Consensus Recommendations for the Management of High-Risk Biochemical Recurrence in Prostate Cancer

A Modified Delphi Study by the Arab Association of Urology

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Abstract

Biochemical recurrence (BCR) after radical prostatectomy (RP) or radiotherapy (RT) is common and biologically heterogeneous, yet definitions and management strategies remain inconsistent across clinical practice. A multidisciplinary panel of regional experts convened to develop consensus recommendations for the definition, risk stratification, imaging, and treatment of high-risk BCR. The group reviewed contemporary evidence on PSA kinetics, Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography (PSMA PET/CT), androgen deprivation therapy (ADT) strategies, novel androgen receptor pathway inhibitors (ARPIs), and local salvage options. A modified Delphi process was used to draft, refine, and vote on candidate statements, with consensus defined a priori as ≥80% agreement. The panel defined high-risk BCR primarily by PSA kinetics, with a Prostate-Specific Antigen Doubling Time (PSADT) ≤9 months as the core criterion, in combination with post-RP PSA ≥1 ng/mL or post-RT PSA ≥2 ng/mL above nadir and/or adverse pathological features. PSMA PET/CT was endorsed as the preferred imaging modality for staging and localizing disease in BCR, given its superior detection rates and impact on salvage radiotherapy planning and metastasis-directed strategies. For systemic treatment, the group supported intermittent ADT in appropriately selected non-metastatic high-risk BCR and recommended enzalutamide plus ADT as a standard of care in men meeting high-risk criteria, with enzalutamide monotherapy as an alternative for those unable or unwilling to receive castration-based therapy, within a structured monitoring framework. Implementation recommendations emphasized multidisciplinary team management and the need for supportive reimbursement and formulary pathways to ensure equitable access to advanced imaging and ARPIs. Adoption of these recommendations, coupled with ongoing research into optimal sequencing and real-world implementation, may help standardize care and improve long-term outcomes for men with high-risk BCR.

Keywords: Prostate Cancer, High-risk Biochemical recurrence, Prostate-Specific Membrane Antigen, androgen deprivation therapy, enzalutamide

1. Introduction

Prostate cancer (PC) represents a significant global health burden, standing as the most common solid organ malignancy for men in many parts of the world and a leading cause of cancer-related mortality [1,2]. Following primary definitive therapy with radical prostatectomy (RP) or radiation therapy (RT), a substantial proportion of men, estimated at 20–40%, will experience a biochemical recurrence (BCR) [3,4]. BCR, defined by a rising prostate-specific antigen (PSA) level, often precedes clinically detectable metastatic disease by several years [5]. However, it is a critical prognostic marker; the development of BCR is strongly associated with a heightened risk of distant metastasis, reduced metastasis-free survival (MFS), and increased PC–specific mortality [6,7]. The natural history following BCR is heterogeneous, largely dictated by factors such as Gleason score at diagnosis, time from primary therapy to recurrence, and the kinetics of the PSA rise [5].

The management of BCR is complicated by a historical lack of consensus on its fundamental definition. Major international guidelines have proposed different criteria; for instance, the American Urological Association (AUA) has defined BCR post-RP as a PSA ≥0.2 ng/mL with a subsequent confirmatory value, whereas post-RT recurrence is often defined by the ASTRO-Phoenix criteria as a rise of ≥2 ng/mL above the PSA nadir [8,9]. This heterogeneity creates challenges in comparing clinical trial outcomes and standardizing patient care.

Furthermore, the term “high-risk” BCR, which identifies patients most likely to progress and benefit from early systemic therapy, lacks a universally accepted definition. Risk stratification often relies on a combination of PSA doubling time (PSADT), absolute PSA values, and primary tumor pathology, but the specific cut-offs used vary across guidelines and clinical trials [5,9]. This inconsistency can lead to variable timing for the initiation of imaging and treatment, complicating trial eligibility and making it difficult to provide clear prognostic counsel to patients. To address

these limitations and provide a pragmatic framework for modern management, a clear and clinically meaningful definition of both BCR and high-risk BCR is required.

The landscape of BCR management is rapidly evolving, driven by two major advances: the widespread adoption of highly sensitive prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) imaging and the emergence of novel, potent androgen-receptor pathway inhibitors (ARPIs) [10,11]. Data from recent phase III clinical trials have established new standards of care, demonstrating significant improvements in MFS for patients with high-risk BCR treated with intensified systemic therapy [12]. This consensus initiative was convened to synthesize this new evidence and address the existing ambiguities in the field. The objectives were to develop a set of clear, evidence-based, and regionally relevant recommendations for the definition, diagnostic work-up, systemic and local treatment strategies, and practical implementation of care for patients with high-risk BCR.

2. Methods

An expert panel was convened, comprising seven urologists from the Arab Association of Urology (AAU), with recognized expertise in the management of PC. Members were selected from diverse geographic regions and practice settings (academic and community-based) to ensure the final recommendations would be broadly applicable. The scope of this consensus was strictly limited to the management of patients with high-risk BCR following definitive local therapy (RP or RT) for non-metastatic PC. The management of de novo metastatic disease or low-risk BCR was outside the scope of this project. A comprehensive literature review was conducted to inform the development of the consensus statements. Searches were performed in PubMed, MEDLINE, and the Cochrane Library for articles published up to October 2025. Key search terms included "prostate cancer," "biochemical recurrence," "PSA recurrence," "salvage therapy," "PSMA PET,"

"androgen deprivation therapy," "intermittent," "enzalutamide," "apalutamide," and "darolutamide." Priority was given to evidence from phase III randomized controlled trials, high-quality prospective and retrospective observational cohorts, systematic reviews, meta-analyses, and major international guideline documents relevant to the diagnosis and management of high-risk BCR.

A modified two-round Delphi approach was employed to achieve consensus. An initial set of draft statements was developed by a steering committee based on the literature review. These statements were then distributed electronically to the entire expert panel for anonymous voting in the first round. Panelists indicated their response to each statement by selecting one of three options: Agree, Abstain, or Disagree. A pre-specified consensus threshold was set at ≥80% agreement. Panelists were also invited to provide open-text comments and suggest modifications for each statement. Statements that did not reach the consensus threshold or those with significant qualifying comments were revised by the steering committee. The revised statements, along with a summary of the first-round voting results and anonymized comments, were then circulated for a second and final round of voting.

3. Results and Discussions

A total of 13 statements were developed and discussed. Of these, 9 statements achieved 100% consensus and 4 achieved 86% consensus, all meeting the pre-specified threshold (**Table 1**).

