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Risk Stratification for Biochemical Recurrence among Men with Positive Surgical Margins or Extracapsular Disease after Radical Prostatectomy: Results from the SEARCH Database

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Abstract

Purpose—Among men with either extracapsular disease or positive surgical margins after radical prostatectomy, immediate adjuvant therapy decreases the risk of biochemical recurrence at the cost of increased toxicity. We sought to further stratify these men into a low-risk group in whom watchful waiting after surgery may be preferred and a high-risk cohort in whom adjuvant therapy may be preferred.

Materials and Methods—We performed a retrospective analysis of 902 men treated by radical prostatectomy in the SEARCH database between 1988 and 2007 with positive surgical margins and/or extracapsular disease without seminal vesicle invasion or lymph node metastasis. The significant independent predictors of biochemical recurrence were determined using a multivariate Cox proportional hazards model. Based upon the recurrence risk generated from the multivariate

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Cox proportional hazards regression model, we generated tables to estimate the risk of recurrence at 1, 3 and 5 years after surgery.

Results—After a median of 3 years of follow-up, 346 (39%) patients developed a biochemical recurrence. On multivariate analysis, the significant predictors of biochemical recurrence included age >60 years, PSA >10 ng/ml, Gleason score 4+3 and 8–10, 2 or more sites of positive surgical margins and prostate specimen weight ≤30 grams. The overall predictive accuracy of the model as determined by the Concordance Index C was 0.67, which compared to 0.60 for the post-operative “Kattan nomogram” for this patient population.

Conclusions—We have developed a simple instrument, which once validated, may aid in the postoperative decision making process for men with intermediate risk of recurrence after prostatectomy.

Keywords

Prostate cancer; radical prostatectomy; biochemical recurrence

Introduction

The number of new cases of prostate cancer projected for 2007 is 218,890, which accounts for almost a third of all cancers in men excluding skin cancers. Radical prostatectomy is one of the most accepted and widely practiced management strategies for localized prostate cancer. Though survival rates for prostate cancer continue to be exceptionally good in comparison with other cancers, biochemical recurrence occurs in up to 30% of all men undergoing surgical treatment.^{1, 2} It is acknowledged those with organ confined cancer are least likely to recur while those with seminal vesicle invasion or lymph node metastases are at the highest risk for recurrence.³ It seems intuitive that men with organ-confined disease would benefit most from a watchful waiting approach while prior studies have shown that early aggressive treatment for the latter group improves overall survival, at least for those with lymph node involvement.⁴ However, for men with intermediate risk – those with either a positive surgical margin or extracapsular extension without seminal vesicle invasion – the optimal management remains unclear.

Recently, two large prospective clinical trials investigated the role of immediate adjuvant radiation therapy for men with either extracapsular disease or a positive surgical margin following radical prostatectomy.^{5, 6} Both studies found adjuvant therapy decreased the risk of prostate specific antigen (PSA) recurrence but at the cost of increased toxicity. While no metastasis-free or overall survival benefit was seen in either study, it is unknown whether this represents a lack of true long-term benefit from adjuvant treatment or was a function of modest patient numbers without sufficient follow-up time. Ultimately, balancing the benefit of reduced biochemical recurrence must be weighed against the potential for decrements in quality of life. Therefore, we sought to identify among those men with either extracapsular disease or a positive surgical margin, patients who were at low risk of recurrence and in whom close observation may be the preferred management approach while also identifying those who are at high-risk and in whom adjuvant therapy may be warranted. To accomplish this, we used the multi-center multi-ethnic Shared Equal-Access Regional Cancer Hospital (SEARCH) Database of men treated with radical prostatectomy at multiple Veterans Affairs Medical Centers across the United States.

Methods

Study population

After obtaining Institutional Review Board approval from each institution to abstract and combine data, data from patients undergoing radical prostatectomy at the Veterans Affairs Medical Centers in West Los Angeles, Palo Alto, San Francisco, and Augusta, Georgia, and Durham, North Carolina were combined into the SEARCH database.⁷ This database includes information on patient age at surgery, race, height, weight, clinical stage, grade of cancer on diagnostic biopsies, preoperative PSA, surgical specimen pathology (specimen weight, tumor grade, stage, and surgical margin status), and follow-up PSA data. Patients treated with preoperative androgen deprivation or radiation therapy were excluded. Of the 2,062 men within the SEARCH Database, we excluded 32 and 205 men who were at very high-risk of recurrence due to lymph node metastasis and seminal vesicle invasion, respectively. Due to the very low-risk of recurrence, we excluded men with organ confined disease and negative margins. This resulted in a study population of 902 men. Biochemical recurrence was defined as a single PSA >0.2 ng/ml, 2 concentrations at 0.2 ng/ml, or secondary treatment for an elevated postoperative PSA. The prostatectomy specimens were sectioned per each institution's protocol.⁷ Margins were categorized as positive or negative at each given anatomic location (i.e. apex, bladder neck, left peripheral or right peripheral). Information regarding the number of positive foci at each location was not available, thus patients were defined as either positive or negative at each location. The number of positive margins was computed by adding the number of locations with a positive margin. Each location was considered mutually exclusive. For example, a man with an isolated left apical margin was considered to have a positive apical margin, but not a left lateral margin, for a total of one positive margin.

