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Brief Correspondence

Prostate-specific Membrane Antigen–radioguided Surgery in an EMBARK-like Cohort of Patients with Oligorecurrent Hormone-sensitive Prostate Cancer: Delay in Systemic Treatment

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Abstract

We analyzed data for a cohort of 111 patients with EMBARK-like biochemical recurrence (BCR) of prostate cancer (prostate-specific antigen [PSA] doubling time ≤9 mo, PSA ≥1 ng/ml) after radical prostatectomy and localized oligorecurrence on prostate-specific membrane antigen (PSMA)-based imaging. All patients underwent PSMA-radioguided surgery (RGS). At PSMA-RGS, the median PSA was 1.95 ng/ml (interquartile range [IQR] 1.36–3.20) ng/ml and the median PSA doubling time was 4.0 mo (IQR 2.5–5.5). Clavien-Dindo grade >IIIa complications occurred in nine of 111 patients (8.1%). A complete biochemical response (cBR; PSA decline ≤0.2 ng/ml after PSMA-RGS) was observed in 53 patients (47.7%). In the cBR group (equivalent to the treatment suspension criterion in EMBARK), estimated survival rates at 2 yr were 49.9% (95% confidence interval [CI] 37.2–67.1%) for BCR-free survival and 65.2% (95% CI 52.2–81.4%) for treatment-free survival. A relevant proportion of our PSMA-RGS cohort with localized oligorecurrence on PSMA-based imaging fulfilled the EMBARK criteria. PSMA-RGS yielded meaningful biochemical responses that translated to long-lasting treatment-free periods.

Patient summary: For some patients with prostate cancer and no evidence of metastasis on conventional imaging but high risk of metastatic progression, modern molecular imaging identifies small cancer deposits that can be removed via targeted surgery.

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This surgery led to a significant decrease in PSA (prostate-specific antigen) levels, which allowed a longer break from further treatment.

Biochemical recurrence (BCR) of prostate cancer (PCa) after radical prostatectomy (RP) is a frequent event [1]. Patients with BCR and negative conventional imaging results but high risk of metastatic progression may be offered early intensification of systemic therapy according to the EMBARK trial [1,2]. However, if staged with prostate-specific membrane antigen (PSMA)-based imaging instead, a substantial proportion of such patients would exhibit oligorecurrent PCa [3], which might be targetable via PSMA-radioguided surgery (RGS) [4]. Moreover, a short prostate-specific antigen (PSA) doubling time (PSADT), a key inclusion criterion for the EMBARK trial, was not a predictor of adverse cancer control outcomes after PSMA-RGS [2,5]. Therefore, we hypothesized that some EMBARK-like patients would be candidates for PSMA-RGS. Our aim was to quantify the effect of PSMA-RGS on treatment-free survival (TFS) in this cohort, analogous to treatment suspension in the EMBARK trial.

We identified patients with hormone-sensitive BCR who met the EMBARK inclusion criteria (PSADT ≤9 mo, PSA ≥1 ng/ml, Eastern Cooperative Oncology Group performance status score of 0, and adenocarcinoma without atypical transdifferentiation) before PSMA-RGS. All PSMA-RGS procedures were performed for local recurrences and/or nodal oligorecurrence within the pelvis and/or retroperitoneum, as identified via PSMA-based imaging. All patients initially underwent RP with or without additional radiotherapy. The PSMA-RGS procedure has already been reported [4]. In brief, after injection with technetium-labeled PSMA-targeting agents, regional excision of local recurrences or template-based lymph-node dissection of nodal recurrences was performed using intraoperative γ-probe measurements. We assessed the rate of complete biochemical response (cBR; PSA <0.2 ng/ml), BCR-free survival (BCRFS; PSA <0.2 ng/ml without further treatment), and TFS. The Kaplan-Meier method was used to estimate survival.

Of 681 eligible patients who underwent PSMA-RGS between 2014 and 2024 at two centers, 111 (16.3%) fulfilled the EMBARK criteria (Supplementary Fig. 1). At PSMA-RGS, median PSA was 1.95 ng/ml (IQR 1.36–3.20) and median age was 67 yr (IQR 62–71; Table 1). Median PSADT was 4.0 mo (IQR 2.5–5.5). On preoperative PSMA imaging, most patients had one lesion (70/111, 63.1%) within the pelvis (83/111, 74.8%).

