Should we redefine the Phoenix criteria for biochemical recurrence after primary radiotherapy?

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Purpose of review
The Phoenix criteria, which define biochemical recurrence (BCR) after radiotherapy as a prostate specific antigen (PSA) rise of at least 2 ng/ml above nadir, were developed to improve consistency in outcome reporting and distinguish genuine cancer recurrence from transient, noncancerous PSA fluctuations, commonly referred to as PSA "bounces". However, in the current era of advanced imaging and precision oncology, this definition is increasingly viewed as inadequate. This review critically examines recent evidence challenging the clinical utility of the Phoenix definition and explores potential alternatives that better reflect disease biology and patient outcomes.

Recent findings
Modern imaging techniques, particularly prostate-specific membrane antigen (PSMA) PET/computed tomography (CT), have demonstrated the ability to detect recurrent prostate cancer at PSA levels well below the Phoenix threshold, allowing for earlier salvage interventions. Additionally, PSA kinetics such as nadir levels and doubling time provide superior prognostic information compared to static PSA thresholds. Multiparametric risk models that also incorporate PSMA PET/CT findings, PSA kinetics and clinical features may enable more accurate stratification of patients into low-risk and high-risk BCR categories. This evolving approach supports the notion that early, risk-adapted treatment can improve outcomes in high-risk patients, while reducing overtreatment in those at low risk.

Summary
The Phoenix criteria no longer align with the capabilities of current diagnostic and prognostic tools. Redefining BCR using dynamic PSA metrics and advanced imaging could facilitate timely salvage treatment in patients at a high risk and allow surveillance strategies in those unlikely to progress. Prospective validation is warranted to inform future clinical guidelines.

Keywords
biochemical recurrence, phoenix criteria, prostate cancer, PSA kinetics, PSMA PET/CT, radiotherapy

INTRODUCTION

Biochemical recurrence (BCR) after primary radiotherapy represents a critical clinical event that impacts patient outcomes and subsequent therapeutic strategies. Unlike patients who undergo radical prostatectomy, where prostate specific antigen (PSA) levels become undetectable following complete surgical removal of the prostate [1], those treated with radiotherapy may still produce small amounts of PSA, even when the treatment is considered radical. PSA levels gradually decline, eventually reaching their lowest point, referred to as the PSA nadir. BCR has then been defined by the Phoenix criteria, specifying an increase of at least 2 ng/ml above the PSA nadir [2]. This definition was originally established to distinguish genuine cancer recurrence from transient, noncancerous PSA fluctuations, commonly referred to as PSA "bounces" [3]. At the time of adoption, the Phoenix criteria significantly improved consistency in reporting recurrence rates, facilitating more accurate comparisons of therapeutic efficacy across various clinical studies and allowing detection of metastatic disease on conventional radiology. Over the past two decades, substantial

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KEY POINTS

- The Phoenix criteria for biochemical recurrence after radiotherapy is inadequate in the context of modern imaging and clinical risk stratification.
- PSMA PET/CT can detect recurrent disease at PSA levels below the Phoenix threshold, enabling earlier salvage interventions.
- PSA kinetics, including nadir levels and doubling time, offer superior prognostic value over absolute PSA thresholds alone.
- Multiparametric risk models incorporating PSA dynamics, imaging, and clinical variables may better distinguish between low-risk and high-risk recurrence.
- Redefining BCR thresholds could reduce overtreatment in low-risk patients and facilitate timely salvage therapy in high-risk cases.

advances have occurred in prostate cancer (PCa) diagnostics, including the introduction of sensitive imaging techniques such as prostate-specific membrane antigen PET/computed tomography (PSMA PET/CT), along with significant developments in molecular profiling and biomarker discovery. These innovations have altered the understanding of PCa biology, emphasizing the considerable heterogeneity in disease progression and treatment response. Recent evidence suggests that Phoenix criteria may no longer adequately capture this complexity. For example, PSMA PET/CT frequently identifies clinically significant recurrent disease at PSA levels below the traditional Phoenix threshold, indicating that the criteria's sensitivity may be insufficient for early detection. Conversely, concerns regarding specificity have also emerged, as some patients meeting the Phoenix definition for BCR might not experience clinically meaningful progression, potentially leading to unnecessary interventions. This review evaluates recent literature addressing the limitations of the Phoenix criteria and discusses the rationale for potentially redefining BCR based on current technological and clinical advancements.

