Optimizing therapy for high-risk biochemically recurrent non-metastatic prostate cancer

Current and emerging strategies

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Cite as: Kollmannsberger C, Finelli A, Loblaw A, et al. Optimizing therapy for high-risk biochemically recurrent non-metastatic prostate cancer: Current and emerging strategies. *Can Urol Assoc J* 2025;19(8):282-8. http://dx.doi.org/10.5489/cuaj.9100

Published online April 17, 2025

ABSTRACT

Prostate cancer is a leading malignancy affecting men globally and in Canada. Biochemical recurrence (BCR), marked by rising prostate-specific antigen (PSA) levels post-curative-intended local treatment, is prevalent in nearly one-third of prostate cancer patients and is associated with increased risk of metastases and mortality. The management of patients with BCR is evolving rapidly, highlighting the need for practical guidance. This review aims to provide guidance to clinicians on the use and subsequent implications of advanced imaging results in patients with BCR. In addition, current management approaches, including salvage therapies post-radical prostatectomy, as well as the integration of androgen deprivation therapy (ADT) plus androgen receptor pathway inhibitors (ARPI), are explored.

INTRODUCTION

The purpose of this review is to provide clinical management support to physicians managing patients with high-risk biochemically recurrent non-metastatic castrate-sensitive prostate cancer (nmCSPC). Emerging treatment strategies, challenging clinical questions, and key considerations are discussed. The key considerations provided are not guideline statements, but a review of factors to consider for managing clinical scenarios in patients with high-risk biochemical recurrence (BCR).

In Canada, prostate cancer is the most commonly diagnosed and third leading cause of death in men. It is estimated that 27 900 men will be diagnosed with prostate cancer in 2024, with 5000 succumbing to the disease.[1] Globally, prostate cancer remains a significant health concern, with an estimated 1.5 million new cases diagnosed annually.[2]

BCR of prostate cancer, defined by rising levels of prostate-specific antigen (PSA) without detectable metastases following primary definitive treatment with radical prostatectomy (RP) and/or radiation therapy (RT), occurs in almost one-third of patients.[3,4] Patients with BCR are at an increased risk of eventual metastases and mortality, especially in those with poor prognostic indicators.

Recent findings from phase 3 clinical trials in patients who have failed locoregional therapies without metastatic disease on conventional imaging but with high-risk characteristics support early treatment intensi-

KEY MESSAGES

- A key consideration for ordering a PSMA-PET imaging is whether the information PSMA-PET provides will influence the treatment approach.
- Patients with high-risk BCR are candidates for PSMA-PET, as more sensitive imaging may influence disease classification and treatment options.
- Adding an ARPI to ADT has become a potential treatment option for patients with non-metastatic high-risk prostate cancer with BCR (PSADT ≤9 months) who have failed locoregional primary and salvage therapies.

fication with next-generation hormonal therapies, such as enzalutamide, with or without androgen deprivation therapy (ADT), and apalutamide with ADT.[5,6] In addition, advances in imaging techniques, such as prostate-specific membrane antigen positron emission tomography (PSMA-PET), have enhanced the detection of metastatic/recurrent disease at earlier stages.[7,8]

The evolving treatment landscape for patients with non-metastatic high-risk BCR, in combination with the advent of more sensitive imaging techniques, highlights a unique therapeutic situation in the management of patients with BCR. This review examines the latest data on treatment strategies for patients with BCR, with a focus on high-risk BCR, who have failed locoregional therapies, and discusses the impact PSMA-PET may have on the clinical management of these patients.