Histologically confirmed cancer was removed in 109/111 patients (98.2%). A total of 53/111 patients (47.7%) achieved cBR, and PSA declined to <0.1 ng/ml in 40/111 patients (36.0%). Estimated 2-yr survival rates were 25.8% (95% confidence interval [CI] 18.2–36.4) for BCRFS and 45.4% (95% CI 35.8–57.5%) for TFS in the overall cohort, and 49.9% (95% CI 37.2–67.1%) for BCRFS and 65.2% (95% CI 52.2–81.4) for TFS in the cBR group (Fig. 1). In the cBR group, median BCRFS was 22 mo (IQR 15–55) and median TFS was not reached by 5 yr. Clavien-Dindo grade >IIIa complications occurred in nine of 111 patients (8.1%) and included three ureteral injuries, three bowel injuries, two bleeding complications requiring surgical revision, and one wound infection.

The optimal treatment modality for conventional non-metastatic hormone-sensitive recurrent PCa in the PSMA era remains controversial. While these patients may benefit from early intensification of systemic therapy and, if applicable, subsequent treatment suspension, some may also be candidates for local therapies instead. Our analysis yielded several important results.

First, nearly one-sixth of the PSMA-RGS cohort met the EMBARK criteria. Most patients had one lesion within the pel-

Table 1 – Baseline characteristics and results for 111 patients treated with PSMA-RGS for EMBARK-like biochemical recurrence of prostate cancer with evidence of oligorecurrence on PSMA imaging between 2014 and 2024

Parameter	Result
Median age at PSMA-RGS, yr (IQR)	67 (62–71)
Median PSA before PSMA-RGS, ng/ml (IQR)	1.95 (1.36–3.20)
Median PSA doubling time, mo (IQR)	4.0 (2.5–5.5)
Median time between radical prostatectomy and PSMA-RGS, mo (IQR)	41 (25–70)
Radiotherapy after radical prostatectomy, *n* (%)	71 (64.0)
Number of PSMA-avid lesions on PET, *n* (%)	
Inconclusive/mild PSMA uptake	2 (1.8)
1 lesion	70 (63.1)
2 lesions	27 (24.3)
≥3 lesions	12 (10.8)
Location of PSMA-avid lesions on PET, *n* (%)	
Pelvis	83 (74.8)
Retroperitoneum	11 (9.9)
Retroperitoneum and pelvis	13 (11.7)
Other sites	4 (3.6)
Surgical approach, *n* (%)	
Open	109 (98.2)
Robot-assisted	2 (1.8)
Number of pathologically positive specimens, *n* (%)	
No cancer removed	2 (1.8)
1 positive specimen	37 (33.3)
2 positive specimens	23 (20.7)
≥3 positive specimens	49 (44.1)
Median first PSA after PSMA-RGS, ng/ml (IQR)	0.18 (0.04–0.96)
Biochemical response status, *n* (%)	
Complete (PSA <0.2 ng/ml)	53 (47.7)
PSA ≥ 0.2 ng/ml	48 (43.2)
Not assigned	10 (9.0)
Median operative time, min (IQR)	115 (91–150)
Median estimated blood loss, ml (IQR)	100 (50–200)
Clavien-Dindo grade >IIIa complications, *n* (%)	9 (8.1)
Median follow-up after PSMA-RGS, mo (IQR)	37 (22–58)
BCR-free survival rate at 2 yr, % (95% CI)	25.8 (18.2–36.4)
Treatment-free survival rate at 2 yr, % (95% CI)	45.4 (35.8–57.5)

BCR = biochemical recurrence; CI = confidence interval; IQR = interquartile range; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.

