Predictors of time to biochemical recurrence in a radical prostatectomy cohort within the PSA-era

Ahva Shahabi, MPH, PhD;[1] Raj Satkunasivam, MD;[2*] Inderbir S. Gill, MD;[2] Gary Lieskovsky, MD;[2] Sia Daneshmand, MD;[2] Jacek K. Pinski, MD, PhD;[3] Mariana C. Stern, PhD[1]*

[1]Department of Preventive Medicine, Keck School of Medicine of USC; [2]Department of Urology, USC Institute of Urology and Norris Comprehensive Cancer Center, Keck School of Medicine of USC; [3]Department of Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine of USC, Los Angeles, CA, U.S.A. *These authors contributed equally to this work.

Cite as: *Can Urol Assoc J* 2016;10(1-2):E17-22. http://dx.doi.org/10.5489/cuaj.3163
Published online January 14, 2016.

Abstract

Introduction: We sought to determine predictors for early and late biochemical recurrence following radical prostatectomy among localized prostate cancer patients.

Methods: The study included localized prostate cancer patients treated with radical prostatectomy (RP) at the University of Southern California from 1988 to 2008. Competing risks regression models were used to determine risk factors associated with earlier or late biochemical recurrence, defined using the median time to biochemical recurrence in this population (2.9 years after radical prostatectomy).

Results: The cohort for this study included 2262 localized prostate cancer (pT2-3N0M0) patients who did not receive neoadjuvant or adjuvant therapies. Of these patients, 188 experienced biochemical recurrence and a subset continued to clinical recurrence, either within (n=19, 10%) or following (n=13, 7%) 2.9 years after RP. Multivariable stepwise competing risks analysis showed Gleason score ≥7, positive surgical margin status, and ≥pT3a stage to be associated with biochemical recurrence within 2.9 years following surgery. Predictors of biochemical recurrence after 2.9 years were Gleason score 7 (4+3), preoperative prostate-specific antigen (PSA) level, and ≥pT3a stage.

Conclusions: Higher stage was associated with biochemical recurrence at any time following radical prostatectomy. Particular attention may need to be made to patients with stage ≥pT3a, higher preoperative PSA, and Gleason 7 prostate cancer with primary high-grade patterns when considering longer followup after RP.

Introduction

Radical prostatectomy (RP) remains a mainstay of treatment for localized prostate cancer (PCa). However, up to 30% of patients will experience biochemical recurrence (BCR) following RP,[1-4] of which 20–30% will progress to clinical metastasis or recurrence (CR).[4, 5] Although guidelines are available for post-RP surveillance, there is no clear consensus on an optimal followup strategy.[6, 7] Optimal risk stratification is crucial to avoid patient anxiety while tailoring risk-adapted surveillance and potentially earlier adjuvant therapy in those who require it.

Existing models and nomograms using preoperative or postoperative clinical and pathologic data provide risk estimates of recurrence.[8-12] Few studies have further examined the timing of BCR after surgery as a possible predictor of metastatic disease and PCa-related mortality [4,5,13-15] or the association of potential risk factors with earlier or later BCR.[1,16,17] Approximately 27% of BCR patients have been reported to experience late BCR.[13] In this study, we sought to determine clinical and pathologic characteristics predictive of early BCR vs. late BCR in a large cohort of patients treated with RP for localized PCa.

Methods

Patient population

The University of Southern California maintained an institutional review board-approved database that included prospectively collected clinical data for 4063 males who underwent open radical retropubic prostatectomy with bilateral pelvic lymph node dissection (RRP/PLND) from 1972 to 2009. We excluded patients who did not consent to participate in the database (n=85), non-adenocarcinoma pathology (n=7), salvage cases (n=23), laparoscopic cases (n=39), patients who were treated before July 1, 1988 in the pre-PSA era or after June 30, 2008 to ensure at least two years of followup on patients (n=375). Further exclusions (not mutually exclusive) included PSA-era cases with clinical stage cTX or cT4 (n=2), lymph node metastasis (n=344), neoadjuvant hormonal therapy (n=703), neoadjuvant chemotherapy (n=7), patients classified as never having "no evidence of disease" after surgery (n=110), patients with any adjuvant therapy (hormone therapy only, n=13; radiation only, n=373; hormone and radiation, n=13; and

chemotherapy, n=8), and patients who were recorded as having a clinical recurrence without a prior biochemical recurrence (n=51). The final study population used for the analyses included 2262 patients who achieved undetectable PSA after surgery.

