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Definition of biochemical recurrence after radical prostatectomy does not substantially impact estimates for prognostic factors

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Abstract

Purpose—Biochemical recurrence (BCR) is used as a surrogate endpoint following radical prostatectomy. A large number of different definitions of BCR are currently used in the research literature. We examine various definitions of BCR in a large clinical cohort to explore whether estimation differs by definition.

Materials and Methods—The cohort included 5473 patients who underwent radical prostatectomy from 1985 to 2007 at Memorial Sloan-Kettering Cancer Center. Separate analyses were performed using 12 definitions of BCR that have been used in published studies. Cox regression was used to estimate hazard ratios for established predictors. Predictive accuracy was determined using the concordance index.

Results—Depending on the definition used, the recurrence-free probability ranged from 86% to 91% at 3 years and from 81% to 87% at 5 years. Hazard ratios tended to be smaller for the most inclusive definitions, but were fairly similar across all definitions. The univariate hazard ratio for log PSA ranged from 2.1 to 2.4; for clinical stage T2b vs $\leq$ T2a from 2.4 to 2.5; and for biopsy Gleason grade ≥ 8 vs ≤ 6 from 9.8 to 15. Multivariable hazard ratios were more homogeneous across the definitions. The concordance index ranged from 0.80–0.83 for the preoperative nomogram and from 0.83–0.88 for the postoperative nomogram.

Conclusions—Estimates of risk ratios and predictive accuracy are generally robust to the definition of BCR. For clinical research, papers using different definitions will come to similar conclusions on prognostic factors. The definition should be factored into papers comparing overall recurrence probabilities.

Keywords

prostate; prostatic neoplasms; prostatectomy; prostate-specific antigen; biological markers; recurrence

Introduction

Clinically relevant outcomes such as distant metastases and death from prostate cancer do not occur for many years after radical prostatectomy^{1–2}. With the development of prostate specific antigen (PSA) as a marker in the mid-1980's came the concept of “biochemical” recurrence, an event that precedes clinical recurrence by many years, and thus can function as a surrogate endpoint for treatment efficacy^{3–5}.

The definition of this surrogate, however, is open to discussion. PSA is a continuous variable and there is no clear agreement as to what level of PSA would constitute a recurrence. A large number of different definitions of biochemical recurrence have been published^{6–7} and these differ in a variety of ways, such as in terms of PSA level (e.g. 0.2 vs. 0.4 ng/ml) and whether

a single value indicates recurrence or a confirmatory test is required. For example, when examining the prognostic significance of tertiary Gleason pattern 5 in Gleason 7 prostate cancer, Sim et al defined biochemical recurrence as a serum PSA > 0.2 ng/ml, as confirmed by repeat measurement⁸, whereas Hattab et al explored exactly the same issue defining biochemical recurrence as two consecutive serum PSA measurements > 0.1 ng/ml⁹.

Biochemical recurrence is used for both research and clinical purposes. The predominant clinical use of biochemical recurrence is to identify candidates for additional therapy, who would benefit from early initiation of salvage treatment. The most useful definition of biochemical recurrence is that with the optimal relationship with prostate cancer metastasis or death from prostate cancer, leading to a suitable balance between early treatment of a high proportion of men otherwise destined to have the worst oncologic outcome (i.e. high sensitivity) without unnecessarily treating a large number men who would not develop clinical recurrence (i.e. good specificity).

However, it is unclear whether the most clinically useful definition of biochemical recurrence would also be the most useful definition for research purposes, or even whether different definitions of biochemical recurrence would influence the results of research. Here, we examine various definitions of biochemical recurrence in a large clinical cohort to explore whether estimation for prognostic factors differs by definition used.

Material and Methods

We identified 6545 patients who underwent primary radical prostatectomy from January 1985 to September 2007 at Memorial Sloan-Kettering Cancer Center. Patients who received neoadjuvant therapy (n=823) or who were lost to follow up on their date of surgery (n=249) were excluded. The final cohort for analysis included 5473 patients (Table 1). Patients were generally followed for disease recurrence postoperatively with serum PSA measurements and clinical assessments every 3 months for the first three years, semiannually during the next two years, and annually thereafter. This study was approved by the Institutional Review Board.

