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PSMA PET-guided management in high-risk biochemical recurrence after radical prostatectomy: Pros and cons from the experience of a tertiary referral center

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ABSTRACT

Background: High-risk biochemical recurrence (BCR) after radical prostatectomy identifies patients at increased risk of metastatic progression and prostate cancer-specific mortality. Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) is increasingly used to localize recurrence and guide treatment; however, its implications for oncologic endpoints and their interpretation in routine practice remain uncertain.

Methods: We retrospectively analyzed consecutive patients with high-risk BCR after radical prostatectomy who were discussed within a multidisciplinary tumor board at a tertiary referral center. All patients underwent PSMA PET/CT at recurrence, and imaging findings informed subsequent treatment allocation. Outcomes of interest were second BCR-free survival and progression-free survival (PFS). Survival outcomes were evaluated using Kaplan–Meier estimates, restricted mean survival time (RMST), and multivariable Cox proportional hazards regression. For external contextualization, Kaplan–Meier curves from pivotal randomized trials in this setting were reconstructed and used as benchmark references.

Results: Overall, 136 patients were included. At PSMA PET/CT, 35% had negative findings or isolated local recurrence, 18% had nodal-only disease (miN1M0), and 47% had metastatic disease (miNanyM1). Both second BCR-free survival and PFS differed significantly across PSMA PET categories. Compared with patients with PET-negative/local recurrence, those with miNanyM1 disease had significantly shorter RMST for second BCR-free survival −11.6 months; $p < 0.01$ and PFS −7.8 months; $p < 0.01$, whereas miN1M0 disease showed an intermediate-risk profile. In multivariable models, PSMA PET category was the strongest independent predictor of progression. Compared with reconstructed randomized-trial benchmarks, this real-world cohort showed earlier biochemical and radiographic progression. Among patients experiencing second BCR, median time to PET-detected progression was 4.3 months.

Conclusion: PSMA PET/CT provides clinically meaningful prognostic stratification in high-risk BCR after radical prostatectomy and supports individualized management. However, PSMA PET-guided surveillance may anticipate progression detection, leading to apparent shortening of intermediate endpoints through lead-time bias and stage migration.

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List of abbreviations:

PSMA	prostate-specific membrane antigen
PET	positron emission tomography
CT	computed tomography
BCR	biochemical recurrence
RMST	restricted mean survival time
RP	radical prostatectomy
PFS	progression-free survival
PSA	prostate-specific antigen
EAU	European Association of Urology
SABR	stereotactic ablative radiotherapy
MDT	metastasis-directed therapy
ADT	androgen deprivation therapy
ARTA	androgen receptor-targeted agents
PSADT	PSA doubling time

1. Introduction

High-risk biochemical recurrence (BCR) after radical prostatectomy (RP) represents a clinically relevant disease state associated with an increased risk of metastatic progression and prostate cancer-specific mortality [1,2]. In this setting, early risk stratification is essential to identify patients at highest risk of clinical progression and to guide treatment intensification [3].

Randomized trials such as PRESTO [4] and EMBARK [5] have demonstrated improved outcomes with systemic treatment escalation in selected patients with high-risk BCR. However, these studies were conducted in highly controlled settings with predefined imaging strategies and treatment algorithms, and their results may not fully capture contemporary real-world practice, where prostate-specific membrane antigen positron emission tomography (PSMA PET) is increasingly incorporated into clinical decision-making.

The widespread adoption of PSMA PET has profoundly reshaped the clinical management of BCR by enabling the early detection of nodal and distant disease and by informing personalized, imaging-guided treatment strategies. At the same time, this paradigm shift raises important methodological and clinical concerns. In particular, PSMA PET-detected clinical recurrence may represent a less robust surrogate for overall survival than progression defined by conventional imaging, as earlier detection does not necessarily indicate a worsened long-term prognosis. Moreover, the increased sensitivity of PSMA PET may expose patients to a risk of overtreatment, especially in the setting of low-volume or indolent disease identified at very early stages [6]. Finally, the use of molecular imaging introduces the possibility of lead time bias and stage migration, complicating the interpretation of intermediate endpoints and limiting comparability with historical cohorts and randomized trials conducted in the pre-PSMA PET era.

In this context, the present study aims to evaluate oncologic outcomes in a consecutive cohort of patients with high-risk BCR after RP, all managed according to a PSMA PET–guided, multidisciplinary treatment algorithm. Specifically, we aimed to confirm the prognostic value of PSMA PET findings in this clinical setting while simultaneously exploring the potential limitations of PSMA PET-driven management, including its impact on biochemical and progression endpoints. This study provides a balanced assessment of both the opportunities and the pitfalls associated with PSMA PET in high-risk BCR.

2. Materials and methods

2.1. Study population

After Institutional Review Board approval (IISR-2016-101720), we retrospectively analyzed consecutive patients experiencing BCR after RP, discussed within a dedicated multidisciplinary tumor board at a tertiary referral center between June 2020 and January 2024. Written informed consent for data collection was obtained at the time of the initial outpatient visit. Biochemical recurrence was defined according to the European Association of Urology (EAU) Guidelines as a confirmed rise in prostate-specific antigen (PSA) $\geq$0.2 ng/mL, following RP. Patients were classified as having high-risk BCR based on the presence of one or more adverse clinical or biochemical features (PSA doubling time $<$12 months, and/or ISUP grade group 4 or 5) [1].

2.2. PSMA PET-guided treatment strategy

All patients underwent restaging according to the EANM guidelines [7] with [18F]PSMA PET/CT either with [18F]PSMA-1007 (activity 210-280 MBq, uptake time 90-120 min) or [18F]DCFPyL, (dosage 296-370 MBq, uptake time 60 min). Imaging was performed using integrated PET/CT system (Biograph64_mCT 4R, Siemens Healthineers, Erlangen, Germany) at our institution. Low-dose CT from vertex to mid tight was performed using 35 mA tube current and 120 kVp tube voltage, followed by PET acquisition with flowmotion of 1.6 mm/s. Image readout was performed on syngo.via Client 8.9 by two nuclear medicine physicians and were interpreted using a structured reporting framework based on the PROMISE criteria, as well as the standardized reporting template from Esfahani et al. [8]. Disease was categorized as follows.