Statistical analysis

Significant risk factors for time to biochemical recurrence were examined using log-rank survivorship analysis and Cox proportional hazards regression. The variables considered for entry into the model included age, race, body mass index (BMI), year of surgery, SEARCH site, pre-operative serum PSA, pathological Gleason score, extracapsular extension, number of positive surgical margins, and prostate specimen weight. As our goal was to develop easy to use tables, this necessitated identifying cut-points to categorize the significant prognostic characteristics. Therefore, we performed univariate exploratory analyses among the identified significant variables using multiple clinically relevant cut points for each variable (e.g. age ≤ 50 vs. age >50, age ≤ 60 vs. age >60, etc.) and determined that grouping age ≤ 60 vs. >60, Gleason score as ≤3+4, 4+3, vs. 8–10, preoperative PSA ≤ 10 vs. >10 ng/ml, prostate specimen weight ≤ 30 vs. >30 grams and number of positive margins locations ≤ 2 vs. >2 provided the maximum likelihood χ^2 ratio for estimating time to biochemical recurrence; therefore, these groupings were used in the multivariate model. For multivariable analysis, a step-wise Cox proportional hazards model was used with $p < 0.15$ to determine which variables should be entered into the model at each step. The variable with the highest p value was then successively deleted until only variables with a $p < 0.1$ remained. The predictive performance of the model was assessed and compared with the post-operative "Kattan nomogram"⁸ using the concordance index C .⁹ Tables were generated to predict the 1, 3 and 5-year actuarial risk of biochemical recurrence free survival using the coefficients of the multivariable Cox model. All statistical analyses were performed using STATA 9.2 (STATA Corp; College Station, TX) or SAS 9.1.3 (SAS Institute; Cary, NC) and $P < 0.05$ was considered statistically significant.

Results

Table 1 lists the demographic and clinicopathological characteristics of the patients. Most patients were below 60 years of age (61%, n=554) had preoperative PSA values 10 ng/mL (65%, n= 586) and had a pathological Gleason score of 7 or less (87%, n=760). A relatively large proportion of the men were African American (40%, n=358). The mean (SD) and median follow-up among men who did not recur was 4.0 years (3.6) and 3.0 respectively. Overall, 346 (39%) patients experienced biochemical recurrence (figure 1). The 1-, 3-, and 5-year overall risk of biochemical recurrence was 19, 34 and 48%.

On univariate exploratory analysis, the number of positive surgical margins, pathological Gleason score and pre-operative serum PSA levels were significantly associated with biochemical relapse ($p<0.001$ for all three) as was prostate specimen weight ($p=0.002$) and age at the time of surgery ($p=0.03$). No other variables were significantly associated with time to biochemical recurrence. On multivariate analysis, similar to the univariate analysis, only age at the time of surgery, pathological Gleason score, number of positive margins, PSA and prostate weight were significantly predictive of biochemical recurrence (table 2). The overall accuracy of this multivariate model to predict biochemical recurrence, as defined by the Concordance index C, was 0.67. This compared favorably with the post-operative “Kattan nomogram”⁸, which had a Concordance index C of 0.60 in our subset of patients.

We used the significant risk factors identified in table 2 to generate tables to estimate the risk of biochemical recurrence free survival at 1-, 3-, and 5-years after surgery (table 3). For example, the 1-, 3-, and 5-year risk of biochemical recurrence for a man with age ≤ 60 , preoperative serum PSA level ≤ 10 ng/mL, pathological Gleason score of 3+4 or lower, with ≤ 2 positive margins and a prostate specimen weight of >30 g are 93, 87 and 79%, respectively. This compares to a 1-, 3-, and 5-year risk of PSA recurrence of 26, 7, and 1%, respectively, for a man with age >60 , preoperative serum PSA level >10 ng/mL, pathological Gleason score ranging from 8 through 10, with >2 positive margins and a prostate specimen weight of ≤ 30 g.