3.1. Definition and Risk Stratification of High-Risk BCR

3.1.1. Consensus definition of BCR

BCR after definitive local therapy is traditionally defined by rising PSA in a patient whose PSA initially became undetectable after RP or reached a post-radiotherapy nadir. Contemporary

guidelines from AUA/ASTRO/SUO and other societies commonly define BCR after RP as a PSA ≥0.2 ng/mL confirmed by a second value, while after external-beam radiotherapy (EBRT) the Phoenix definition (nadir + 2.0 ng/mL) is widely accepted as the standard criterion for biochemical failure [13,9]. However, these thresholds were developed in the era of less sensitive PSA assays and primarily for prognostication, and there is increasing recognition that earlier PSA rises below 0.2 ng/mL may still herald clinically relevant recurrence, particularly in men at higher risk of progression. Recent guidance on salvage therapy after RP explicitly acknowledges that men with a detectable ultrasensitive PSA that does not yet meet the classic ≥0.2 ng/mL definition may nonetheless warrant evaluation and consideration of early salvage strategies [13]. In the view of this background, and recognizing the widespread clinical use of ultrasensitive PSA in the Gulf region, the panel agreed to adopt a more sensitive working definition for this consensus, whereby BCR after RP is defined as an undetectable PSA with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or that increases to PSA >0.1 ng/mL. Following RT, with or without HT, BCR is defined as a PSA level ≥2 ng/mL above the nadir (**Statement 1**).

3.1.2. Defining high-risk BCR

Risk stratification of BCR patients is critical for determining the appropriate intensity of salvage treatment, as long-term outcomes vary substantially according to PSA kinetics and pathological features [14]. A short PSADT after primary therapy is considered the most robust prognostic factor for adverse outcomes and is independently associated with an increased risk of distant recurrence, metastatic progression, and PC-specific mortality [15,16]. In this context, a rapid PSADT of ≤15 months signals an urgency for intervention [17], and high-risk BCR is generally defined by a PSADT ≤12 months [18], while trials targeting the most aggressive disease, such as EMBARK, have employed a stricter threshold of ≤9 months combined with a screening PSA ≥2 ng/mL above

nadir after radiotherapy or ≥1 ng/mL after RP and have demonstrated substantial MFS benefit with enzalutamide-based therapy in this population. In the post-RP setting, even relatively low but rising PSA values are prognostically important. A PSA ≥0.5 ng/mL is an independent predictor of metastatic disease in men with PSADT <12 months, and a PSA ≥0.7 ng/mL is frequently used as a practical high-risk threshold when considering systemic augmentation of salvage therapy [13,18]. Guideline-based schemas are concordant with this PSA- and pathology-driven approach: the EAU defines high-risk post-RP BCR by PSADT ≤1 year or pathological Grade Group (GG) 4–5 (Gleason score 8–10) , and high-risk post-RT by a short interval to biochemical failure (IBF) ≤18 months or biopsy GG 4–5 [19,20]. On the other hand, the NCCN classifies high-risk disease based on initial PSA ≥20 ng/mL, clinical T3 stage, and Gleason score ≥8, noting that patients with two or more of these factors have a markedly increased hazard of subsequent BCR [21]. Consistent with this body of evidence and the EMBARK high-risk definition, our expert panel agreed that high-risk BCR should be defined primarily by PSA kinetics, with PSADT ≤9 months as the core criterion; in our framework, patients with a post-RP PSA ≥1.0 ng/mL or a post-RT PSA ≥2.0 ng/mL above nadir and PSADT ≤9 months, particularly when accompanied by adverse pathological features (e.g. pT3 disease, positive margins, or Gleason Grade Group ≥3), are considered to have high-risk BCR and to warrant early, proactive consideration of systemic therapy and/or intensified local treatment (**Statement 2**).

3.2. Diagnostic Evaluation and Imaging

3.2.1. Role and limitations of conventional imaging

Conventional imaging techniques, including computed tomography (CT) and bone scintigraphy, have a low diagnostic yield for detecting recurrent PC, particularly at low PSA levels characteristic of early BCR [22,3,23]. For bone scans, the likelihood of a positive finding is low, specifically less

than 5% when the PSA level is below 7 ng/mL following RP [24,25]. Similarly, CT scans exhibit low sensitivity, detecting local recurrence or lymph node metastases in only approximately 11−14% of patients within this lower PSA range [25,26]. Historically, the low sensitivity of conventional imaging in the BCR setting frequently led to the misclassification of many high-risk patients as having "non-metastatic" disease, underestimating the true extent of cancer spread [19]. This inherent technical limitation is insufficient for guiding modern, precision-focused treatment decisions, as accurate anatomical and pathological localization is critical for optimizing salvage RT (SRT) planning or identifying candidates for metastasis-directed therapy (MDT) [22].

3.2.2. PSMA PET/CT as the preferred imaging modality in BCR

PSMA PET/CT has revolutionized the diagnostic evaluation of BCR due to its significantly superior sensitivity for disease localization compared to conventional imaging modalities (CT and bone scintigraphy) [27–29]. The efficacy of PSMA PET/CT detection is directly correlated with the measured PSA level. Detection rates range from 50% to 60% even within the critical salvage window, where PSA is <0.5 ng/mL, a performance rate superior to that of other conventional imaging modalities and earlier PET tracers like choline PET/CT [29–31]. Even at ultra-low PSA levels (≤0.2 ng/mL) following RP, the pooled detection rate remains substantial at 29.6% [32]. In prospective BCR cohorts with negative or equivocal conventional imaging, ^{18}F-DCFPyL PET/CT (CONDOR study) and other PSMA ligands have demonstrated high localization rates (typically >80%) and generated “clinically meaningful and actionable” findings that directly alter salvage treatment plans [27].

Integration of PSMA PET/CT findings is therefore critical for guiding precise therapeutic decision-making. Detailed lesion localization is indispensable for customizing salvage radiotherapy (SRT), informing whether to treat the prostate bed alone or to extend fields to include

PSMA-positive pelvic lymph nodes [22], and its sensitivity for low-volume (oligometastatic) disease underpins the use of metastasis-directed therapy (MDT), typically with stereotactic body radiotherapy (SBRT), to ablate discrete lesions and delay the need for continuous systemic therapy [33]. Practical considerations include the timing of imaging; ideally, PSMA PET/CT should be performed before initiating new androgen deprivation therapy (ADT), as hormonal suppression may reduce PSMA expression and diminish diagnostic sensitivity [34,35]. Currently available PSMA radiotracers, such as ^{68}Ga-PSMA-11, ^{68}Ga-PSMA I&T, and ^{18}F-PSMA-1007, demonstrate broadly comparable detection performance in the ultra-low PSA setting. Importantly, a negative PSMA PET/CT, particularly at low PSA levels, does not rule out microscopic disease, and curative-intent SRT should generally proceed in high-risk patients with adverse prognostic features even in the absence of visible lesions [13]. Reflecting this evidence, recent AUA/ASTRO/SUO and EAU guidance recommend PSMA PET/CT as the most sensitive modality for detecting biochemically recurrent disease and emphasize its central role in recurrent staging and treatment planning [13,36]. On this basis, and consistent with the broader evidence base, the expert panel agreed that PSMA PET/CT should be regarded as the preferred imaging modality for staging and localizing disease in patients with BCR, offering superior detection rates and clinically impactful information compared with conventional imaging (**Statement 3**).

