Long-Term Risk of Clinical Progression After Biochemical Recurrence Following Radical Prostatectomy: The Impact of Time from Surgery to Recurrence

Stephen A. Boorjian\textsuperscript{a,}\textsuperscript{*}, R. Houston Thompson\textsuperscript{a}, Matthew K. Tollefson\textsuperscript{a}, Laureano J. Rangel\textsuperscript{b}, Eric J. Bergstrahl\textsuperscript{b}, Michael L. Blute\textsuperscript{c}, R. Jeffrey Karnes\textsuperscript{a}

\textsuperscript{a} Department of Urology, Mayo Clinic, Rochester, MN, USA
\textsuperscript{b} Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA
\textsuperscript{c} Division of Urology, UMass Memorial Medical Center, Worcester, MA, USA

Abstract

\textbf{Background:} The natural history of biochemical recurrence (BCR) after radical retropubic prostatectomy (RRP) is variable and does not always translate into systemic progression or prostate cancer (PCa) death.

\textbf{Objective:} To evaluate long-term clinical outcomes of patients with BCR and to determine predictors of disease progression and mortality in these men.

\textbf{Design, setting, and participants:} We reviewed our institutional registry of 14,632 patients who underwent RRP between 1990 and 2006 to identify 2,426 men with BCR (prostate-specific antigen [PSA] levels \(\geq 0.4\) ng/ml) who did not receive neoadjuvant or adjuvant therapy. Median follow-up was 11.5 yr after RRP and 6.6 yr after BCR.

\textbf{Intervention:} RRP.

\textbf{Measurements:} Patients were grouped into quartiles according to time from RRP to BCR. Survival after BCR was estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard regression models were used to analyze clinicopathologic variables associated with systemic progression and death from PCa.

\textbf{Results and limitations:} Median systemic progression-free survival (PFS) and cancer-specific survival (CSS) had not been reached after 15 yr of follow-up after BCR. Cancer-specific mortality 10 yr after BCR was 9.9%, 9.3%, 7.8%, and 4.7% for patients who experienced BCR <1.2 yr, 1.2–3.1 yr, 3.1–5.9 yr, and >5.9 yr after RRP, respectively (\(p=0.10\)). On multivariate analysis, time from RRP to BCR was not significantly associated with the risk of systemic progression (\(p=0.50\)) or cancer-specific mortality (\(p=0.81\)). Older patient age, increased pathologic Gleason score, advanced tumor stage, and rapid PSA doubling time (DT) predicted systemic progression and death from PCa. Limitations included retrospective design, varied utilization of salvage therapies, and the inclusion of few patients with positive lymph nodes.

\textbf{Conclusions:} Only a minority of men experience systemic progression and death from PCa following BCR. The decision to institute secondary therapies must balance the risk of disease progression with the cost and morbidity of treatment, independent of time from RRP to BCR.
1. Introduction

Despite the stage migration that has been noted in prostate cancer (PCa) over the prostate-specific antigen (PSA) era, biochemical recurrence (BCR) continues to be reported in up to 35% of men undergoing radical retropubic prostatectomy (RRP) [1–4]. Although BCR does not always translate into clinical progression [1,5], it does precede systemic relapse in the majority of cases, and patients with BCR have been shown to be at increased risk for subsequent metastases and mortality [6]. BCR has also been associated with the use of additional cancer treatments, as approximately a third of men who experience BCR receive a secondary therapy such as external-beam radiation therapy (RT) or androgen-deprivation therapy (ADT) [7].

Defining the natural history of patients with BCR after RRP is therefore relevant for patient counseling, clinical trial enrollment, and the judicious application of secondary therapies. Interestingly, reports to date have documented a relatively heterogeneous natural history of BCR [1,5,8,9]. In addition, as men with PCa are generally >60 yr of age, it has been suggested that competing causes of mortality may obscure the ability of BCR to predict death from PCa [10]. In fact, men have been found to be as likely to die within 15 yr of BCR from competing causes as from PCa [11].

However, whether the outcomes from previous cohorts, which were largely composed of men treated during the pre-PSA and early PSA eras [1,5,8], can be extrapolated to the current PCa population has not been established. Moreover, the majority of patients from prior studies [5,8], in contrast to common clinical practice [6,7,12], did not receive salvage therapy until the time of systemic progression. Therefore, the potential impact of secondary treatments on PCa mortality in men with BCR remains to be defined.

