A risk-adjusted definition of biochemical recurrence after radical prostatectomy

TM Morgan¹, MV Meng²,³, MR Cooperberg²,³, JE Cowan², V Weinberg³, PR Carroll²,³ and DW Lin⁴,⁵

BACKGROUND: To determine whether a variable definition of biochemical recurrence (BCR) based on clinicopathologic features facilitates early identification of patients likely to suffer from disease progression. The definition of BCR after radical prostatectomy (RP) bears important implications for patient counseling and management; however, there remains a significant debate regarding the appropriate definition.

METHODS: The study cohort consisted of 3619 men who underwent RP for localized prostate cancer from 1989 to 2007, with data abstracted from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry. Patients were stratified into three risk groups according to Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score. Three single threshold PSA cut-points for BCR were evaluated (PSA ≥ 0.05, ≥ 0.2 and ≥ 0.4 ng ml⁻¹) as well as a variable cut-point defined by risk group. After reaching the cut-points, patients were followed for further PSA progression.

RESULTS: The proportion of patients with BCR differed by cut-point and risk group, ranging from 7 to 37% (low risk), 22 to 58% (intermediate risk) and 60 to 86% (high risk). The positive-predictive value (PPV) for predicting further PSA progression was 49% for the PSA ≥ 0.05 ng ml⁻¹, 62% for the PSA ≥ 0.2 ng ml⁻¹, 65% for the PSA ≥ 0.4 ng ml⁻¹ and 68% for the risk-adjusted definition. Five-year progression-free survival was 39% for the risk-adjusted definition compared with 45–52% for the other definitions of BCR.

CONCLUSIONS: These data suggest that a variable definition of BCR determined by clinicopathologic risk may improve the identification of early recurrence after RP without increasing the overdiagnosis of BCR. By using a risk-adjusted BCR definition, clinicians can better predict future PSA progression and more appropriately counsel patients regarding salvage therapies.

Keywords: biochemical recurrence; radical prostatectomy; risk stratification

INTRODUCTION
After radical prostatectomy (RP), a detectable level of serum PSA is generally thought to represent local or distant recurrent disease—and sometimes both.¹ However, time to clinical progression after biochemical recurrence (BCR) can be prolonged, with metastasis following BCR by a median of 8 years and prostate cancer (PCa)-specific death by another 5 years.²,³ The natural history of BCR after RP is incompletely understood and may depend both on the definition of BCR utilized and on the rate of PSA change after BCR, as well as the time from RP to recurrence.⁴⁻⁷

The definition of BCR after RP continues to be controversial and impacts reported long-term outcomes and patient consultation in the office.⁶ In an American Urological Association consensus panel review, 53 definitions of post-RP BCR were identified, and none have gained universal acceptance due to substantial limitations of each.⁹ Candidate definitions have ranged from specific PSA thresholds (for example, PSA ≥ 0.2 ng ml⁻¹) to definitions requiring further verification at or above the threshold (for example, PSA ≥ 0.2 ng ml⁻¹ with a second level > 0.2 ng ml⁻¹).⁴,⁵ Additionally, the ultrasensitive PSA assay, detecting PSA levels below 0.1 ng ml⁻¹, was developed for surveillance after RP. The importance of these low, but detectable, ultrasensitive PSA values is controversial, however, because a substantial proportion of patients with ultrasensitive PSA levels will not exhibit further PSA progression.¹⁰⁻¹³ Thus, the utilization of lower PSA thresholds increases the sensitivity for further disease progression, but there is a concomitant decrease in specificity. As a result, implementation of lower thresholds may lead to overuse of secondary treatments such as salvage radiation or hormone therapy. Conversely, while higher PSA thresholds will more accurately predict future clinical progression, there is a potential delay in the time to salvage therapy when higher thresholds are used.

The ideal definition of BCR after RP would identify patients likely to experience future clinically significant disease progression, such as systemic metastasis, and do so at the lowest possible PSA values. Although it is not known whether identification of PSA failure at extremely low PSA levels (for example, 0.05 ng ml⁻¹) will lead to a survival advantage with earlier use of salvage therapies, knowledge of the natural history of PSA progression will aid in patient consultation in the event of a detectable PSA after RP. We hypothesized that adjusting PSA cutoffs based on clinical and pathologic features of the primary tumor would result in improved performance characteristics for predicting further PSA progression, enabling earlier identification of BCR in high-risk patients without a decrease in the predictive value of the test.