- Negative: No PSMA-avid lesions detected above background.
- Local recurrence: PSMA-avid uptake confined to the prostatic bed without nodal or distant spread.
- Nodal-only disease (miN1M0): PSMA-avid lesions restricted to pelvic or regional lymph nodes below the common iliac bifurcation, with no evidence of distant metastases.
- Metastatic disease (miNanyM1): Presence of PSMA-avid lesions outside regional nodal basins, including bone, visceral organs, or distant lymph nodes.

Lesions were considered positive if showing focal PSMA uptake exceeding surrounding tissue and corresponding to an anatomical abnormality on CT, excluding benign causes of uptake. Equivocal lesions were reviewed within a multidisciplinary tumor board for consensus interpretation.

The PSMA PET/CT results directly informed treatment allocation according to a predefined MDT-based algorithm, consistent with European Association of Urology (EAU) Guidelines available at the time of patient evaluation. According to PSMA PET/CT results, patients received the following treatment strategies.

1) Negative PET/local recurrence only [8]. Patients with negative PSMA PET findings or isolated local recurrence were treated with salvage radiotherapy (SRT) to the prostatic bed combined with the addition of androgen deprivation therapy (ADT) left at the discretion of treating physician [9–11]. A small proportion of patients received stereotactic ablative radiotherapy (SABR) as a part of a clinical trial [12,13].
2) miN1M0 disease (nodal recurrence) [8]. Patients with nodal disease received pelvic radiotherapy with a boost to involved lymph nodes and/or SABR to PET-positive nodes, in combination with ADT. In selected cases with oligometastatic nodal disease, metastasis-directed therapy (MDT) alone was considered as an alternative strategy to delay the initiation of systemic therapy, based on evidence from prospective trials such as STOMP and ORIOLE [14,15], and in accordance with MDT consensus.
3) miNanyM1 disease [8]. Patients with metastatic disease were primarily managed with systemic therapy, with or without metastasis-directed therapy, according to disease burden and MDT

recommendation. In patients with oligometastatic miM1 disease, MDT alone represented a potential treatment option aimed at postponing systemic treatment initiation, supported by data from phase II randomized studies, including STOMP, ORIOLE, and SABR-COMET [14–16]. The addition of ADT [17] and/or androgen receptor-targeted agents (ARTA) was evaluated on a case-by-case basis, considering disease extent, PSA kinetics, patient comorbidities, and MDT judgment.

2.3. Outcomes definition

The primary endpoints of the study were second biochemical recurrence-free survival and progression-free survival (PFS). For both endpoints, time-to-event was calculated from the date of the first PSMA PET/CT performed at the time of biochemical recurrence, which represented the standardized clinical decision point for treatment allocation within the multidisciplinary tumor board. This approach was chosen to ensure consistency across patients and to allow comparability with randomized clinical trials, in which time-to-event analyses are typically anchored to the time of randomization.

Second biochemical recurrence-free survival was defined as the time from the first PSMA PET/CT to the occurrence of a subsequent PSA relapse (PSA level $\geq$0.2 ng/mL, confirmed by a second consecutive value $\geq$ 0.2 ng/mL) following salvage or metastasis-directed therapy, after achievement of a post-treatment PSA nadir. Although second biochemical recurrence is not formally defined as a distinct endpoint in current EAU guidelines, this operational definition is consistent with EAU criteria for biochemical recurrence and is widely adopted in contemporary literature to describe biochemical failure after salvage treatment [18].

Radiographic progression was assessed by PSMA PET/CT using the PSMA PET Progression (PPP) criteria [19]. Progression was defined by the appearance of one or more new PSMA-avid lesions or a clear increase in size and/or PSMA uptake intensity of pre-existing lesions compared with prior imaging. For each patient, progression status was confirmed by consensus reading among nuclear medicine specialists and discussed within the multidisciplinary team. This standardized approach ensured consistent categorization of disease extent at recurrence and objective criteria for progression, minimizing inter-reader variability and enabling robust prognostic stratification [18].

Secondary analyses explored several clinically relevant aspects of disease evolution: i) the prognostic value of PSMA PET findings, assessed by stratifying patients according to PET-defined disease extent at recurrence; ii) temporal patterns between biochemical failure and radiographic progression, focusing on the interval between second BCR and PET-detected progression; iii) contextual comparison of oncological outcomes in our cohort with those reported in randomized controlled trials enrolling patients with high-risk biochemical recurrence.

2.4. Statistical analysis

Time-to-event outcomes were estimated using the Kaplan–Meier method and compared across subgroups descriptively. In addition to conventional survival summaries, between-group differences were quantified using the restricted mean survival time (RMST) framework over prespecified time horizons, to provide an absolute and model-robust measure of treatment-free time. To identify independent predictors of clinical progression, multivariable Cox proportional hazards regression models were fitted. Model covariates were selected a priori based on clinical relevance and included PSMA PET/CT category and key biochemical parameters. The proportional hazards assumption was assessed using Schoenfeld residuals. The relationship between PSA at first BCR, ADT duration, and the risk of subsequent clinical progression was explored using locally weighted scatterplot smoothing (LOWESS) curves. Predicted probabilities of progression at 36 months were estimated and visualized separately according to PSMA PET/CT subgroups, without imposing linearity assumptions. A sensitivity analysis excluding patients receiving ARTAs was performed.