As previously described,[18,19] all specimens were assessed using consistent pathological reporting, and followup at our institution was standardized, with patients monitored every four to six months in the first year after RP, every six months in the following second and third years, and annually thereafter. Patients were recommended adjuvant radiotherapy for positive surgical margins and/or ≥pT3 disease and salvage radiotherapy was offered to those with BCR or CR with evidence supporting of local disease.

Patient followup was completed through chart review of patient medical records and phone calls to the patients or the patient's primary care provider. Cause of death was confirmed through review of medical records or direct contact with the primary physician or the patient's family. The date of death was confirmed in all patients using the Social Security Death Index. Last followup of patients was completed in May 2010.

Biochemical recurrence (BCR) was defined as a detectable PSA level based on the era-specific assay's detectability limit, verified by two consecutive increased PSA tests, with three to four months in between blood draws.[20] The current National Comprehensive Cancer Network (NCCN) guidelines recommend followup until five years post-surgery, when annual PSA testing is then recommended.[21] However, guidelines for the management of patients following BCR have evolved during the course of followup within the time period reflected in this cohort. Therefore, for this study, we used the cutoff point indicating early and late biochemical recurrence using the characteristics of the cohort itself. To distinguish early vs. late BCR, we used the median time to biochemical recurrence (2.91 years) as the cutoff within this population. This time frame is consistent with other work that showed a three-year cutoff was the best indicator of prostate cancer-specific mortality following BCR.[14] Time to BCR was calculated as the time from RP to the time when BCR was documented based on physician's evaluation of the two consecutive PSA tests. Patients were defined as having a CR after the detection of recurrent local or distant disease by imaging.

Statistical analyses

Demographic and clinical characteristics were evaluated and presented as counts and percentages for categorical variables and medians, interquartile ranges, and ranges for continuous variables. To account for the possible risk of either early or late recurrence for each patient, rather than one mutually exclusive event, multivariable competing risks regression models were used to determine sub hazard ratios (SHR) for risk, taking into account all clinical variables from the univariable analyses that showed associations with $p<0.2$. Clinical variables considered include age at surgery, preoperative PSA, pathologic Gleason score, surgical margin status, pathologic stage, and operation year. Race/ethnicity was not included, since most of the categories did not reach significance ($p<0.2$) in the univariable analyses. All analyses were performed using Stata (Stata 12, StataCorp LP, College Station, TX).

Results

Characteristics of all study patients (n=2262) are presented in Table 1. The median followup after RP of patients who did not experience any recurrence (n=2074) was 6.55

Table 1. Characteristics of radical prostatectomy patients in the study cohort (N=2262)

Total (N)	2262
Age at RP (years)	
Median	63
IQR	57–68
Range	35–83
Race/ethnicity, n (%)	
Non-Hispanic White	1948 (86)
Hispanic	118 (5)
African-American	91 (4)
Asian/PI	77 (3)
Missing	27 (1)
PSA before surgery (ng/ml)	
Median	6.36
IQR	4.70–8.94
Range	0.40–109
Clinical stage, n (%)	
cT1	1676 (74)
cT2	581 (26)
cT3	5 (<1)
D'Amico risk classification,* n (%)	
Low	1033 (53)
Intermediate	680 (35)
High	247 (13)
Prostatectomy year, n (%)	
07/1988–07/1994	302 (13)
07/1994–03/2005	1448 (64)
03/2005–06/2008	511 (23)
Pathologic Gleason score, n (%)	
≤6	1091 (48)
(3+4)	799 (35)
(4+3)	238 (11)
8–10	126 (6)
Missing	8 (<1)

*Risk categories were determined for clinically localized PCa patients who had all preoperative variables available: PSA, biopsy Gleason score, and clinical stage. BCR: biochemical recurrence; IQR: interquartile range; PI: RP: radical prostatectomy.