We examined 12 definitions of biochemical recurrence that have previously been used in published studies (table 2)^{6–7, 10–16}. In addition, we studied another definition that we constructed (i.e. one that has not been used in the literature), a single detectable postoperative PSA. This definition served as a positive control: if results did not differ between this definition and more commonly used definitions of recurrence, we would conclude that our study method was insensitive for determining differences between definitions. PSA assays used at our institution are as follows: Hybritech Tandem-E (lower detection limit, 0.3 ng/ml; Beck-man Coulter Inc, Fullerton, CA) before 1996; Tosoh AIA (lower detection limit, 0.05 ng/ml; Tosoh USA Inc, Grove City, OH) from 1996 to 1997, and Bayer Immuno-1 (lower detection limit, 0.05 ng/ml; Bayer Diagnostics, Tarrytown, NY) since 1997. Patients were considered to have a documented biochemical recurrence on the date on which they fulfilled the criteria, or the date of initiation of secondary therapy, whichever was earliest. Secondary therapy was given at the discretion of the treating physician and to a minority of patients before a documented recurrence (Table 2). The median follow up for patients without recurrence (according to the definition with the fewest events) was 3 years. 1612 (29%) patients were followed for at least 5 years.

The probability of freedom from biochemical recurrence following radical prostatectomy was estimated using Kaplan-Meier methods. Univariate and multivariable Cox proportional hazards regression were used to estimate hazard ratios with 95% confidence intervals for established predictors, such as PSA, stage, grade, and positive surgical margins. The predictive accuracy of the preoperative¹⁷ and postoperative¹⁸ nomograms were calculated using the

concordance index. The concordance index is used to quantify the discriminative ability of a Cox regression model, and ranges from 0.5 (indicating lack of discrimination, equivalent to a coin flip) to 1.0 (indicating perfect discrimination). Separate analyses were conducted for each definition of biochemical recurrence. Patients were excluded from an analysis if they were missing data for the predictor variables in that specific analysis. We performed a sensitivity analysis where patients who have secondary therapy before documented biochemical recurrence are censored at the time that they receive secondary therapy. Although the ordering of the definitions with the least to most number of events changed slightly, none of the trends observed were impacted (data not shown). All statistical analyses were conducted using Stata 10.0 (StataCorp LP, College Station, TX).

Results

Estimates of recurrence-free probabilities at 3 and 5 years are given in Table 2 for each definition. As expected, these estimates varied based on the restrictiveness of the definition. At 3 years, the recurrence-free probability was 91.1% for the definition with the fewest events (PSA ≥ 0.4 and rising) compared to 86.1% for the definition with the most events (single PSA ≥ 0.2); at 5 years, the corresponding probabilities were 86.7% and 80.6%. The positive control had much lower estimates, with 3- and 5-year recurrence-free probabilities of 70.3% and 60.4%, respectively.

Hazard ratios for established prognostic factors are given in Tables 3 and 4. A few patterns can be observed from these results. First, all univariate (and multivariable) associations were statistically significant. Therefore, hypothesis testing was not affected by the definition of biochemical recurrence in this cohort. Second, the risk factors with moderate hazard ratios (for example, clinical stage T2b vs $\leq$ T2a with a hazard ratio ~ 2.5 on univariate analysis) had very similar hazard ratios for every definition except for the positive control. The risk factors with large hazard ratios (for example, biopsy Gleason grade ≥ 8 vs ≤ 6 with a univariate hazard ratio of ~ 11 to 15) had fairly consistent hazard ratios for every definition except for the positive control. However, we observed more variability in these hazard ratios, with the higher hazard ratios tending to occur with the more strict definitions. These differences were smaller on multivariable analysis: for example, the hazard ratio for pathology Gleason grade ≥ 8 vs ≤ 6 ranged from 18 to 29 on univariate analysis and from 6.3 to 10 on multivariable analysis (excluding the positive control).

The predictive accuracies of the preoperative and postoperative nomograms are given in Table 4. These results were similar to what was observed for multivariable regression: the concordance index was similar for all definitions except for the positive control. The preoperative nomogram had concordance index of 0.66 for the positive control and ranged from 0.79–0.83 for all other definitions; the corresponding values for the postoperative nomogram were 0.69 and 0.83 to 0.87.