For contextual comparison with pivotal randomized trials, Kaplan–Meier curves from the ADT of PRESTO and EMBARK trials were reconstructed from published figures using a validated algorithm for individual patient data reconstruction [20–22]. Digitized time–survival coordinates and reported numbers at risk were used to generate reconstructed individual patient time-to-event datasets, which were then used to overlay Kaplan–Meier estimates against the current cohort for descriptive benchmarking.

Analyses were conducted using R software (version 4.2.1 www.r-project.org). The code generated for the analysis is made available in Supplementary Materials and Methods. All tests were two-sided with a significance level set at $p = 0.05$.

3. Results

3.1. Patient characteristics

A total of 136 consecutive patients with high-risk biochemical recurrence after radical prostatectomy were included. Baseline clinicopathologic characteristics of the overall cohort, stratified according to PSMA PET/CT findings, are summarized in Table 1. At first PSMA PET/CT evaluation, 48 patients (35%) had negative PET findings or isolated local recurrence, 24 patients (18%) had pelvic nodal recurrence (miN1M0), and 64 patients (47%) had distant metastatic disease (miNanyM1). Patients with miNanyM1 disease showed higher PSA levels at first BCR and shorter PSA doubling time compared with the other groups. Adverse pathological features, including lymph node invasion and positive surgical margins, were more frequently observed among patients with PET-detected metastatic disease. At a median follow-up of 37 months, 72 patients developed a second biochemical recurrence, 68 experienced disease progression on subsequent PSMA PET/CT evaluation, and 7 patients died.

3.2. Second biochemical recurrence-free survival

Second BCR-free survival differed across PSMA PET/CT categories (Fig. 1). Patients with negative PET/local recurrence showed the most favorable outcomes, while those with miNanyM1 disease experienced early second biochemical recurrence; miN1M0 disease demonstrated intermediate outcomes. RMST analysis confirmed these findings (Table 2).

3.3. Progression-free survival

PFS varied substantially according to PSMA PET/CT findings (Fig. 2). Patients with miNanyM1 disease experienced rapid progression, while PET-negative/local recurrence was associated with the most favorable PFS; miN1M0 disease showed intermediate risk (Table 2).

On multivariable Cox regression analysis (Table 3), PSMA PET/CT findings were the strongest independent predictors of PSMA PET/CT progression. Compared with PET-negative/local recurrence, miN1M0 disease was associated with an increased risk of progression (HR 2.53; 95% CI 1.05–6.10 $p = 0.036$), while miNanyM1 disease conferred a markedly higher risk (HR 5.07; 95% CI 2.51 – 10.21; $p < 0.001$).

LOWESS plots demonstrated an increasing predicted probability of clinical progression at 36 months with rising PSA levels at first BCR, and ADT duration with marked differences according to PSMA PET/CT findings (Figs. 3 and 4). When modeled as a function of ADT duration, PSMA PET/CT results stratified patients into three distinct prognostic groups across the entire range of ADT exposure: individuals with miNanyM1 disease consistently exhibited the highest predicted risk of progression, followed by those with miN1M0 disease, whereas patients with negative PET or isolated local recurrence demonstrated the lowest risk. These patterns suggest that the duration of ADT could not compensate

Table 1
Descriptive statistics of the study population.

	Total	Negative/ local recurrence	Pelvic nodal recurrence (miN1 M0)	Distant recurrence (miNany M1)
N	136	48	24	64
Median Age (years) [IQR]	73 [67; 76]	70 [65; 74]	74 [65; 76]	73 [68; 78]
iPSA (ng/ml) [IQR]	9.7 [5.8; 14.2]	9.1 [5.0; 11.0]	9.7 [6.8; 14.3]	11.4 [5.7; 17.5]
ISUP Grade Group (%)				
1	6 (4)	4 (9)	0 (0)	2 (3)
2	29 (21)	15 (32)	4 (17)	10 (16)
3	38 (28)	17 (36)	9 (38)	12 (19)
4	28 (21)	5 (11)	4 (17)	19 (30)
5	34 (25)	6 (13)	7 (29)	21 (33)
Unknown	1	1	0	0
pT stage (%)				
pT2	37 (27)	18 (38)	4 (17)	15 (24)
pT3a	50 (37)	20 (42)	10 (42)	20 (32)
pT3b	42 (31)	9 (19)	9 (38)	24 (38)
pT4	6 (4)	1 (2)	1 (4)	4 (6)
Unknown	1	0	0	1
Lymph node invasion (%)	43 (32)	8 (17)	8 (33)	27 (43)
Positive margins (%)	60 (45)	17 (35)	9 (39)	34 (54)
PSA (ng/ml) at BCR [IQR]	0.5 [0.3; 1.1]	0.3 [0.2; 0.7]	0.4 [0.3; 0.6]	0.7 [0.4; 2.0]
PSA doubling time (months) [IQR]	4.4 [2.3; 7.0]	4.8 [2.5; 8.1]	6.0 [3.3; 10.5]	3.7 [2.0; 6.2]
Time to first BCR (months) [IQR]	38 [15; 94]	43 [15; 89]	33 [11; 60]	37 [17; 105]
Salvage RT	49 (36)	28 (58)	13 (54)	8 (13)
Metastasis Directed Therapy/ Stereotactic Ablative RT	68 (50)	5[a] (10%)	18 (75)	45 (71)
Concomitant ADT	78 (58)	20 (42)	10 (42)	48 (76)
ADT duration (months) [IQR]	25 [22; 39]	24 [13; 30]	24 [15; 28]	29 [24; 41]
Concomitant ARTA	16 (12)	1 (2)	0	16 (25)
Concomitant Chemotherapy	2 (2)	0	0	2 (3)

[a] Participants of the POPART trial.

for underlying differences in biological disease aggressiveness as captured by PSMA PET status.

Regarding PSA at first BCR, higher values were associated with an increased predicted probability of clinical progression at 36 months. Throughout most of the PSA range, patients with miNanyM1 disease exhibited the highest predicted risk, followed by those with miN1M0 and negative PET/local recurrence. At higher PSA levels, however, the risk estimates for patients with miN1M0 disease converged toward those of patients with miNanyM1 disease.

