Impact of Biochemical Recurrence in Prostate Cancer Among US Veterans

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Background: Among men treated for prostate cancer, increasing prostate-specific antigen (PSA) is known as biochemical failure or biochemical recurrence (BCR). The impact of BCR on subsequent mortality is uncertain, however, especially given competing causes of death.

Methods: To describe patterns of BCR and subsequent mortality, we conducted an observational study in a community-based, “high-comorbidity” setting of 623 US veterans diagnosed as having prostate cancer from 1991 to 1995 and receiving radical prostatectomy or radiation therapy. The main outcome measures were BCR, defined as a PSA level of 0.4 ng/mL or higher (treated with surgery) or “PSA nadir + 2 ng/mL” (treated with radiation therapy), and prostate cancer mortality, determined through 2006.

Results: With 5-, 10-, and 15-year follow-up periods, respectively (for all results shown herein), the cumulative incidence of BCR after prostatectomy (n=225) was 34%, 37%, and 37%; prostate cancer mortality among men who failed treatment (n=81) was 3%, 11%, and 21%. Among men receiving radiation therapy (n=398), the cumulative incidence of BCR was 35%, 46%, and 48%; prostate cancer mortality among those who failed treatment (n=161) was 11%, 20%, and 42%. Overall, BCR was associated with an increased risk of death from prostate cancer in the study population, but the individual probability of this outcome was relatively low.

Conclusions: Biochemical recurrence is associated with increased prostate cancer mortality, yet when BCR occurs only a minority of men subsequently die of their disease. The phrase “most men die with prostate cancer, not of it” applies to elderly veterans, even after failure of primary treatment. New strategies for defining and managing treatment failure in prostate cancer are needed.

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Among men diagnosed as having prostate cancer, assessment of disease recurrence after primary treatment typically includes periodic measurement of prostate-specific antigen (PSA). A detectable PSA level after radical prostatectomy, or an increasing PSA level following radiation therapy, is considered biochemical recurrence (BCR) or “PSA failure.”1,2 Biochemical recurrence can indicate disease progression years before clinical signs or symptoms develop,3 but specific criteria for determining BCR in prostate cancer differ according to the type of treatment received.

After radical prostatectomy, PSA usually becomes undetectable within 6 weeks after surgery because the major source of PSA (the prostate gland) has been removed. Detectable PSA following prostatectomy most likely implies residual or recurrent prostate cancer. A PSA level cut point of 0.2 ng/mL or higher was the most commonly used criterion among 53 definitions identified by an American Urological Association guideline panel in 2007,4 but this cut point can identify BCR that is clinically insignificant.5 Accordingly, a cut point of 0.4 ng/mL or higher has been recommended to define BCR after radical prostatectomy.6,7 (To convert PSA to micrograms per liter, multiply by 1.0.)

After radiation therapy, residual functioning epithelium leads to a gradual decline in PSA before reaching a posttreatment nadir. In this context, the American Society for Therapeutic Radiation Oncology has promulgated definitions of BCR among patients treated with radiation therapy.1 Owing to concerns with a prior definition,6,9 however, a PSA level greater than absolute nadir plus 2 ng/mL has been adopted as the current criterion of BCR.10

See also pages 1396 and 1397
In clinical care, BCR often triggers secondary therapy for prostate cancer, including salvage treatment or androgen deprivation. In research activities, BCR is often used as a surrogate outcome, assuming a direct progression from PSA-defined recurrence to subsequent prostate cancer mortality. This sequence of events may not occur, however, especially among older men with competing causes of mortality, such as US veterans. Our objective was to identify patterns of BCR among men treated for localized prostate cancer, focusing on prostate cancer mortality as the health-related outcome, thereby providing clinicians with a better understanding of the clinical course of this common malignant disease.