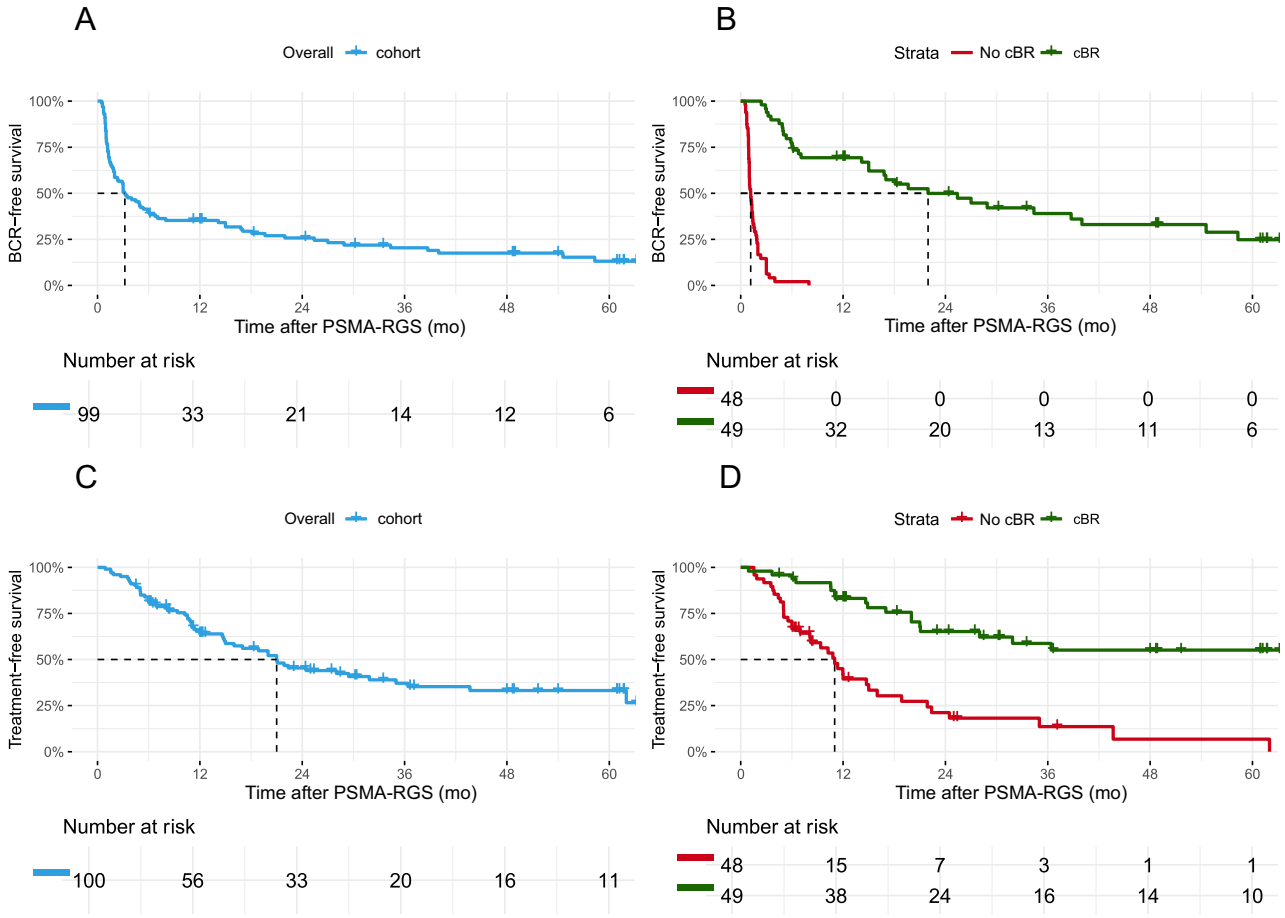

Fig. 1 – Kaplan-Meier analyses of (A,B) BCR-free survival and (C,D) treatment-free survival for patients with follow-up† treated with PSMA-RGS for EMBARK-like BCR with evidence of oligorecurrence on PSMA imaging between 2014 and 2024 in (A,C) the overall cohort and (B,D) stratified for cBR (prostate-specific antigen <0.2 ng/ml). Note: for one patient, follow-up was only available for treatment-free survival and not BCR-free survival. cBR status after PSMA-RGS was not available for two patients with follow-up. Therefore, these two patients were included in the overall cohort, but not in cBR analysis. BCR = biochemical recurrence; cBR = complete biochemical response; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.

