Are Biochemical Recurrence Outcomes Similar After Radical Prostatectomy and Radiation Therapy? Analysis of Prostate Cancer–Specific Mortality by Nomogram-predicted Risks of Biochemical Recurrence

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Abstract

Background: Due to the protracted natural history of the clinical progression of prostate cancer, biochemical recurrence (BCR) is often used to compare treatment modalities. However, BCR definitions and posttreatment prostate-specific antigen kinetics vary considerably among treatments, calling into the question the validity of such comparisons.

Objective: To analyze prostate cancer–specific mortality (PCSM) according to treatment-specific nomogram-predicted risk of BCR for men treated by radical prostatectomy (RP), external-beam radiation therapy (EBRT), and brachytherapy.


Intervention: RP, EBRT, and brachytherapy.

Outcome measurements and statistical analysis: The 5-yr progression-free probability (5Y-PFP) was calculated for each patient based on the treatment received using a validated treatment-specific nomogram. Fine and Gray competing risk analysis was then used to estimate PCSM by a patient’s predicted 5Y-PFP. Multivariable competing risk regression analysis was used to determine the association of treatment with PCSM after adjusting for nomogram-predicted 5Y-PFP.

Results and limitations: Men receiving EBRT had higher 10-yr PCSM compared with those treated by RP across the range of nomogram-predicted risks of BCR: 5Y-PFP >75%, 3% versus 0.9%; 5Y-PFP 51–75%, 6.8% versus 5.9%; 5Y-PFP 26–50%, 12.2% versus 10.6%; and 5Y-PFP ≤25%, 26.6% versus 21.2%.

After adjusting for nomogram-predicted 5Y-PFP, EBRT was associated with a significantly increased PCSM risk compared with RP (hazard ratio: 1.5; 95% confidence interval, 1.1–2.0; p = 0.006). No statistically significant difference in PCSM was observed between patients treated by brachytherapy and RP, although patient selection factors and lack of statistical power limited this analysis.

Conclusions: EBRT patients with similar nomogram-predicted 5Y-PFP appear to have a significantly increased risk of PCSM compared with those treated by RP. Comparison of treatments using nomogram-predicted BCR end points may not be valid.

Patient summary: Biochemical recurrence (BCR) outcomes after external-beam radiation therapy and radical prostatectomy are associated with different risks of subsequent prostate cancer–specific mortality. Physicians and patients should cautiously interpret BCR end points when comparing treatments to make treatment decisions.

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Radical prostatectomy (RP), external-beam radiation therapy (EBRT), and brachytherapy are considered standard treatments for clinically localized prostate cancer (PCa) with several observational studies showing similar rates of biochemical recurrence (BCR) among patients stratified by prostate-specific antigen (PSA) levels, clinical stage, and biopsy Gleason score [1–3]. To counsel patients about treatment outcomes from local therapy, several pretreatment nomograms have been developed and validated to predict the long-term risk of BCR for RP, EBRT, and brachytherapy [4–9]. Patients and physicians may use these predicted risks of BCR to make comparisons regarding treatment efficacy. BCR after RP, EBRT, and brachytherapy may not be associated with similar risks of subsequent metastatic progression and prostate cancer–specific mortality (PCSM) and may thereby prevent meaningful comparisons between treatments. Using BCR end points to compare treatments is problematic given that different BCR definitions are used. BCR after RP is typically defined as a rising PSA level $\geq 0.2$ or $\geq 0.4$ ng/ml, and a PSA $\geq 2$ ng/ml above the PSA nadir (nadir + 2) is the standard BCR definition for EBRT [10–13]. Hernandez et al examined the impact of applying the nadir + 2 BCR definition to surgically treated patients and found that it resulted in a delay of determining BCR by 5 yr [14]. Differences in posttreatment PSA kinetics may also have an impact on observed BCR rates after RP and EBRT because the cytotoxic effects of the latter may occur over months to years, and it does not eliminate all prostatic sources of PSA. After RP, the posttreatment PSA nadir occurs within 4–6 wk and typically occurs 18–36 mo after EBRT (although it may take as long as 8–10 yr) [15,16]. Likewise, any detectable PSA $>0.1$ ng/ml after RP is thought to indicate recurrent PCa, whereas the nadir PSA is associated with variable risks of subsequent disease progression after EBRT [15,16]. Benign PSA bounces can occur for several years in up to 10–30% of patients receiving brachytherapy (less commonly with EBRT) that may also confuse patients and physicians [17–19]. Another factor confounding comparisons of RP and EBRT using BCR end points is the frequent use of androgen deprivation therapy (ADT) in the latter group (particularly among intermediate- and high-risk patients) that may significantly delay the time to BCR while testicular androgen production is suppressed.