MATERIALS AND METHODS

A literature search was conducted in PubMed to identify relevant studies published between January 2020 and March 2025. The keywords used included "prostate cancer," "biochemical recurrence," "Radiotherapy," "Phoenix criteria," "PSMA PET/CT," "salvage therapy," and "PSA kinetics." Only clinical trials, reviews, meta-analyses, and cohort studies published in English were included.

To provide clinically meaningful insights, we evaluated the utility of BCR as an early indicator of potential relapse by examining its incidence, prognostic value and risk stratification, associated imaging and biopsy findings, and potential as a surrogate endpoint in clinical trials.

EVIDENCE SUMMARY

Incidence of biochemical recurrence according to different definitions of biochemical recurrence

The incidence of BCR after radiotherapy ranges between 15 and 55% [4–6]. Recent literature indicates considerable variability in BCR rates depending on clinical risk at diagnosis, the BCR definition used, and according to primary treatment modality. Table 1 summarizes BCR definitions used in clinical practice and trials.

In a Swedish population-based cohort, the observed 15-year cumulative incidence of BCR (Phoenix Criteria) after radiotherapy was 18% [95% confidence interval (95% CI), 15–21] in the D'Amico low-risk group, 24% (95% CI, 21–26) in the intermediate-risk group, and 36% (95% CI, 33–39) in the high-risk group [7▪].

Studies comparing the Phoenix definition with alternative criteria consistently demonstrate significant differences in reported BCR-free survival rates. In particular, the Phoenix criteria generally yield lower reported BCR rates compared to stricter definitions [8,9]. For example, in one randomized study comparing radiotherapy treatments at different doses according to the 1997 American Society for Therapeutic Radiology and Oncology definition (ASTRO), the 5-year biochemical relapse rates were 39 and 28% for the 70-Gy and 80-Gy arms, respectively ($P=0.036$). Using the Phoenix definition, the corresponding rates were 32 and 24% ($P=0.09$) [5].

Gul *et al.* [8] compared the incidence of BCR defined by the Phoenix criteria versus the American Urological Association (AUA) criteria (PSA >0.2 ng/ml) in a cohort of 2634 patients who underwent permanent brachytherapy for PCa. They reported that 11% of patients met the Phoenix criteria compared to 17% meeting the AUA criteria. The study noted that while the differences in BCR rates were statistically significant at 5 and 10 years, they were not significant at 15 years. Notably, 64 patients (2.4%) died of PCa, with a median time from BCR to death of 3.7 years using the Phoenix definition and 5.8 years using the AUA definition. Another study compared the incidence of BCR based on the AUA criteria with that defined by the Japanese Prostate Cancer Outcomes Study (J-POPS), which considers a PSA level more than

Table 1. Comparison of biochemical recurrence definitions used in clinical practice and trials

Definition	PSA threshold	Context of use	Pros	Cons
ASTRO Criteria	3 consecutive PSA rises	Older EBRT studies	Simple	Influenced by PSA bounce
Phoenix Criteria	Nadir + 2 ng/ml	Current RT standard	Reduces false positives	May miss early recurrences
PSMA PET-guided	Imaging-based (positive PET scan)	Modern practice, recurrence localization	High sensitivity and specificity	Not universally available
EAU High Risk BCR	Nadir + 2 ng/ml and time to BCR < 18 months or ISUP GG 4–5	Identifies patients at a high risk after recurrence	Guides early salvage therapy	Complex criteria, less validated
EMBARK High Risk BCR	Nadir + 2 ng/ml and PSADT < 9 months	Clinical trials for treatment intensification post-BCR	Identify a subset of patients that benefits treatment intensification	Very high risk of being already metastatic

1.0 ng/ml on at least three measurements. Similar findings were observed by Takeuchi *et al.* [9], with BCR rates of 15.5% according to the AUA definition and 4.2% according to the J-POPS criteria.