3.3. Management of High-risk BCR

3.3.1. Goals of therapy and general treatment framework in BCR

In men with BCR after definitive local therapy, the principal management goals are to delay metastasis and PC-specific mortality, minimise disease-related symptoms, and preserve health-related quality of life (QoL), while avoiding overtreatment in those with indolent disease [37]. Contemporary reviews and guidelines emphasise that BCR represents a heterogeneous state in

which long-term outcomes are driven by PSA kinetics, pathological risk factors, and the timing and pattern of recurrence, rather than PSA alone. Accordingly, treatment intensity should be tailored to individual risk; low-risk patients may be safely managed with surveillance or local salvage alone, whereas high-risk BCR warrants earlier consideration of systemic therapy [38]. In this framework, SRT with or without ADT is the preferred approach for eligible men after RP, while after primary radiotherapy, further local salvage, systemic treatment, or clinical trial enrolment is considered according to risk stratification and modern imaging findings [13]. Overall, management decisions in BCR should integrate risk category, comorbidities, life expectancy, imaging (including PSMA PET/CT), and patient preferences to balance oncologic benefit against the long-term toxicities of systemic therapy.

3.3.2. ADT Strategies in BCR

Intermittent versus continuous ADT in BCR: Several randomised trials and meta-analyses have compared intermittent ADT (IADT) with continuous ADT (CAD) in men with non-metastatic or BCR PC. The landmark NCIC CTG PR7 trial randomised 1,386 men with a rising PSA (>3 ng/mL) more than one year after radiotherapy to intermittent versus continuous ADT and demonstrated non-inferiority of IADT for overall survival, with better erectile function and mental health scores during off-treatment periods [39]. Additionally, a systematic review, including pooled analysis of non-metastatic and BCR populations, reports no significant difference in overall survival between IADT and CAD, while highlighting potential quality-of-life advantages (sexual function, physical well-being) and reduced treatment exposure with IADT [40]. IADT results in superior patient-reported outcomes (PROs), with improvements in specific functional domains, such as sexual activity and physical functioning, and reduced hot flashes, primarily mediated by partial testosterone recovery during off-treatment cycles [41]. Furthermore, population-based cohort

studies strongly support the safety profile of I-ADT concerning chronic morbidities, demonstrating a significantly lower risk of fractures (HR 0.52) and serious cardiovascular events, particularly heart failure (HR 0.62), compared to C-ADT [42]. A recent narrative review on BCR management similarly concludes that IADT is an acceptable alternative to continuous therapy in appropriately selected men, especially those with higher-risk BCR but without radiographic metastases, provided that patients are closely monitored and restarted on therapy when predefined PSA or clinical criteria are met.

Treatment interruption after response to ADT: Treatment interruption, often termed a drug holiday, following an induction phase allows clinicians to mitigate the cumulative long-term toxicity and burden of therapy while maintaining durable disease control [43]. This approach was successfully integrated into the design of the Phase 3 EMBARK trial, which used intensified systemic therapy (Enzalutamide plus ADT) for high-risk BCR. The trial protocol defined an induction duration of 37 weeks (approximately 9 months) of therapy. If patients achieved a deep and favorable PSA response, specifically a nadir PSA <0.2 ng/mL (post-RP), treatment could be safely suspended [12]. This intermittent approach maximized QoL by providing extended treatment-free intervals (median up to 20.2 months for combination responders), demonstrating that early, intensive therapy can achieve durable disease suppression that permits subsequent periods off treatment. This strategy significantly benefits patients by substantially reducing cumulative exposure to chronic ADT toxicities (e.g., bone density loss and cardiovascular risk) [44]. Achieving this deep PSA response after the initial induction phase allows for safe treatment breaks without compromising overall survival benefits. Clinicians should therefore offer ADT interruption (i.e., a drug holiday) to patients with BCR who achieve a nadir PSA <0.2 ng/mL after approximately 36 weeks of induction therapy, as this approach maintains therapeutic effectiveness

and enhances patient QoL (**Statement 4**). This approach is specifically useful for managing non-metastatic BCR following RT, serving as a reasonable option for patients who wish to minimize side effects (**Statement 5**)

Criteria for discontinuing intermittent ADT and resuming therapy: The decision to discontinue IADT is based on progression markers, including rising PSA kinetics, the appearance of new or progressing lesions on imaging, or the emergence of intolerable side effects. Monitoring absolute PSA thresholds is critical for triggering the return to therapy for patients treated under intermittent protocols like EMBARK [12]. Treatment is typically resumed when PSA levels rise to predefined, high thresholds:≥2.0 ng/mL following RP or ≥5.0 ng/mL following RT (**Statement 6**). Furthermore, the observation of definitive radiographic progression should prompt a shift in management strategy. Ignoring these progression signals while continuing ineffective ADT exposes the patient to the accumulated burden of toxicity, such as bone density loss and cardiovascular risk, without achieving any meaningful oncologic benefit [45,46]. Moreover, a continuous, albeit ineffective, exposure to hormonal treatment accelerates the time to Castration-Resistant PC (CRPC) and depletes future therapeutic options [47]. Thus, prompt resumption or alteration of therapy based on defined triggers is crucial to maintaining therapeutic benefit and preserving future treatment effectiveness.

3.3.3. Indications for prostate re-irradiation

In men with high-risk BCR after definitive RT, local salvage may be considered when recurrence is confirmed as viable intraprostatic/prostate-bed disease on biopsy and comprehensive imaging ensures no distant metastases, preferably with PSMA PET/CT to localize recurrence and exclude M1 disease. PSMA PET/CT data in high-risk BCR indicate that, even with adverse PSA kinetics,

a considerable subset of patients (20-30%) have recurrence confined to the prostate/prostate bed or pelvis [48], supporting consideration of curative-intent local salvage rather than defaulting to immediate lifelong systemic therapy [13]. Available salvage modalities include salvage RP (sRP), cryoablation, high-intensity focused ultrasound (HIFU), and contemporary re-irradiation approaches (high- or low-dose-rat [HDR/LDR] brachytherapy or SBRT), with selected-series outcomes suggesting 5-year biochemical/relapse-free survival of approximately 50–60%, broadly comparable across re-irradiation and ablative strategies in appropriately selected patients [49].