3.4. Contextual comparison with randomized trials

Kaplan–Meier curves reconstructed from the ADT monotherapy arm

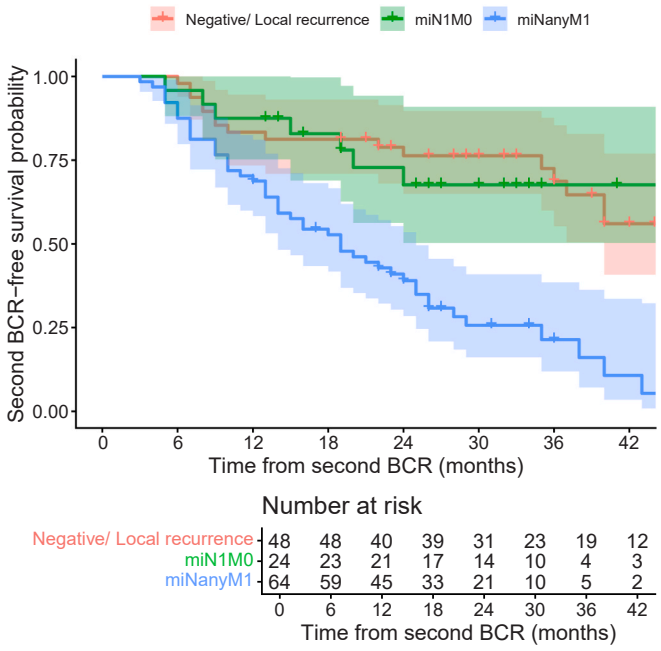

Fig. 1. Second biochemical recurrence–free survival according to PSMA PET/CT findings.

Table 2
Difference in RMST for second BCR and clinical progression according to PSMA PET/CT results.

RMST for 2nd BCR	Δ RMST	95% CI	p value
Negative PET/Local recurrence	Ref	-	-
miN1M0	−1.3	−6.2 4.1	0.67
miNanyM1	−11.6	−15.0 -7.9	<0.01
RMST for Clinical progression	**Δ RMST**	**95% CI**	**p value**
Negative PET/Local recurrence	Ref	-	-
miN1M0	−3.5	−7.7 -0.7	0.04
miNanyM1	−7.8	−11.0 -4.7	<0.01

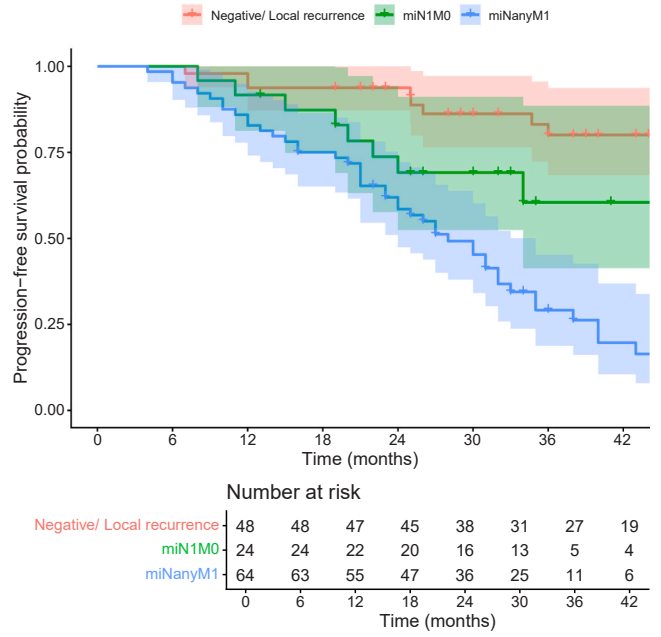

Fig. 2. Progression-free survival according to PSMA PET/CT findings.

Table 3
Multivariable Cox Regression Analysis predicting the risk of Clinical Progression.

Variabile	HR	95% CI	p value
PSMA PET/CT result			
Negative/Local recurrence	ref	-	-
miN1M0	2.53	1.05 – 6.10	0.036
miNanyM1	5.07	2.51 – 10.21	<0.001
Concomitant ADT			
No	ref	-	-
Yes	0.70	0.51 – 0.89	<0.001
PSA at first BCR (ng/mL)	1.07	1.00 – 1.15	0.049
PSAdt (months)	0.99	0.93 – 1.05	0.621

of published data were used for descriptive benchmarking against randomized trials enrolling patients with high-risk BCR. Compared with the PRESTO trial [4], patients in the present cohort exhibited earlier second biochemical recurrence, with a steeper decline in second BCR-free survival over the first 6 months (Fig. S1). Similarly, when compared with the EMBARK trial [5], progression-free survival appeared shorter in the present cohort, with earlier occurrence of radiographic or clinical progression (Fig. S2). Among patients who experienced second biochemical recurrence, post-second BCR progression-free survival declined rapidly, with a median time to progression of 4.3 months (Fig. 5). This time span is comparable to the expected time to second PSA testing and subsequent waiting time for PSMA PET/CT in routine clinical practice, suggesting that approximately half of patients already had radiographic disease progression at the time of second BCR detection.

3.5. Sensitivity analysis

The sensitivity analysis excluding patients who received ARTAs confirmed the robustness of the results (Fig. S3, Table S1). Notably, as ARTAs were administered almost exclusively in miM1 patients (with a single exception), univariate subgroup analyses showed comparable second BCR-free survival and PSMA progression-free survival between patients who did and did not receive ARTAs (all $p > 0.05$; Fig. S4 and S5).