METHODS

PATIENTS AND CLINICAL INFORMATION

Among 64,545 male veterans at least 50 years old receiving care at any of 9 Department of Veterans Affairs (VA) facilities in New England in 1990, 1313 men developed incident prostate cancer during 1991 to 1995. A comprehensive review of medical records and death registries, available for 1270 men (96.7%), determined each patient’s clinical characteristics and mortality follow-up. For analyses of BCR, complete data were available for 1156 men (91.0%) regarding date of treatment (“zero-time”), type of treatment, date of BCR, and date and cause of death (if applicable). A more complete discussion of the clinical information available was included in a previous report; pertinent aspects include a source population of patients who used the VA as their primary site for health care (minimizing non-VA testing of PSA) and a systematic approach to determine cause of death (using medical records rather than death certificates).

DESCRIPTIVE ANALYSES

Although choice of therapy in prostate cancer is influenced by age, clinical stage, histologic grade, comorbidity, and other factors, results obtained from clinical practice provide an overview of real-world events. We therefore generated initial survival curves, showing prostate cancer mortality according to treatment received, reflecting global outcomes. The main focus of subsequent analyses was on patients receiving surgery (prostatectomy) or radiation (external beam or brachytherapy), with or without neoadjuvant/adjuvant therapy, based on evidence in the medical record that such treatment was intended as primary “curative” therapy. These patients could also receive subsequent, “secondary” therapy, usually on the basis of new clinical evidence of disease, such as BCR or metastatic lesions.

PATTERNS OF BCR

For the relevant study population of men receiving primary treatment with curative intent, we first generated Kaplan-Meier time-to-event curves for BCR, based on the type of treatment received and with the clinically applicable definition of BCR, evaluated starting 6 weeks after therapy. We also examined a time-vs-PSA plot for each patient, and reviewed medical records when necessary, to manually verify BCR status. Next, for each treatment group, we generated Kaplan-Meier survival curves for cause-specific death according to BCR status, and we also calculated a log-rank test to evaluate the (unadjusted) association of BCR with prostate cancer mortality. Of note, to account for censoring owing to causes of death other than prostate cancer, BCR and cause-specific death are reported as cumulative incidence (percent-age), based on the Kaplan-Meier calculations, rather than as proportions (n/N) at the end of follow-up.

SECONDARY ANALYSES

As a secondary analysis, we evaluated the adjusted association between BCR and cause-specific death—accounting for age, comorbidity, histologic grade, and anatomic stage—to confirm the independent impact of BCR on prostate cancer mortality. In addition, to highlight the clinical implications of our data, we calculated the predicted survival for a representative, hypothetical patient receiving either prostatectomy or radiation therapy and based on whether or not they experienced BCR. Finally, although our focus on cause-specific death avoided the added complexity of conducting formal competing risk analyses, we reran our analyses focusing on overall mortality as the outcome. These calculations were performed to confirm biologic plausibility; a diminution in the strength of association was expected, if BCR increases the risk specifically for prostate cancer mortality and if non–prostate cancer deaths occur.

BASELINE CHARACTERISTICS AND INTERVAL FOLLOW-UP

Initial treatment for the source population (N=1156) included prostatectomy (n=231 [36%]), radiation therapy (n=412 [36%]), hormonal ablation (n=200 [17%]), or “watchful waiting” or none (n=313 [27%]). The pattern of prostate cancer mortality based on treatment is shown in Figure 1; this descriptive information is provided with the caveat that patient characteristics vary widely across treatment groups, precluding any assessment of therapeutic effectiveness. (Data for men receiving hormonal therapy or watchful waiting were not analyzed further.) Among the 643 men receiving prostatectomy or radiation therapy with curative intent, 623 (97%) had at least 2 follow-up PSA values, representing the study population for subsequent analyses (Table). The median age was 70 years (interquartile range, 67–74 years), most patients were white (n=556 [89%]), and comorbidity scores were none (n=194 [31%]), mild (n=201 [32%]), or moderate...
to severe (n=228 [37%]). The median PSA value at diagnosis was 8.9 ng/mL, most (n=595 [96%]) of the cancers were localized, and most (n=401 [64%]) had moderate tumor differentiation. Although not a focus of our analysis, patients receiving radiation therapy, compared with patients receiving surgery, tended to be older with more comorbidities, and have more extensive cancer, higher Gleason scores, and higher PSA values.