PROGNOSTIC VALUE OF PHOENIX CRITERIA

Patients who meet BCR endpoints have per definition disease progression. However, meeting the Phoenix criteria does not necessarily indicate clinically significant recurrence or progression to PCa-specific mortality (PCSM) [10,11]. The European Association of Urology (EAU) guidelines recently introduced a novel stratification system distinguishing low-risk and high-risk biochemical recurrence (HR-BCR) based on PSA kinetics and standard clinical variables [12,13,14▪]. This stratification has been validated in retrospective cohort studies, demonstrating that low-risk patients, particularly after radical prostatectomy, have a very low risk of mortality and may not require immediate intervention [7▪,15]. Conversely, the evidence of the clinical utility of the EAU-BCR risk stratification in patients undergoing radiotherapy is largely unexplored.

A recent population-based analysis by our group showed that cumulative incidences of PCSM 10 years after BCR adjusted for salvage treatment were 24% (95% CI, 19–29) for patients with low-risk EAU-BCR and 46% (95% CI, 40–51) for patients with high-risk EAU-BCR. Multivariable competing risks regression analysis showed both low-risk BCR (sHR, 1.34; 95% CI, 1.22–1.47) and high-risk BCR (sHR, 1.45, 95% CI, 1.32–1.60) to be significant risk factors of PCSM [7▪]. These findings suggest that these criteria may need improvements, that is incorporating PSA kinetics and reducing PSA cut-off levels to distinguish patients at true low-risk BCR after radiotherapy who do not have higher risk of PCSM.

IMAGING FINDINGS IN PATIENTS WITH BIOCHEMICAL RECURRENCE AFTER RADIOTHERAPY

After radiotherapy, MRI and target biopsies have shown excellent results in detecting local recurrences and guiding salvage therapies. The FORECAST trial (NCT01883128) was a prospective cohort diagnostic study that recruited patients with suspected radiorecurrence at six UK centres. Of 144 patients, 111 (77%) had cancer detected on biopsy. MRI sensitivity and specificity at the patient level were 0.95 (95% CI 0.92–0.99) and 0.21 (95% CI 0.07–0.35), respectively [16▪].

Given the morbidity of post-RT local salvage treatments, distant metastases should also be checked in patients with local recurrences and who are fit for these salvage therapies. Choline-, fluciclovine- or PSMA-PET/CT can be used to detect metastases, but for this indication, PSMA PET/CT shows the highest sensitivity, improving recurrence detection at PSA levels below the Phoenix criteria threshold [17,18]. van Altena *et al.*[19▪▪] compared PSMA findings and outcomes in patients not yet meeting Phoenix criteria with patients undergoing PSMA after Phoenix criteria. Patients were detected earlier and were more frequently eligible for local salvage therapy [75.9 vs. 45.0%; odds ratio (OR 3.84); $P < 0.001$]. Distant metastases were less frequent in patients not meeting Phoenix criteria ($n = 37$, 21.8%) than in those who met Phoenix criteria ($n = 157$, 48.8%; OR 0.29; $P < 0.001$). Similarly, survival analyses revealed longer times to ADT (re)initiation and progression to CRPC, as well as lower overall mortality, in patients not meeting Phoenix criteria (log-rank $P < 0.001$) [19▪▪]. Perera

et al.[20] evaluated the diagnostic performance and clinical predictors of ^{68}Ga-PSMA PET in advanced PCa. Among 1309 patients, the overall detection rate was 76% in the setting of BCR. PSMA Positivity correlated with pre-PET PSA levels and PSA doubling time (PSAdt) [20]. Notably, PSMA PET detected recurrence in 42% of patients with PSA less than 0.2 ng/ml, 58% with PSA 0.2–1.0, and 95% when PSA exceeded 2 ng/ml. Per-lesion specificity reached 97%, significantly outperforming choline-based PET and conventional imaging.