The key challenge in this high-risk, previously irradiated population is balancing oncologic benefit with the risk of late genitourinary (GU) and gastrointestinal (GI) toxicity. A recent systematic review and meta-analysis reported that salvage re-irradiation (SBRT or brachytherapy) is associated with lower rates of severe GU toxicity (approximately 5.6–9.6%) compared with ablative modalities such as sRP or HIFU, where grade ≥3 GU events of 21–23% have been described, while maintaining similar long-term local control [49]. Modern focal or partial-gland approaches, adherence to strict cumulative dose constraints, and careful patient selection are essential to minimise toxicity. Given the complexity and potential morbidity of retreatment after RT, these decisions should be made in a multidisciplinary setting and embedded within shared decision-making, with clear discussion of benefits, risks, and alternatives. In line with this evidence, the expert panel concluded that prostate re-irradiation (using SBRT or brachytherapy) may be offered to highly selected, non-metastatic high-risk BCR patients with biopsy- and/or PSMA PET/CT–confirmed local recurrence after prior RT, following multidisciplinary review and thorough counselling regarding potential late toxicity **(Statement 7).**

3.3.4. Novel ARPIs in High-Risk BCR

Enzalutamide plus ADT as standard of care in high-risk BCR (Statement 8)

The phase III EMBARK trial established ARPI with enzalutamide plus ADT as a new standard of care for men with high-risk, non-metastatic castration-sensitive PC presenting with BCR [12]. In EMBARK, 1,068 patients with high-risk BCR (PSADT ≤9 months and PSA ≥2 ng/mL above nadir after radiotherapy or ≥1 ng/mL after prostatectomy) were randomised to enzalutamide plus leuprolide, enzalutamide monotherapy, or leuprolide alone [12]. Enzalutamide plus leuprolide significantly improved MFS versus leuprolide alone, with a hazard ratio (HR) for metastasis or death of 0.42 (95% CI 0.30–0.61), and 5-year MFS rates of 87.3% vs 71.4%, respectively [12]. Moreover, enzalutamide plus leuprolide significantly improved overall survival (OS). In the recent OS analysis presented at ESMO Congress 2025, 8-year OS was 78.9% (95% CI, 73.9–83.1) with enzalutamide–leuprolide versus 69.5% (95% CI, 64.0–74.3) with leuprolide alone; 73 versus 111 deaths occurred, corresponding to a stratified HR for death of 0.60 (95% CI, 0.44–0.80; P=0.0006) and a 40% relative reduction in mortality risk [50]. This efficacy positions the doublet therapy superiorly to older systemic strategies; notably, enzalutamide is the only ARI-based regimen proven to extend OS in nmHSPC with high-risk BCR, a benefit previously uncertain or modest with older antiandrogens like bicalutamide, which provided a lower absolute OS improvement over observation alone in the salvage setting [51]. Taken together, these data support enzalutamide plus ADT as the preferred systemic option for men with high-risk BCR who are candidates for intensified ARI. In line with this evidence, the expert panel endorsed enzalutamide plus ADT as a standard-of-care systemic strategy for high-risk BCR (**Statement 8**), while acknowledging the need to individualize use based on comorbidities, tolerability, and patient preference.

Enzalutamide monotherapy as an alternative strategy: Enzalutamide monotherapy is a viable option for patients with high-risk BCR who may be intolerant to, or wish to avoid, the full side-effect profile of standard ADT. In the EMBARK trial, ENZA monotherapy demonstrated superiority over ADT alone for MFS (HR 0.63; P=0.005), achieving a 5-year MFS rate of 80.0% compared with 71.4% for ADT alone. While ENZA monotherapy significantly delayed the time to metastasis, the improvement in OS trended favorably but did not reach statistical significance compared to ADT alone [12]. The main advantage of this strategy is its differentiated tolerability profile, as testosterone levels are largely preserved, patients experience fewer classical castration-related symptoms such as severe hot flushes, loss of libido, and marked bone demineralization, although enzalutamide monotherapy introduces a distinct spectrum of AR-targeted toxicities, including gynecomastia, breast tenderness, fatigue, and hypertension, which must be carefully discussed and monitored [12,52,53]. In high-risk BCR, this trade-off may be particularly attractive for men who priorities preservation of sexual function and refuse or cannot tolerate LHRH therapy, provided they are suitable for close surveillance of PSA kinetics and cardiovascular/metabolic risk factors [54]. Emerging analyses from EMBARK further suggest that PSA nadir depth and time to nadir under enzalutamide are powerful prognostic markers, supporting the rationale for future intermittent, PSA-guided enzalutamide-based strategies (with or without background ADT) analogous to established intermittent ADT paradigms [55]. On this basis, the expert panel concluded that enzalutamide monotherapy is a reasonable alternative to enzalutamide plus ADT for carefully selected high-risk BCR patients who decline or cannot tolerate castration-based therapy, provided its use is embedded within a structured follow-up framework with predefined PSA- and imaging-based triggers for treatment adaptation (**Statement 9**), and if patients achieved a deep PSA response (<0.2 ng/mL) after approximately 36 weeks of therapy, treatment suspension

(intermittent therapy) could be guided by this response, maintaining a significant MFS benefit (**Statement 10**).

Safety, tolerability, and monitoring of enzalutamide: Enzalutamide plus ADT, while highly effective for high-risk BCR, is associated with a distinct profile of adverse events (AEs) that require proactive management. Common treatment-emergent AEs (≥10% incidence) include fatigue and hot flashes [12]. More serious risks target cardiovascular and bone health: pooled randomized trials indicated that 14.2% of enzalutamide-treated patients developed hypertension compared to 7.4% on placebo, and enzalutamide carried an increased risk of ischemic heart disease [12]. Furthermore, falls occurred in 12% of patients receiving enzalutamide versus 6% on placebo, and fractures occurred in 13% versus 6%, respectively [12]. Rarer but severe events include seizures (occurring in 0.6% of patients, with a rate of 2.2% in those with predisposing factors) and reports of Posterior Reversible Encephalopathy Syndrome (PRES) [12]. To mitigate these risks, management must prioritize consistent monitoring, meaning that clinicians should perform a DEXA scan at the start of enzalutamide plus ADT (and routinely thereafter, at least every two years if bone-protective agents are not used) to evaluate fracture risk [36,56,57]. Cardiovascular and metabolic monitoring should occur every three to six months, including checks of blood pressure (BP), fasting glucose, HbA1c, and blood lipid levels [36]. Management of pre-existing cardiovascular risk factors (e.g., hypertension, diabetes) must be optimized to reduce the risk of ischemic heart disease. Finally, due to potential drug interactions (e.g., involving CYP3A4, CYP2C9, and CYP2C19 enzymes), co-administration of certain medications should be avoided or monitored closely. By employing regular monitoring and proactive management of common toxicities, enzalutamide is generally well tolerated during long-term therapy (**Statement 11**).