TREATMENT OPTIONS FOR PRIMARY DEFINITIVE THERAPY

Initial treatment of prostate cancer depends on a host of clinical factors, as well as the patient's overall health and preference. For patients with lower-risk prostate cancer, treatment options include active surveillance, where the cancer is closely monitored with regular PSA tests, digital rectal exams (DREs), and biopsies, and may include magnetic resonance imaging (MRI) and PSMA-PET scans.[9] For higher-risk patients, primary treatment with curative intent, such as RP or RT with or without ADT, is typically recommended (Figure 1).[10-12] After initial treatment, patients enter a followup phase, which includes regular PSA testing, clinical visits, and imaging studies to monitor signs of recurrence. Despite curative-intent primary treatment of prostate cancer, BCR is common, with up to 27–53% of patients experiencing BCR.[13]

RISK STRATIFICATION FOR PATIENTS WITH BCR

Treatment strategies are based on risk stratification using clinical factors such as PSA levels, PSA doubling time (PSADT), tumor staging, surgical margin and node status, post-prostatectomy PSA, genomic classifier risk, PET imaging results, time from local therapy to BCR, and International Society of Urological Pathology (ISUP) grade (Gleason score [GS]/sum). Generally, BCR is defined by a PSA increase above 0.1 or 0.2 ng/mL following RP or a PSA rise of 2.0 ng/mL above nadir post-external beam radiotherapy (EBRT);[3] however, if PSA levels persist and do not drop to undetectable levels post-RP, it is indicative of residual disease rather than PSA recurrence.

A rapid rise in PSA is suggestive of a higher risk of distant metastases, whereas a slow rise in PSA more likely reflects local recurrence.[3] High-risk BCR post-RP can be defined as PSADT ≤9 months or a pathologic ISUP grade 4–5 (GS 8–10), and low risk if they have both a PSADT >9 months and an ISUP grade <4 (GS <8). Post-RT, high-risk BCR can be defined as an interval to BCR ≤18 months or a clinical ISUP grade 4–5 (GS 8–10), and low-risk BCR is defined as an interval to BCR >18 months and an ISUP grade <4 (GS <8).[3]

TREATMENT OPTIONS FOR PATIENTS WITH BCR FOLLOWING PRIMARY DEFINITIVE THERAPY

Salvage (s) EBRT after RP

Salvage EBRT is an important treatment option for patients with rising PSA levels after RP. This approach can be curative and may delay the need for long-term ADT.[14] Adjuvant EBRT (aEBRT) and early sEBRT are similarly effective, but aEBRT requires treatment for patients with high-risk features, although more than 50% would never need early salvage RT.[15] aEBRT has higher rates of adverse events (AEs), such as genitourinary and gastrointestinal toxicity, and erectile dysfunction.[16,17] PSA levels and PSADT at the time of sEBRT are crucial prognostic factors.[18,19] The European guidelines recommend sEBRT for high-risk BCR patients with PSA levels ≤0.5 ng/mL.[20] Canadian guidelines suggest consideration of salvage therapy at the earliest possible time when PSA becomes detectable >0.1 ng/mL.[13]

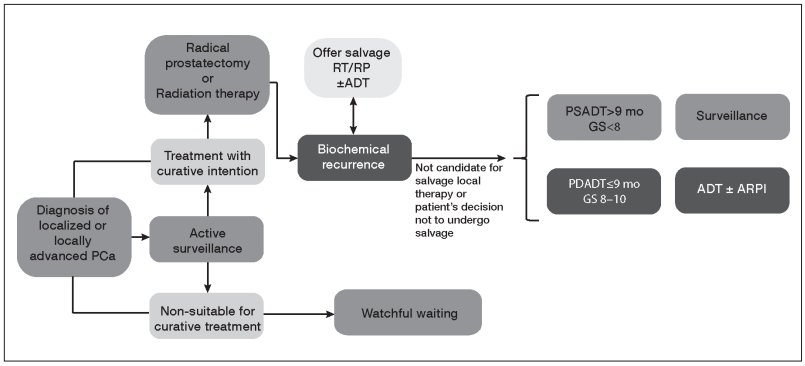

Figure 1. Patient journey to treatment for biochemical recurrence. For patients diagnosed with localized or locally advanced prostate cancer, initial treatment options are guided by factors such as cancer stage, PSA levels, surgical margin and node status, post-RP PSA, genomic classifier risk, PET imaging results, time from local therapy to BCR, ISUP grade group (or Gleason score), and the patient's overall health and preferences. Lower-risk patients may opt for active surveillance, while higher-risk patients are generally advised to pursue curative treatments such as radical prostatectomy or radiation therapy, with or without ADT. Following the initial treatment, patients enter a follow-up phase, which includes regular PSA testing, clinical visits, and imaging studies to monitor for signs of recurrence. For those with biochemical recurrence GS<8 and PSADT >9 months, options include salvage radiation or surgery (with or without ADT). In patients with GS>8 and PSADT ≤9 months, ADT with or without ARPI, is recommended. ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; GS: Gleason score; PCa: prostate cancer; PSADT: prostate-specific antigen doubling time; PSA: prostate-specific antigen; RP: radical prostatectomy; RT: radical therapy.

