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Prostate Cancer

Better Oncological Outcomes After Prostate-specific Membrane Antigen Positron Emission Tomography–guided Salvage Radiotherapy Following Prostatectomy

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Abstract

Background and objective: Up to 50% of patients with prostate cancer experience prostate-specific antigen (PSA) relapse following primary radical prostatectomy (RP). Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) is increasingly being used for staging after RP owing to its high detection rate. Our aim was to compare outcomes for patients who received salvage radiotherapy (sRT) with versus without PSMA PET guidance.

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Methods: In this observational case-control study, the control group consisted of 344 patients from the SAKK09/10 trial (sRT without PSMA PET guidance from 2011 to 2014). The treatment group consisted of 1548 patients from a retrospective multicenter cohort (PSMA PET-guided sRT from July 2013 to 2020). Data were collected up to November 2023. Patients with pN1 status at RP, initial cM1 status, cM1 status on PET, or PSA >0.5 ng/ml were excluded. Patients with detectable PSA after RP who were treated with sRT were eligible. We assessed 3-yr biochemical recurrence-free survival (BRFS) and metastasis-free survival (MFS).

Key findings and limitations: The study population of 717 patients comprised a control group (n = 255) with median follow-up of 75 mo and a PSMA PET group (n = 462) with median follow-up of 31 mo. In the PSMA PET cohort, 103 patients (22.3%) had PSMA-positive pelvic lymph nodes (PLNs), 85 (18.4%) received androgen deprivation therapy (ADT), and 104 (22.5%) underwent PLN irradiation. The BRFS rate at 3 yr was 71% (95% confidence interval [CI] 64–78%) for the control group and 77% (95% CI 72–82%) for the PSMA PET group. The PSMA PET group had favorable BRFS at 18–24 mo after sRT (hazard ratio 0.32, 95% CI 0.0.14–0.75; p = 0.01) and a lower rate of lymph node relapse after sRT (standardized mean difference 0.603). The MFS rate at 3 yr was 89.2% (95% CI 84.6–94.1%) for the control group and 91.2% (95% CI 88.1–94.4%) for the PSMA PET group.

Conclusions and clinical implications: Our results suggest a moderate improvement in short-term BRFS if PSMA PET is used to guide sRT. One possible reason is individualized PLN coverage facilitated by PET. MFS was not improved by PSMA PET guidance for sRT.

Patients' summary: For patients who experience recurrence of prostate cancer after surgical removal of their prostate, salvage radiotherapy (sRT) is a further treatment option. We found that a type of scan called PSMA PET (prostate-specific membrane antigen positron emission tomography) to identify recurrence and guide sRT can improve recurrence-free survival because of better targeting of pelvic lymph nodes that may contain cancer cells.

1. Introduction

Up to 50% of patients with prostate cancer experience prostate-specific antigen (PSA) relapse or persistence after primary radical prostatectomy (RP) [1,2], for which salvage radiation therapy (sRT) ± androgen deprivation therapy (ADT) is a viable treatment option [3]. At present, prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET) is used for staging in the post-RP setting owing to its high detection rate [4,5], and significantly influenced treatment decisions for 33% of patients in the prospective PSMA-SRT trial [6,7]. Retrospective studies revealed favorable biochemical recurrence (BCR)-free survival (BRFS) rates after PSMA PET-guided sRT [8–10]. Two ongoing phase 3 randomized controlled trials (NCT03582774, n = 193; NCT04794777, n = 450) are investigating whether PSMA PET guidance improves oncological outcomes after sRT [11–13].

Our aim was to compare the efficacy of sRT ± ADT in patients with BCR or PSA persistence after RP, with versus without PSMA PET guidance, in a large, well-balanced cohort.