We then explored whether the definitions with more events also had greater statistical power. Statistical significance in a Cox model is determined by the z-score, which is calculated by dividing the estimated log hazard ratio by the standard error of the estimate; higher z-scores in absolute value have lower p-values. Although the numerator (the log hazard ratio estimate) decreased with more events, the denominator (the standard error of the estimate) decreased more proportionately. This results in a lower z score and a lower p-value for the definition with more events. For example, the z score of pathology Gleason grade ≥ 8 vs ≤ 6 was $\log(28.9)/0.16 = 21.0$ for the definition with the fewest events, and $\log(18.3)/0.12 = 24.2$ for the definition with the most events.

Discussion

Biochemical recurrence has been widely used as an endpoint in studies examining prognostic factors associated with disease progression following radical prostatectomy. Yet the definition of biochemical recurrence used for each study varies, making the validity of comparisons between studies unclear. Less restrictive definitions of biochemical recurrence, such as those with a low trigger PSA or that do not require a confirmatory rise, will naturally have lower recurrence-free probabilities compared to more restrictive definitions. In this study, we demonstrate that the definition of biochemical recurrences does not have a large impact on estimates of risk ratios, such hazard ratios, if the definition is reasonably chosen.

We observe two general trends from our results. First, the hazard ratios tended to be smaller for the more inclusive definitions. A smaller risk ratio indicates a smaller relative separation in risk between those with and without the risk factor. With a more inclusive definition, more patients will meet the criteria for recurrence; this tends to have a disproportionate effect on the estimates of risk for those without the risk factor. Since patients without the risk factor are typically represented in the denominator of the risk ratio, the more inclusive definitions will have smaller risk ratios.

Second, the predictive accuracy of the nomogram tended to be higher for the more restrictive definitions. We hypothesize that this is because worse events are easier to predict, and that meeting the criteria for the more restrictive definitions is typically indicative of a worse failure. For example, a patient with $\text{PSA} \geq 0.4$ with a confirmatory rise probably has more aggressive disease compared to a patient with a single $\text{PSA} \geq 0.2$. Of note, the concordance indices were very high (generally >0.8) for both nomograms. This is primarily because a high proportion of patients in this cohort were treated in recent years (31% from 2005 to 2007). With a mature cohort, we would expect the nomograms to have slightly lower predictive accuracy than that reported here.

With acknowledgement of these trends, we also observe that the relative risks and hazard ratios were fairly consistent between the 12 definitions examined. The univariate hazard ratio for positive surgical margins was ~ 3 and the univariate hazard ratio for clinical stage T2b vs $\leq$ T2a was ~ 2.5 . The only definition to provide a substantially different result was the positive control, which lends support to our study method.

In this large cohort, statistical inferences on established prognostic factors were not impacted by the definition of biochemical recurrence. We have not focused on this result because it is unlikely that hypothesis testing would be a problem in our particular setting. First, we analyzed very strong predictors of outcome; second, the number of events ranged from 600 to 800, and therefore all definitions had very high power to detect statistical differences. It is plausible that the definition of biochemical recurrence would have an impact on hypothesis testing when examining a novel marker in a smaller data set, where one might find a statistically significant difference using the most inclusive definition but not the least inclusive definition. This suggests that investigators should use a relatively inclusive – but reasonable – definition of biochemical recurrence when evaluating novel markers in small data sets. What would constitute a reasonable definition of biochemical recurrence is an area of debate, but is out of the scope of this paper to discuss. An important distinction to make is between studies of prognostic factors, such as molecular markers, and studies of treatments for prostate cancer. For example, in studies where patients will receive a treatment after biochemical recurrence, the definition should be based on considering the harms and benefits of the particular treatment. A more liberal definition of biochemical recurrence might be selected for a well tolerated treatment, whereas a more restrictive definition might be selected for a toxic treatment.