ADT and sEBRT

ADT has significant AEs, including cardiovascular risks, osteoporosis, sexual dysfunction, and quality of life impacts.[21] Additionally, 20–50% of patients can develop permanent castration with ADT treatments of 6–36 months.[22] Despite these negative effects, ADT can prolong survival in high-risk patients, especially for patients with high-risk disease and long life expectancy.[23] Intermittent ADT (iADT) offers a way to mitigate these AEs while delaying disease progression, and the Canadian PR.7 study confirmed that iADT is not inferior to continuous ADT (cADT) in terms of overall survival (OS) and demonstrated quality-of-life improvements in patients with BCR post-EBRT.[24]

ADT is often combined with sEBRT to reduce the likelihood of disease progression.[21,25] The RTOG 9601 trial demonstrated that the addition of 24 months of bicalutamide to sEBRT significantly improved OS in patients with BCR post-RP (a 25% 12-year absolute benefit; hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.25–0.81 in patients with PSA stratum >1.5 ng/mL); however, the survival benefit of adding bicalutamide was notably observed only in patients with a pre-EBRT PSA level >0.6 ng/mL, highlighting the importance of risk stratification in optimizing treatment strategies.[26,27]

The GETUG-AFU 16 trial found that combining six months of ADT with goserelin and sEBRT significantly improved progression-free survival (PFS) compared to sEBRT alone in patients with BCR. The PFS benefit was seen in both high-risk and low-risk subgroups (120-month PFS was 61% in the sEBRT group vs. 74% in the sEBRT plus goserelin group for patients in the low-risk subgroup, and 43% vs. 60% for patients in the high-risk subgroup), although metastasis-free survival (MFS) was comparable between the treatment groups for both subgroups.[28]

The NRG 0534 (SPPORT) trial evaluated 1792 patients randomized to three treatment arms: sEBRT to the prostate bed alone (arm 1), sEBRT to the prostate bed with six months of ADT (arm 2), or sEBRT to the prostate bed and pelvic lymph nodes with six months of ADT (arm 3). With a median followup of 8.2 years, five-year freedom from progression rates were 70.9%, 81.3%, and 87.4% for arms 1, 2, and 3, respectively. While acute toxicities were higher in arm 3 compared to arm 2 and in arm 2 compared to arm 1, no significant differences in late toxicities were observed.[29]

Life expectancy should also be considered when deciding on ADT, as patients with severe disease and short life expectancy may prefer observation to avoid overtreatment and preserve quality of life.

Surgical and non-surgical salvage treatments after definitive EBRT

Options for localized BCR post-EBRT include salvage RP (sRP), cryotherapy, high-intensity focused ultrasound (HIFU), stereotactic body radiotherapy (SBRT), and brachytherapy.[3] Meta-analyses show similar five-year relapse-free survival rates for these treatment options, with the lowest rates for HIFU.[30] Low-dose-rate (LDR), high-dose-rate (HDR) brachytherapy, and SBRT re-irradiation are associated with late treatment-related grade 2–3 gastrointestinal/genitourinary toxicities.[30-33]

European guidelines suggest sRP for patients with a long life expectancy, low pre-sRP PSA, and no metastases.[20] National Comprehensive Cancer Network guidelines recommend sRP with pelvic lymph node dissection (LND) for highly selected patients in the absence of metastases.[4] Canadian guidelines suggest sRP, brachytherapy, or cryotherapy for patients with a PSA threshold <5 ng/mL and biopsy-proven local recurrence.[13] sRP is associated with a high risk of incontinence and other functional complications; however, recent studies suggest that robot-assisted sRP may reduce adverse outcomes and improve recovery, as well as functional outcomes, compared to open sRP.[34]

SYSTEMIC TREATMENT INTENSIFICATION FOR PATIENTS WITH HIGH-RISK BCR

PSA doubling time and Gleason score are strong predictors of metastases and mortality in patients with

BCR.[35-37] Patients with BCR should be risk-stratified prior to undergoing additional treatments.[11,36]

Recent clinical trials using conventional imaging have underscored the importance of early systemic treatment intensification in patients with high-risk BCR following primary definitive therapy for localized prostate cancer.