A further issue of contention in men with BCR following RRP has been the importance of the time interval from surgery to BCR. Although several series have noted that patients who experience BCR early after RRP are at higher risk for clinical progression and death from PCa [5,8,13], others have found that patients who experience BCR earlier after RRP are not at greater risk for subsequent adverse outcomes [1,9]. Determining the prognostic impact of the disease-free interval after surgery is important, for example, when considering secondary treatments, as a shorter disease-free interval after RRP has been shown to predict receipt of salvage therapy [14]. Here, then, we evaluated long-term clinical outcomes in a large contemporary cohort of patients with BCR after RRP and determined predictors of disease progression and mortality in these men, including the importance of time from RRP to BCR and the impact of secondary cancer therapies.

2. Methods

After institutional review board approval was obtained, we reviewed our Prostatectomy Registry to identify 14 632 consecutive patients who underwent RRP at the Mayo Clinic between 1990 and 2006 (Table 1). Men who received neoadjuvant (n = 1625) or adjuvant (n = 1921) therapy were excluded from study, as were men who refused release of their records (n = 29) and 639 foreign patients without known follow-up.

Surgical procedures were performed by different surgeons using standardized techniques. The extent of pelvic lymph node dissection varied by individual surgeon and over the time period of study. Median follow-up after RRP was 11.5 yr (interquartile range [IQR]: 7.8–14.7). Patients who experienced postoperative BCR, defined as a PSA ≥0.4 ng/ml [15,16], were identified for further analysis. PSA doubling time (DT) was assessed in patients with at least two valid PSA measurements (n = 1732). PSA DT was calculated by the natural log of 2 divided by the slope of the linear regression line of log PSA over time [1,5,17]. PSA DT was categorized as <6 mo, 6 mo–1 yr, 1–10 yr, and ≥10 yr [17]. Patients with a negative or zero PSA DT were classified as having a DT ≥10 yr for ease of calculations.
Systemic progression and salvage therapy use were recorded. Secondary treatments were given at the discretion of the treating physician, and men receiving salvage therapies were censored at the time of treatment. Systemic progression involved demonstrable metastases on radionucleotide bone scan or on biopsies outside of the prostatic bed. Vital status was identified from death certificates or physician correspondence.

Patients were grouped into quartiles according the timing of BCR after RRP. Postoperative survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Patients were censored at last follow-up or death if the end point of interest had not been attained. Cox proportional hazard regression models were used to analyze clinicopathologic variables associated with systemic progression and death from PCa. In addition, cumulative incidence estimates were performed to assess the impact of deaths not related to PCa on PCa mortality.

All tests were two sided, with a $p$ value $\leq 0.05$ considered significant. Statistical analyses were performed using SAS version 9.1.3 statistical software (SAS Institute, Cary, NC, USA).

Fig. 1 – Kaplan-Meier curve showing estimated 15-yr systemic progression-free survival after biochemical recurrence (BCR). PFS = progression-free survival.

Fig. 2 – Kaplan-Meier curve showing estimated 15-yr prostate cancer (PCa)–specific survival after biochemical recurrence (BCR).
3. Results

We identified 2426 men who experienced BCR following RRP and who did not receive neoadjuvant or adjuvant therapy (Table 1). Median age at surgery was 64 yr of age (IQR: 59–69), and median preoperative PSA was 7.9 ng/ml (IQR: 5.2–12.4). Approximately a third of patients had extraprostatic disease at RRP, and half had pathologic Gleason score $\geq 7$ tumors. The fact that only a few men were included with positive lymph nodes (1.4%) reflects our common institutional practice of adjuvant treatment in these patients [19]. Indeed, among the 1921 patients who received adjuvant treatment after RRP (and were therefore excluded from study here), the number of men with positive lymph nodes (433 [22.5%]), pathologic Gleason score $\geq 8–10$ (347 [18.1%]), and extraprostatic disease (1220 [63.5%]) was significantly greater ($p < 0.0001$ for all) than in the present cohort.

Median follow-up after BCR was 6.6 yr (IQR: 3.3–10.1). During this time, 375 men (15.5%) received salvage RT, and 264 men (10.9%) were treated with salvage ADT, which was therapy delivered at BCR but before systemic progression. Overall, 284 patients (11.7%) with BCR experienced systemic progression free survival (PFS; Fig. 1) and cancer-specific survival (CSS; Fig. 2) had not been reached at 15 yr after BCR, such that the estimated 15-yr systemic PFS and CSS after BCR was 75.8% and 83.6%, respectively.