¹Department of Urology, University of Michigan, Ann Arbor, MI, USA; ²Department of Urology, University of California at San Francisco, San Francisco, CA, USA; ³Helen Diller Family Comprehensive Cancer Center, Biostatistics Core, University of California at San Francisco, San Francisco, CA, USA; ⁴Department of Urology, University of Washington School of Medicine, Seattle, WA, USA and ⁵Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. Correspondence: Dr TM Morgan, Department of Urology, University of Michigan, 1500 E. Medical Center Drive, CCC, 7308, Ann Arbor, MI 48109-5330, USA. E-mail: tomorgan@med.umich.edu

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MATERIALS AND METHODS

The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) is a longitudinal, observational database of men with biopsy-proven PCA. Patients were recruited prospectively by participating urologists, and collected variables include screening, diagnostic, treatment-related and clinical outcomes. This study was approved by the University of California, San Francisco institutional review board.

As of September 2010, 13,893 men with newly diagnosed PCs had enrolled at 34 community-based, 3 Veteran’s and 3 academic urology practices nationwide. All follow-up, including PSA testing, was performed by the individual centers according to their local practices. Patients included in this analysis were diagnosed between 1989 and 2007 and underwent RP as a primary treatment for clinically localized PCs without neoadjuvant treatment. There were 5598 patients who met these criteria (Figure 1). A total of 261 patients were excluded because they received adjuvant therapy within 6 months of RP, and 784 with incomplete pathologic data were excluded. Finally, 934 patients were excluded because they did not have at least three PSA values after RP, leaving 3619 patients for analysis.

Patients were stratified into three risk groups based on the Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score, a validated instrument for post-operative risk stratification after RP. As previously described, patients were considered as low risk for a CAPRA-S score of 0–2, intermediate risk given a score of 3–5 and high risk given a score of ≥6. All but 129 patients had complete component data to compute CAPRA-S scores; multiple imputation was used to compute CAPRA-S for those 129 patients having missing one component. We evaluated three single threshold PSA cut-points to define BCR: PSA ≥ 0.05 ng ml⁻¹, PSA ≥ 0.2 ng ml⁻¹ and PSA ≥ 0.4 ng ml⁻¹, all occurring at least 4 weeks after surgery with previous nadir PSA below the limits of the detection assay (typically <0.1 ng ml⁻¹). We chose these commonly used values a priori, after a review of the literature, as they are commonly evaluated single threshold definitions and represent a range of cut-points.

A fourth BCR definition used a variable PSA cut-point defined by CAPRA-S risk group: PSA ≥ 0.05 ng ml⁻¹ in high-risk patients, PSA ≥ 0.2 ng ml⁻¹ in intermediate-risk patients and PSA ≥ 0.4 ng ml⁻¹ in low-risk patients. This was termed the risk-adjusted cut-point. Five-year recurrence-free survival (RFS) rate was defined as the Kaplan–Meier probability of patients not meeting a given PSA cut-point by 5 years post-RP.

The primary end point was confirmation of biochemical failure after reaching each PSA cut-point. This was defined as any rise in PSA above the cut-point for patients with at least one post-cut-point PSA. All serum PSA values measured after the initiation of secondary treatments were excluded, and patients without at least one post-cut-point PSA were not included in the analysis of the primary end point. The median numbers of PSA measurements available after reaching each cut-point were 5 (PSA ≥ 0.05 ng ml⁻¹), 6 (PSA ≥ 0.2 ng ml⁻¹), 6 (PSA ≥ 0.4 ng ml⁻¹) and 6 (risk-adjusted), with a median of 6 months (interquartile range 3–8 months) between PSA tests, minimizing the risk of ascertainment bias. The median PSA follow-up since RP was 38 months (interquartile range 20–61 months) for Kaplan–Meier analyses—that is, accounting for censoring.

