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Optimal Definition of Biochemical Recurrence After Radical Prostatectomy Depends on Pathologic Risk Factors: Identifying Candidates for Early Salvage Therapy

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Abstract

Background: The use of prostate-specific antigen (PSA) thresholds (<0.2 ng/ml) below currently accepted biochemical recurrence (BCR) definitions for patients treated with radical prostatectomy may be useful in the identification of candidates for early salvage therapy with improved outcome; however, the practice risks overtreatment, as the risk of subsequent PSA progression may be low.
Objective: To analyze 14 BCR definitions for their association with subsequent PSA and treatment progression among subgroups of patients at varying risk of prostate cancer–specific mortality.
Design, setting, and participants: The subsequent risk of PSA and treatment progression after BCR based on 14 BCR definitions (six standard definitions and eight definitions requiring one or more successive PSA rises ≤0.1 ng/ml) was analyzed according to various clinicopathologic risk criteria among 2348 patients with a detectable PSA ≥0.03 ng/ml at least 6 wk after radical prostatectomy.
Intervention: Radical prostatectomy.
Outcome measurements and statistical analysis: Probability of subsequent PSA progression after BCR, defined as a PSA rise >0.1 ng/ml above BCR PSA, initiation of secondary treatment, or clinical progression.
Results and limitations: Using standard BCR definitions, the risk of PSA progression was >70%, regardless of clinicopathologic features. A single PSA ≤0.1 ng/ml was associated with PSA progression in only 30–55% of patients but ranged from 18–25% to 73–88% for patients without and with adverse pathologic features, respectively. Based on discrimination and calibration analysis, the optimal BCR definition for patients with 5-yr progression-free probability of <50%, 50–75%, 76–90%, and >90% was a single PSA ≥0.05 ng/ml, two or more rising PSAs ≥0.05 ng/ml, PSA ≥0.2 ng/ml and rising, and PSA ≥0.4 ng/ml and rising.
Conclusions: BCR definitions below currently accepted PSA thresholds appear to be valid for selecting patients with adverse clinicopathologic risk factors for secondary therapy. This information may be useful in selecting for early salvage radiotherapy to improve clinical outcome.

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1. Introduction

Approximately 25–35% of patients will develop evidence of a rising prostate-specific antigen (PSA) level after radical prostatectomy for clinically localized prostate cancer (PCa) [1–3]. While a standard definition of biochemical recurrence (BCR) has been adopted for patients treated with external-beam radiotherapy [4], several BCR definitions are in use for patients treated with radical prostatectomy. The European Association of Urology and the American Urological Association define BCR as a single PSA >0.2 ng/ml followed by a subsequent rise [5,6]. The National Comprehensive Cancer Network guidelines define BCR as either a failure of PSA to decline to undetectable levels or a rising PSA on two or more subsequent determinations, without specifying a minimum threshold [7]. Stephenson et al. identified a PSA ≥0.4 ng/ml followed by a subsequent rise to be the BCR definition that best explained the risk of metastasis progression [8].

A single BCR definition may not be appropriate for all patients, as detectable PSA levels may have a different prognostic significance based on a man's clinicopathologic risk factors and probability of cancer recurrence/progression. PSA changes above the threshold of detection may be highly meaningful for men with high pretest probability (eg, a PSA level of 0.05 ng/ml 2 mo postoperatively in a man with Gleason 9 PCa with seminal vesicle invasion) but might not be meaningful for men with low pretest probability (eg, a PSA level of 0.05 ng/ml 4 yr postoperatively in a man with organ-confined, Gleason 6 PCa), as the latter may have a higher likelihood of being a laboratory error or a detectable PSA from a benign source or an indolent focus of PCa.

Identifying appropriate BCR definitions below currently accepted PSA thresholds (<0.2 ng/ml) is important, given the accumulating evidence of improved outcomes when salvage radiotherapy is administered at lower PSA levels [9–11]. Contemporary PSA assays with improved sensitivity can be used to select patients at risk for prostate cancer–specific mortality (PCSM) for salvage therapy at lower PSA levels. However, BCR based on a single PSA rise is problematic, as Amling et al. reported a high rate of PSA nonprogression among men with a single elevated PSA level <0.4 ng/ml using older assays [12].We endeavored to identify the most suitable threshold for BCR among 14 definitions (six standard definitions and eight definitions requiring one or more successive PSA rises ≤0.1 ng/ml) that best predicts subsequent PSA progression and treatment progression after radical prostatectomy according to clinicopathologic risk factors.