The phase 3 randomized control trial EMBARK demonstrated that the second-generation androgen receptor pathway inhibitors (ARPI) enzalutamide, either alone or in combination with ADT, delayed radiographic progression in patients with high-risk BCR who failed locoregional primary and salvage therapies, or that were not candidates for salvage therapies. The interventions were administered intermittently, and treatment was suspended at week 37 if the PSA was below 0.2 ng/mL and restarted upon PSA rise.

The trial reported five-year MFS rates of 87.3% (HR 0.42, 95% CI 83.0–90.6, p<0.001) for the enzalutamide plus leuprolide combination, 80.0% (HR 0.63, 95% CI 75.0–84.1, p=0.005) for enzalutamide monotherapy, and 71.4% (95% CI 65.7–76.3) for leuprolide-alone.[5] An interim analysis also indicated a trend toward improved survival in the combination group. EMBARK also showed that enzalutamide plus ADT and enzalutamide monotherapy preserved health-related quality of life, underscoring the benefits of ARPI treatment.[38]

The phase 3, open label, randomized controlled trial PRESTO demonstrated that adding apalutamide to ADT with or without abiraterone extended PSA-PFS in patients with high-risk BCR without adversely affecting time to testosterone recovery. Specifically, PSA-PFS was 24.9 months for ADT plus apalutamide vs. 20.3 months for ADT alone (HR 0.52, p=0.00047) and 26.0 months for ADT plus apalutamide plus AAP vs. 20 months for ADT alone (HR 0.48, p=0.00008). No other endpoints, such as OS or MFS, were reported for this trial.[6]

These trials collectively highlight the potential benefits of early systemic intensification with hormonal therapies in managing patients with high-risk BCR.

IMAGING FOR PATIENTS WITH BCR AND THE ROLE OF PSMA-PET

PSMA-PET is a more sensitive imaging modality compared to conventional imaging that uses radiolabelled molecules to bind the PSMA surface protein highly expressed in prostate cancer cells.[7,8,39] PSMA-PET imaging allows for earlier detection of metastases and supports the identification of patients who may benefit from early treatment intensification.[8]

The clinical impact of PSMA-PET extends beyond diagnostic accuracy, as clinical management decisions are significantly influenced when using these technologies. In Canada, a PSMA-PET computed tomography (CT) registry observed that imaging-based changes in management occurred in over half of the men imaged within the first two years.[40] The impact was even greater in patients with BCR after primary definitive treatment, with a 62% change in management intent.[41] These findings align with multiple systematic reviews, with meta-analyses indicating that PSMA-PET imaging results in a change in management in over 50% of patients with BCR.

Moreover, BCR-free survival after PET-based management at a median of 20 months post-salvage therapy was 60%, with up to 25% of men achieving a complete biochemical response.[42,43] In a retrospective study where men underwent ^{68}GaPSMA-PET/CT following EBRT or brachytherapy, 75.3% had positive scans despite having pre-scan PSA values below the Pheonix criteria for BCR, nadir +2.0 ng/mL. In this subgroup, 52.1% of patients were identified as suitable candidates for salvage therapy.[44] Finally, it was shown that molecular imaging helps clinicians identify patients who may benefit from ADT intensification in a prospective cohort of patients who were candidates to salvage RT after RP.[45] These results highlight the clinical value of PSMA-PET imaging in the management of patients with BCR.