vis. Median PSADT (4.0 vs 4.9 mo) and age at PSMA-RGS (67 vs 69 yr) were similar between our cohort and the EMBARK population. Absolute PSA levels could not be compared because a quarter of EMBARK patients did not undergo RP, and subgroup PSA levels were not reported. In a post hoc analysis of patients undergoing PSMA-based imaging for BCR, 85.2% of those who met the EMBARK criteria had positive PSMA imaging finding [3]. The most common location for PCa lesions was nodal drainage sites (85.2%), predominantly within the pelvis (55.7%) [3]. With the recent advent of PSMA-based imaging, conventional assessment of non-metastatic status is no longer sensitive enough, especially in patients with low PSA but a short PSADT [6,7]. The high prevalence of metastatic disease on PSMA imaging in these otherwise similar cohorts raises questions regarding the applicability of results from studies that used conventional imaging in the PSMA era. Post hoc analyses of such cohorts are necessary until prospective trials incorporating PSMA-based imaging have emerged, which is a methodology that has previously been applied [3,8]. According to these observations, a relevant proportion of EMBARK-like patients may harbor oligorecurrent PCa lesions on PSMA imaging that can be targeted via PSMA-RGS.

Second, we are the first to report on a nonsystemic treatment for a specific EMBARK-like cohort. Histologically confirmed cancer was removed in all but two patients. Nearly half of the patients exhibited cBR after PSMA-RGS. In EMBARK, the proportion of patients with PSA <0.2 ng/ml at week 36 was 67.8%, for leuprolide alone, 85.9% for enzalutamide alone, and 90.9% for leuprolide + enzalutamide. Effective surgical targeting of lesions via PSMA-RGS could further improve outcomes by expanding local treatment options, even with repeated procedures [9], and complement systemic treatment. In the ongoing ARASTEP trial (NCT05794906; darolutamide for high-risk BCR) metastasis-directed therapy options such as PSMA-RGS are not prohibited. Even in patients for whom PSMA-RGS fails, repeat surgery, radiotherapy, or, finally, EMBARK-like systemic treatment is feasible.

Third, prolonged BCRFS and TFS were observed when cBR was achieved. In the cBR group, median BCRFS was 22 mo and the 2-yr TFS rate was 65.2%. Median TFS was not reached by 5 yr. These findings are consistent with results from recent multicenter analyses of all PSMA-RGS patients [4]. Treatment suspension was considered a key advantage of the EMBARK trial, with median treatment suspension

periods of 17 mo for leuprolide alone, 11 mo for enzalutamide alone, and 20 mo for leuprolide + enzalutamide. Of note, the delayed testosterone recovery after suspension of regimens that include leuprolide may have artificially inflated the treatment suspension duration in the PSA-based restarting regimen in EMBARK, while testosterone levels remain unaffected by PSMA-RGS. Therefore, cross-study comparisons indicate that PSMA-RGS can maintain similar or even superior treatment-free periods in some patients without any hormone-related detrimental effects on overall quality of life [10]. Hypothetically, this delay in systemic treatment may also prolong the time to castration resistance. However, patient selection remains challenging.

Limitations of our study include the retrospective design and universal use of PSMA-based imaging, which limits its comparability with the EMBARK trial.

Our results indicate that a relevant proportion of our PSMA-RGS cohort of patients with localized oligorecurrence on PSMA-based imaging met the EMBARK criteria. PSMA-RGS achieved meaningful biochemical responses, which translated into prolonged treatment-free periods.

Author contributions: Fabian Falkenbach had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Falkenbach, Heck, Maurer.
Acquisition of data: Falkenbach, Lischewski, Koehler, Heck, Maurer.
Analysis and interpretation of data: Falkenbach, Knipper.
Drafting of the manuscript: Falkenbach, Maurer.
Critical revision of the manuscript for important intellectual content: Knipper, Karakiewicz, Tian, Saad, Tilki, Budäus, Steuber, Mandel, Wenzel, Gschwend, Graefen, Heck.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2025.01.006.

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