4. Discussion

In this real-world, single-center cohort of patients with high-risk biochemical recurrence (BCR) after radical prostatectomy managed within a PSMA PET-guided multidisciplinary framework, we investigated how contemporary molecular imaging shapes treatment decisions, and its impact on intermediate oncologic endpoints. Overall, our findings underscore the central clinical role of PSMA PET at the time of recurrence, while also highlighting important conceptual and practical challenges in interpreting outcomes when highly sensitive imaging is systematically integrated into patient management.

The most consistent and clinically relevant observation of this study is the robust risk stratification provided by PSMA PET at the time of BCR. Patients with negative PSMA PET findings or isolated local recurrence experienced the most favorable outcomes, whereas those with PET-detected metastatic disease, particularly miNanyM1, had substantially higher risks of second biochemical recurrence and radiographic

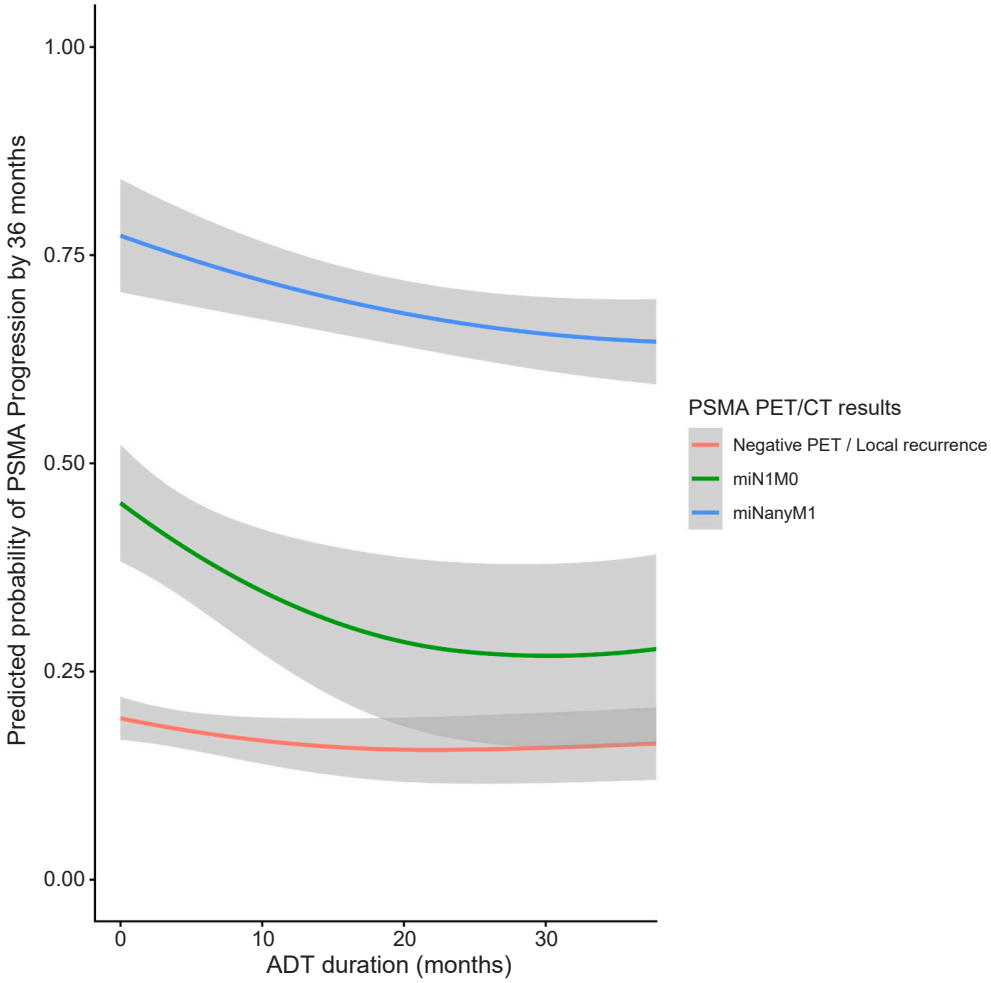

Fig. 3. Predicted probability of clinical progression according to ADT duration and PSMA PET/CT findings.