3.4. Health-System and Implementation Considerations

Effective management of high-risk BCR relies on the ability to deliver proven systemic therapies, such as enzalutamide plus ADT, which has demonstrated significant benefits in MFS and OS [12,50]. Analyses of this intensified combination therapy have established a robust health-economic justification, demonstrating significantly higher Quality-Adjusted Life Years (QALYs) (8.96 QALYs) compared to ADT monotherapy (6.24 QALYs) over a 30-year horizon [58]. However, realizing this long-term patient value requires overcoming substantial implementation challenges related to equitable access and cost coverage for novel agents and the sophisticated diagnostics (like PSMA PET/CT) needed for appropriate patient selection. The value of precision diagnostics, for instance, has also been shown to be maximized when applied early (PSA 0–1.99 ng/mL), yielding more favorable cost-effectiveness ratios (ICER of $39,730/QALY) than later applications (ICER over $144,000/QALY), supporting the early use of novel technologies [59]. This cost disparity emphasizes the critical need for aligning formulary inclusion and reimbursement policies with the clinical evidence derived from high-risk BCR trials (such as EMBARK) to ensure that the proven survival advantages are not limited to specific populations or practice settings (**Statement 12**). Equitable deployment of enzalutamide, therefore, requires supportive reimbursement policies and formulary inclusion across diverse practice settings to ensure timely access to these evidence-based treatments.

3.5. Multidisciplinary team–based management

Multidisciplinary Team–based management is strongly recommended for patients with high-risk BCR to ensure individualized, evidence-based care. The complex nature of high-risk BCR, characterized by nuanced risk stratification (e.g., integrating PSADT and Grade Group) and the

proliferation of advanced diagnostic imaging, necessitates the integrated expertise provided by a multidisciplinary team. Multidisciplinary team consultation ensures that diagnostic findings, particularly the detection of occult systemic disease (miM1 status) via highly sensitive PSMA PET/CT, are correctly interpreted and translated into optimal treatment sequencing, such as integrating local SRT, MDT, and systemic intensification strategies. The core composition of an effective multidisciplinary team for high-risk BCR must at a minimum include expertise from urology, radiation oncology, and medical oncology (**Statement 13**). Depending on institutional resources and the complexity of the specific patient case, this core team should be augmented by specialists, including radiology, nuclear medicine, and pathology experts, to accurately stage disease, as well as supportive care or geriatric oncology specialists to address the significant physical and quality of life burdens associated with long-term therapy. This approach ensures that competing risks, such as managing long-term side effects and balancing patient preferences between intermittent and continuous therapy, are comprehensively addressed, maximizing the potential for durable control while preserving patient health and function.

4. Future directions and research priorities

Despite substantial advances in imaging and systemic therapy, high-risk BCR remains a heterogeneous and incompletely defined disease state, and several key questions emerged during the consensus process. Long-term follow-up of EMBARK and other ARPI studies will be essential to clarify the durability of metastasis-free and overall survival benefits, the optimal duration of enzalutamide-based therapy, and evidence-based sequencing once progression occurs on enzalutamide + ADT or monotherapy [60]. Current practice largely extrapolates from metastatic hormone-sensitive and non-metastatic castration-resistant settings, yet robust data on post-

enzalutamide sequencing in high-risk BCR are lacking. Existing evidence on timing and intensity of ADT in BCR also remains mixed, underscoring the need for modern trials that integrate risk stratification by PSADT, contemporary imaging, and quality-of-life end points, and that prospectively evaluate continuous versus intermittent ARPI-based strategies rather than ADT alone [41,61,62].

The widespread adoption of PSMA PET/CT has identified a growing cohort of men with oligometastatic or loco-regional recurrence at low PSA levels, but the optimal management of PSMA-defined disease remains unclear. Early randomised trials such as STOMP and ORIOLE showed that metastasis-directed therapy can delay progression and defer systemic treatment in oligometastatic recurrence, but these studies were conducted before routine PSMA imaging and with limited integration of modern systemic agents [63,64]. Recent reviews of PSMA-guided MDT emphasise the need to define standardised oligometastatic criteria, clarify the incremental benefit of combining MDT with ARPIs, and evaluate the role of novel radioligand approaches such as ^{177}Lu-PSMA earlier in the disease course [65–67]. In parallel, guidelines highlight persistent gaps in real-world implementation, including variable access to PSMA PET/CT, advanced systemic therapies and re-irradiation across regions, which require prospective registries and health-services research to understand barriers, equity, and cost-effectiveness in diverse healthcare systems [68,69].

Table 1. Consensus statements on the definition, diagnostic evaluation, and management of high-risk biochemical recurrence (BCR) of prostate cancer and the achieved level of agreement

Number	Statement	Consensus Level
Definition		
1	BCR is defined as undetectable prostate-specific antigen (PSA) after radical prostatectomy with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or that increases to PSA >0.1 ng/mL. A PSA level ≥2 ng/mL above the nadir following radiation therapy (RT), with or without HT.	86%
2	High-risk BCR is characterized by adverse prognostic factors, primarily a rapid PSA doubling time (PSADT) of ≤9 months, in addition to a post-RP PSA ≥1 ng/mL or a post-RT PSA ≥2 ng/mL above nadir.	86%
Diagnostic Evaluation		
3	Prostate-specific membrane antigen (PSMA) PET/CT is the preferred imaging modality for staging and localizing disease in patients with BCR, offering superior detection rates to conventional imaging (CT and bone scan).	100%
Management of BCR		
4	For patients with BCR managed with ADT, treatment interruption (i.e., a drug holiday) should be offered to those who achieve an PSA response (e.g., nadir PSA <0.2 ng/mL) after 36 weeks of therapy to improve quality of life without compromising overall survival (OS).	100%
5	Intermittent ADT can be considered for BCR post-RT in patients with non-metastatic disease and a preference to minimize side effects.	100%
6	Intermittent ADT should be discontinued if there is evidence of disease progression, rising PSA despite therapy, or intolerable side effects.	100%
7	Prostate re-irradiation may be considered in highly selected patients with local recurrence, confirmed by imaging and/or biopsy, and without distant metastasis.	100%
8	Enzalutamide plus ADT should be adopted as standard of care in high-risk BCR, as it significantly improves metastatic-free survival (MFS) and overall survival (OS) compared to ADT alone.	86%
9	Enzalutamide monotherapy represents a viable alternative for patients with high-risk BCR, particularly for those who are intolerant to, or wish to avoid, the side effects of ADT (e.g., hot flushes, bone demineralization). It has demonstrated superior MFS compared to ADT alone	100%
10	In patients with high-risk BCR treated with enzalutamide-based therapy, treatment suspension (intermittent therapy) can be guided by achieving a deep PSA response (e.g., PSA <0.2 ng/mL at 36 weeks), as this approach maintained a significant MFS benefit.	100%
11	Timely and equitable access to novel, evidence-based therapies such as enzalutamide for high-risk BCR requires supportive reimbursement policies and formulary inclusion to ensure these treatments can be implemented across diverse practice settings.	100%
12	Enzalutamide is generally well tolerated. Regular monitoring and proactive management of common toxicities are recommended to optimize safety and maintain quality of life during long-term therapy.	100%
Multidisciplinary team-based management		