MORTALITY OUTCOMES

After follow-up through December 2006, ranging from 11 to 16 years per patient, 387 of 623 patients in the study population (62%) had died from any cause, with 48 of 387 of the deaths (12%) attributed to prostate cancer.

BCR and Mortality After Prostatectomy

Among men receiving prostatectomy (n=225), the pattern of BCR is shown in Figure 2A. The cumulative incidence of BCR, accounting for censoring, was 34%, 37%, and 37%, at 5, 10, and 15 years, respectively. The median PSA value at the time of BCR was 0.50 ng/mL, and secondary treatment was received by 42 men (18.7%) as either androgen deprivation therapy (n=32) or radiation therapy (n=10).

As shown in Figure 2B, the cumulative mortality due to prostate cancer among men who did not experience BCR (n=144) at 15 years was 0%, whereas among men (n=81) who failed treatment, subsequent prostate cancer mortality at 5, 10, and 15 years was 3%, 11%, and 21%, respectively (P < .001).

BCR and Mortality After Radiation Therapy

Among men receiving radiation therapy (n=398), the pattern of BCR is shown in Figure 2C. The cumulative incidence of BCR, accounting for censoring, was 35%, 46%, and 48%, at 5, 10, and 15 years, respectively. The median PSA value at the time of BCR was 4.3 ng/mL, and secondary treatment was received by 88 men (22.1%), mainly as androgen deprivation therapy.

As shown in Figure 2D, the cumulative mortality due to prostate cancer among men who did not experience BCR (n=237) at 15 years was 1%, whereas among men (n=161) who failed treatment, subsequent prostate cancer mortality at 5, 10, and 15 years was 11%, 20%, and 42%, respectively (P < .001).

ADDITIONAL ANALYSES

The association of BCR and prostate cancer mortality remained statistically significant (P < .001) after adjusting for age, comorbidity, histologic grade, and anatomic stage (data not shown). These results confirm the independent prognostic impact of BCR in the study population.

To highlight the clinical relevance of our data, we used the same multivariable (Cox) models to predict out-