2. Patients and methods

2.1. Control cohort

The external control cohort consisted of the per-protocol population (n = 344) of the phase 3 Swiss Group for Clinical Cancer Research (SAKK) 09/10 trial. Previous analyses included all patients and reported on the primary study endpoint [14]. All 28 study centers in three countries received approval from the local ethics committee, and all participants signed written informed consent. Before randomization, magnetic resonance imaging (MRI) or computed tomography (CT) was mandatory to exclude patients with macroscopic local recurrence or pelvic/distant metastases. sRT to the prostate bed was administered between February 2011 and April 2014 to a total dose of 64 or 70 Gy in 2 Gy per fraction. Follow-up visits were scheduled 3 mo after completion of sRT and then every 6 mo for 3 yr and every 12 mo thereafter. Regular PSA testing was performed, with subsequent staging via imaging (modality not defined) in BCR cases.

2.2. PSMA PET cohort

Eleven centers from five countries participated in a retrospective multicenter study after obtaining ethics committee approval. Written consent was waived owing to the retrospective nature of the study. Previous reports on analyses that included patients from this cohort analyzed novel risk factors for treatment failure after PSMA PET-guided sRT [15–18]. The study included patients who had undergone RP and were subsequently managed with PSMA PET-guided sRT for PSA persistence or recurrence (PSA ≥0.1 ng/ml for both) between July 2013 and June 2020. In total, 1548 patients met the inclusion criteria. PET protocols are presented in Supplementary Table 1. An integrated boost to local recurrence, elective inclusion of pelvic lymph nodes (PLNs) in the radiation field, and ADT administration were implemented according to risk factors for individual patients and institutional practice (Supplementary Table 2). Follow-up included PSA testing and restaging in cases with BCR after sRT (Supplementary Table 3).

2.3. Exclusion criteria

The exclusion criteria were as follows: missing information for the stratification variables, PSA >0.5 ng/ml before sRT, pT4 disease, R2 or unknown resection margin status, and/or unknown pN status. To fulfill

the positivity assumption for the weighting approach, the age in the two cohorts was set to a common range between 48 yr (lowest age in the control cohort) and 75 yr (exclusion criterion for the control cohort). A total of 1892 patients were screened, of whom 717 (255 control, 462 PSMA PET) were deemed to be eligible (Supplementary Fig. 1).

2.4. Statistical analysis

Statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [19]. A p value of 0.05 was set as the level for statistical significance. The standardized mean difference (SMD) measure of effect was used to compare outcome variables between the two groups. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed [20].

2.4.1. Selection of balancing variables

Before data extraction, the study team (C.Z., P.S., M.W., S.H., P.G., M.S.) determined which clinical variables to include for balancing of the two cohorts. On the basis of previous publications on sRT [15,21], the International Society of Urological Pathology (ISUP) grade group for the RP specimen, pT stage and resection status at RP, serum PSA before sRT, and PSA persistence (PSA >0.1 ng/ml 6–20 wk after RP) versus recurrence were included in the modeling. The analysis did not include PSA doubling time or preoperative PSA because of their limited predictive value in previous studies [10,21].

2.4.2. Balancing

We combined two weighting techniques. First, patient characteristics were not balanced at the start of follow-up, so entropy balancing weights were calculated for the baseline balancing variables [22]. This allowed estimation of a marginal treatment effect that would have been measured in a randomized study with a cohort with similar patient characteristics as the PSMA PET cohort (average treatment effect in the treated population). Using weights instead of matching allowed the inclusion of as many patients as possible in the analysis. In other words, entropy reweighting is used to balance covariate distributions in observational studies with a binary treatment for which the control group data can be reweighted to match the covariate distributions in the treatment group. Second, as the two cohorts had different censoring patterns, the probability of being censored over time was estimated in each cohort separately using a Cox proportional-hazards model. ISUP grade group was included as a single independent variable in the regression, with censoring as the event. ISUP grade group was included with a ratio scale for the control cohort, as the presence of only a few censoring events did not allow for a complex model. For the PSMA PET cohort, ISUP grade group was included as a categorical variable. We started with a more complicated model with all the balancing variables, but model selection (*mfp* package for R, fractional polynomial for age; selection level = 0.05 [23]) suggested use of ISUP grade group as a single predictor. From these probabilities, we calculated a second time-varying weight for each patient to counteract the different patient groups that were preferably censored and developed imbalances over time.