Table 1. Characteristics of radical prostatectomy patients in the study cohort (N=2262) (cont'd)

Total (N)	**2262**
Pathologic stage	
pT2a–pT2c	1900 (84)
pT3a–pT4a	362 (16)
Surgical margin status, n (%)	
Negative	1935 (86)
Apex only	154 (7)
Other with +/- apex	135 (6)
Positive but missing location	38 (2)
Recurrence status	
No recurrence	2074 (92)
Only BCR	156 (7)
BCR and CR	32 (1)
Followup for patients without any recurrence following surgery (years)	
Median	6.55
IQR	3.92–10.05
Range	0–20.35
Time from surgery to biochemical recurrence (years)	
Median	2.91
IQR	1.67–4.55
Range	0.17–13.69
Clinical recurrence based on median time to BCR (2.91 years after RP)	
Early BCR (≤2.91 years after RP)	19 (59)
Late BCR (>2.91 years after RP)	13 (41)

BCR: biochemical recurrence; IQR: interquartile range; RP: radical prostatectomy.

years (interquartile range [IQR]=3.92-10.05) and 2.91 years (IQR=1.67-4.55) to BCR after surgery. A total of 188 (8.3%) patients experienced disease recurrence: 156 with only BCR, and 32 with BCR followed by CR.

Table 2 presents characteristics stratified by early or late BCR categorized based on the median years until BCR (2.91 years). The majority of early BCR patients had pathologic Gleason score of 7 (3+4) (41%) whereas the majority of late BCR patients had pathologic Gleason score ≤6 (40%). As expected, late BCR patients were more likely to have a negative surgical margin status (80%) than early BCR patients (62%). Of the 32 with CR, 19 were early BCR patients (20%) and 13 were late BCR patients (14%). There were a total of 11 patients who experienced PCa-related mortality after CR (5.8%), of which six had BCR ≤2.91 years after surgery and five deaths >2.91 years after surgery (data not shown).

All clinical variables evaluated except race/ethnicity were associated with early BCR in the competing risks models for univariable and multivariable analyses shown in Table 3. By using competing risks models, we accounted for the additional possible risk of late recurrence for each patient rather than one mutually exclusive event. In multivariable

Table 2. Characteristics of localized prostate cancer patients based on biochemical recurrence status

	Time of biochemical recurrence		
	No BCR	**Early BCR (≤2.91 years after RP)**	**Late BCR (>2.91 years after RP)**
Total (N)	2074	94	94
Age at surgery (years)			
Median (IQR)	62.5 (57–68)	66 (58–70)	63 (60–68)
Race/ethnicity			
Non-Hispanic White	1787 (86)	80 (85)	81 (86)
Hispanic	106 (5)	6 (6)	6 (6)
African-American	85 (4)	2 (2)	4 (4)
Asian/PI	68 (3)	6 (6)	3 (3)
Missing	27 (1)	0 (0)	0 (0)
Pathologic Gleason score			
≤6	1033 (50)	20 (21)	38 (40)
(3+4)	732 (35)	38 (40)	29 (31)
(4+3)	203 (10)	18 (19)	17 (18)
8–10	98 (5)	18 (19)	10 (11)
PSA before surgery (ng/ml)			
Median (IQR)	6.27 (4.67–8.71)	7.25 (5.5–10.4)	7.65 (5.7–11.7)
D'Amico risk classification*			
Low	990 (55)	21 (25)	22 (31)
Intermediate	609 (34)	40 (48)	31 (43)
High	206 (11)	22 (27)	19 (26)
Surgical margin status			
Negative	1802 (87)	58 (62)	75 (80)
Apex only	133 (6)	14 (15)	7 (7)
Other with +/- apex	101 (5)	22 (23)	12 (13)
Positive but missing location	38 (2)	0 (0)	0 (0)
Clinical stage			
cT1	1551 (75)	66 (70)	59 (63)
cT2	519 (25)	27 (29)	35 (37)
cT3	4 (<1)	1 (1)	0 (0)
Prostatectomy year			
07/1988–07/1994	253 (12)	15 (16)	34 (36)
07/1994–03/2005	1316 (63)	72 (77)	60 (64)
03/2005–06/2008	504 (24)	7 (7)	0 (0)
Pathologic stage			
pT2a-pT2c	1780 (86)	58 (62)	62 (66)
pT3a-pT4a	294 (14)	36 (38)	32 (34)
Clinical recurrence			
No	2074 (100)	75 (80)	81 (86)
Yes	0 (0)	19 (20)	13 (14)