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Table. Baseline Characteristics Among 623 Men Receiving Surgery or Radiation Therapy for Curative Intent and With Complete Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Surgery (n=225)</th>
<th>Radiation (n=398)</th>
<th>P Valueb</th>
<th>Both Groups (n=623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>19 (8.4)</td>
<td>8 (2.0)</td>
<td>&lt;.001</td>
<td>27 (4.3)</td>
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<td>60-69</td>
<td>143 (63.6)</td>
<td>134 (33.7)</td>
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<td>277 (44.5)</td>
</tr>
<tr>
<td>70-79</td>
<td>65 (28.9)</td>
<td>242 (60.8)</td>
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<td>305 (49.0)</td>
</tr>
<tr>
<td>≥80</td>
<td>0</td>
<td>14 (3.5)</td>
<td></td>
<td>14 (2.2)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>25 (11.1)</td>
<td>42 (10.6)</td>
<td>.83</td>
<td>67 (10.8)</td>
</tr>
<tr>
<td>All other</td>
<td>200 (88.9)</td>
<td>356 (89.4)</td>
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<td>556 (89.2)</td>
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<td>Comorbidity (Charlson score)</td>
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<td></td>
</tr>
<tr>
<td>0 (none)</td>
<td>91 (40.4)</td>
<td>103 (25.9)</td>
<td>&lt;.001</td>
<td>194 (31.1)</td>
</tr>
<tr>
<td>1 (mild)</td>
<td>70 (31.1)</td>
<td>131 (32.9)</td>
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<td>201 (32.3)</td>
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<td>2 (moderate)</td>
<td>47 (20.9)</td>
<td>93 (23.4)</td>
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<td>140 (22.5)</td>
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<tr>
<td>≥3 (severe)</td>
<td>17 (7.5)</td>
<td>71 (17.8)</td>
<td>.04</td>
<td>88 (14.1)</td>
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<td>Anatomic stage</td>
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<td></td>
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<td>Localized (T1, T2)</td>
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<td>374 (94.0)</td>
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<td>595 (95.5)</td>
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<td>24 (6.0)</td>
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<td>28 (4.5)</td>
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<td>Differentiation (Gleason score)</td>
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<tr>
<td>Well differentiated (2-4)</td>
<td>57 (25.3)</td>
<td>81 (20.4)</td>
<td>.046</td>
<td>138 (22.2)</td>
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<td>Moderately differentiated (5-7)</td>
<td>147 (65.3)</td>
<td>254 (63.8)</td>
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<td>401 (64.4)</td>
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<tr>
<td>Poorly differentiated (8-10)</td>
<td>21 (9.4)</td>
<td>63 (15.8)</td>
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<td>84 (13.5)</td>
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<tr>
<td>Baseline PSA level, ng/mL</td>
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<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>0 to &lt;4.0</td>
<td>39 (17.3)</td>
<td>38 (9.5)</td>
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<td>77 (12.4)</td>
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<tr>
<td>4.0 to &lt;10.0</td>
<td>105 (46.7)</td>
<td>157 (39.5)</td>
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<td>262 (42.1)</td>
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<td>10.0 to &lt;20.0</td>
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<td>118 (29.6)</td>
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<td>167 (26.8)</td>
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<td>29 (12.9)</td>
<td>84 (21.1)</td>
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<td>113 (18.1)</td>
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<td>1 (0.3)</td>
<td></td>
<td>4 (0.6)</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.

SI conversion factor: To convert PSA to micrograms per liter, multiply by 1.0.

Data are presented as number (percentage) unless otherwise indicated.

P value is for χ² test comparing patients receiving surgery vs radiation therapy.

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comes for hypothetical patients aged 65 years, with characteristics including a baseline PSA value of 6.0 ng/mL, a Gleason score of 7, and "moderate" comorbidity as per the Charlson index. First, in a scenario involving prostatectomy for localized disease, a hypothetical patient would have a projected 10-year prostate cancer mortality of 0% if he does not experience BCR, compared with 3% if BCR occurs. Second, for a similar hypothetical patient receiving radiation therapy, the projected 10-year prostate cancer mortality is 2% if he does not experience BCR, compared with 14% if BCR is documented. Finally, the association of BCR with all-cause mortality was not statistically significant for men receiving surgery ($P = .40$) or radiation therapy ($P = .33$) (data not shown). Thus, the predictive ability of BCR was reduced when outcomes were redefined to include non-prostate-related causes of death.

**COMMENT**

Among men receiving surgery or radiation therapy with curative intent, we found that BCR of prostate cancer occurred in 37% to 48% of patients over 15 years of follow-up. Regardless of the type of primary treatment and the corresponding definition of failure, a plateau in BCR was observed approximately 5 years after treatment, indicating that "late failures" are relatively uncommon. Biochemical recurrence itself was associated (as expected) with an increased likelihood of dying from prostate cancer. Yet, even among the treatment groups with biochemical failure, death caused by prostate cancer was seen in less than half of men.

Prior reports on BCR tended to focus on 1 treatment modality and to be based on the experience at "referral" centers. For example, an early report establishing BCR as an independent predictor of metastatic disease used data from patients receiving prostatectomy from 1 surgeon. Another frequently cited report compared different definitions of BCR but used data from patients post-prostatectomy at a single academic institution. These and similar reports are both pertinent and important, but the results may not be generalizable to patients receiving other treatments nor to community-based practice. In particular, the incidence and impact of BCR will vary with the population of men receiving treatment and the definition of biochemical failure.