Regarding local staging, Rasing *et al.*[21] evaluated the diagnostic performance of combined PSMA PET/CT and mp-MRI in detecting radio-recurrent PCa in 41 patients undergoing evaluation for focal salvage HDR brachytherapy. Targeted biopsies – guided by mp-MRI and PSMA PET/CT fusion – confirmed recurrence in 97.6% of cases with a lesion visible on both modalities, supporting a high positive predictive value (PPV). All five patients with initially negative biopsies had low PSMA uptake or ambiguous MRI findings, and four were later confirmed positive upon rebiopsy [21].

These findings underscore the clinical utility of PSMA PET for early localization of recurrence, even at low PSA thresholds, potentially challenging the adequacy of current biochemical definitions like the Phoenix criteria which may delay imaging and treatment in early BCR.

BIOPSY FINDINGS IN PATIENTS WITH BIOCHEMICAL RECURRENCE AFTER RADIOTHERAPY

In addition to advanced imaging, prostate biopsy remains an important diagnostic tool to confirm local recurrence, particularly in patients considered for salvage therapies. Histological confirmation is often required prior to initiating local salvage treatments such as salvage prostatectomy or reirradiation. Studies have shown that post-radiotherapy biopsies carry prognostic significance. At 2 years after treatment, the rate of positive biopsies ranges from approximately 10 to 30%, depending on radiation dose and technique [22,23]. In the setting of BCR, targeted biopsies performed at the time of PSA rise showed a higher positivity rate ranging between 30 and 60% [24,25]. Positive findings are strongly associated with increased risks of metastasis and cancer-specific mortality, emphasizing their role in patient stratification and salvage treatment planning [23].

SALVAGE TREATMENTS POST-RADIOTHERAPY

Emerging evidence supports multiple local salvage treatment strategies after radiotherapy, including SBRT, cryotherapy, brachytherapy, focal therapies (e.g., HIFU), and salvage prostatectomy [26,27▪,28▪,29]. A recent systematic review and meta-analysis compared the oncological and functional outcomes of these approaches [30]. No significant differences were found regarding recurrence-free survival (RFS) between these modalities with the 5-year RFS ranging from 50 to 60%. Due to the low quality of the evidence, no strong recommendation regarding the choice of any of these techniques can be made and salvage treatment strategies after radiotherapy are often underutilized. In a multicentre cohort of 978 men with radiorecurrent high risk PCa who previously received either EBRT (n = 654, 67%) or EBRT + BT (n = 324, 33%), local salvage therapies were delivered to only 21 men after EBRT, and eight men after EBRT + BT [31].

In patients undergoing radical prostatectomy, increasing evidence suggest better outcomes if radiotherapy is delivered at lower PSA cut-offs (early salvage radiotherapy). Question remains about the perfect timing of salvage treatments after radiotherapy and the impact of different definitions of BCR on long term oncological outcomes. High PSA values at recurrence may indicate a higher tumour burden resulting in lower efficacy of salvage treatments.

PSA-BASED SURROGATE ENDPOINTS

Literature supports the utility of PSA-based surrogate endpoints for predicting clinical outcomes post-radiotherapy. PSA kinetics, including nadir values and doubling time, reliably predict metastasis and PCa-specific mortality [31]; however, BCR, as it is currently defined, cannot be used as an intermediate surrogate endpoint for PCSM [32]. Xie *et al.* [32], on behalf of the ICECaP Working Group, evaluated whether event-free survival (EFS) – a composite PSA-based endpoint including biochemical failure, local/regional recurrence, distant metastasis, or death – can serve as a surrogate for overall survival (OS) in men with localized PCa treated with primary radiotherapy. Using individual patient data from 10 350 men across 15 trials, they found that EFS had only a weak correlation with OS at both patients (Kendall's tau = 0.43) and trial level (R^2 = 0.35). In contrast, metastasis-free survival (MFS) showed a significantly stronger correlation with OS ($R^2 > 0.8$ in prior ICECaP work). These findings confirm that PSA-based definitions of recurrence, including the Phoenix criteria, are insufficient surrogates for OS, and caution against their use as primary endpoints in trials evaluating (neo)adjuvant therapies [32].