To evaluate the primary end point, we analyzed the performance characteristics of each BCR definition for predicting further PSA progression, including positive-predictive value (PPV), and the 5-year progression-free survival (PFS) rate after reaching each BCR cut-point. Only patients meeting the cut-point being evaluated and having at least one post-cut-point PSA available were included in this analysis. Sensitivity and negative-predictive values were not evaluable since patients not reaching a cut-point cannot suffer from further PSA progression (causing both sensitivity and negative-predictive value to equal 100%). Specificity testing was not appropriate for this observational study because the cohort subjects were not selected as cases vs controls. Rates of further progression after reaching a given PSA cut-point were estimated and graphed using the Kaplan–Meier product limit method. The secondary end point of the study was the development of bone metastasis or PCa-specific mortality (PCSM). We performed Cox regression to analyze the relationship between each definition of BCR as a time-varying covariate and bone metastasis or PCSM. Follow-up began at date of surgery for all Kaplan–Meier and Cox analyses. Demographic, clinical and pathologic variables were compared among risk groups using a chi-square test for categorical variables and analysis of variance for continuous variables. Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA) and Stata 11 (StataCorp, College Station, TX, USA).

Figure 1. Flow of patients in the study and distribution of evaluable patients reaching the specified cut-points. Patients are delineated in each risk group according to whether or not their PSA reached 0.05 ng ml⁻¹ and which of the single threshold PSA cut-points they fulfilled. CAPRA-S, Cancer of the Prostate Risk Assessment post-Surgical; RP, radical prostatectomy.
RESULTS

Of the 3619 patient cohort, 2412 (67%) were low risk, 960 (26%) were intermediate risk and 247 (7%) were high risk at surgery. Median age was 62 years (interquartile range 56–66 years) and median PSA at diagnosis was 5.6 ng ml\(^{-1}\) (interquartile range 4.4–7.8 ng ml\(^{-1}\)). Patient stratification by clinicopathologic characteristics is given in Table 1. Comparison of clinicopathologic features between the final patient set and those excluded due to incomplete pathologic or post-RP PSA data demonstrated that the final cohort had lower clinical disease risk characteristics than the excluded patient set, but there were no differences in surgical pathology or CAPRA-S risk distribution. Excluded patients had a higher PSA at diagnosis (\(P<0.01\)) and a higher clinical T stage (\(P<0.01\)) as well as a higher percentage of African-American patients (\(P<0.01\)).

The proportion of patients reaching the four BCR cut-points was assessed within each risk group (Table 2). Few low-risk patients fulfilled any but the lowest cut-point, with increasing proportions of patients reaching the cut-points in the intermediate- and high-risk groups. The proportion of patients reaching the highest threshold (PSA \(\geq 0.4\) ng ml\(^{-1}\)) was lower in the low-risk group (7%) than in the intermediate- (22%) and high- (60%) risk groups (\(P<0.01\)). Similarly, the PSA \(\geq 0.2\) ng ml\(^{-1}\) and PSA \(\geq 0.05\) ng ml\(^{-1}\) cut-points were reached by greater percentages of patients as CAPRA-S score increased. RFS at 5 years was lower with increasing risk category as well as with decreasing PSA thresholds for BCR. The risk-adjusted cut-point, by incorporating different data components from each of the single-threshold cut-points, yielded the highest proportion of high-risk patients reaching the definition of BCR (86%) with the lowest proportion of low-risk patients reaching the definition of BCR (7%). Since patients were censored at the time of administration of any secondary therapy, some patients meeting the PSA \(\geq 0.05\) ng ml\(^{-1}\) and PSA \(\geq 0.2\) ng ml\(^{-1}\) cut-points were censored before they could reach a higher cut-point. This occurred infrequently, with 203 patients (19 high risk) meeting the PSA \(\geq 0.05\) ng ml\(^{-1}\) receiving secondary therapy at a PSA of \(<0.4\) ng ml\(^{-1}\) (103 of these with a PSA of \(<0.2\) ng ml\(^{-1}\)), and 118 patients meeting the PSA \(\geq 0.2\) ng ml\(^{-1}\) cut-point receiving secondary therapy at a PSA of \(<0.4\) ng ml\(^{-1}\).