Despite the demonstrated superiority of detecting metastatic lesions, the clinical application of PSMA-PET faces several challenges. There is low sensitivity of PSMA-PET to detect lesions when PSA ≤0.2 ng/mL after RP (plus/minus sRT). Ontario PREP registry data observed the PET positivity rate was 26% (38 of 148 men) for PSA ≤0.2 ng/mL, 41% (89 of 216 men) for PSA >0.2 ng/mL and ≤0.4 ng/mL, and 55% (33 of 60 men) for PSA >0.4 ng/mL and <0.5 ng/mL.[46]

Clear guidance on interpreting PSMA-PET results and managing patients accordingly is lacking, and few studies have validated PSMA-PET-positive findings. Evidence on how these findings impact patient outcomes is limited, with most studies being retrospective or having short followup periods.[47] The limited availability of PSMA-PET in Canada further complicates its routine use in clinical practice, posing a significant barrier to widespread adoption.[40] In Canada, PSMA-based imaging is categorized under investigational new drug, limiting its use.[40] To address these challenges, practical guidance on the appropriate use of PSMA-PET in high-risk BCR patients is essential.

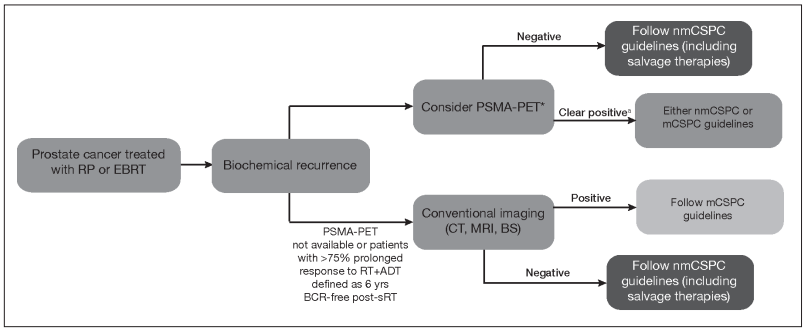

Figure 2. Management of patients with biochemical recurrence based on imaging results. Patients with high-risk BCR may be candidates for PSMA-PET imaging. For patients showing clear metastatic disease on PSMA-PET, combined with aggressive clinical features, treatment may follow either nmCSPC or mCSPC guidelines. If PSMA-PET is unavailable, treatment decisions should rely on conventional imaging and clinical nomograms. Positive findings on conventional imaging should be managed according to mCSPC guidelines, while negative results should follow nmCSPC guidelines. BS: bone scan; CT: computed tomography; EBRT: external beam radiation therapy; mCSPC, metastatic castration-sensitive prostate cancer; MRI: magnetic resonance imaging; nmCSPC: non-metastatic castration-sensitive prostate cancer; PSMA-PET: prostate-specific membrane antigen positron emission tomography; RP: radical prostatectomy.

PRACTICAL GUIDANCE AND CONSIDERATIONS

Several key considerations can be taken into account when determining the best approach for patients with high-risk BCR. The following considerations are not guideline statements but instead outline factors clinicians may consider when managing a patient with high-risk BCR.

Consideration #1

Given the heterogeneity in clinical practice and the limited availability of PSMA-PET in Canada, a key consideration for ordering a PSMA-PET is whether the information it provides will influence the treatment approach. For patients with rapidly rising PSA following primary definitive therapy, immediate treatment may be necessary, bypassing PSMA-PET if it is not readily available. For patients with a high probability of response to sRT calculated by validated nomograms, such as the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram, PSMA-PET could also be omitted.

Consideration #2

If a patient with high-risk BCR is negative for metastatic disease on conventional imaging but is positive for nodal or extranodal metastatic disease on PSMA-PET (with aggressive clinical features), the patient could either be managed as a patient with nmCSPC, or mCSPC (Figure 2). The decision to upstage the patient to mCSPC should be a shared decision with the patient, as upstaging will lead to lifelong ADT but also offer additional treatment options.

Consideration #3

For patients with non-metastatic high-risk prostate cancer with BCR that have failed locoregional primary and salvage therapies, the goal is to delay progression to metastasis and improve survival without exposing patients to unnecessary toxicity. Given the MFS benefit observed with enzalutamide alone or in combination with leuprolide in the EMBARK trial, and the PSA-PFS observed when adding apalutamide to ADT in the PRESTO trial, adding an ARPI to ADT has become a potential treatment option for these patients. Intensifying with an ARPI should be a shared decision with these patients and may be favored in patients with good life expectancy.