*Risk categories were determined for clinically localized PCa patients who had all preoperative variables available: PSA, biopsy Gleason score, and clinical stage. Time of biochemical recurrence based on median years after surgery until biochemical recurrence (2.91 years) BCR: biochemical recurrence; IQR: interquartile range; RP: radical prostatectomy.

Table 3. Competing risks analysis to determine predictors of earlier biochemical recurrence with later recurrence being the competing risk

	Univariable			Multivariable		
	SHR	95%CI	*p* value	SHR	95%CI	*p* value
Age at surgery (years)	1.04	1.01–1.07	0.006			
Pathologic Gleason score						
≤6	1.0[REF]			1.0[REF]		
(3+4)	2.74	1.60–4.71	<0.001	2.23	1.30–3.85	0.004
(4+3)	4.41	2.34–8.33	<0.001	3.17	1.60–6.29	0.001
8-10	8.66	4.37–16.43	<0.001	6.01	2.97–12.16	<0.001
PSA before surgery (ng/ml)	1.02	1.01–1.04	0.003			
Surgical margin status						
Negative	1.0[REF]			1.0[REF]		
Positive: Apex only	2.95	1.64–5.29	<0.001	2.75	1.53–4.96	0.001
Positive other location with +/- apex	5.48	3.36–8.95	<0.001	3.42	1.92–6.10	<0.001
Pathologic T stage						
pT2a–pT2c	1.0[REF]			1.0[REF]		
pT3a–pT4a	3.42	2.25–5.18	<0.001	1.75	1.05–2.92	0.032
Race/ethnicity						
Non-Hispanic White	1.0[REF]					
Hispanic	1.28	0.56–2.93	0.558			
African-American	0.57	0.14–2.34	0.438			
Asian/PI	2.00	0.87–4.58	0.102			
Prostatectomy year						
07/1988–07/1994	1.0[REF]					
07/1994–03/2005	1.01	0.58–1.76	0.957			
03/2005–06/2008	0.36	0.15–0.87	0.024			

BCR: Biochemical recurrence; CI: confidence interval; PI: PSA: prostate-specific antigen; SHR: subdistribution hazard ratio.

analysis, pathologic Gleason score >6 (7(3+4) SHR=2.23, 95%CI: 1.30–3.85; 7(4+3) SHR=3.17, 95%CI: 1.60–6.29; 8-10 SHR=6.01, 95%CI: 2.97–12.16), positive surgical margin status (apex only SHR=2.75, 95%CI: 1.53–4.96; apex and another location SHR=3.42, 95%CI: 1.92–6.10), and stage ≥pT3 disease (SHR=1.75, 95%CI: 1.05–2.92) were statistically significantly associated with earlier BCR.

Table 4 presents univariable and multivariable competing risks analyses for late BCR. Similar to early BCR, all clinical variables evaluated except race/ethnicity were associated with early BCR in univariable analysis. Multivariable analysis shows pathologic Gleason score 7(4+3) (SHR=2.11, 95%CI: 1.11–4.01), preoperative PSA (SHR=1.02, 95%CI: 1.00–1.04), and stage ≥pT3 disease (SHR=2.40, 95%CI: 1.47–3.93) to be associated with risk of later BCR.

Figure 1 shows the estimated cumulative incidence curves with earlier biochemical recurrence as the competing risk. Patients with Gleason (4+3) and stage ≥pT3 had the highest cumulative incidence of later BCR, followed by patients with Gleason (3+4) and stage ≥pT3 disease, then patients with Gleason (4+3) and stage pT2 disease, with patients with Gleason (3+4) and stage pT2 disease having the lowest cumulative incidence of later BCR.