13	Whenever available, multidisciplinary team–based management is preferred for patients with high-risk BCR of PC, integrating expertise from urology, radiation oncology, and medical oncology to individualize treatment decisions.	100%

ADT, androgen deprivation therapy; BCR, biochemical recurrence; BP, blood pressure; HT, hormonal therapy; MFS, metastasis-free survival; OS, overall survival; PC, prostate cancer; PET/CT, positron emission tomography/computed tomography; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy.

5. Conclusions

High-risk BCR of PC is a distinct and clinically important state that demands harmonised definitions and risk stratification. In this consensus, the panel highlights the central role of PSMA PET/CT for accurate staging and treatment planning, the value of risk-adapted local salvage, including carefully selected re-irradiation, and the growing importance of systemic strategies that incorporate intermittent ADT and enzalutamide-based regimens for appropriate patients. Enzalutamide plus ADT is endorsed as the standard of care for fit men with high-risk non-metastatic BCR, with enzalutamide monotherapy as an alternative in selected individuals, provided that safety, tolerability, and structured monitoring are prioritised. Equitable access to advanced imaging and therapies, systematic toxicity surveillance, and multidisciplinary team–based decision-making are essential to ensure that the benefits of these evolving approaches are realised consistently across practice settings, while ongoing clinical trials and real-world research address the remaining gaps in evidence.

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Conflict of Interest

The authors declare no conflicts of interest related to the development, content, or publication of this manuscript.

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References

1. Schafer EJ, Jemal A, Wiese D, et al.: Disparities and Trends in Genitourinary Cancer Incidence and Mortality in the USA. Eur Urol. 2023, 84:117–26. 10.1016/j.eururo.2022.11.023

2. Siegel RL, Miller KD, Wagle NS, Jemal A: Cancer statistics, 2023. CA Cancer J Clin. 2023, 73:17–48. 10.3322/caac.21763

3. Morawitz J, Kirchner J, Lakes J, et al.: PSMA PET/CT vs. CT alone in newly diagnosed biochemical recurrence of prostate cancer after radical prostatectomy: Comparison of detection rates and therapeutic implications. Eur J Radiol. 2021, 136:109556. 10.1016/j.ejrad.2021.109556

4. McPherson V, Nair SM, Tin AL, et al.: Comparison of salvage radical prostatectomy vs. salvage ablation therapy for biopsy-proven radio-recurrent localized prostate cancer. Can Urol Assoc J = J l'Association des Urol du Canada. 2024, 18:41–6. 10.5489/cuaj.8373

5. Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S: Management of Biochemical Recurrence after Primary Curative Treatment for Prostate Cancer: A Review. Urol Int. 2018, 100:251–62. 10.1159/000481438

6. Moreira DM, Howard LE, Sourbeer KN, et al.: Predicting Time From Metastasis to Overall Survival in Castration-Resistant Prostate Cancer: Results From SEARCH. Clin Genitourin Cancer. 2017, 15:60–66.e2. 10.1016/j.clgc.2016.08.018

7. Antonarakis ES, Feng Z, Trock BJ, et al.: The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int. 2012, 109:32–9. 10.1111/j.1464-410X.2011.10422.x

8. Lowrance WT, Breau RH, Chou R, et al.: Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II. J Urol. 2021, 205:22–9. 10.1097/JU.0000000000001376

9. Roach M 3rd, Hanks G, Thames HJ, Schellhammer P, Shipley WU, Sokol GH, Sandler H: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006, 65:965–74. 10.1016/j.ijrobp.2006.04.029

10. Fendler WP, Eiber M, Beheshti M, et al.: PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. Eur J Nucl Med Mol Imaging. 2023, 50:1466–86. 10.1007/s00259-022-06089-w

11. Cornford P, van den Bergh RCN, Briers E, et al.: EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2021, 79:263–82. 10.1016/j.eururo.2020.09.046

12. J. FS, Murilo de AL, Ugo DG, et al.: Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. N Engl J Med. 2023, 389:1453–65. 10.1056/NEJMoa2303974

13. Morgan TM, Boorjian SA, Buyyounouski MK, et al.: SALVAGE THERAPY FOR PROSTATE CANCER : AUA / ASTRO / SUO GUIDELINE ಸ 2024 ಸ Guideline Panel Staff and Consultants TREATMENT DECISION-MAKING AT THE TIME OF SUSPECTED BIOCHEMICAL. Am Urol Assoc. 2024, 1–39.

14. Tourinho-Barbosa R, Srougi V, Nunes-Silva I, et al.: Biochemical recurrence after radical prostatectomy: what does it mean? Int Braz J Urol. 2018, 44:14–21. 10.1590/S1677-

5538.IBJU.2016.0656

15. Patel A, Dorey F, Franklin J, deKernion JB: Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol. 1997, 158:1441–5. 10.1016/s0022-5347(01)64238-1

16. Shore ND, Moul JW, Pienta KJ, Czernin J, King MT, Freedland SJ: Biochemical recurrence in patients with prostate cancer after primary definitive therapy: treatment based on risk stratification. Prostate Cancer Prostatic Dis. 2024, 27:192–201. 10.1038/s41391-023-00712-z

17. Crawford ED, Harris RG, Slovin SF, et al.: Synthesizing and Applying Molecular Targeted Imaging Results in Patients With Prostate Cancer (RADAR VII). JU Open Plus. 2023, 1:.

18. Markowski MC, Chen Y, Feng Z, et al.: PSA Doubling Time and Absolute PSA Predict Metastasis-free Survival in Men With Biochemically Recurrent Prostate Cancer After Radical Prostatectomy. Clin Genitourin Cancer. 2019, 17:470–475.e1. 10.1016/j.clgc.2019.08.002

19. Sayyid RK: APCCC Diagnostics 2025: Biochemical Recurrence: When Do You Image? UroToday. (2025). Accessed: https://www.urotoday.com/conference-highlights/apccc-diagnostics-2025/158651-apccc-diagnostics-2025-biochemical-recurrence-when-do-you-image.html.