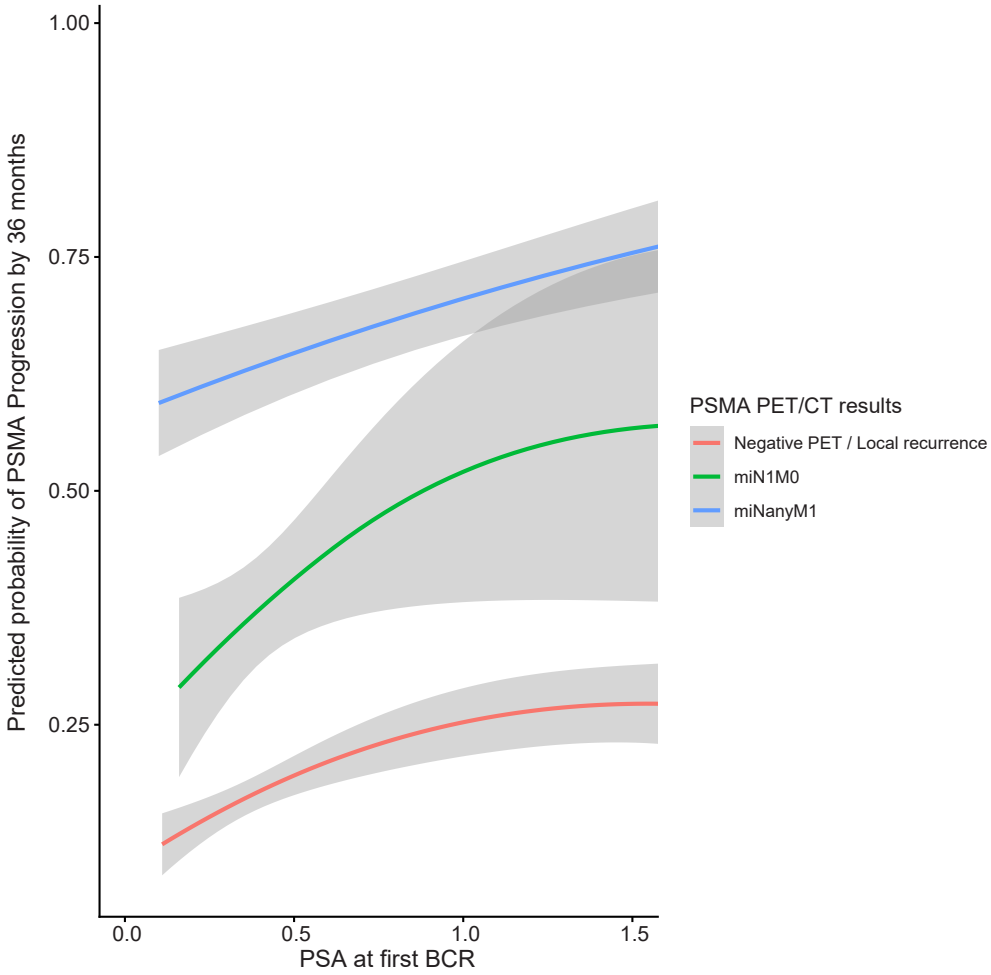

Fig. 4. Predicted probability of clinical progression according to PSA and PSMA PET/CT findings.

progression. Importantly, the PSMA PET category remained an independent predictor of progression in multivariable analyses, after adjusting for biochemical parameters and ADT duration. These results suggest that PSMA PET is not merely a staging tool but a meaningful surrogate of underlying tumor biology at the time of recurrence, capturing heterogeneity that is not fully reflected by PSA kinetics or pathological features. From a clinical standpoint, this reinforces the value of incorporating PSMA PET into multidisciplinary decision-making for patients with high-risk BCR, particularly when considering systemic therapy and metastasis-directed treatment.

In this context, it is important to recognize that the European Association of Urology definition of high-risk BCR encompasses a heterogeneous group of patients with variable underlying disease biology. In patients with high-risk recurrence but low absolute PSA values, PSADT may appear artificially rapid because the available formulas tend to overestimate PSA growth velocity at very low levels [23]. Consequently, classification as high risk based solely on PSADT may not always reflect truly aggressive tumor biology. The same category also includes patients with genuinely aggressive disease, making it difficult to provide a uniform treatment recommendation for all individuals labeled as high risk. These considerations further support the role of PSMA PET as a complementary tool to refine risk stratification beyond biochemical criteria alone and emphasize that not all patients with high-risk BCR necessarily require the same therapeutic intensity.

Patients with nodal-only disease (miN1M0) represent a particularly important and clinically challenging subgroup [24]. In our cohort, these patients consistently demonstrated an intermediate risk profile between localized disease and metastatic spread, supporting the concept that miN1M0 should be considered a biologically distinct state rather than a simple anatomical category. Notably, when PSA at first BCR was higher, the predicted risk of progression in miN1M0 patients approached that observed in miNanyM1 disease, suggesting that nodal-only involvement may behave similarly to metastatic disease in the setting of high-PSA recurrence. Clinically, this finding raises the possibility that selected miN1M0 patients (particularly those with higher PSA levels) may benefit from more aggressive treatment strategies, such as the combination of ADT and ARTAs.

Despite the clear prognostic discrimination afforded by PSMA PET, patients in our cohort experienced earlier second biochemical recurrence and shorter progression-free survival compared with pivotal randomized trials in high-risk BCR (PRESTO [4] and EMBARK [25] trials). Rather than reflecting inferior oncologic outcomes, we believe this discrepancy primarily reflects differences in imaging sensitivity, patient selection, and treatment strategies. The systematic use of PSMA PET inevitably introduces stage migration and lead time bias, enabling detection of metastatic disease at much lower PSA levels than conventional imaging. Consequently, radiographic progression defined by PSMA PET may appear to occur earlier without necessarily indicating more aggressive disease biology or worse long-term prognosis [26,27].

The comparatively early biochemical failure observed in our cohort should also be interpreted in light of treatment intensity. Among patients with negative/local PSMA PET findings or miN1M0 disease, 58% did not receive concomitant ADT. Furthermore, 24% of patients with miNanyM1 disease received no systemic therapy, most commonly because metastasis-directed therapy alone was selected to postpone systemic treatment, in line with available evidence at the time of