Many investigators have examined the appropriate definition of biochemical recurrence for clinical purposes. For example, the American Urological Association Prostate Cancer Guidelines Panel recommended defining biochemical recurrence after radical prostatectomy as an initial serum PSA ≥ 0.2 ng/ml, with a second confirmatory level of PSA of > 0.2 ng/ml⁶. This recommendation was based on a literature review of studies published from 2001 to 2004, but without any formal comparative statistical analysis. Stephenson et al subsequently examined the correlation between 10 definitions of biochemical recurrence with metastatic progression in a clinical cohort, and proposed that biochemical recurrence should be defined as a PSA > 0.4 ng/ml with a confirmatory rise⁷. We found only one paper that also examined the effects of the definition on clinical research. In this study of 2782 men who underwent radical prostatectomy between 1987 and 1993, Amling et al looked at five definitions of biochemical recurrence and concluded that hazard ratios and statistical significance of Gleason grade, PSA doubling time, surgical margin status, and seminal vesicle invasion were not impacted by the definition¹⁹. Our study confirms the findings of Amling et al, with over 5000 patients, 12 commonly used definitions of biochemical recurrence, and including other established prognostic factors such as pathologic stage.

One limitation of any study on recurrence definitions is the use of secondary therapy. Depending on the definition of biochemical recurrence, 10–30% of patients received secondary therapy prior to the documented recurrence and were considered as events when they started secondary therapy. This could produce bias because these patients were not followed to their true failure time. However, hazard ratios were fairly similar when comparing the results of the most and least inclusive definitions, which correspond to 10% versus 30% of patients having secondary therapy. Accordingly, any bias is likely to be minimal. Other limitations are the retrospective nature of the data, the inherent inaccuracies and natural variability of serum PSA measurements, and the short length of follow up. It is possible that longer follow up would modify the results. However, we believe that any modification would be small since the data set contained approximately 1500 patients followed for at least 5 years following surgery. The strength of our study is that we comprehensively examined 13 definitions of biochemical recurrence, including a positive control. Importantly, substantial differences in estimation were observed for the positive control. We can therefore be confident that we would have identified differences in estimation between the 12 reasonable definitions, if true differences existed.

Conclusions

Estimates of risk ratios and predictive accuracy are generally robust to the definition of biochemical recurrence. These results by no means imply that the clinical usefulness of the definitions is similar – only that research results do not differ importantly by definition. The definition of biochemical recurrence used for clinical purposes should be based on clinical judgment, with a consideration of patient risk factors and after thorough discussion about the potential risks and benefits of the treatment. For clinical research, the definition of biochemical recurrence should be factored into comparative papers on overall recurrence probabilities; however, papers using different definitions will come to similar conclusions on prognostic factors. For trial design, studies of prognostic factors are likely to have increased power if a more inclusive, but reasonable, definition of biochemical recurrence is used.

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Table 1

Clinical and pathological patient characteristics

Characteristic	Median (IQR) or Frequency (%)
Age at surgery (years)	60 (55, 65)
Pretreatment PSA (ng/ml) *	5.77 (4.20, 8.30)
Preoperative nomogram 5-year PFP (%) *	94 (88, 96)
Postoperative nomogram 5-year PFP (%) *	97 (92, 98)
Biopsy Gleason grade	
≤6	2946 (54%)
7	1585 (29%)
≥8	353 (6%)
Unknown	589 (11%)
Clinical Stage	
≤T2a	4138 (76%)
T2b	703 (13%)
≥T2c	427 (8%)
Unknown	205 (4%)
Pathology Gleason grade	
≤ 6	1967 (36%)
7	2835 (52%)
≥8	377 (7%)
Unknown	294 (5%)
Extracapsular extension	
No	3860 (71%)
Yes	1512 (28%)
Unknown	101 (2%)
Seminal vesicle invasion	
No	5062 (92%)
Yes	355 (6%)
Unknown	56 (1%)
Surgical margin status	
Negative	4326 (79%)
Positive	1089 (20%)
Unknown	58 (1%)
Lymph node involvement	
Not done	500 (9%)
No	4727 (87%)
Yes	226 (4%)

IQR: interquartile range; PSA: prostate specific antigen; PFP: progression free probability

* Pretreatment PSA was available for 5299 patients; preoperative nomogram for 4525; and postoperative nomogram for 4870.

Table 2

Kaplan-Meier recurrence-free probability for various definitions of biochemical recurrence. Definitions are listed in the order of the definition with the least number of events to the definition with the most number of events.