We next sought to investigate the impact of time interval from RRP to BCR on the risk of subsequent disease progression. The median time from RRP to BCR in our series was 3.1 yr (IQR: 1.2–5.9). Table 2 compares the characteristics of patients who experienced BCR $<3.1$ yr after RRP (early cohort) to patients who experienced BCR $>3.1$ yr after RRP (late cohort). Median follow-up after BCR

<table>
<thead>
<tr>
<th>Years from RRP to BCR</th>
<th>No. of patients</th>
<th>% with PCa-specific mortality</th>
<th>% with non-PCa deaths</th>
<th>% with all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;1.2$</td>
<td>607</td>
<td>9.1</td>
<td>15</td>
<td>24.1</td>
</tr>
<tr>
<td>1.2–3.1</td>
<td>606</td>
<td>8.4</td>
<td>17.8</td>
<td>26.2</td>
</tr>
<tr>
<td>3.1–5.9</td>
<td>606</td>
<td>6.7</td>
<td>25.3</td>
<td>31.9</td>
</tr>
<tr>
<td>$&gt;5.9$</td>
<td>607</td>
<td>3.8</td>
<td>36.1</td>
<td>39.9</td>
</tr>
</tbody>
</table>

RRP = radical retropubic prostatectomy; BCR = biochemical recurrence; PCa = prostate cancer

Table 3 – Actuarial competing risk estimate of prostate cancer–specific mortality, non–prostate cancer death, and all-cause mortality 10 yr after biochemical recurrence (BCR) stratified by time from radical retropubic prostatectomy to BCR
was 8.3 yr (IQR: 4.6–12.2) for the early cohort and 5.2 yr (IQR: 2.5–8.2) for the late cohort (p < 0.0001). We noted that patients with early BCR had a significantly more advanced tumor stage, higher Gleason score, and greater preoperative PSA levels. Men who experienced early BCR also had more rapid PSA DT and were more likely to receive salvage therapy.

Patients were divided evenly into quartiles according to time from RRP to BCR. Using actuarial competing risks analysis, the estimates of PCa-specific and all-cause mortality, stratified by time from RRP to BCR, are shown in Table 3. On univariate analysis, a longer time from RRP to BCR was associated with a significantly decreased risk of systemic progression (hazard ratio [HR]: 0.93; 95% confidence interval [CI], 0.88–0.97; p = 0.002), such that the 10-yr rate of systemic progression for patients who experienced BCR >5.9 yr after RRP was 10% versus 19% for patients who experienced BCR <1.2 yr after RRP (p = 0.02; Fig. 3). Likewise, the incidence of death from PCa also tended to be lower among patients with a longer interval from RRP to BCR (HR: 0.92; 95% CI, 0.85–1.00; p = 0.05), with the 10-yr PCa mortality for patients with BCR <1.2 yr after RRP (9.9%) more than double that for patients with BCR >5.9 yr after RRP (4.7%; p = 0.01; Fig. 4).

However, on multivariate analysis (Table 4), the time interval from RRP to BCR was not independently associated with the risks of systemic progression (p = 0.50) or death from PCa (p = 0.81). Instead, we found that older patient age, increased pathologic Gleason score, advanced tumor stage, and rapid PSA DT predicted systemic progression and death from PCa in men who experienced BCR after RRP. In addition, we noted that receipt of salvage therapy did not significantly affect the risks of systemic progression or PCa mortality.

Table 4 – Multivariate Cox proportional hazards regression analysis of systemic progression and death from prostate cancer after biochemical recurrence

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Systemic progression</th>
<th>Death from PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Patient age at BCR</td>
<td>1.02 (0.99–1.04)</td>
<td>0.13</td>
</tr>
<tr>
<td>Year of RRP</td>
<td>0.96 (0.91–1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pathologic Gleason score</td>
<td>1.33 (1.16–1.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pathologic tumor stage</td>
<td>1.19 (1.03–1.38)</td>
<td>0.02</td>
</tr>
<tr>
<td>Time interval from RRP to BCR, continuous</td>
<td>0.98 (0.91–1.04)</td>
<td>0.50</td>
</tr>
<tr>
<td>PSA DT (relative to ≥10 yr):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>4.91 (2.88–8.38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥6 mo to &lt;1 yr</td>
<td>2.38 (1.37–4.11)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥1 yr to &lt;10 yr</td>
<td>1.51 (0.83–2.75)</td>
<td>0.18</td>
</tr>
<tr>
<td>Receipt of salvage RT*</td>
<td>0.90 (0.58–1.37)</td>
<td>0.61</td>
</tr>
<tr>
<td>Receipt of salvage ADT*</td>
<td>0.69 (0.36–1.30)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

PCa = prostate cancer; HR = hazard ratio; CI = confidence interval; BCR = biochemical recurrence; RRP = radical retropubic prostatectomy; PSA = prostate-specific antigen; DT = doubling time; RT = radiation therapy; ADT = androgen-deprivation therapy.