Several attempts have been made over the years to find novel PSA-based surrogate endpoints. Royce et al. conducted a secondary analysis of a randomized trial involving 157 men with unfavourable-risk PCa

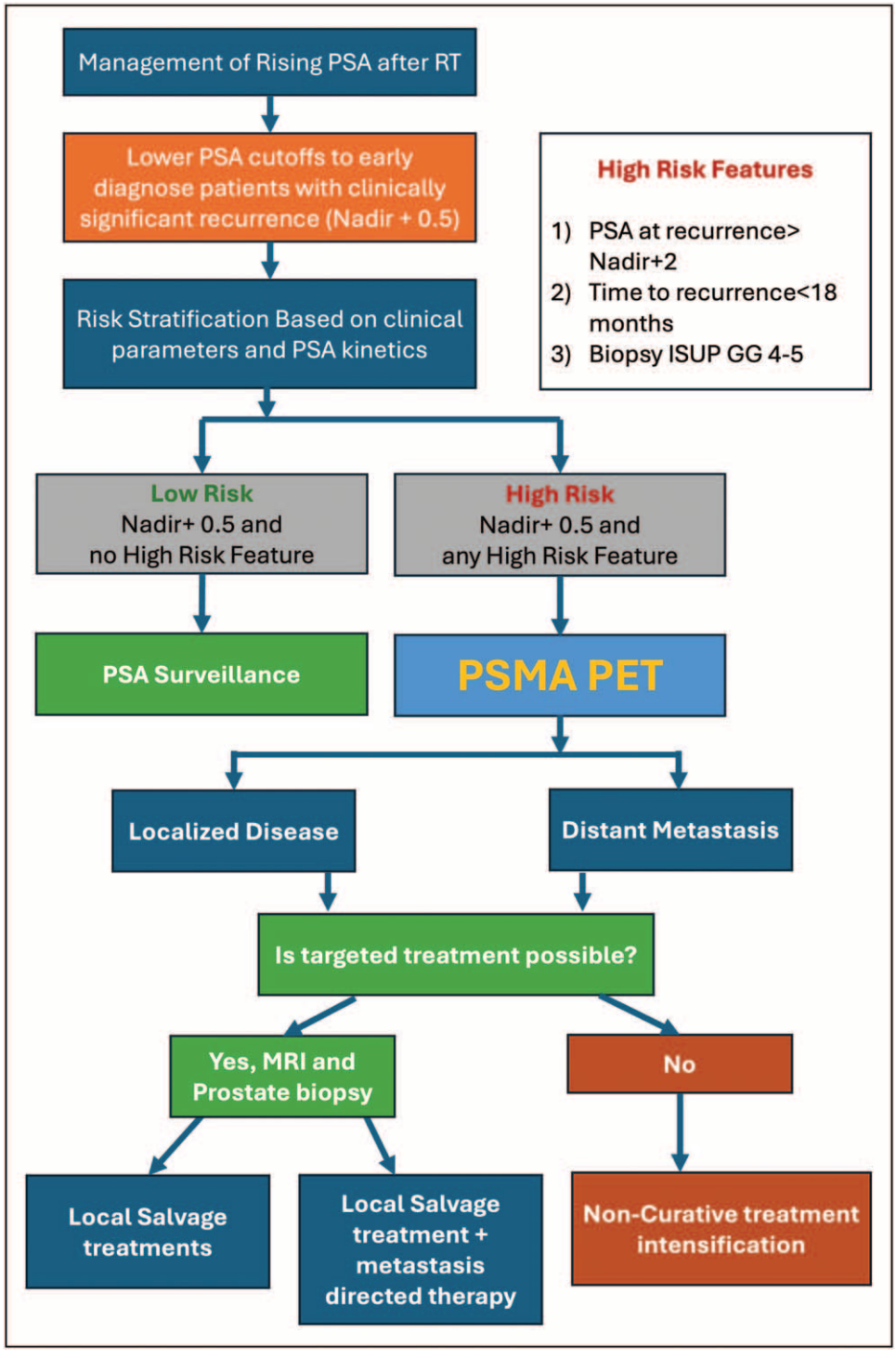

FIGURE 1. Proposed multiparametric early definition of biochemical recurrence – flowchart integrating lower PSA values at recurrence, doubling time, clinical parameters, and PSMA imaging.