Discussion

In this study, we sought to understand the clinical factors associated with early or late biochemical recurrence among a cohort of localized PCa patients who underwent RP. Our results show that there are similarities and also differences in patient characteristics among those who are at risk of earlier vs. later BCR after surgery. Stage ≥pT3 disease is consistently a risk factor BCR any time after surgery, while any Gleason score >6 and positive surgical margin status independently predict earlier BCR, and Gleason score of 7 (4+3) and higher pre-operative PSA predict later BCR.

These findings further support ongoing followup for these patients, particularly for stage ≥T3a disease, who had a higher risk of BCR any time after surgery. While higher Gleason score and positive surgical margin status are known risk factors for early recurrence after surgery,[13, 17] these factors may not be associated with patients who are at risk for later biochemical recurrence of disease and subsequent clinical recurrence. According to our results, having a primary Gleason 4 pattern in a Gleason score 7 tumour continues to be associated with an increased risk of later BCR after surgery. Previous studies have shown that a Gleason score of 7 with a primary Gleason 4 pattern is an independent

Table 4. Competing risks analysis to determine predictors of later biochemical recurrence with earlier recurrence being the competing risk

	Univariable			Multivariable		
	SHR	95%CI	*p* value	SHR	95%CI	*p* value
Age at surgery (years)	1.01	0.99–1.03	0.393			
Pathologic Gleason score						
≤6	1.0[REF]			1.0[REF]		
(3+4)	1.33	0.82–2.16	0.242	1.14	0.68–1.90	0.621
(4+3)	2.98	1.68–5.26	<0.001	2.11	1.11–4.01	0.022
8-10	2.68	1.34–5.35	0.005	1.83	0.85–3.96	0.122
PSA before surgery (ng/ml)	1.03	1.01–1.04	0.001	1.02	1.00–1.04	0.021
Surgical margin status						
Negative	1.0[REF]					
Positive: Apex only	1.23	0.57–2.67	0.600			
Positive other location with +/- apex	2.23	1.22–4.09	0.009			
Pathologic T stage						
pT2a-pT2c	1.0[REF]			1.0[REF]		
pT3a-pT4a	2.95	1.92–4.52	<0.001	2.40	1.47–3.93	<0.001
Race/ethnicity						
Non-Hispanic White	1.0[REF]					
Hispanic	1.52	0.67–3.44	0.318			
African-American	1.53	0.56–4.20	0.406			
Asian/PI	1.05	0.33–3.40	0.934			
Prostatectomy year						
07/1988–07/1994	1.0[REF]					
07/1994–03/2005	0.49	0.33–0.75	0.001			
03/2005–06/2008						

BCR: Biochemical recurrence; CI: confidence interval; PI: PSA: prostate-specific antigen; SHR: subdistribution hazard ratio.

risk factor for BCR and recurrence-free survival continues to be lower than that of tumours with primary Gleason 3 at any time after RP.[22,23]

Our results are comparable to other studies that have sought to identify predictors of early and late BCR following RP for localized PCa.[1,5,13,16,17] Specifically, Gleason score of >6, positive surgical margin, and extracapsular extension have been previously shown to be independently associated with earlier recurrence.[17, 24] Ward et al also found that Gleason, pre-operative PSA, and positive surgical margins were associated with an increased risk of BCR within five years after RP in multivariable analyses; late BCR was associated with Gleason score and preoperative PSA.[13] These same variables for late BCR also reached statistical significance in our study, in addition to stage. Our results showed pathologic stage to be a strong predictor of both early and late BCR, supporting findings from previous reports.[1,16] Loeb et al additionally showed that the actuarial probability of BCR and CR increased among men BCR-free at 10 years after surgery with increasing Gleason score, particularly among patients with stage pT3.[5]

Our results are in agreement with a previous study that suggests that low-risk patients, such as patients with organ-confined disease (stage pT2) without high Gleason scores or high PSA levels may not need annual lifelong PSA followup.[25] However, patients with stage ≥pT3a disease are at risk for both early and late BCR, and therefore, appropriate followup should be maintained after approximately three years from surgery for these patients. Differences in the study populations, (such as inclusion of cases with lymph node involvement in some studies) should be noted, as these may contribute to the differences in findings across studies.[13,17]

Strengths of our study include the use of a large cohort of patients who were treated and actively followed at a single institute with standardized operative technique, along with a standardized pathologic evaluation by dedicated genitourinary pathologists and a meticulous postoperative followup protocol. Limitations of our study included the use of a single institutional dataset with a small number of recurrences without pathologic re-review of the prostatectomy specimens to confirm the reported Gleason score. We were also not able to consider PSA doubling time and details on tumour volume as possible predictors of timing of BCR.