* Salvage therapy defined for analysis here as treatment received within 90 d of BCR.
4. Discussion

We report that, at 15 yr following BCR, only 24% of patients had systemic progression, and 16% had died from PCa. In addition, we noted that although early BCR after RRP was associated with adverse clinicopathologic features, the time from surgery to BCR did not independently predict systemic progression or cancer-specific mortality. Instead, pathologic Gleason score, tumor stage, and PSA DT were significantly associated with systemic progression and death from PCa after BCR.

Our findings regarding the prognostic importance of pathologic tumor variables and postoperative PSA kinetics for predicting death from PCa after BCR are consistent with prior series [1,5,8,9,20,21]. At the same time, however, our data regarding the lack of impact of time from RRP to BCR on clinical progression support the results from Zhou et al. [9] but are in contrast to the findings from other studies [5,8,13]. In addition, the 15-yr systemic PFS and CSS among men with BCR noted here (76% and 84%, respectively) differ from the results of Pound et al. [8], who reported a 15-yr metastases-free survival of just over 25% after BCR, as well as the data from Freedland and colleagues [13], who, in 379 men with BCR after RRP, found a 15-yr CSS of 53%.

Several explanations can be offered for these disparate outcomes, including differences in the clinicopathologic variables of the patients studied (ie, 86% of patients in one of these series [13] had a pathologic Gleason score ≥7 vs 49.1% here). Moreover, given our institution's frequent use of adjuvant therapy, we included only a small number of patients with lymph node–positive disease (n = 35). Thus, the ability to extrapolate the outcomes noted here to all patients with BCR as well as whether additional patients with BCR here would experience clinical progression with continued extended follow-up remains to be determined.

Another important potential explanation for the differences in survival between centers may be the impact of differences in secondary therapy utilization. That is, in previous studies [5,8,13], men were not treated with salvage therapy prior to systemic progression, whereas in our cohort, 24% of patients received salvage treatments for BCR and prior to systemic progression. Although salvage therapy usage was not independently associated with improved outcomes on our multivariate analysis, patients who received salvage therapies had a significantly higher rate of adverse clinicopathologic features (Table 2), reflecting the limits of a nonrandomized study design. Likewise, the association of older patient age with increased risk of death from PCa noted here, while possibly demonstrating an interaction of age with tumor biology, may also reflect the inability of our model to completely control for the known association of age with adverse clinicopathologic features [22,23].

The optimal timing and treatment choice for patients with BCR after RRP remain controversial [24], largely because a survival benefit for salvage treatments has not been clearly established. Indeed, Moul et al. [25] noted that ADT at BCR following RRP but before systemic progression did not affect metastases-free survival in their overall cohort of 1352 men, although in those patients with a pathologic Gleason score ≥7 or PSA DT ≤12 mo, early ADT delayed clinical progression. Meanwhile, Siddiqui and colleagues [26], in a matched cohort analysis, demonstrated that ADT given at BCR did not improve systemic PFS or CSS.

Interestingly, a single recent series did report a survival benefit to salvage RT for BCR [27], with salvage RT associated with a threefold increase in CSS. Our current results, consistent with previous data from our group [26,28] and others [6], demonstrated that salvage therapy was not associated with a decrease in PCa mortality. These discrepant findings may again reflect differences in patient populations as well as differences in the use of ADT with salvage RT [29] and therefore require further investigation—ideally, in a prospective trial format.

We recognize that our study is limited by its retrospective, nonrandomized design. As such, the decisions to institute secondary treatments as well as the time to initiate therapy were based on patient preference and physician counseling and thus were subject to an inherent selection bias. Nevertheless, we believe this reflects “real-world” clinical practice, where the application of postoperative RT and ADT are not standardized.

5. Conclusions

Only a minority of men experience systemic progression and death from PCa following BCR after RRP for primarily lymph node–negative disease. Nevertheless, an increased interval from RRP to BCR is not independently associated with diminished risks of progression or mortality. Regardless of the timing of BCR, then, the decision to institute secondary therapies must balance the risk of disease progression based on clinical parameters—in particular, Gleason score, pathologic tumor stage, and PSA DT—with the cost and potential morbidity of treatments.

Author contributions: Stephen A. Boorjian had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Boorjian, Karnes.
Acquisition of data: Rangel, Bergstralh.
Analysis and interpretation of data: Boorjian, Rangel, Bergstralh.
Drafting of the manuscript: Boorjian.
Critical revision of the manuscript for important intellectual content: Thompson, Tollefson, Blute, Karnes.
Statistical analysis: Rangel, Bergstralh.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Karnes.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.
References