We assessed the balance between the two cohorts over time via the SMD for each variable to evaluate whether, conditional on the true propensity score, distributions observed for the baseline covariates were similar for treated and untreated subjects [24]. Weights were combined by multiplication and weighted Kaplan-Meier curves were derived.

2.4.3. Effect of PSMA PET on BRFS

To estimate the effect of PSMA PET guidance for sRT on BRFS, we used a Cox proportional-hazards model with PMSA PET imaging as a covariate and included the time-varying weights. BCR after sRT was defined as an increase in PSA to the nadir + 0.2 ng/ml. As survival curves suggested time dependence of the PSMA PET influence on BRFS, we fitted a separate model for each year after completion of sRT. Follow-up time was censored administratively 3 yr after sRT as median follow-up for the PSMA PET cohort was 31 mo (interquartile range [IQR] 21–44). BRFS was selected as the primary combined endpoint, and no competing-risk analysis was performed as only one patient died before experiencing BCR. A competing-risk sensitivity analysis was performed in the original study for the control cohort and yielded similar results to the primary analysis [14].

2.4.4. Metastasis-free survival

For analysis of metastasis-free survival (MFS), an additional 30 patients whose metastatic status was unknown were excluded. Weights were recalculated for this reduced cohort.

3. Results

3.1. Patient and treatment characteristics

Patient and treatment characteristics are shown in Table 1. The weighted cohorts were well balanced for all stratification variables (all SMD < 0.1; Supplementary Fig. 2). Entropy balancing weights ranged from 0.25 to 4.71. No patient in the control cohort received ADT. Among the 85 patients (18.4%) in the PSMA PET cohort who received ADT, the duration was <6 mo for 13 (2.8%), 6–12 mo for 25 (5.4%), 12–24 mo for 11 (2.4%), and >24 mo for 11 (2.4%). None of the patients in the control cohort received sRT to the PLNs, whereas 104 patients (22.5%) in the PSMA-PET cohort underwent PLN irradiation. In the PSMA PET cohort, local failure was detected in 156 patients (33.8%) and PLN metastasis in 103 (22.3%), as detailed in Table 2.

3.2. BRFS results

In the weighted comparison, median follow-up was 75.3 mo (IQR 72.1–86.2) for the control cohort and 31 mo (IQR 21–44) for the PSMA PET cohort. The 3-yr BRFS rates were 71% (95% CI 64–78%) for the control cohort and 76.8% (95% CI 72–82%) for the PSMA PET cohort (Fig. 1A). The effect of PSMA PET varied over time (Fig. 2 and Supplementary Table 4).

During the first year after sRT, patients in the PSMA PET group exhibited a 50% reduction in the risk of PSA relapse or mortality (weighted HR 0.51, 95% CI 0.28–0.93; $p = 0.027$) in comparison to the control group. For patients who were event-free for the first year, there was no evidence of an effect of PSMA PET at 12–18 mo after sRT (weighted HR 1.36, 95% CI 0.52–3.55; $p = 0.53$). At 18–24 mo after sRT, an effect of PSMA PET was evident again (weighted HR 0.32, 95% CI 0.14–0.75; $p = .009$). At 24–36 mo after sRT, the effect of PSMA PET was undetectable.

A sensitivity analysis excluding patients who received ADT ($n = 85$) was performed to avoid the interplay of ADT in the analysis. The effect was slightly reduced but was still apparent (Supplementary Table 5). Some patients in the PSMA PET cohort did not receive sRT to the fossa; as this could have influenced the effect, we excluded these 13 patients in a second sensitivity analysis, which did not affect the results (Supplementary Table 5).

Table 1 – Characteristics of the study population [a]