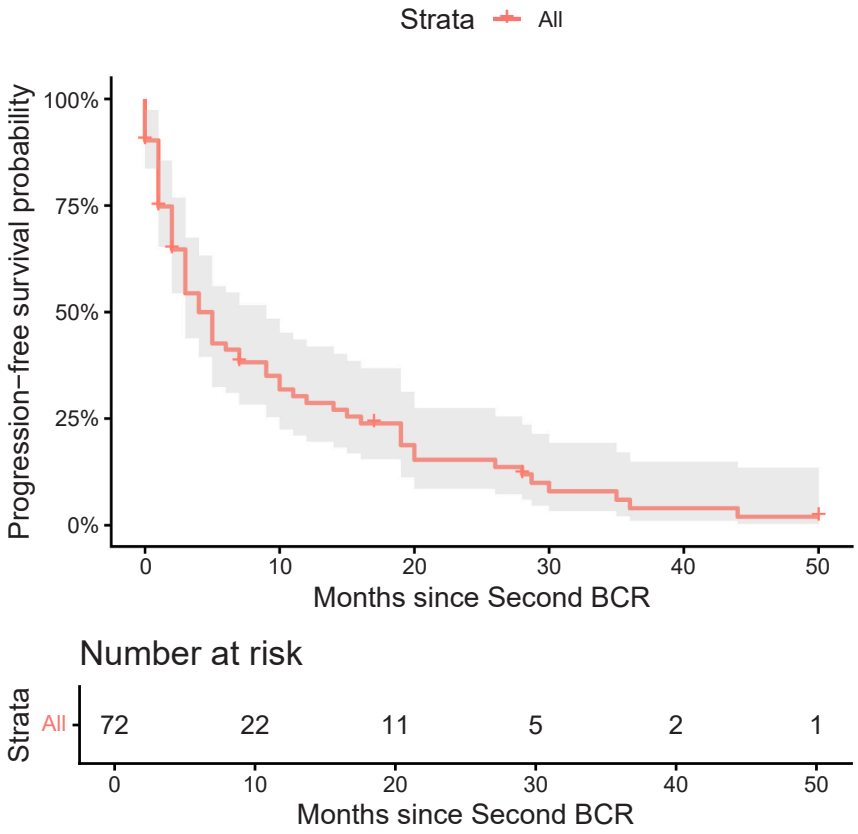

Fig. 5. Progression-free survival after second biochemical recurrence.

treatment initiation, from metastasis directed therapy studies such as STOMP, ORIOLE, SABR COMET [14–16]. Although these strategies reflected multidisciplinary decisions and the evidence available at the time of treatment, they may represent relative undertreatment compared with contemporary standards and likely contributed to the shorter intermediate oncological endpoints observed in this cohort. Similarly, a subset of patients with negative PSMA PET findings or isolated local recurrence were treated with salvage radiotherapy alone, without systemic therapy escalation. These heterogeneous, real-world treatment patterns, driven by multidisciplinary decision-making, likely contributed to differences in observed biochemical and radiographic outcomes when compared with more standardized trial protocols.

An additional methodological consideration relates to the intrinsic relationship between PSMA PET-guided management and PSMA PET-defined endpoints. In this study, PSMA PET not only informed treatment allocation but also defined radiographic progression, introducing a degree of self-referentiality inherent to imaging-driven management strategies [28,29]. Progression-free survival should therefore be interpreted as a PSMA PET-defined imaging endpoint rather than as a direct surrogate for overall survival [30]. This interpretation is further supported by the short interval observed between second biochemical recurrence and PSMA PET-detected progression. Among patients experiencing second BCR, the median time to radiographic progression was approximately five months, a time span comparable to the expected waiting time for PSMA PET imaging in routine clinical practice. This finding suggests that a substantial proportion of patients already harbor radiographically evident disease at the time second BCR is detected.

Finally, several limitations should be acknowledged. First, the retrospective, single-center design and relatively limited sample size restrict causal inference and generalizability. Treatment allocation and follow-up imaging were not standardized, and residual confounding by indication and surveillance intensity cannot be excluded. Therefore, the treatment-related analyses presented in this study should be considered exploratory and hypothesis-generating. Second, PSMA PET-defined disease extent provided clinically relevant prognostic stratification and informed individualized treatment selection. However, the observed differences in intermediate outcomes cannot be attributed exclusively to disease biology, as treatment heterogeneity and non-protocolized imaging intensity may have contributed to earlier biochemical and radiographic event detection. PSMA PET-defined PFS should therefore be interpreted cautiously, particularly when compared with outcomes from trials employing standardized conventional imaging and treatment protocols.

5. Conclusions

In our series of patients with high-risk biochemical recurrence after radical prostatectomy, PSMA PET provided powerful prognostic stratification and directly informed personalized treatment allocation within a multidisciplinary framework. At the same time, PSMA PET–guided strategies were associated with earlier detection of second biochemical and radiographic progression, resulting in apparent shortening of intermediate endpoints when compared with historical randomized trials. These findings are most consistent with lead-time bias and stage migration rather than true deterioration of long-term prognosis. Careful interpretation of PSMA PET-defined endpoints are therefore warranted, and future studies should prioritize long-term survival and patient-centered outcomes to fully define the clinical value of PSMA PET-guided management.

CRediT authorship contribution statement

Daniele Robesti: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Marco Roscigno:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **Suela Vukcaj:** Conceptualization, Data curation, Methodology,

Writing – review & editing. **Michele Catellani:** Conceptualization, Data curation. **Giovanni La Croce:** Data curation, Methodology. **Irene Gotuzzo:** Data curation, Methodology. **Lucia Bonomi:** Data curation, Investigation, Methodology. **Federico Garrou:** Data curation, Methodology. **Michele Donadoni:** Conceptualization, Data curation, Methodology. **Alberto Pelizzola:** Conceptualization, Data curation, Methodology. **Maurizio Giovanni Portaluri:** Conceptualization, Data curation, Supervision, Writing – review & editing. **Stefano Arcangeli:** Supervision, Writing – review & editing. **Alberto Zambelli:** Supervision, Writing – review & editing. **Paola Erba:** Supervision, Writing – review & editing. **Luigi Filippo Da Pozzo:** Supervision, Writing – review & editing.

Ethics statement

The study was approved by the institutional review board (IISR-2016-101720) on 28 September 2017. All subjects/patients/participants signed an informed consent form".

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eanmi.2026.100302.

Data availability

Data will be made available on request.

References

[1] Van den Broeck T, van den Bergh RCN, Arfi N, et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. Eur Urol 2019;75(6):967–87. https://doi.org/10.1016/j.eururo.2018.10.011.

[2] 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(2):148–63. https://doi.org/10.1016/j.eururo.2024.03.027.

[3] Group EYPCW, Preisser F, Abrams-Pompe RS, et al. European association of urology biochemical recurrence risk classification as a decision tool for salvage radiotherapy—A multicenter study. Eur Urol 2024;85(2):164–70. https://doi.org/10.1016/j.eururo.2023.05.038.

[4] 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 2024;42(10):1114–23. https://doi.org/10.1200/JCO.23.01157.