BCR Definition	Number of Events	Number with secondary therapy*	Kaplan-Meier recurrence-free probability (%)	
			3-year	5-year
1 PSA $\geq$ 0.4 ng/ml and rising ^{6-7, 10}	610	207 (34%)	91.1 (90.2, 91.9)	86.7 (85.4, 87.8)
2 Single PSA $\geq$ 0.6 ng/ml ⁶⁻⁷	657	180 (27%)	90.6 (89.7, 91.5)	85.7 (84.5, 86.9)
3 PSA $\geq$ 0.2 ng/ml and rising ^{6-7, 11}	663	192 (29%)	90.4 (89.5, 91.3)	84.8 (83.5, 86.0)
4 3 consecutive PSA rises ^{7, 12}	680	139 (20%)	90.2 (89.3, 91.1)	85.1 (83.9, 86.3)
5 2 consecutive PSA values $\geq$ 0.2 ng/ml ^{6, 13}	697	131 (19%)	89.9 (88.9, 90.7)	84.9 (83.6, 86.1)
6 Initial PSA $\geq$ 0.2 ng/ml with successive PSA $>$ 0.2 ng/ml ^{6**}	702	129 (18%)	89.8 (88.8, 90.7)	84.8 (83.5, 85.9)
7 Single PSA $\geq$ 0.4 ng/ml ^{6-7, 14}	732	152 (21%)	89.4 (88.5, 90.3)	84.4 (83.1, 85.6)
8 2 successive PSA rises, final PSA $\geq$ 0.2 ng/ml ⁷	760	110 (14%)	88.7 (87.7, 89.6)	83.5 (82.2, 84.7)
9 3 successive PSA rises $\geq$ 0.1 ng/ml ⁷	793	132 (17%)	88.3 (87.2, 89.2)	83.1 (81.7, 84.3)
10 PSA $\geq$ 0.1 ng/ml and rising ^{7, 15}	801	79 (10%)	87.9 (86.9, 88.8)	82.4 (81.0, 83.6)
11 3 successive PSA rises ⁷	817	129 (16%)	88.0 (87.0, 88.9)	81.6 (80.2, 82.9)
12 Single PSA $\geq$ 0.2 ng/ml ^{6-7, 16}	889	87 (10%)	86.1 (85.0, 87.1)	80.6 (79.3, 81.9)
13 Single detectable PSA	1848	22 (1%)	70.3 (68.9, 71.7)	60.4 (58.7, 62.0)

BCR: biochemical recurrence

* Number with secondary therapy before documented biochemical recurrence, that is, the documented event was caused by initiation of secondary therapy

** Definition recommended by the American Urological Association Prostate Cancer Guidelines Panel

Table 3

Univariate hazard ratios and p-values for the association with various BCR definitions. All associations were statistically significant at $p < 0.001$. Definitions are listed in the order of the definition with the least number of events to the definition with the most number of events.

Predictor	BCR definition												
	1*	2	3	4	5	6**	7	8	9	10	11	12	13
Log PSA (ng/ml)	2.40 (2.14, 2.69)	2.42	2.32	2.40	2.42	2.40	2.31	2.34	2.17	2.36	2.10	2.23	1.54
Biopsy Gleason grade													
7 vs ≤ 6	3.89 (3.12, 4.87)	3.81	3.77	3.88	3.89	3.87	3.52	3.73	3.38	3.73	3.21	3.32	1.72
≥8 vs ≤ 6	14.7 (11.5, 18.7)	13.4	12.0	13.3	13.1	13.1	11.9	12.5	11.1	12.3	9.79	10.5	3.69
Clinical stage													
T2b vs ≤ T2a	2.53 (2.09, 3.06)	2.63	2.49	2.48	2.52	2.52	2.39	2.43	2.42	2.35	2.39	2.46	1.60
≥T2c vs ≤ T2a	3.54 (2.86, 4.37)	3.69	3.45	3.41	3.48	3.44	3.37	3.29	3.11	3.21	2.97	3.25	2.19
Pathology Gleason grade													
7 vs ≤ 6	5.15 (3.82, 6.96)	4.73	4.65	4.74	4.89	4.73	4.19	4.58	4.02	4.63	4.10	3.46	1.61
≥8 vs ≤ 6	28.9 (21.1, 39.5)	26.8	22.8	25.7	26.7	26.0	22.8	23.5	20.2	23.4	18.4	18.3	5.21
ECE (yes vs no)	4.55 (3.87, 5.36)	4.45	4.60	4.59	4.64	4.63	4.27	4.34	3.93	4.27	4.05	3.70	2.16
SVI (yes vs no)	6.76 (5.64, 8.09)	6.87	6.36	6.83	7.01	6.87	6.59	6.51	6.02	6.43	5.78	5.93	3.54
LNI (yes vs no/not done)	9.54 (7.73, 11.8)	10.26	8.18	9.35	9.69	9.65	9.49	8.70	9.07	8.73	7.69	8.43	4.89
PSM (yes vs no)	3.18 (2.71, 3.73)	3.09	2.96	3.18	3.15	3.13	2.98	3.12	2.89	3.14	2.89	2.99	2.05