We analyzed data for a representative spectrum of patients treated at 9 sites in the VA health care system. Our study population was therefore regional rather than national, yet our approach is more rigorous than case series.
of patients receiving 1 type of treatment at a single institution. Of note, US veterans receiving care from the VA have an approximately 2-fold higher burden of comorbid illness compared with patients in nonveteran health care systems. This distinction is an important consideration in patient care and research on prostate cancer, owing to a relatively long clinical course of screening, diagnosis, treatment, and outcomes. Although age-comorbidity distributions may differ in nonveteran populations, older and sicker men with prostate cancer are treated in most nonacademic settings, and our findings are therefore relevant to virtually all patient populations.

Prostate cancer mortality occurs less often among men diagnosed as having prostate cancer today, compared with our data from early in the era in which PSA values began to be used to detect prostate cancer. Specifically, a shift has occurred over time toward more limited burden of disease at detection—often attributed to increased screening and treatment for prostate cancer, although both topics are the subject of some controversy. Our results therefore provide an important opportunity to examine the association of BCR with prostate cancer mortality at a time when BCR was more prevalent, allowing us to more readily evaluate the corresponding relationship. As another conceptual point, prior published reports suggest a relatively modest benefit of secondary therapy on prostate cancer mortality. Nonetheless, assuming such benefits existed in our study population, the effect of treatments (given preferentially to men with BCR) would tend to lessen the influence of BCR status on prostate cancer mortality, yet we were able to discern an impact.

Differing definitions of BCR based on the type of treatment can be viewed as a study limitation, yet that very issue was the motivation for our analyses, and the same problem of different thresholds for biochemical failure exists for any study that examines populations of men receiving a full spectrum of treatments for prostate cancer. Although beyond the scope of our work, a related issue involves selecting the “best” definition of BCR. We made a decision to focus on definitions of BCR that are contemporary as well as commonly used in clinical practice, for patients after either surgery or radiation treatment. (For example, 0.4 ng/mL has been considered preferable to 0.2 ng/mL as a threshold for determining BCR after prostatectomy, yet our results were similar when a post hoc analysis used 0.2 ng/mL as a definition of BCR; data not shown.)

Finally, multiple other issues can be raised in the context of assessing the topic of prognosis after primary treatment with curative intent. For example, molecular markers or other factors may provide independent information regarding prognosis, even after accounting for clinical characteristics, including BCR. Yet, our analyses of BCR help to describe and explain real-world scenarios that are often encountered during the clinical care of patients with prostate cancer.

The patterns of BCR we observed, including the “expected” population-based association between BCR and long-term prostate cancer mortality, confirm the importance of the disease and the continued need for vigilance among clinicians and patients. From an individual patient’s viewpoint, however, BCR after primary surgery or radiation therapy usually occurs—if it occurs—within 5 years and is followed by death caused by prostate cancer in a minority of men, especially when a high burden of comorbidity exists. The relatively low probability of prostate cancer mortality (exemplified by the analyses describing hypothetical patients) may provide some reassurance, and perhaps improve the quality of life, among men facing this situation.

Clinicians and patients should be aware of these issues, and our research emphasizes the need for an improved approach to assessing prognosis in prostate cancer. Regarding PSA measurements per se, strategies to evaluate the trajectory of PSA during or after the occurrence of BCR (“PSA kinetics” involving velocity/slope or doubling time) are suitable but are typically examined in separate populations of patients treated with surgery or radiation therapy. Future work can help to define BCR in a manner that is applicable to different treatment groups and also predicts prostate cancer mortality.

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Data collection: Uchio, Wells, and Concato.

Analysis and interpretation of data: Uchio, Aslan, Wells, and Concato.

Drafting of the manuscript: Uchio, Wells, Calderone, and Concato.

Critical revision of the manuscript for important intellectual content: Uchio, Aslan, Wells, and Concato.

Statistical analysis: Aslan, Wells, and Concato.

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