Discussion

Despite being one of the most effective methods for managing organ confined disease radical prostatectomy is still plagued with a recurrence rate ranging from 15 – 40 percent.^{1, 2} While pathological stage and grade are useful determinants of recurrence risk, many men will find themselves in an intermediate risk group based upon standard pathological features. For these men, adjuvant radiation has been suggested as a potential modality to reduce biochemical recurrence risk though at the cost of increased toxicity.^{5, 6} In order to better risk stratify these men, we examined men with extracapsular disease or a positive margin after radical prostatectomy and determined significant risk factors for biochemical recurrence. We found that along with the standard prognostic variables of PSA and Gleason grade, that the number of positive margins as well as prostate size and patient age were all significant predictors of biochemical recurrence. Using these features, we developed tables that estimate the risk of biochemical recurrence at 1-, 3-, and 5-years after surgery. It is hoped that once these tables are validated, that their use can help guide men and their physicians toward identifying those at the greatest and lowest need for adjuvant therapy.

In the current study of men with intermediate risk, the overall 5-year biochemical recurrence free survival was 55%. Therefore, nearly half the men in this group will recur while half will not by 5-years. This is in line with prior studies that found the risk of recurrence among men

with positive surgical margins was similarly near 50%.¹⁰ This highlights the uncertain future for these men who are at high-risk of recurrence.

Analogous to multiple prior studies, we found men with higher pre-operative PSA and higher grade disease were at increased risk of biochemical recurrence.^{11, 12} Apart from these well discussed variables, we found the number of margins to be strongly associated with the risk of biochemical failure. Specifically, the risk of recurrence rose in those with 2 or more positive margins while men with 1 or 0 positive margins had similar outcomes. Across many studies positive margins have been strongly associated with recurrence,^{12, 13} but studies reporting the number of margins as a risk factor for recurrence are infrequent.^{14, 15} Lowe et al found that men with more than one positive margins were at increased risk of recurrence in univariate analysis.¹⁴ However, no multivariate analysis was performed. In the current study, the number of positive margins remained a significant predictor of recurrence on multivariate analysis. Our findings are similar to those by Obek et al who found that 2 or more positive margins were associated with 2.5 times increased risk for biochemical recurrence.¹⁵ Therefore, future studies should include not just whether the overall surgical margins are positive, but the number of positive margins.

Several prior studies have found that younger men tend to have more favorable clinical outcomes after radical prostatectomy.^{16, 17} In agreement with these prior studies including a prior study from the SEARCH database,¹⁷ we also found younger men had better outcomes. Though invariably age is on a continuum, we found that a cut-off of age 60 provided the best separation between “young” and “old”. However, in different patient populations the exact cutoff may vary. Whether age 60 is truly the optimal cut-off remains to be determined.

We¹⁸ and others¹⁹ have previously found that men with smaller prostates are at increased risk of recurrence. The current study lends further support to the growing literature suggesting a clinically important and statistically significant association between small prostate size and poor outcome. It has previously been suggested much of this association may be driven by larger prostates producing more PSA from the benign elements leading to early detection creating a lead time bias.¹⁹ However, it has also been suggested there may be a true biological link between small prostate size and aggressive prostate cancer. If true, it is unknown whether this results from a local paracrine effect of the benign elements suppressing the aggressive cancer or a small prostate creating a hostile environment where only the most aggressive cancers can survive¹⁸ or an alternative explanation. However, regardless of the reason why, the clinical significance is that small prostate size appears to be associated with poorer outcomes among men with prostate cancer.

Ultimately, putting all of the significant risk factors together we derived tables to estimate the risk of recurrence at 1-, 3-, and 5-years after surgery. The tables have the advantage of being able to estimate the risk of biochemical recurrence based on easily available clinicopathological characteristics and does not involve complex calculations. The accuracy of these tables was 67% for predicting time to biochemical recurrence. Overall, this compared well with the Kattan postoperative nomogram which had a predictive accuracy of only 60% among our patients.⁸ However, the modest predictive accuracy of 67% highlights the difficulty in predicting outcome among men who are intermediate risk. It is hoped that in the future, molecular markers will be available to further aide risk stratification within this group.