Several theoretical reasons support the concept that patients treated with EBRT are significantly more advanced in the course of progressive disease when BCR is declared compared with RP patients and are therefore at higher risk of developing clinical progression and dying from PCa. To investigate this hypothesis, we compared PCSM rates after RP, EBRT, and brachytherapy according to treatment-specific nomogram-predicted probabilities of BCR [5,7,9]. If BCR end points after RP, EBRT, and brachytherapy are similar (and thus valid for treatment comparisons), one would anticipate that the predicted BCR risk would be associated with a similar probability of PCSM, regardless of the treatment received.

2. Patients and methods

After institutional review board approval, clinical information and follow-up data were obtained for 13 803 consecutive men who underwent definitive therapy for clinically localized PCa at Barnes-Jewish Hospital (St. Louis, MO, USA) or the Cleveland Clinic (Cleveland, OH, USA) by RP ($n = 8308$), EBRT ($n = 2839$), or brachytherapy ($n = 2656$) between 1995 and 2008. All information was obtained from prospectively maintained PCa databases approved by institutional review board. The patient population was described previously [20]. All pathologic specimens were reviewed by genitourinary pathologists at each institution before initiation of treatment. Open retropubic, laparoscopic, or robot-assisted approaches were used to perform RP. Three-dimensional conformal radiotherapy (3DCRT) was performed from 1995 to 1999, and intensity-modulated radiotherapy (IMRT) was performed from 1999 to 2008 at Barnes-Jewish Hospital. At Cleveland Clinic, four-field conventional EBRT was performed in 1995 only, 3DCRT was performed from 1995 to 1997, and IMRT was performed after 1997. The median EBRT dose at Barnes-Jewish Hospital and Cleveland Clinic was 7400 cGy (interquartile range [IQR]: 7070–7400) and 7800 cGy (IQR: 7000–8000), respectively. Transperineal permanent interstitial prostate brachytherapy was delivered using intraoperative treatment planning with ultrasound guidance. At Barnes-Jewish Hospital, 103 of 542 men (19%) who underwent EBRT and 29 of 350 (8%) who underwent brachytherapy received concomitant ADT. At Cleveland Clinic, 1041 of 2305 men (45%) who underwent EBRT and 423 of 2309 (18%) who underwent brachytherapy received concomitant ADT. Among patients receiving radiation therapy, neoadjuvant, concurrent, and/or adjuvant ADT was administered to 12% (median duration: 6 mo [IQR: 3–6]), 45% (median duration: 6 mo [IQR: 6–6]), and 82% (median duration: 6 mo [IQR: 6–12]) of those classified as low, intermediate, and high risk by D’Amico criteria [20].

We obtained survival information through three sources: review of the medical record, patient correspondence, and the Social Security Death Index. Death was attributed to PCa if there was evidence of castration-resistant metastatic disease and PCa was listed on the death certificate as the cause or the patient died of complications of PCa treatment.

2.1. Statistical analysis

The 5-yr progression-free probability (5Y-PFP) was calculated for each patient based on the treatment received using one of three validated treatment-specific nomograms [5,7,9]. In the RP nomogram, BCR was defined as a serum PSA value of $\geq 0.4$ ng/ml (confirmed by a second PSA value higher than the first by any amount), secondary therapy, clinical recurrence, or aborted RP for lymph node metastases [5,13]. In the EBRT and brachytherapy nomograms, BCR was defined using the nadir + 2 definition [7,9,10]. PCSM was estimated using Fine and Gray competing risk analysis stratified by quartiles of 5Y-PFP calculated from the nomograms. Multivariable competing risk regression analysis was used to determine the association of treatment type with PCSM after adjusting for nomogram-predicted 5Y-PFP. All statistical analyses were performed using R v2.8.1 software (R Foundation for Statistical Computing, Vienna, Austria) with additional packages (Design and cmpsk) added.