20. Chavarriaga J: EAU 2025: High-Risk Biochemical Recurrence with Positive PSMA PET: Systemic Treatment Intensification Is the Way to Go. UroToday. (2025). .

https://www.urotoday.com/conference-highlights/eau-2025/eau-2025-prostate-cancer/159136-eau-2025-high-risk-biochemical-recurrence-with-positive-psma-pet-systemic-treatment-intensification-is-the-way-to-go.html

21. Schaeffer EM, Srinivas S, Adra N, et al.: NCCN Guidelines® Insights: Prostate Cancer, Version 3.2024: Featured Updates to the NCCN Guidelines. J Natl Compr Cancer Netw. 2024, 22:140–50. 10.6004/jnccn.2024.0019

22. Bouchelouche K, Choyke PL: Advances in prostate-specific membrane antigen PET of prostate cancer. Curr Opin Oncol. 2018, 30:189–96. 10.1097/CCO.0000000000000439

23. Rouvière O, Vitry T, Lyonnet D: Imaging of prostate cancer local recurrences: why and how? Eur Radiol. 2010, 20:1254–66. 10.1007/s00330-009-1647-4

24. Gomez P, Manoharan M, Kim SS, Soloway MS: Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? BJU Int. 2004, 94:299–302. 10.1111/j.1464-410X.2004.04927.x

25. Beresford MJ, Gillatt D, Benson RJ, Ajithkumar T: A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. Clin Oncol (R Coll Radiol). 2010, 22:46–55. 10.1016/j.clon.2009.10.015

26. Kane CJ, Amling CL, Johnstone PAS, et al.: Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology. 2003, 61:607–11. 10.1016/s0090-4295(02)02411-1

27. Morris MJ, Rowe SP, Gorin MA, et al.: Diagnostic Performance of (18)F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clin cancer Res an Off J Am Assoc Cancer Res.

2021, 27:3674–82. 10.1158/1078-0432.CCR-20-4573

28. McCarthy M, Francis R, Tang C, Watts J, Campbell A: A Multicenter Prospective Clinical Trial of (68)Gallium PSMA HBED-CC PET-CT Restaging in Biochemically Relapsed Prostate Carcinoma: Oligometastatic Rate and Distribution Compared With Standard Imaging. Int J Radiat Oncol Biol Phys. 2019, 104:801–8. 10.1016/j.ijrobp.2019.03.014

29. Yuminaga Y, Rothe C, Kam J, et al.: (68)Ga-PSMA PET/CT versus CT and bone scan for investigation of PSA failure post radical prostatectomy. Asian J Urol. 2021, 8:170–5. 10.1016/j.ajur.2020.02.001

30. Eiber M, Maurer T, Souvatzoglou M, et al.: Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med. 2015, 56:668–74. 10.2967/jnumed.115.154153

31. Morigi JJ, Stricker PD, van Leeuwen PJ, et al.: Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. J Nucl Med. 2015, 56:1185–90. 10.2967/jnumed.115.160382

32. Burgard C, Frei M, Blickle A, et al.: PSMA PET/CT in biochemical recurrence of prostate cancer with PSA levels ≤ 0.2 ng/mL: a German multicenter analysis of conventional PSMA tracers, including [(68)Ga]Ga-PSMA-11, [(68)Ga]Ga-PSMA I&T, and [(18)F]PSMA-1007. Eur J Nucl Med Mol Imaging. 2025, 52:4368–76. 10.1007/s00259-025-07292-1

33. AIZAWA R, OGATA T, GOTO T, et al.: Clinical Outcomes of Metastasis-directed

Therapy for Oligo-metastatic Prostate Cancer Diagnosed Using PSMA-PET/CT or Whole-body MRI. Anticancer Res. 2025, 45:2515 LP-2525. 10.21873/anticanres.17623

34. Emmett L, Yin C, Crumbaker M, et al.: Rapid Modulation of PSMA Expression by Androgen Deprivation: Serial (68)Ga-PSMA-11 PET in Men with Hormone-Sensitive and Castrate-Resistant Prostate Cancer Commencing Androgen Blockade. J Nucl Med. 2019, 60:950–4. 10.2967/jnumed.118.223099

35. Onal C, Guler OC, Torun N, Reyhan M, Yapar AF: The effect of androgen deprivation therapy on (68)Ga-PSMA tracer uptake in non-metastatic prostate cancer patients. Eur J Nucl Med Mol Imaging. 2020, 47:632–41. 10.1007/s00259-019-04581-4

36. 2025 EAU PCa Guidelines update: High risk, locally advanced and biochemical recurrence. Uroweb - Eur. Assoc. Urol. (2025). Accessed: https://uroweb.org/education-events/2025-eau-pca-guidelines-update-high-risk-locally-advanced-and-biochemical-recurrence-2.

37. Paller CJ, Antonarakis ES: Management of biochemically recurrent prostate cancer after local therapy: evolving standards of care and new directions. Clin Adv Hematol Oncol. 2013, 11:14–23.

38. Simon NI, Parker C, Hope TA, Paller CJ: Best Approaches and Updates for Prostate Cancer Biochemical Recurrence. Am Soc Clin Oncol Educ book Am Soc Clin Oncol Annu Meet. 2022, 42:1–8. 10.1200/EDBK_351033

39. M. CJ, J. OC, Graeme D, et al.: Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy. N Engl J Med. 2025, 367:895–903. 10.1056/NEJMoa1201546

40. Magnan S, Zarychanski R, Pilote L, et al.: Intermittent vs Continuous Androgen

Deprivation Therapy for Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2015, 1:1261–9. 10.1001/jamaoncol.2015.2895

41. Crook JM, O'Callaghan CJ, Duncan G, et al.: Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med. 2012, 367:895–903. 10.1056/NEJMoa1201546

42. Tsai H-T, Pfeiffer RM, Philips GK, et al.: Risks of Serious Toxicities from Intermittent versus Continuous Androgen Deprivation Therapy for Advanced Prostate Cancer: A Population Based Study. J Urol. 2017, 197:1251–7. 10.1016/j.juro.2016.12.022

43. Karim MU, Tisseverasinghe S, Cartes R, Martinez C, Bahoric B, Niazi T: Early Versus Delayed Androgen Deprivation Therapy for Biochemical Recurrence After Local Curative Treatment in Non-Metastatic Hormone-Sensitive Prostate Cancer: A Systematic Review of the Literature. Cancers (Basel). 2025, 17:. 10.3390/cancers17020215

44. Bryce AH, Agarwal N, Beltran H, et al.: Implementing evidence-based strategies for men with biochemically recurrent and advanced prostate cancer: Consensus recommendations from the US Prostate Cancer Conference 2024. Cancer. 2025, 131:e35612. 10.1002/cncr.35612

45. Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS: Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005, 352:154–64. 10.1056/NEJMoa041943