Our study has several limitations. First and foremost, though our model to predict recurrence appeared to perform better than the commonly used Kattan nomogram, this was based upon the same population from which our model was derived. Therefore, external validation will be required to assess whether this holds true in other populations as well. Also, in many of

the subsets in table 3, the confidence intervals are wide. This likely reflects small patient numbers, but also the fact that currently available clinical and pathological information is inexact in predicting outcome. Future studies are needed to better identify molecular markers that can improve risk stratification. The follow-up of our patients is relatively short. Longer follow-up with more individuals in the higher risk categories will enable us to derive more robust conclusions. We must bear in mind that although an acceptable clinical endpoint, biochemical recurrence is not a perfect surrogate for more concrete endpoints like metastases or cancer specific death since biochemical recurrence has a highly variable natural history. However, early biochemical recurrence is linked with increased risk for prostate cancer death.²⁰ The current study used non-centralized pathologic evaluation of surgical specimens from multiple institutions by multiple pathologists, which may make pooling of pathologic findings problematic. However, this may better represent what most practicing urologists can expect in their practice and as such, may have broader applicability than single institutional series. Finally, while our model may be able to better risk stratify patients the amount of risk which should be the threshold to treat is difficult to determine. This decision may be influenced by a multitude of factors including life expectancy, comorbidities and individual patient preference. Ultimately, it is the discretion of the patient and treating physician to decide on treatment options.

Conclusions

In conclusion, we have developed an easy to use device which after validation in other patient populations should enable both physicians and patients to assess the risk of recurrence in a subgroup of patients with intermediate risk after radical prostatectomy. This will serve to guide the decision making process specifically regarding the need for adjuvant therapy.

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Key for Abbreviations

CI	confidence interval
OR	odds ratio
PSA	prostate-specific antigen
SD	standard deviation
SEARCH	Shared Equal-Access Regional Cancer Hospital

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Figure 1.
Actuarial 10-year Kaplan-Meier estimates of biochemical recurrence rates in patients

Table 1

Preoperative clinical and pathological characteristics of men from the SEARCH database with either a positive surgical margin or extracapsular extension

Characteristics	No. (%)
No. of patients	902
Age at time of surgery, mean (SD)	62.0 (6.6)
Preoperative PSA, ng/mL	
Mean (SD)	10.5 (11.0)
Median (Range)	7.5 (0.56 – 140)
Race	
White	493 (55)
Black	358 (40)
Other	45 (5)
Clinical stage	
T1	422 (52)
T2	379 (47)
T3	5 (1)
Biopsy Gleason score	
2–6	526 (60)
3+4	208 (24)
4+3	69 (8)
8–10	68 (8)
Pathological Stage	
pT2+	544 (60)
pT3	135 (15)
pT3+	223 (25)
Pathological Gleason score	
2–6	283 (32)
3+4	384 (44)
4+3	93 (11)
8–10	114 (13)
Extracapsular extension	364 (43)
Positive surgical margins	715 (84)
Prostate specimen weight, g	
Mean (SD)	40.9 (20.0)
Median (Range)	36.7 (8.2 – 232.5)
Lymph Node Status	
Negative	643
Unknown	259

Table 2

Cox proportional hazards analysis of factors estimating time to biochemical recurrence following radical prostatectomy

Variables	Hazard Ratio (95% CI)	Coefficient β	P value
Patient age >60 vs. ≤ 60	1.57 (1.17 – 2.11)	0.45	0.003
Preoperative PSA >10 vs. ≤ 10 ng/mL	1.59 (1.21 – 2.09)	0.46	0.001
Pathological Gleason score (vs. $\leq 3+4$)			
4+3	1.57 (1.06 – 2.32)	0.45	0.025
8 – 10	2.17 (1.51 – 3.10)	0.77	<0.001
Number of positive margins >2 vs. ≤ 2	1.96 (1.49 – 2.57)	0.67	<0.001
Prostate weight ≤ 30 vs. >30g	1.72 (1.29 – 2.30)	0.55	<0.001

Abbreviations: CI – Confidence Interval; PSA – Prostate Specific Antigen

Table 3

Estimate of risk of biochemical recurrence free survival following prostatectomy*

YEAR 1			Risk Estimate, % (95% Confidence Interval)			
			Margins ≤ 2		Margins > 2	
			Prostate weight >30g	Prostate weight ≤ 30g	Prostate weight >30g	Prostate weight ≤ 30g
Age ≤ 60	PSA ≤ 10 ng/mL	Gleason score ≤ 3+4	93 (91–95)	88 (84–92)	87 (82–91)	78 (72–86)
		Gleason score 4+3	89 (84–94)	82 (75–91)	80 (72–89)	68 (56–82)
		Gleason score 8–10	85 (79–92)	76 (67–87)	74 (64–85)	59 (46–75)
	PSA > 10 ng/mL	Gleason score ≤ 3+4	89 (85–93)	82 (76–89)	80 (73–87)	68 (58–79)
		Gleason score 4+3	83 (76–91)	73 (62–86)	70 (59–83)	54 (40–74)
		Gleason score 8–10	78 (69–88)	65 (53–80)	61 (49–77)	43 (29–63)
Age > 60	PSA ≤ 10 ng/mL	Gleason score ≤ 3+4	89 (86–92)	82 (77–88)	80 (74–86)	68 (59–78)
		Gleason score 4+3	84 (78–90)	74 (64–85)	71 (60–83)	55 (41–73)
		Gleason score 8–10	78 (71–86)	65 (54–78)	62 (50–76)	43 (30–63)
	PSA > 10 ng/mL	Gleason score ≤ 3+4	83 (79–88)	73 (65–82)	70 (62–79)	54 (43–69)
		Gleason score 4+3	75 (67–85)	61 (48–78)	57 (45–73)	38 (24–61)
		Gleason score 8–10	68 (58–79)	51 (38–69)	46 (34–63)	27 (15–48)