In summary, identified clinical and pathologic characteristics among patients who experience earlier or late BCR after RP support risk-adapted surveillance. Based on the results from this cohort, followup should be maintained, especially for patients with high-stage disease, higher preoperative PSA level, and tumours with higher primary Gleason pattern.

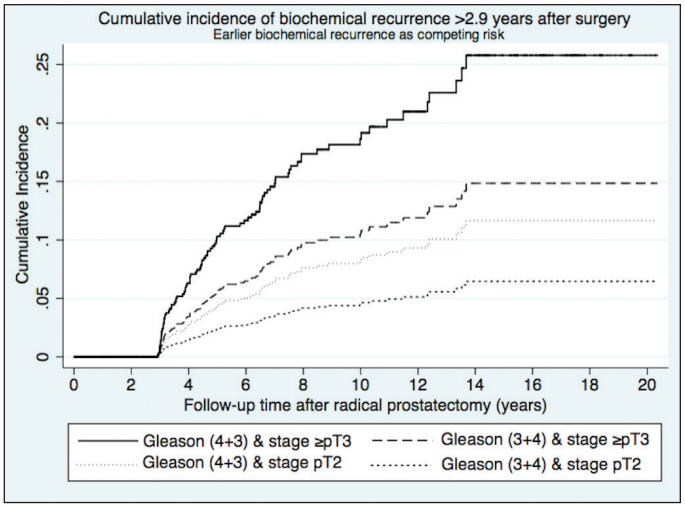

Fig. 1. Estimated cumulative incidence of late biochemical recurrence after radical prostatectomy based on combinations of pathologic Gleason score and stage.

Competing interests: Dr. Shahabi, Dr. Satkunasivam, Dr. Lieskovsky, and Dr. Stern declare no competing financial or personal interests. Dr. Gill has served on Advisory Boards for EDAP TMS, Mimic, and Hansen Medical. Dr. Daneshmand has received grant(s) or honoraria from Photocure and Taris, and is currently or has participated in a clinical trial for Photocure. Dr. Pinski is a member of a Speakers' Bureau for Janssen, Astellas, and Dendreon and is currently or has participated in clinical trials for Xanthus Life Sciences, Sanofi-Aventis, Eli Lilly, Cougar Biotechnology, and Millenium Pharmaceuticals.

This paper has been peer-reviewed.

Acknowledgements: AS was financially supported by the National Institutes of Health (NIH) through Grant Award Number TL1RR031992.We acknowledge Jie Cai and Tracy Campanelli Palmer for their help in the maintenance of the clinical database at the USC Institute of Urology.