3. Results

Table 1 lists the baseline clinical characteristics by treatment group. Men who were treated by EBRT were older and tended to have higher risk features on the basis of PSA, clinical stage, and biopsy Gleason score ($p < 0.05$ for all parameters). When
treatment-specific nomograms were used to calculate 5Y-
PFP, the EBRT cohort had the highest risk of BCR; the
brachytherapy cohort had the lowest risk of BCR. The median
nomogram-predicted 5Y-PFP was 89% (IQR: 82–92) for
RP, 79% (IQR: 58–87) for EBRT, and 92% (IQR: 87–94) for
brachytherapy (p < 0.001). Because brachytherapy was
generally reserved for low-risk patients and those with
favorable intermediate-risk features, only 9 (0.4%) and 116
(4.4%) had 5Y-PFP/C20 50% and 51–75%, respectively.

Over a median follow-up of 60 (IQR: 29–97), 75 (IQR: 43–109),
and 37 mo (IQR: 14–65) after RP, EBRT, and brachytherapy,
respectively, 249 men died from PCa including 93 after RP,
144 after EBRT, and 12 after brachytherapy. Follow-up information
/C21 10 yr for eligible survivors was available for 1572 of 2762 men (57%)
included in this study. In the RP versus EBRT comparison,
the 10-yr PCSM according to treatment-specific nomogram-
predicted BCR was 21.2% versus 26.6% for those with 5Y-PFP/C20 25%,
10.6% versus 21.2% for those with 5Y-PFP 26–50%,
5.9% versus 6.8% for those with 5Y-PFP 51–75%, and 0.9% versus 3% for those with 5Y-PFP >75%, respectively. Thus
EBRT patients had higher estimated PCSM compared with RP across the spectrum of predicted BCR risks. The analysis
of 10-yr PCSM by nomogram-predicted BCR risk for
brachytherapy and RP patients was restricted to those with
5Y-PFP >75% due to the few patients (and events) in the
former group with 5Y-PFP ≤75%. Among those with 5Y-PFP
>75%, a higher 10-yr PCSM was observed for brachytherapy
compared with RP (2.8% vs 0.9%).

Figure 1 shows the estimated 10-yr PCSM for RP and
EBRT based on the treatment-specific nomogram-predicted
5Y-PFP on a continuous scale. In multivariable analysis after
adjusting for nomogram-predicted 5Y-PFP, EBRT was
associated with a significantly increased risk PCSM compared
with RP (hazard ratio [HR]: 1.5; 95% confidence interval [CI], 1.1–2.0; p = 0.006). No significant difference in
PCSM was observed between patients treated by brachy-
therapy and RP (HR: 1.4; 95% CI, 0.7–2.5; p = 0.3), although
the few PCSM events (n = 12) and high-risk patients in the

![Fig. 1 – Estimated 10-yr prostate cancer-specific mortality according to treatment-specific nomogram-predicted 5-yr progression-free probability [5,7] for men treated by radical prostatectomy (blue) and external-beam radiation therapy (orange). Dashed lines represent the 95% confidence interval for the survival estimates.](image-url)
brachytherapy group (n = 125) limited the statistical power of the analysis.

4. Discussion

A man diagnosed with screen-detected clinically localized PCAs faces a complicated treatment decision about whether radical local therapy should be pursued and, if so, what treatment will give him the highest likelihood of achieving his long-term treatment goals. RP, EBRT, and brachytherapy are accepted treatment options, and none has been definitively proven to be superior in terms of quantity or quality of life. The protracted treated natural history of screen-detected PCa has necessitated the use of BCR end points to assess treatment success and is frequently used to compare treatments. The results of the analysis.

In a contemporary cohort of patients treated by RP, EBRT, and brachytherapy at two high-volume US hospitals according to current treatment standards, men receiving EBRT had higher 10-yr PCSM compared with RP across the range of nomogram-predicted risks of BCR. The few high-risk patients receiving brachytherapy and few PCSM events limit the ability to identify similar differences. This study provides convincing evidence that BCR end points after EBRT and RP are not equivalent. Thus comparison of treatments using nomogram-predicted BCR end points may not be valid.