To assess the performance of each BCR definition for predicting further PSA progression, we evaluated the PPV of each definition for the primary end point. Table 3 gives the distribution of patients according to whether or not they reached a given PSA cut-point and whether or not those who reached the cut-point experienced further PSA progression. PPV was 49% for the PSA \(\geq 0.05\) ng ml\(^{-1}\), 62% for the PSA \(\geq 0.2\) ng ml\(^{-1}\), 65% for the PSA \(\geq 0.4\) ng ml\(^{-1}\) and 68% for the risk-adjusted definition. Comparing the rates of further progression for each of the definitions demonstrated that the highest progression rates are observed with the risk-adjusted definition (Figure 2). Five-year PFS was 39% with the risk-adjusted definition compared with 46, 45 and 52% for the 0.4, 0.2 and 0.05 ng ml\(^{-1}\) definitions of BCR. A total of 80 patients suffered from bone metastasis or PCSM. In the Cox analysis, the PSA \(\geq 0.4\) ng ml\(^{-1}\) (hazard ratio (HR) 2.67, 95% confidence interval 1.68–4.23), PSA \(\geq 0.2\) ng ml\(^{-1}\) (HR 2.42, 95% confidence interval 1.65–3.54) and risk-adjusted (HR 2.32, 95% confidence interval 1.57–3.45) cut-points were all similarly associated with these end points, whereas the PSA \(\geq 0.05\) ng ml\(^{-1}\) definition was less strongly associated with bone metastasis/PCSM (HR 1.38, 95% confidence interval 1.18–2.11).

Table 1. Distribution by surgical pathology in each risk group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients, N = 3619</th>
<th>Low risk, N = 2412</th>
<th>Intermediate risk, N = 960</th>
<th>High risk, N = 247</th>
</tr>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;55</td>
<td>646 (18)</td>
<td>478 (20)</td>
<td>143 (15)</td>
<td>25 (10)</td>
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<tr>
<td>55–64</td>
<td>1716 (47)</td>
<td>1173 (49)</td>
<td>442 (46)</td>
<td>101 (41)</td>
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<tr>
<td>65+</td>
<td>1257 (35)</td>
<td>761 (31)</td>
<td>375 (39)</td>
<td>121 (49)</td>
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<tr>
<td>Race</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3227 (90)</td>
<td>2190 (91)</td>
<td>830 (87)</td>
<td>207 (85)</td>
</tr>
<tr>
<td>African American</td>
<td>285 (8)</td>
<td>163 (7)</td>
<td>89 (9)</td>
<td>33 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>90 (2)</td>
<td>52 (2)</td>
<td>34 (4)</td>
<td>4 (2)</td>
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<td>PSA at diagnosis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0–6 ng ml(^{-1})</td>
<td>2027 (58)</td>
<td>1645 (70)</td>
<td>362 (39)</td>
<td>20 (9)</td>
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<tr>
<td>6.1–10 ng ml(^{-1})</td>
<td>959 (27)</td>
<td>565 (24)</td>
<td>327 (35)</td>
<td>67 (29)</td>
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<tr>
<td>10.1–20 ng ml(^{-1})</td>
<td>399 (12)</td>
<td>127 (6)</td>
<td>193 (21)</td>
<td>79 (34)</td>
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<tr>
<td>&gt;20 ng ml(^{-1})</td>
<td>110 (3)</td>
<td>3 (0)</td>
<td>45 (5)</td>
<td>65 (28)</td>
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<td>Surgical Gleason sum</td>
<td></td>
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<tr>
<td>2–6</td>
<td>2007 (55)</td>
<td>1747 (72)</td>
<td>242 (25)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>7</td>
<td>1389 (39)</td>
<td>665 (28)</td>
<td>612 (64)</td>
<td>112 (45)</td>
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<tr>
<td>8–10</td>
<td>223 (6)</td>
<td>0 (0)</td>
<td>106 (11)</td>
<td>117 (48)</td>
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<td>Pathologic stage</td>
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<td></td>
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<tr>
<td>T2</td>
<td>2976 (82)</td>
<td>2301 (95)</td>
<td>629 (66)</td>
<td>46 (19)</td>
</tr>
<tr>
<td>T3a</td>
<td>457 (13)</td>
<td>103 (4)</td>
<td>271 (28)</td>
<td>83 (34)</td>
</tr>
<tr>
<td>T3b</td>
<td>173 (5)</td>
<td>5 (0)</td>
<td>53 (5)</td>
<td>115 (46)</td>
</tr>
<tr>
<td>T4</td>
<td>13 (&lt;1)</td>
<td>3 (&lt;1)</td>
<td>7 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Surgical margins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>2677 (74)</td>
<td>2242 (93)</td>
<td>384 (40)</td>
<td>51 (21)</td>
</tr>
<tr>
<td>Positive</td>
<td>942 (26)</td>
<td>170 (7)</td>
<td>576 (60)</td>
<td>196 (79)</td>
</tr>
</tbody>
</table>

