PSA less than 0.2 ng./ml.) survival probability following radical retropubic prostatectomy for men with nonorgan confined disease

Postop. Yr.	Probability (95% CI)			
	PSA 0-4	PSA 4.1-10	PSA 10.1-20	PSA Greater Than 20
Surgery Gleason score 5:				
3	0.99 (0.95 1.00)	0.97 (0.92 0.99)	0.95 (0.85 0.98)	0.90 (0.70 0.97)
5	0.98 (0.93 0.99)	0.95 (0.87 0.98)	0.91 (0.77 0.97)	0.83 (0.56 0.95)
7	0.97 (0.89 0.99)	0.93 (0.82 0.98)	0.87 (0.67 0.95)	0.77 (0.42 0.92)
10	0.96 (0.86 0.99)	0.91 (0.77 0.97)	0.84 (0.60 0.94)	0.71 (0.33 0.90)
Surgery Gleason score 6:				
3	0.97 (0.90 0.99)	0.94 (0.84 0.98)	0.90 (0.74 0.96)	0.83 (0.58 0.94)
5	0.94 (0.84 0.98)	0.90 (0.75 0.96)	0.84 (0.61 0.94)	0.74 (0.41 0.90)
7	0.92 (0.78 0.97)	0.86 (0.66 0.95)	0.77 (0.48 0.91)	0.64 (0.26 0.86)
10	0.89 (0.72 0.96)	0.82 (0.58 0.93)	0.72 (0.39 0.89)	0.56 (0.18 0.83)
Surgery Gleason score 3 + 4:				
3	0.92 (0.79 0.97)	0.88 (0.70 0.95)	0.82 (0.57 0.93)	0.74 (0.42 0.90)
5	0.87 (0.67 0.95)	0.81 (0.55 0.93)	0.72 (0.40 0.89)	0.61 (0.23 0.84)
7	0.81 (0.55 0.93)	0.73 (0.41 0.89)	0.62 (0.26 0.84)	0.48 (0.12 0.78)
10	0.76 (0.46 0.91)	0.66 (0.32 0.86)	0.53 (0.17 0.80)	0.38 (0.06 0.72)
Surgery Gleason score 4 + 3:				
3	0.81 (0.56 0.93)	0.75 (0.46 0.90)	0.68 (0.35 0.87)	0.60 (0.23 0.84)
5	0.71 (0.38 0.89)	0.63 (0.28 0.85)	0.54 (0.17 0.80)	0.43 (0.09 0.75)
7	0.60 (0.24 0.84)	0.51 (0.15 0.79)	0.40 (0.08 0.73)	0.29 (0.03 0.66)
10	0.52 (0.16 0.79)	0.42 (0.08 0.73)	0.31 (0.03 0.66)	0.20 (0.01 0.58)
Surgery Gleason score 8-10:				
3	0.60 (0.23 0.84)	0.55 (0.18 0.81)	0.49 (0.13 0.78)	0.43 (0.08 0.75)
5	0.44 (0.09 0.75)	0.37 (0.06 0.71)	0.31 (0.03 0.67)	0.25 (0.02 0.63)
7	0.30 (0.03 0.66)	0.24 (0.02 0.60)	0.18 (0.01 0.55)	0.13 (0.00 0.51)
10	0.21 (0.01 0.59)	0.15 (0.00 0.52)	0.11 (0.00 0.46)	0.07 (0.00 0.42)

diagnosed with higher Gleason scores. Yang et al suggested that small foci of Gleason score 8 to 10 cancer on biopsy do not necessarily indicate advanced pathological stage at surgery, and that those with higher Gleason score diseases may fare well following surgery as long as there is no evidence of lymph node metastases.²² Therefore, men with higher grade cancer suitable for surgery should undergo radical retropubic prostatectomy as long as the pelvic lymph nodes are without metastasis, since they may be cured with surgery.

As our patient population represents mostly white men treated by a single surgeon at a single institution, future validations of the nomograms using independent patient cohorts, including nonwhite races, from different surgeons or institutions will be necessary. However, actuarial comparison of our nomograms with retrospective data on a cohort of men who underwent surgery in the 1980s and 1990s would be underserved since our models are developed to predict the biochemical recurrence-free outcome following surgery in the PSA era (1999). We will only know the true accuracy of the current models with time as prospective data accumulate on men who have undergone surgery in the modern era.

A man with newly diagnosed prostate cancer has to make important decisions regarding treatment. The Partin nomograms enabled physicians and patients to make more informed treatment decisions based on the probability of pathological stage for clinically localized prostate cancer.²³ When a patient experiences biochemical recurrence following radical retropubic prostatectomy, the recent study by Pound et al can be informative as well as comforting regarding the interval from PSA detection to evidence of metastasis.¹ They demonstrated that disease progression from an isolated PSA increase to metastasis and cancer specific mortality is generally a protracted process.¹ The algorithm in their study provided the risk for developing metastatic cancer so that patients and physicians could decide on the need for and timing of the most appropriate adjuvant therapy following postoperative biochemical recurrence.

In addition to the Partin nomograms and the Pound algorithm, the nomograms in the present study can help patients rationally decide on the best treatment options depending on the probability of recurrence-free survival following radical prostatectomy according to disease characteristics in the modern era. In addition, these nomograms can guide physi-

cians caring for men with prostate cancer in determining how often and what type of monitoring tests should be performed following surgery. Finally, the nomograms can help physicians determine whether adjuvant therapy may be beneficial or which patients would benefit from novel adjuvant therapy.

CONCLUSIONS

We reviewed a large series of men who underwent radical prostatectomy for clinically localized prostate cancer to identify indicators of biochemical recurrence. Using 3 preoperative or postoperative variables, we developed multivariate proportional hazards models to determine the 3, 5, 7 and 10-year biochemical recurrence-free survival probabilities among men who undergo radical prostatectomy for clinically localized prostate cancer. These nomograms were adjusted for the decreasing relative risk of biochemical recurrence over time. They may be helpful in guiding treatment decisions for men who are considering or have undergone radical prostatectomy for clinically localized prostate cancer in the modern era.

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