BCR: Biochemical recurrence; PSA: prostate specific antigen; ECE: extracapsular extension; SVI: seminal vesicle invasion; LNI: lymph node involvement; PSM: positive surgical margin.

* For reference, 95% confidence intervals are given in parentheses

** Definition recommended by the American Urological Association Prostate Cancer Guidelines Panel

Table 4

Multivariable hazard ratios and concordance index for preoperative and postoperative models. All associations were significant at $p < 0.001$. Definitions are listed in the order of the definition with the least number of events to the definition with the most number of events.

	1*	2	3	4	5	6**	7	8	9	10	11	12	13
BCR definition													
Preoperative model													
Log PSA (ng/ml)	2.07 (1.79, 2.38)	2.02	2.00	2.08	2.08	2.08	1.97	2.04	1.91	2.04	1.83	1.94	1.42
Biopsy Gleason grade													
7 vs ≤ 6	3.21 (2.55, 4.05)	3.20	3.03	3.17	3.18	3.16	2.97	3.02	2.83	3.05	2.64	2.77	1.56
≥8 vs ≤ 6	10.7 (8.26, 13.9)	9.78	8.82	9.81	9.50	9.54	8.89	9.21	8.28	9.12	7.41	7.76	3.00
Clinical stage													
T2b vs ≤ T2a	1.94 (1.55, 2.44)	1.93	2.04	2.00	2.00	2.00	1.82	2.01	1.95	1.96	2.07	1.94	1.45
≥T2c vs ≤ T2a	2.09 (1.63, 2.68)	2.17	2.20	2.08	2.16	2.15	2.10	1.99	2.01	1.98	2.01	2.02	1.74
Concordance index	0.825	0.817	0.814	0.824	0.823	0.823	0.806	0.814	0.800	0.813	0.790	0.798	0.659
Postoperative model													
Log PSA (ng/ml)	1.42 (1.23, 1.63)	1.42	1.40	1.45	1.46	1.46	1.41	1.44	1.39	1.44	1.31	1.45	1.20
Pathology Gleason grade													
7 vs ≤ 6	3.47 (2.51, 4.79)	3.10	3.03	3.15	3.27	3.14	2.80	3.07	2.77	3.12	2.78	2.29	1.29
≥8 vs ≤ 6	10.0 (6.99, 14.4)	9.25	7.87	8.73	9.14	8.89	8.13	8.04	7.52	8.07	6.75	6.34	2.61
ECE (yes vs no)	2.08 (1.69, 2.55)	2.00	2.21	2.09	2.02	2.05	1.96	1.99	1.76	1.95	1.93	1.80	1.35
SVI (yes vs no)	1.93 (1.54, 2.41)	2.02	1.88	1.97	2.01	1.98	2.00	1.96	1.89	1.89	1.81	1.96	1.71
LNI (yes vs no/not done)	2.50 (1.93, 3.23)	2.75	1.99	2.40	2.53	2.52	2.70	2.30	2.56	2.33	2.16	2.56	2.24
PSM (yes vs no)	1.74 (1.44, 2.10)	1.67	1.69	1.79	1.74	1.74	1.65	1.79	1.68	1.78	1.73	1.79	1.52
Concordance index	0.872	0.861	0.858	0.868	0.869	0.868	0.850	0.857	0.842	0.855	0.834	0.833	0.686

BCR: Biochemical recurrence; PSA: prostate specific antigen; ECE: extracapsular extension; SVI: seminal vesicle invasion; LNI: lymph node involvement; PSM: positive surgical margin.

* For reference, 95% confidence intervals are given in parentheses

** Definition recommended by the American Urological Association Prostate Cancer Guidelines Panel