Abbreviation: CAPRA-S, Cancer of the Prostate Risk Assessment post-Surgical.

\(^{a}\)No \(\chi^2\) testing because CAPRA-S risk categories are defined by PSA, grade, stage and margins.
that low cutoffs such as a single PSA of 0.2 ng ml \(^{-1}\) may not experience any further PSA rise. These reports suggest disease progression, they also include a large percentage that underestimate progression rates after RP. Conversely, while lower PSA thresholds will have greater sensitivity for future disease/PSA progression, they may underestimate progression rates after RP. Conversely, while lower cut-points capture more patients who suffer from continued disease progression, they also include a large percentage that may not experience any further PSA rise. These reports suggest that low cutoffs such as a single PSA of 0.2 ng ml \(^{-1}\), widely used for counseling patients and in clinical trials, are not sufficiently specific for future disease progression. According to our data, both the percentage of patients at risk meeting a PSA cut-point and the rates of RFS varied depending on the risk group and the definition of BCR. Importantly, the risk-adjusted definition is simultaneously associated with the lowest rate of RFS in high-risk patients (10%) and the highest rate of RFS in low-risk patients (91%). While this is naturally true given how the risk-adjusted thresholds are defined, the key point is that the risk-adjusted thresholds result in a more inclusive definition of BCR in the higher risk patients who are more likely to progress to clinical end points.

The primary outcome of the study was further PSA progression after reaching the BCR cut-point, as we sought to test whether altering the definition of BCR according to clinicopathologic risk provides improved predictive accuracy for further progression compared with single PSA thresholds. Although not a standard trial end point, further PSA rise often impacts decisions regarding salvage therapy and offers an intermediate end point given the low number of clinical events (for example, metastasis or PCSM) present even in a large cohort with extensive follow-up. Among the three single threshold definitions, PPV for further PSA progression increased as the PSA threshold was increased. For the risk-adjusted cut-point, the PPV exceeded the PSA 0.4 ng ml \(^{-1}\) definition (68 vs 65%). That is, of the patients who reached a cut-point, patients meeting the risk-adjusted cut-point were the most likely to experience further PSA progression. This is also illustrated by the PPV rates according to each of the BCR definitions. Five-year PFS for patients meeting the risk-adjusted cut-point was 39%, compared with 45–52% for the other definitions of BCR. Finally, in predicting the development of bone metastasis or PCSM, the HR for the risk-adjusted definition approached that of the most restrictive threshold definition (0.4 ng ml \(^{-1}\)) while enabling earlier identification of BCR in higher risk patients.