Parameter	Unweighted cohort				Weighted cohort		
	Overall	PSMA PET for staging		SMD	PSMA PET for staging		SMD
		No	Yes		No	Yes	
Patients (*n*)	717	255	462		255	462	
Mean age at sRT, yr (SD)	66 (6.1)	66 (5.6)	66 (6.3)	0.05	66 (5.4)	66 (6.3)	<0.001
ISUP grade group, *n* (%)				0.34			<0.001
1–2	339 (47.3)	141 (55.3)	198 (42.9)		109 (42.9)	198 (42.9)	
3	228 (31.8)	81 (31.8)	147 (31.8)		81 (31.8)	147 (31.8)	
4	78 (10.9)	17 (6.7)	61 (13.2)		34 (13.2)	61 (13.2)	
5	72 (10.0)	16 (6.3)	56 (12.1)		31 (12.1)	56 (12.1)	
Resection status, *n* (%)				0.44			<0.001
R0	464 (64.7)	131 (51.4)	333 (72.1)		184 (72.1)	333 (72.1)	
R1/Rx	253 (35.3)	124 (48.6)	129 (27.9)		71 (27.9)	129 (27.9)	
pT stage, *n* (%)				0.19			<0.001
pT2	387 (54.0)	151 (59.2)	236 (51.1)		130 (51.1)	236 (51.1)	
pT3a	242 (33.8)	81 (31.8)	161 (34.8)		89 (34.8)	161 (34.8)	
pT3b	88 (12.3)	23 (9.0)	65 (14.1)		36 (14.1)	65 (14.1)	
PSA before sRT, *n* (%)				0.05			<0.001
0.01–0.2 ng/ml	282 (39.3)	104 (40.8)	178 (38.5)		98.2 (38.5)	178 (38.5)	
0.21–0.5, ng/ml	435 (60.7)	151 (59.2)	284 (61.5)		157 (61.5)	284 (61.5)	
PSA persistence, *n* (%)				0.04			<0.001
No	589 (82.1)	212 (83.1)	377 (81.6)		208 (81.6)	377 (81.6)	
Yes	128 (17.9)	43 (16.9)	85 (18.4)		47 (18.4)	85 (18.4)	
Time from RP to BCR, *n* (%)				0.56			0.62
0–1 yr	231 (32.2)	47 (18.4)	184 (39.8)		41 (16.1)	184 (39.8)	
>1 yr	474 (66.1)	208 (81.6)	266 (57.6)		214 (83.9)	266 (57.6)	
Data not available	12 (1.7)	0	12 (2.6)		0	12 (2.6)	
PSA doubling time, *n* (%) [b]				0.92			0.945
0–6 mo	223 (31.1)	84 (32.9)	139 (30.1)		76 (29.8)	139 (30.1)	
6–12 mo	172 (24.0)	81 (31.8)	91 (19.7)		80 (31.2)	91 (19.7)	
>12 mo	189 (26.4)	90 (35.3)	99 (21.4)		99 (38.9)	99 (21.4)	
Data not available	133 (18.5)	0	133 (28.8)		0	133 (28.8)	
sRT dose to the fossa, *n* (%) [c]				1.46			1.439
<66 Gy	166 (23.2)	126 (49.4)	40 (8.7)		123 (48.2)	40 (8.7)	
66–70 Gy	363 (50.6)	129 (50.6)	234 (50.6)		132 (51.8)	234 (50.6)	
>70 Gy	167 (23.3)	0	167 (36.1)		0	167 (36.1)	
Data not available	21 (2.9)	0	21 (4.5)		0	21 (4.5)	
PSA relapse, *n* (%)				0.45			0.574
No	490 (68.3)	140 (54.9)	350 (75.8)		125 (49.0)	350 (75.8)	
Yes	227 (31.7)	115 (45.1)	112 (24.2)		130 (51.0)	112 (24.2)	
Distant metastases, *n* (%)				0.4			0.434
No	606 (84.5)	215 (84.3)	391 (84.6)		209 (81.8)	391 (84.6)	
Yes	83 (11.6)	40 (15.7)	43 (9.3)		47 (18.2)	43 (9.3)	
Data not available	28 (3.9)	0	28 (6.1)		0	28 (6.1)	
Death from PC, *n* (%)				1.24			1.236
Yes	1 (0.1)	0	1 (0.2)		0	1 (0.2)	
No	517 (72.1)	255 (100)	262 (56.7)		255 (100)	262 (56.7)	
Data not available	199 (27.8)	0	199 (43.1)		0	199 (43.1)	
Dead at last FU, *n* (%)				0.24			0.243
Yes	14 (2.0)	11 (4.3)	3 (0.6)		11 (4.5)	3 (0.6)	
No	703 (98.0)	244 (95.7)	459 (99.4)		244 (95.5)	459 (99.4)	
Time to last FU (mo)				2.37			2.442
Mean (SD)	48 (26.0)	74.33 (17.9)	33 (16.7)		75 (17.2)	33.29 (16.8)	
Median (IQR)	43 (26–73)	75 (71–86)	31 (21–44)		75 (72.1–86.2)	31 (21–44)	
ADT, *n* (%)				0.67			0.672
Yes	85 (11.9)	0	85 (18.4)		0	85 (18.4)	
No	377 (52.6)	0	377 (81.6)		0	377 (81.6)	
Data not available	255 (35.6)	255 (100)	0		255 (100)	0	

