

Should we embark on “EMBARK”?

Reassessing the Role of RT and ARPI in the Era of Next-Generation Imaging on behalf of the Urology Focus Group of the European Society for Radiotherapy and Oncology

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Background

Patients with biochemical recurrence (BCR) represent a heterogeneous population, and many will not go on to develop metastatic disease. In fact, only one-third of patients with BCR progress to metastases, and approximately one-fifth ultimately die from prostate cancer¹. As a result, efforts have been made to stratify this population based on risk. A systematic review by Van den Broeck et al. introduced the concept of BCR risk stratification in the European Association of Urology (EAU) guidelines². A PSA doubling time (PSADT) greater than 12 months and a baseline Gleason score of 7 or less are used to identify patients with low-risk BCR after radical prostatectomy (RP), distinguishing them from those at high risk. The association between high-risk BCR and increased rates of metastasis and prostate cancer-specific mortality was further validated in a large European cohort³. A more recent systematic review identified pT3 stage, ISUP (International Society of Urological Pathology) grade group 4, negative surgical margins, and a PSA level >0.5 ng/mL prior to salvage therapy as prognostic factors associated with oncologic outcomes, although supported by moderate evidence⁴.

How to apply these prognostic factors in clinical decision-making remains complex. Patients without adverse prognostic features may be appropriate candidates for initial observation rather than immediate imaging or treatment. For others—once local therapies have been exhausted—ADT has historically been the primary therapeutic option. However, ADT is associated with significant adverse effects on quality of life (QoL), particularly in terms of sexual function and hot flashes. In recent years, studies such as TOAD (immediate vs. deferred ADT) and PR7 (continuous vs. intermittent ADT) have gained significant attention for demonstrating the feasibility of reducing exposure to hormonal therapy while preserving QoL and maintaining oncologic control^{5,6}.

The recent results from the EMBARK trial have renewed interest in systemic treatment intensification for a highly selected subgroup of patients with high-risk BCR. While eligibility criteria included PSA >1 ng/mL and PSADT ≤9 months, the enrolled population had a median PSA of 5.5 ng/mL and PSADT of 5 months indicating a markedly aggressive disease subset. In this population, enzalutamide plus ADT significantly prolonged metastasis-free survival compared to ADT alone, setting a new standard supported by level 1 evidence. However, extrapolating these results to broader BCR cohorts must be done with caution. The trial showed that the addition of enzalutamide to standard ADT significantly prolonged metastasis-free survival compared to ADT alone. Notably, even if it was an experimental part of the study, enzalutamide monotherapy also outperformed ADT alone in this setting⁷.

In parallel, the BCR treatment landscape has been significantly reshaped in recent years by the widespread adoption of next-generation imaging (NGI). Furthermore, salvage treatment strategies—traditionally limited to prostate bed irradiation—have evolved to incorporate systemic therapies, dose escalation strategies and extended lymph node radiation volumes. The integration of EMBARK trial findings into this modern therapeutic context warrants careful consideration. In this editorial, we advocate for an individualized, risk-adapted approach to the management of high-risk BCR.

Limitations of Conventional Imaging and the Role of PSMA PET/CT

A recent post hoc analysis of 182 patients enrolled across four prospective trials, all with high-risk BCR according to EMBARK criteria and with no evidence of metastatic disease by CI, revealed that 84% had PSMA PET-CT-detectable disease. Among these, 9% had local recurrence, 29% had pelvic nodal involvement, and 46% had distant metastases (with only 24% having >5 lesions)⁸.

This suggests that a substantial proportion of patients classified as high-risk BCR using CI may have limited loco-regional or oligometastatic disease which can be detected using PET-CT. In selected patients outside the EMBARK population, typically with lower PSA and longer PSADT, pelvic RT and/or MDT may offer a prolonged disease-free interval.

These strategies, however, remain investigational and should not be generalized to patients eligible for EMBARK. Recent data also suggest a role for systemic treatment intensification with salvage RT, targeting local and micro-metastatic disease, but this is hypothesis-generating and not definitive.

Use of elective regional radiotherapy for patients with BCR

The EMBARK trial offers compelling, level 1 evidence for systemic intensification in patients with aggressive PSA kinetics and high-risk features. Importantly, patients were excluded if the investigator considered them candidates for post-operative radiotherapy.

The question whether a proportion of patients in the EMBARK trial might have benefited from locoregional therapy remains unknown. It could be speculated, based on PSMA PET-CT data in an EMBARK-like population, that up to 40% of patients still had locoregional disease and might have benefitted from the addition of locoregional therapy to systemic therapy.

The closest evidence to this hypothesis is the PEACE-V STORM trial, which compared two local therapy strategies for patients with pelvic nodal recurrences at NGI in combination with 6 months of ADT. In this trial, 90% of the patients were high-risk BCR according to the EMBARK inclusion criteria. Nevertheless, the STORM patients had more favorable PSA values (median of 1ng/ml) as compared to EMBARK patients (median around 5ng/ml), but comparable doubling times. Elective nodal radiotherapy and only 6 months of ADT resulted in a median 4-year metastasis-free survival of 76%⁹. Importantly, the trial also suggested that omission of local prostate bed salvage RT increases the risk of subsequent prostate bed relapse.