[5] De Giorgi U, Freedland SJ, Rannikko A, et al. Enzalutamide in patients with high-risk biochemically recurrent prostate cancer according to the european association of urology definition: a post hoc analysis of EMBARK. Prostate Cancer Prostatic Dis 2025. https://doi.org/10.1038/s41391-025-00959-8. Published online.

[6] Madan RA, Mena E, Lindenberg L, Choyke PL. With new technology comes great responsibility: prostate-specific membrane antigen imaging in recurrent prostate cancer. J Clin Oncol 2022;40(26):3015–9. https://doi.org/10.1200/JCO.22.00493.

[7] 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 Imag 2023;50(5):1466–86. https://doi.org/10.1007/s00259-022-06089-w.

[8] Esfahani SA, Morris MJ, Sartor O, et al. Standardized template for clinical reporting of PSMA PET/CT scans. Eur J Nucl Med Mol Imag 2024;52(1):335–41. https://doi.org/10.1007/s00259-024-06857-w.

[9] Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol 2016;17(6):747–56. https://doi.org/10.1016/S1470-2045(16)00111-X.

[10] Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376(5):417–28. https://doi.org/10.1056/NEJMoa1607529.

[11] Le QC, Siech C, Hoeh B, et al. Influence of concomitant androgen deprivation therapy and its duration for salvage radiation after radical prostatectomy: a systematic review and network meta-analysis according to published data. Eur Urol Oncol 2025;8(5):1406–15. https://doi.org/10.1016/j.euo.2025.05.006.

[12] Ferrario F, Franzese C, Faccenda V, et al. Toxicity profile and patient-reported outcomes following salvage stereotactic ablative radiation therapy to the prostate bed: the POPART multicentric prospective study. Clin Transl Radiat Oncol 2024;44. https://doi.org/10.1016/j.ctro.2023.100704.

[13] Ferrario F, Franzese C, Vukcaj S, et al. Predictors of toxicities and oncological outcomes following postoperative ablative radiotherapy (POPART) for biochemical recurrence. Radiother Oncol 2025;211. https://doi.org/10.1016/j.radonc.2025.111072.

[14] 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 2018;36(5):446–53. https://doi.org/10.1200/JCO.2017.75.4853.

[15] 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(5):650–9. https://doi.org/10.1001/jamaoncol.2020.0147.

[16] Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 2020;38(25):2830–8. https://doi.org/10.1200/JCO.20.00818.

[17] Marvaso G, Corrao G, Zaffaroni M, et al. ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial. Lancet Oncol 2025;26(3):300–11. https://doi.org/10.1016/S1470-2045(24)00730-7.

[18] Di Giorgio A, Siepe G, Serani F, et al. Long-term outcomes of PSMA PET/CT-guided radiotherapy in biochemical failure patients post-radical prostatectomy: a 5-year follow-up analysis. Eur J Nucl Med Mol Imag 2025;52(10):3720–9. https://doi.org/10.1007/s00259-025-07255-6.

[19] Fanti S, Hadaschik B, Herrmann K. Proposal of systemic therapy response assessment criteria in time of PSMA PET/CT imaging: PSMA PET progression (PPP). Published online J Nucl Med December 1, 2019. https://doi.org/10.2967/jnumed.119.233817. jnumed.119.233817.

[20] Robesti D, Micheli F, Rai SN, et al. Trimodal treatment vs radical cystectomy for muscle-invasive bladder cancer: the neglected impact of informative censoring. A systematic review and meta-analysis. Crit Rev Oncol Hematol 2025;214:104815. https://doi.org/10.1016/j.critrevonc.2025.104815.

[21] Martini A, Yu M, Raggi D, et al. Adjuvant immunotherapy in patients with high-risk muscle-invasive urothelial carcinoma: the potential impact of informative censoring. Cancer 2022;128(15):2892–7. https://doi.org/10.1002/cncr.34255.

[22] Robesti D, Micheli F, Rai SN, et al. Addressing uneven treatment discontinuation rate in the chemotherapy arm of the EV-302 phase 3 randomized clinical trial: implications for outcome interpretation. Clin Genitourin Cancer 2025:102423. https://doi.org/10.1016/j.clgc.2025.102423. Published online.

[23] Vickers AJ, Brewster SF. PSA velocity and doubling time in diagnosis and prognosis of prostate cancer. Br J Med Surg Urol 2012;5(4):162–8. https://doi.org/10.1016/j.bjmsu.2011.08.006.

[24] Karpinski MJ, Civan C, Rauscher I, et al. New prostate cancer risk groups by PSMA-PET (PPP3): an international, retrospective, registry-based cohort study. Lancet Oncol 2026;27(4):480–90. https://doi.org/10.1016/S1470-2045(26)00016-1.

[25] Freedland SJ, de Almeida Luz M, Giorgi U De, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med 2023;389(16):1453–65. https://doi.org/10.1056/NEJMoa2303974.

[26] Jadvar H, Calais J, Fanti S, et al. Appropriate use criteria for prostate-specific membrane antigen PET imaging. J Nucl Med 2022;63(1):59. https://doi.org/10.2967/jnumed.121.263262.

[27] Olson AC, Beriwal S. Is distant metastasis-free survival lead time bias? J Clin Oncol 2021;39(25):2844. https://doi.org/10.1200/JCO.21.00326.

[28] Carpenter CR, Pines JM. Understanding bias in diagnostic research. In: Evidence-based emergency care. John Wiley & Sons, Ltd; 2023. p. 73–92. https://doi.org/10.1002/9781119616870.ch6.

[29] Kea B, Hall MK, Wang R. Recognising bias in studies of diagnostic tests part 2: interpreting and verifying the index test. Emerg Med J 2019;36(8):501. https://doi.org/10.1136/emermed-2019-208447.

[30] Martini A, Gandaglia G, Briganti A. Evidence-based urology: surrogate endpoints – for. Eur Urol Focus 2021;7(6):1217–8. https://doi.org/10.1016/j.euf.2021.09.023.