Table 4

YEAR 3			Risk Estimate, % (95% Confidence Interval)			
			Margins ≤2		Margins>2	
			Prostate weight >30g	Prostate weight ≤ 30g	Prostate weight >30g	Prostate weight ≤ 30g
Age ≤ 60	PSA ≤10 ng/mL	Gleason score ≤3+4	87 (83–91)	78 (72–85)	76 (68–83)	62 (52–73)
		Gleason score 4+3	80 (72–89)	68 (56–82)	64 (52–80)	46 (32–68)
		Gleason score 8–10	73 (63–85)	59 (46–75)	54 (41–72)	35 (22–56)
		Gleason score ≤3+4	80 (73–87)	67 (58–79)	64 (54–75)	47 (34–62)
	PSA> 10 ng/mL	Gleason score 4+3	70 (59–83)	54 (40–74)	50 (36–69)	30 (17–54)
		Gleason score 8–10	61 (49–76)	43 (28–64)	38 (25–58)	19 (9–40)
		Gleason score ≤3+4	80 (75–85)	68 (60–77)	64 (56–74)	47 (36–61)
		Gleason score 4+3	70 (61–81)	54 (41–72)	50 (37–68)	30 (17–54)
Age > 60	PSA 10 ≤ng/mL	Gleason score 8–10	61 (51–74)	43 (30–61)	38 (26–57)	19 (9–39)
		Gleason score ≤3+4	70 (63–78)	54 (43–68)	50 (39–62)	30 (19–48)
		Gleason score 4+3	57 (45–72)	38 (24–60)	33 (21–53)	15 (6–37)
	PSA> 10 ng/mL	Gleason score 8–10	46 (34–62)	26 (15–47)	22 (12–39)	7 (2–23)
		Gleason score ≤3+4				

Table 5

YEAR 5			Risk Estimate, % (95% Confidence Interval)			
			Margins<2		Margins>2	
			Prostate weight >30g	Prostate weight ≤ 30g	Prostate weight >30g	Prostate weight ≤ 30g
Age ≤ 60	PSA ≤ 10 ng/mL	Gleason score ≤3+4	79 (74–86)	67 (59–77)	64 (54–74)	46 (35–60)
		Gleason score 4+3	70 (58–83)	54 (40–73)	49 (35–69)	30 (16–54)
		Gleason score 8–10	61 (48–76)	42 (28–63)	38 (24–59)	18 (9–40)
	PSA> 10 ng/mL	Gleason score ≤3+4	69 (61–79)	53 (42–68)	49 (38–63)	29 (18–47)
		Gleason score 4+3	56 (43–74)	37 (22–61)	32 (19–55)	14 (5–38)
		Gleason score 8–10	45 (31–65)	25 (13–49)	21 (10–42)	7 (2–23)
Age > 60	PSA ≤10 ng/mL	Gleason score ≤3+4	70 (63–76)	53 (44–65)	49 (40–61)	29 (19–45)
		Gleason score 4+3	57 (45–71)	38 (24–59)	33 (20–54)	15 (6–37)
		Gleason score 8–10	45 (33–62)	26 (15–46)	21 (11–40)	7 (2–22)
	PSA> 10 ng/mL	Gleason score ≤3+4	56 (48–66)	37 (26–53)	32 (22–46)	14 (7–30)
		Gleason score 4+3	40 (28–58)	21 (10–44)	17 (8–36)	5 (1–21)
		Gleason score 8–10	29 (18–46)	12 (4–30)	9 (3–23)	1 (<1–9)

* How this should be explained to a patient is that, Mr. X, given your PSA, age, prostate weight, number of positive surgical margins, and your Gleason sum, our best guess is that you have an X (actual value from the table) percentage chance of not developing a PSA recurrence at 1, 3, and 5 years. We are 95% confident that your chances of not recurring are somewhere between x and y (the lower and upper limits of the 95% confidence interval).