treated with radiotherapy or radiotherapy plus 6 months of androgen deprivation therapy (ADT), followed for a median of 16.5 years. The study compared four PSA-based metrics as surrogate endpoints for all-cause mortality (ACM): PSA failure, PSA nadir more than 0.5 ng/ml, PSA doubling time less than 9 months, and interval to PSA failure less than 30 months. Only three met all four Prentice criteria for surrogacy – PSA nadir more than 0.5 ng/ml, PSA DT less than 9 months, and early PSA failure

(<30 months) – with PSA nadir more than 0.5 ng/ml showing the highest proportion of treatment effect explained (103.9%) [33].

Bryant *et al.*[34] proved the prognostic significance of the PSA nadir at 3 months after RT. Furthermore, a PSA nadir more than 0.5 ng/ml showed potential as a surrogate endpoint of overall mortality meeting the Prentice criteria [33].

Finally, using individual patients' data from 16 randomized trials evaluating RT ± ADT for localized PCa, Kwak *et al.*[35▪▪] recently pointed out that PSA at least 0.1 ng/ml within 6 months after radiotherapy completion was prognostic for long-term outcomes in patients treated with RT ± ADT for localized PCa.

DISCUSSION

The Phoenix criteria, originally developed to standardize the assessment of BCR and minimize false positives due to transient PSA fluctuations, now appear insufficient in the era of advanced imaging and molecular profiling. Emerging evidence indicates that most patients undergoing PSMA PET re-staging at the time of PSA nadir +2 present with high-risk, high-volume disease, often limiting opportunities for curative salvage treatments. In contrast, initiating evaluation at lower PSA thresholds may increase the likelihood of negative or false-positive PSMA PET scans; however, it also enables earlier detection of low-volume, clinically meaningful recurrences that could still be amenable to curative intervention. A possible solution could be to reduce PSA thresholds for BCR and introduce a more nuanced and comprehensive post-BCR risk stratification. Incorporating additional parameters – such as PSA kinetics, initial risk classification, and reduced PSA cut-offs – may help identify patients with true low-risk BCR who are not at significant risk of PCSM [31].

Based on current evidence, we propose a novel multiparametric definition of BCR that integrates longitudinal PSA follow-up, clinical risk factors, and advanced imaging findings. This approach is more reflective of contemporary clinical practice and aligns with the broader objective of delivering individualized patient care. The proposed framework, depicted in Fig. 1, seeks to address the limitations of traditional BCR definitions by providing a more refined understanding of disease progression in the context of modern diagnostics and patient-specific prognostic factors.

Within this framework, patients meeting criteria for low-risk BCR may be appropriate candidates for active surveillance. Conversely, those classified as high-risk should undergo prompt re-staging to evaluate the presence and extent of local or distant disease. These patients may benefit from intensified salvage strategies, including salvage radical prostatectomy, targeted radiotherapy modalities (e.g., external beam radiotherapy, HDR, or LDR brachytherapy), or systemic treatment escalation with novel androgen receptor pathway inhibitors [4,36]. Early identification of patients at an increased risk of PCSM is critical for maintaining the window of opportunity for curative intervention. Future prospective studies involving patients with postradiotherapy PSA rises are needed to validate the clinical utility of treatment intensification and de-intensification strategies in patients with BCR. Ultimately, how these trials define patients with BCR and how risk stratification is performed in low-risk or high-risk recurrence will determine changes in diagnostic and treatment paradigms.

CONCLUSION

In the era of advanced diagnostics, the Phoenix criteria are increasingly inadequate for identifying clinically meaningful BCR following radiotherapy for PCa. Modern tools such as PSMA PET/CT, when combined with PSA kinetics and clinical variables, can significantly enhance risk stratification and inform timely salvage therapies.

Redefining BCR to detect recurrence at lower PSA thresholds may allow more patients to be treated with curative intent. At the same time, improved risk stratification can prevent overtreatment in those with indolent disease.

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Conflicts of interest

The authors declare no conflicts of interest.

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