References

1. Amling CL, Blute ML, Bergstralh EJ, et al. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: Continued risk of biochemical failure after five years. *J Urol* 2000;164:101-5. http://dx.doi.org/10.1016/S0022-5347(05)67457-5
2. Blute ML, Bergstralh EJ, Iocca A, et al. Use of Gleason score, prostate specific antigen, seminal vesicle, and margin status to predict biochemical failure after radical prostatectomy. *J Urol* 2001;165:119-25. http://dx.doi.org/10.1097/00005392-200101000-00030
3. Lerner SE, Blute ML, Bergstralh EJ, et al. Analysis of risk factors for progression in patients with pathologically confined prostate cancers after radical retropubic prostatectomy. *J Urol* 1996;156:137-43. http://dx.doi.org/10.1016/S0022-5347(01)65967-6
4. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591-7. http://dx.doi.org/10.1001/jama.281.17.1591
5. Loeb S, Feng Z, Ross A, et al. Can we stop prostate specific antigen testing 10 years after radical prostatectomy? *J Urol* 2011;186:500-5. http://dx.doi.org/10.1016/j.juro.2011.03.116
6. Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and treatment of clinically localised disease. *Eur Urol* 2011;59:61-71. http://dx.doi.org/10.1016/j.eururo.2010.10.039
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®): Prostate Cancer (Version 4.2013).
8. Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: A straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J Urol* 2005;173:1938-42. http://dx.doi.org/10.1097/01.ju.0000158155.33890.e7
9. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-74. http://dx.doi.org/10.1001/jama.280.11.969
10. Kattan MW, Eastham JA, Stapleton AM, et al. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 1998;90:766-71. http://dx.doi.org/10.1093/jnci/90.10.766
11. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 1999;17:1499-507.
12. Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* 2001;58:843-8. http://dx.doi.org/10.1016/S0090-4295(01)01441-8
13. Ward JF, Blute ML, Slezak J, et al. The long-term clinical impact of biochemical recurrence of prostate cancer five or more years after radical prostatectomy. *J Urol* 2003;170:1872-6. http://dx.doi.org/10.1097/01.ju.0000091876.13656.2e
14. Freedland SJ, Humphreys EB, Mangold LA, et al. Time to prostate-specific antigen recurrence after radical prostatectomy and risk of prostate cancer specific mortality. *J Urol* 2006;176:1404-8. http://dx.doi.org/10.1016/j.juro.2006.06.017
15. Caire AA, Sun L, Ode O, et al. Delayed prostate-specific antigen recurrence after radical prostatectomy: How to identify and what are their clinical outcomes? *Urology* 2009;74:643-7. http://dx.doi.org/10.1016/j.urology.2009.02.049
16. Ahove DA, Hoffman KE, Hu JC, et al. Which patients with undetectable PSA levels five years after radical prostatectomy are still at risk of recurrence? Implications for a risk-adapted followup strategy. *Urology* 2010;76:1201-5. http://dx.doi.org/10.1016/j.urology.2010.03.092
17. Walz J, Chun FK, Klein EA, et al. Nomogram predicting the probability of early recurrence after radical prostatectomy for prostate cancer. *J Urol* 2009;181:601-7; discussion 07-8.
18. Daneshmand S, Quek ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: Long-term results. *J Urol* 2004;172:2252-5. http://dx.doi.org/10.1097/01.ju.0000143448.04161.cc
19. Dorin RP, Lieskovsky G, Fairey AS, et al. Outcomes after radical prostatectomy for patients with clinical stages T1-T2 prostate cancer with pathologically positive lymph nodes in the prostate-specific antigen era. *Urol Onc* 2013;31:1441-7. http://dx.doi.org/10.1016/j.urolonc.2012.03.006
20. Dorin RP, Daneshmand S, Lassoff MA, et al. Long-term outcomes of open radical retropubic prostatectomy for clinically localized prostate cancer in the prostate-specific antigen era. *Urology* 2012;79:626-31. http://dx.doi.org/10.1016/j.urology.2011.09.051
21. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®): Prostate Cancer (Version 1.2015).
22. Alenda O, Ploussard G, Mouracade P, et al. Impact of the primary Gleason pattern on biochemical recurrence-free survival after radical prostatectomy: A single-centre cohort of 1,248 patients with Gleason 7 tumours. *World J Urol* 2011;29:671-6. http://dx.doi.org/10.1007/s00345-010-0620-9
23. Tollefson MK, Leibovich BC, Slezak JM, et al. Long-term prognostic significance of primary Gleason pattern in patients with Gleason score 7 prostate cancer: Impact on prostate cancer specific survival. *J Urol* 2006;175:547-51. http://dx.doi.org/10.1016/S0022-5347(05)00152-7
24. Hansen J, Bianchi M, Sun M, et al. Percentage of high-grade tumour volume does not meaningfully improve prediction of early biochemical recurrence after radical prostatectomy compared with Gleason score. *BJU Int* 2014;113:399-407. http://dx.doi.org/10.1111/bju.12424
25. Tollefson MK, Blute ML, Rangel LJ, et al. Lifelong yearly prostate-specific antigen surveillance is not necessary for low risk prostate cancer treated with radical prostatectomy. *J Urol* 2010;184 925-9. http://dx.doi.org/10.1016/j.juro.2010.05.043

Correspondence: Dr. Mariana C. Stern, Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, CA, U.S.A; marianas@usc.edu