46. Keating NL, O'Malley AJ, Smith MR: Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2006, 24:4448–56. 10.1200/JCO.2006.06.2497

47. Yu EY, Gulati R, Telesca D, et al.: Duration of first off-treatment interval is prognostic for time to castration resistance and death in men with biochemical relapse of prostate cancer treated on a prospective trial of intermittent androgen deprivation. J Clin Oncol Off J Am Soc Clin Oncol. 2010, 28:2668–73. 10.1200/JCO.2009.25.1330

48. Handa N, Bennett R 4th, Li E V, et al.: PSMA PET/CT findings in high-risk biochemical recurrence after local treatment of prostate cancer. BJUI compass. 2025, 6:. 10.1002/bco2.70028

49. Valle LF, Lehrer EJ, Markovic D, et al.: A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). Eur Urol. 2021, 80:280–92. 10.1016/j.eururo.2020.11.010

50. Neal D. Shore, Murilo de Almeida Luz, Ugo De Giorgi, Martin Gleave, Geoffrey T. Gotto, Christopher M. Pieczonka, Gabriel P. Haas, Choung-Soo Kim, Miguel Ramirez-Backhaus, Antti Rannikko, Matko Kalac, Swetha Sridharan, Matt Rosales, Yiyun Tang, Ronald F. T SJF: Overall survival with enzalutamide in biochemically recurrent prostate cancer. In: European Society for Medical Oncology Congress. 2025.

51. Shelan M, Achard V, Appiagyei F, et al.: Role of enzalutamide in primary and recurrent non-metastatic hormone sensitive prostate cancer: a systematic review of prospective clinical trials. Prostate Cancer Prostatic Dis. 2024, 27:422–31. 10.1038/s41391-024-00829-9

52. Freedland SJ, Mulhall J, Gleave M, et al.: EMBARK post hoc analysis of sexual activity (SA) patient-reported outcome (PRO) measures. J Clin Oncol. 2024, 42:313. 10.1200/JCO.2024.42.4_suppl.313

53. Erdogan B: Enzalutamide in Prostate Cancer, A Review on Enzalutamide and cancer. EJMO. 2018, 2:121–9.

54. Tombal B, Borre M, Rathenborg P, et al.: Long-term Efficacy and Safety of Enzalutamide Monotherapy in Hormone-naïve Prostate Cancer: 1- and 2-Year Open-label Follow-up Results. Eur Urol. 2015, 68:787–94. 10.1016/j.eururo.2015.01.027

55. Freedland SJ, Giorgi U De, Gleave M, et al.: PD01-06: PROSTATE-SPECIFIC ANTIGEN DYNAMICS FROM THE PHASE 3 EMBARK TRIAL: A POST HOC ANALYSIS. J Urol. Published Online First: 2024. 10.1097/01.JU.0001009540.33579.43.06

56. Sharma A, Garg G, Sadasukhi N, et al.: A prospective longitudinal study to evaluate bone health, implication of FRAX tool and impact on quality of life (FACT-P) in advanced prostate cancer patients. Am J Clin Exp Urol. 2021, 9:211–20.

57. Edmunds K, Tuffaha H, Galvão DA, Scuffham P, Newton RU: Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review. Support care cancer Off J Multinatl Assoc Support Care Cancer. 2020, 28:2079–93. 10.1007/s00520-019-05255-5

58. Aprikian A, Saad F, Wywial E, McLean T, Johnston K, Li Y, Chilelli A: Cost-effectiveness of enzalutamide with androgen-deprivation therapy (ADT) versus ADT alone for the treatment of high-risk biochemically recurrent non-metastatic castration-sensitive prostate cancer in Canada. J Med Econ. 2025, 28:766–77. 10.1080/13696998.2025.2503660

59. Natalia Kunst, Jessica B. Long, Sarah Westvold, Preston Sprenkle, Maximilian Rabil,

Umar Ghaffar, Isaac Y. Kim, Lawrence Saperstein, Shi-Yi Wang, Xiaomei Ma, Cary P. Gross MSL: MP57-08 COST EFFECTIVENESS OF PROSTATE SPECIFIC MEMBRANE ANTIGEN POSITRON EMISSION TOMOGRAPHY (PSMA-PET) FOR THE EVALUATION OF BIOCHEMICAL RECURRENT PROSTATE CANCER IN THE UNITED STATES HEALTHCARE SYSTEM. J Urol. Published Online First: 2024. 10.1097/01.JU.0001009420.83948.eb.08

60. Aggarwal R, Heller G, Hillman DW, et al.: PRESTO: A Phase III, Open-Label Study of Intensification of Androgen Blockade in Patients With High-Risk Biochemically Relapsed Castration-Sensitive Prostate Cancer (AFT-19). J Clin Oncol Off J Am Soc Clin Oncol. 2024, 42:1114–23. 10.1200/JCO.23.01157

61. Duchesne GM, Woo HH, Bassett JK, et al.: Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol. 2016, 17:727–37. 10.1016/S1470-2045(16)00107-8

62. Freedland SJ, de Almeida Luz M, De Giorgi U, et al.: Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. N Engl J Med. 2023, 389:1453–65. 10.1056/NEJMoa2303974

63. Ost P, Reynders D, Decaestecker K, et al.: Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. J Clin Oncol Off J Am Soc Clin Oncol. 2018, 36:446–53. 10.1200/JCO.2017.75.4853

64. Phillips R, Shi WY, Deek M, et al.: Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized

Clinical Trial. JAMA Oncol. 2020, 6:650–9. 10.1001/jamaoncol.2020.0147

65. Konopnicki A, Zaliznyak M, Roy M, Jana B: The therapeutic use of 177 Lu-PSMA-617 radioligand therapy in prostate cancer treatment: a review of literature and ongoing trials. Discov Oncol. 2024, 15:791. 10.1007/s12672-024-01680-z

66. Guckenberger M, Lievens Y, Bouma AB, et al.: Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020, 21:e18–28. 10.1016/S1470-2045(19)30718-1

67. Miszczyk M, Soeterik T, Marra G, Matsukawa A, Shariat SF: Metastasis-directed therapy in oligometastatic prostate cancer. Curr Opin Urol. 2024, 34:178–82. 10.1097/MOU.0000000000001169

68. Cornford P, van den Bergh RCN, Briers E, et al.: EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer-2024 Update. Part I: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2024, 86:148–63. 10.1016/j.eururo.2024.03.027

69. Chiong E, Murphy DG, Akaza H, et al.: Management of patients with advanced prostate cancer in the Asia Pacific region: 'real-world' consideration of results from the Advanced Prostate Cancer Consensus Conference (APCCC) 2017. BJU Int. 2019, 123:22–34. 10.1111/bju.14489