2. Patients and methods

2.1. Patient population

From a prospective database of patients with clinically localized PCa who underwent radical prostatectomy at our institution between 2001 and 2009, 2347 patients had a recorded detectable PSA (≥0.03 ng/ml) ≥6 wk after surgery. PSA ≥0.03 ng/ml was the chosen threshold, as it represents the lower limit of detection for the assay currently used at our institution. The study population did not include any of the 231 patients who received neoadjuvant therapy prior to surgery or any of the 121 patients who received secondary therapy before documented evidence of a detectable postoperative PSA.

A total of 1331 cases were performed by a minimally invasive approach. Pelvic lymph node dissection seldom was performed proximal to the common iliac artery bifurcation. Postoperatively, patients were followed for disease recurrence, with serum PSA determinations at regular intervals. A median of four (range: two to seven) PSA levels were available per patient, of which 95% were performed at Cleveland Clinic laboratories. At Cleveland Clinic, Roche Platform testing had been used since 2001 (lower limit: 0.03 ng/ml). Staging imaging studies and secondary therapy for men with rising PSAs were performed at the discretion of the treating physician.

2.2. Biochemical recurrence definition analysis

We examined 14 definitions of BCR that have been used in published studies or that we believed might be relevant because they were based on PSA thresholds below currently accepted levels (≤0.1 ng/ml). The end points analyzed from the time of BCR based on these 14 definitions included subsequent PSA progression (defined as PSA >0.1 ng/ml above the BCR PSA determination, receipt of secondary therapy, development of distant metastasis, or PC mortality, whichever event was recorded as occurring first) and treatment progression (defined as the use of secondary local or systemic therapy, clinical progression, or PCSM, whichever occurred first). We believe our definition of PSA progression is valid, as virtually all patients classified as such would have rising PSA levels ≥0.2 ng/ml, which has been previously reported to be associated with subsequent PSA progression in >90% of patients [8].

The probability of these events was analyzed according to predefined groups based on the risk of BCR and PCSM, including the presence of unfavorable pathology (pT3B, pN1–3, or Gleason 8–10) and favorable pathology (pT2, Gleason 6 or pT2, Gleason 3 + 4, negative surgical margins) [13] and the 5-yr progression-free probability (PFP) (<50%, 50–75%, 76–90%, and >90%) by a validated postoperative nomogram [14]. For reporting purposes, we grouped the BCR definitions into three categories (A: single PSA thresholds ≤0.1 ng/ml; B: PSA thresholds requiring successive rises ≤0.1 ng/ml; and C: standard BCR definitions [PSA thresholds ≥0.2 ng/ml with or without a subsequent rise]).

2.3. Statistical analysis

The risks of PSA progression and treatment progression were estimated using the Kaplan-Meier method [15].The validity of these 14 BCR definitions was assessed by evaluating the performance characteristics (discrimination and calibration) of a postoperative nomogram for the 5-yr probability of PSA progression after BCR; the postoperative nomogram has been extensively validated in diverse populations for the end point of BCR (defined as PSA ≥0.4 ng/ml followed by a subsequent rise), which is slightly different from the risk of PSA progression after the time of BCR [14,16,17]. The use of the nomogram is valid for this purpose, as the end point of the nomogram (PSA ≥0.4 ng/ml followed by a subsequent rise) occurs at a later point in time compared with all but 1 of the 14 BCR definitions studied (the exception is definition 14—PSA ≥0.4 ng/ml followed by a subsequent rise—as this definition would imply two rises above 0.4 ng/ml). In addition, the BCR end point of the postoperative nomogram has been previously shown to best explain the risk of metastatic progression among standard BCR definitions [8]. The nomogram accurately discriminates among patients for the risk of castration-resistant progressive PCa and PCSM [18].

All analyses and graphics were performed using the statistical software package R v.2.15 (R Development Core Team, www.r-project.org) and its rms package. All statistics were considered significant at the level of $p < 0.05$. The study received institutional review board approval.