Consideration #4

A potential therapeutic option to minimize toxicity without sacrificing efficacy could involve drug holidays. The EMBARK trial investigated this by suspending treatment at week 37 if PSA levels were undetectable (<0.2 ng/mL), with resumption upon PSA increase. Results showed that treatment was suspended in 91% of patients on enzalutamide plus leuprolide for a median of 20.2 months, 68% on leuprolide alone for a median of 16.8 months, and 86% on enzalutamide monotherapy for a median of 11.1 months. Upon re-initiation, 96% of patients on the combination therapy achieved undetectable PSA levels, compared to 73% on leuprolide alone and 90% on enzalutamide monotherapy.

This approach paves the way for intermittent systemic intensification strategies. Drug holidays may reduce the AEs and financial cost of continuous therapy without sacrificing treatment efficacy, while also improving quality of life.[47] If a drug holiday is to be considered, initial treatment with ADT and enzalutamide is recommended based on available phase 3 data.

CONCLUSIONS

Prostate cancer remains a significant health challenge globally, with substantial incidence and mortality rates. Efforts to identify and define patients with high-risk features, combined with sporadic access to advanced imaging techniques, have added complexity to the management of patients with non-metastatic high-risk BCR.

Recent clinical trials in this patient population have demonstrated improved patient outcomes with treatment intensification and the potential therapeutic option of a drug holiday. Continued research and clinical trials are essential for refining treatment strategies and integrating advanced imaging.

COMPETING INTERESTS: Dr. Kollmannsberger has participated in advisory boards for AbbVie, Astellas, Bayer, BMS, BionTech, Eisai, Ipsen, Janssen, Merck, Novartis, and Pfizer; has received honoraria for presentations from AbbVie, Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, Novartis, and Pfizer; and has been a PI or co-PI for clinical trials supported by AbbVie, Astellas, Bayer, BMS, BionTech, Eisai, Ipsen, Janssen, Merck, Novartis, Pfizer, and Roche. Dr. Loblaw has participated in advisory boards for and received honoraria/consulting fees from Astellas, Bayer, J&J, Knight, Sumitomo, Tersera, and Tolmar; has received grants from Astellas, Tersera, and Tolmar; and holds a leadership position with Cure Prostate Cancer Canada Foundation. Dr. Pouliot has participated in advisory boards for Amgen, Astellas, AstraZeneca, Bayer, Merck, Novartis, Pfizer, Roche, Tersera, and Tolmar; has received honoraria from Amgen, Astellas, AstraZeneca, Bayer, Merck, Novartis, Pfizer, Roche, Tersera, and Tolmar; holds investments in Allogene Therapeutics; and is on the boards of the U.S. National Cancer Institute (NCI) Prostate Cancer Task Force, Canadian Urologic Oncology Group, and the GU Trial Development Group-Canadian Clinical Trial Group (CCTG). Dr. Rendon has participated in advisory boards for, is a speakers' bureau member for, and has received honoraria from AbbVie, Amgen, Astellas, Astra Zeneca, Bayer, BMS, EMD Serono, Ferring, Jansen, McKesson, Pfizer, Tersera, and Tolmar; has received honoraria/grants from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, McKesson, Pfizer, Tersera, and Tolmar; holds investments in Myovant; and has participated in clinical trials supported by AAA/Novartis, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Myovant, Pfizer, and Point Biopharma. Dr. Saad has participated in advisory boards for and has received payment/honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Janssen, Merck, Novartis, Pfizer, Tersera, and Tolmar; and has participated in clinical trials supported by AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, ESSA, Janssen, Merck, Novartis, Pfizer, Point Biopharma, Tersera, and Tolmar. The remaining authors do not report any competing personal or financial interests related to this work.

ACKNOWLEDGEMENTS: The authors thank CTC Communications Corporation (Mississauga, Canada) for professional medical writing support.

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