While lower PSA thresholds will have greater sensitivity for disease progression, their specificity is likely to be lower. Possible sources of low detectable PSA levels after RP include recurrent PCa that is slow in growth and potentially indolent, residual benign prostatic tissue, PSA secretion by periurethral glands (or other tumors) and slow-growing or dormant disseminated tumor cells.
CONCLUSIONS

In this study, the risk-adjusted definition of BCR was associated with further PSA progression. As opposed to single threshold definitions, the risk-adjusted definition appears to more accurately identify BCR in higher risk patients while demonstrating a predictive accuracy that matches or exceeds the highest threshold definition. Further validation of the risk-adjusted definition will require a study cohort with higher rates of metastasis and PCSM, as the primary end point here is a surrogate for future objective progression. However, the risk-adjusted definition provides a novel and straightforward way of utilizing PSA to predict disease progression after RP, and our data suggest that this approach may offer substantial benefit in counseling patients after surgery. The earlier identification of PSA failure in patients most likely to experience PSA progression may enable more timely use of secondary therapies, while the ability to reassure patients at lower risk of progression may be of substantial clinical benefit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Address correspondence to: Thomas M Morgan, Department of Urology, University of California, San Francisco, CA 94143, USA. Email: tmorgan@med.ucsf.edu

residing in the bone marrow.19–24 Use of the risk-adjusted BCR definition allows for greater sensitivity at a lower threshold in higher risk patients—detecting recurrences earlier with the risk-adjusted definition than with any of the other definitions of BCR—while maintaining high PPV across the entire cohort. Furthermore, the risk-adjusted definition performed similar to the 0.2 ng ml−1 and 0.4 ng ml−1 cut-points in predicting metastases and PCSM. A key objective for any predictive biomarker is the early identification of patients at high risk of future progression, and the risk-adjusted definition appears to identify these patients earlier than is feasible with the single-threshold definitions evaluated in the present study. This timely recognition of BCR may be critical for patient counseling and decisions regarding biochemical and radiographic surveillance going forward.

In addition, these findings may hold implications for guiding treatment decisions post-RP. For example, increasing evidence indicates that salvage radiotherapy is most effective if administered early, with one report suggesting institution of salvage radiotherapy before PSA reaches 0.5 ng ml−1.25 Utilization of the risk-adjusted definition may improve identification of appropriate salvage radiotherapy patients, rather than using a previously proposed BCR definition of PSA ≥0.4 ng ml−1 and rising in which the median PSA at the time of failure was 1.0 ng ml−1.26 Given concerns about the overuse of adjuvant radiation therapy in appropriate candidates despite level 1 evidence, early salvage radiotherapy using a risk-adjusted definition of BCR could provide a potential alternative means of treating these patients.26

Additionally, a risk-adjusted definition may avoid unnecessary initiation of salvage treatment in low-risk patients with a low detectable PSA who may never experience further PSA progression. Certainly, only a randomized controlled trial could determine the efficacy of this approach to early salvage radiotherapy in comparison with adjuvant radiotherapy. In addition, the risk-adjusted definition may be useful for guiding initiation of other salvage therapies and for defining BCR in phase III clinical trials such as CSP #553 and CALGB 90203 that have PSA progression as the primary end point.27,28 The limitations of current PSA thresholds for defining recurrence in clinical trials are well documented, and a risk-adjusted end point may provide a more accurate assessment of the likelihood of further disease progression.29

There are important limitations to the present study. A number of patients received secondary therapies and were therefore censored within the follow-up time; however, these patients were included up until the time of their secondary therapy. Although some patients meeting the lower cut-points were treated before they could reach a higher BCR definition, this was uncommon and would not be expected to favor the risk-adjusted definition over other definitions of BCR. Importantly, the definition of further PSA progression is not a validated end point and does not take into consideration the rate of PSA rise. Therefore, we have also utilized bone metastasis and PCSM as secondary end points, although there were relatively few events due to the generally prolonged course of disease. Additional follow-up will be required to address how the very variable BCR definition using these end points. Furthermore, as an observational study, there was no standardization of PSA screening post-RP. We could not evaluate or control for variations in ultrasensitive assay use, and this assay was likely utilized to a lesser degree in the earlier years of the study. Interassay variability between commercial PSA assays is also known to exist, and it is unknown how this may have impacted the data. Additionally, as a surgical series, the cohort is shifted toward patients with lower risk disease. Finally, there are no data to support the notion that salvage radiation therapy at very low PSA levels translates to improved efficacy over initiation of salvage therapy at higher PSA levels (for example, PSA = 0.4 ng ml−1), although multiple sources have established that salvage radiation is more durable earlier in the spectrum of PSA recurrence.30,31

The authors declare no conflict of interest.

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