Although BCR universally antedates clinical progression by a median of 5–7 yr [22], it is an imprecise proxy for PCSM due to its variable natural history; at 15 yr after BCR, roughly a third of men will die from PCa, a third will have died of competing causes, and a third are alive [23]. The BCR definitions used in the nomograms we evaluated have proven to better predict clinical progression compared with other BCR definitions [10,13]. However, no study has shown that BCR end points after RP and EBRT are associated with similar risks of clinical progression or PCSM. The nomogram software specifically states in the Frequently Asked Questions section that one cannot simply choose the treatment with the lowest predicted BCR risk and that other outcomes need consideration (available at http://www.nomograms.org). Nevertheless, BCR outcomes are frequently used to compare treatments. The results of our study show that BCR end points after RP and EBRT are not equivalent; the latter is associated with a significantly more ominous prognosis due, in part, to delays in declaring BCR using the nadir + 2 definition compared with RP BCR definitions.

We and others have recently reported that RP is associated with improved all-cause mortality, PCSM, and/or metastatic progression compared with EBRT (IMRT or 3DCRT) among contemporary patients diagnosed in the later PSA era (even among healthy patients) [20,24–27], although others have reported conflicting results [28]. Our study provides further evidence that EBRT patients are at higher risk of PCSM compared with RP because the former was significantly associated with PCSM even after adjusting for nomogram-predicted BCR; the nomograms are all externally validated and consider PSA, clinical stage, biopsy Gleason score, and treatment details (for those receiving EBRT) [5,7,9]. Differences in PCSM between RP and EBRT may be related to a superior ability to achieve local control and/or improved delivery of effective secondary therapy for local recurrence/persistence. There is no conclusive evidence that RP alone achieves superior local control compared with EBRT, although local failure rates of 24% and 33% after IMRT have been reported for intermediate- and high-risk patients, respectively, receiving doses ≥7560 cGy [29]. Survival differences between RP and EBRT may be due to improved ability to deliver timely and effective secondary therapy after RP by enabling a pathologic assessment of the primary tumor and the improved ability to interpret early posttreatment PSA changes [25]. Because secondary treatments in this cohort were seldom administered in the absence of a rising posttreatment level, the improved survival among RP versus EBRT for a given BCR risk may be explained by application of more effective salvage therapy.

This study had several limitations. Our study evaluated PCSM within 10 yr of treatment, but men with localized PCa appear to be at risk for PCSM for up to 20 yr [30,31]. Men in the EBRT group were older and had more adverse disease characteristics (higher PSA, more high-grade cancer, and more advanced clinical stage), although these factors are considered in the 5Y-PFP nomogram predictions. Although the RP nomogram has been shown to discriminate well among patients for clinical progression and PCSM [32], other factors not considered in the nomogram may account for the increased PCSM observed among the EBRT patients. The BCR definition used in the surgery nomogram (postoperative PSA ≥0.4 ng/ml followed by a confirmatory rise) is used less often in current practice in favor of more sensitive definitions (eg, PSA ≥0.2 ng/ml). Thus it is conceivable that larger differences in PCSM by nomogram-predicted BCR end points would have been observed had we used a surgery nomogram based on this BCR definition. Another limitation to our study is the few number of events, especially in the brachytherapy group, that limited our ability to draw statistically significant conclusions in men with 5Y-PFP <75%. Last, although we believe the treatments that patients received in our study reflect contemporary standards, treatments are in constant evolution. In particular, the ADT duration and the radiation dose for many patients treated with EBRT would be considered inadequate by current standards.

5. Conclusions

Men treated with EBRT are at a higher risk of PCSM compared with RP patients with similar nomogram-predicted risks of BCR. This provides convincing evidence that BCR end points after RP and EBRT are not associated with similar clinical consequences in terms of metastatic progression and PCSM and should be used cautiously to
make comparisons between treatment modalities. Functional outcomes, short- and long-term complications, individual preferences, and unique practitioner and institutional expertise should also be considered when making a treatment decision.

Author contributions: Andrew J. Stephenson 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: Lee, Kattan, Kibel, Stephenson.

Acquisition of data: Kibel, Klein, Ciezki, Stephenson, Reddy.

Analysis and interpretation of data: Lee, Kibel, Klein, Ciezki, Reddy, Yu, Kattan, Stephenson.

Drafting of the manuscript: Lee, Stephenson.

Critical revision of the manuscript for important intellectual content: Lee, Kibel, Klein, Ciezki, Reddy, Yu, Kattan, Stephenson.

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