In this particular population of EMBARK suitable patients with better baseline prognostic features. These findings emphasize the potential benefits which may be gained from locoregional disease control, and that merely looking at the marketing authorization criteria of Enzalutamide in BCR would theoretically withhold patients from this option. Whether the addition of androgen receptor pathway inhibitors (ARPIs) to salvage RT with ADT could further improve outcomes in patients with PSMA PET positive disease is being tested in prospective trials like PRIMORDIUM (NCT04557059).

Combined modality therapy for oligometastatic prostate cancer

MDT for high-risk BCR patients with oligometastatic disease detected on NGI represents a promising investigational approach, currently supported by exploratory trials with surrogate endpoints. While it may reduce systemic treatment exposure and toxicity in selected patients, its impact on long-term survival outcomes remains unconfirmed.

As shown by a recent meta-analysis (WOLVERINE) including individual patient data from 5 randomized trials, MDT can significantly improve progression-free survival (PFS), time to castration resistance, and potentially overall survival when compared to standard of care¹⁰. Based on these findings, ongoing randomized clinical trials are investigating MDT as a treatment intensification strategy on top of ADT plus ARPI, with the aim of further improving oncological outcomes in patients with metachronous or synchronous metastatic disease (PERSIAN- NCT03449719, OLIGOPRESTO- NCT04115007).

In the EMBARK trial, treatment was suspended if the PSA level at 9 months was < 0.2 ng/ml and reinitiated when PSA rose to ≥ 2 ng/ml in patients who had undergone RP, or ≥ 5 ng/ml in those treated with definitive RT. These findings reestablish the potential role of an intermittent treatment strategy involving ARPIs. The median duration of the treatment-free interval ranged from 11 months with enzalutamide monotherapy to 20.2 months with the combination of enzalutamide and ADT. Prolonging this off-treatment period has emerged as a new objective for future clinical trials. In the RADIOSA trial, for metachronous metastatic patients, combining SBRT with six months of ADT delayed the need for palliative ADT to 33 months, compared to 18 months with SBRT alone¹¹. In the EXTEND trial, adding SBRT to a short, predefined course of hormone therapy improved both PFS and eugonadal PFS compared to hormone therapy alone, in a mixed population of metachronous and synchronous oligometastatic prostate cancer. Notably, this strategy prolonged the median duration without systemic therapy to over 24 months, compared to 16 months with ADT alone¹². Similarly, in the PEACE-V STORM trial (ref), MDT resulted in a median ADT-free interval of over 48 months following

ADT cessation, with even longer durations observed in patients receiving elective nodal RT, for whom the median was not reached.

These findings provide a rationale for further exploring the integration of MDT with systemic therapies in clinical trials, particularly with the goal of minimizing treatment burden. However, such strategies should be approached cautiously given the lack of phase III validation. The potential of MDT to postpone systemic treatment in high-risk oligometastatic patients undergoing intermittent ARPI, with or without ADT, remains an investigational hypothesis currently under evaluation in prospective trials.

In conclusion, risk stratification after BCR should rely on a combination of PSA level, PSA doubling time, ISUP grade, and next-generation imaging findings. Patients with a high PSA (>4–5 ng/mL), rapid PSA-DT (<6 months), and/or ISUP grade ≥ 4 represent a population in which systemic therapy intensification, as demonstrated by EMBARK, is standard of care. Conversely, patients with lower-risk features or those with limited disease on PSMA-PET may still be considered for salvage radiotherapy or MDT within clinical trials. Finally, a subset of patients with slow PSA kinetics and minimal disease burden may be safely monitored. This stratified framework aims to balance treatment efficacy, toxicity, and healthcare resource use.

Toward a Multidisciplinary Management Paradigm

EMBARK has redefined the BCR treatment paradigm. It supports systemic intensification for high-risk patients, validates ARPI monotherapy as a viable alternative to ADT, and provides a foundation for intermittent treatment strategies. However, these systemic advances should be interpreted within a multidisciplinary framework that considers advanced imaging, MDT, and patient-centered decision-making. Future studies will help refine how best to combine and sequence these therapies to achieve durable control while preserving QoL.

EMBARK has redefined the treatment paradigm for a subset of patients with aggressive biochemical recurrence, providing high-level evidence for systemic intensification with enzalutamide. However, its findings must not be extrapolated to all BCR cases. For patients with less aggressive features, the role of RT, MDT, and NGI-informed strategies remains a subject of ongoing investigation. Future trials should clarify how best to individualize and sequence these therapies across risk groups while preserving quality of life.

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List of abbreviations

ADT: Androgen Deprivation Therapy

ARPI: Androgen Receptor Pathway Inhibitor

BCR: Biochemical Recurrence

CI: Conventional Imaging

MDT: Metastasis-Directed Therapy

MFS: Metastasis-Free Survival

PET/CT: Positron Emission Tomography / Computed Tomography

PSA: Prostate-Specific Antigen

PSA-DT: PSA Doubling Time

PSMA: Prostate-Specific Membrane Antigen

PFS: Progression-Free Survival

QoL: Quality of Life

RT: Radiotherapy

SBRT: Stereotactic Body Radiotherapy