PSMA = prostate-specific membrane antigen; PET = positron emission tomography; SD = standard deviation; SMD = standardized mean difference; sRT = salvage radiotherapy; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; ADT = androgen deprivation therapy; IQR = interquartile range; PC = prostate carcinoma; BCR = biochemical recurrence; FU = follow-up.

[a] Patient characteristics before and after entropy balancing at baseline for the two patient cohorts. SMD = 0.1 indicates balance. Balancing variables with SMD < 0.001 after weighting were selected.

[b] Doubling time was calculated using the Memorial Sloan Kettering Cancer Center nomogram.

[c] Thirteen patients did not receive sRT to the prostate bed.

3.3. *MFS and patterns of recurrence*

The MFS rates at 3 yr were 89.2% (95% CI 84.6–94.1%) for the control cohort and 91.2% (95% CI 88.1–94.4%) for the PSMA PET cohort (Fig. 1B). We found no evidence that PSMA PET imaging altered the risk of metastasis over the first 3 yr (weighted HR 0.83, 95% CI 0.47–1.49).

Table 2 – PET findings and treatment details for the unweighted PSMA PET cohort at the time of salvage radiotherapy

Parameter	Patients, *n* (%)
Local recurrence on PET	
No	306 (66.2)
Yes	156 (33.8)
Nodal recurrence on PET	0
No	359 (77.7)
Yes	103 (22.3)
Elective PLN irradiation	
No	341 (73.8)
Yes, whole pelvis	105 (22.7)
Yes, half pelvis	15 (3.2)
NA	1 (0.2)
Elective PLN dose [a]	
≤50 Gy	53 (11.5)
>50 Gy	22 (4.8)
NA or not applicable	387 (83.8)
Irradiation of PLNs	
No	358 (77.5)
Yes	104 (22.5)
Dose to the PLNs [a]	
<50 Gy	4 (0.9)
50–60 Gy	32 (6.9)
>60 Gy	27 (5.8)
NA or not applicable	399 (86.4)
ADT given	
No	377 (81.6)
Yes	85 (18.4)
ADT duration	
<6 mo	13 (2.8)
6–12 mo	25 (5.4)
12–24 mo	11 (2.4)
>24 mo	11 (2.4)
NA or not applicable	402 (87)

PSMA = prostate-specific membrane antigen; PET = positron emission tomography; PLN = pelvic lymph node; ADT = androgen deprivation therapy; NA = data not available.
[a] Doses are provided as the equivalent dose in 2-Gy fractions (EQD2; $\alpha/\beta = 1.5$ Gy).

The 3-yr recurrence patterns for the balanced cohorts are presented in Table 3. Local 3-yr recurrence rates were similar (4.2% vs 3.7%; SMD 0.025). By contrast, recurrences in any lymph nodes were more frequent in the control group (85.1% vs 59.3%; SMD 0.603). The incidence of bone metastasis was 27.6% in the control group and 37% in the PSMA PET group. In the PSMA PET cohort, 35 patients (46.1%) with relapse within 3 yr underwent PSMA PET/CT or PET/MRI for restaging following sRT; this information was not available for 20 patients (26.3%). The number of patients in the control cohort who underwent PSMA PET for restaging following sRT is also unknown.

4. Discussion

There is insufficient evidence on whether PSMA PET use in planning improves sRT outcomes, as no randomized trial data have been reported. Calais et al [12] estimated a reduction in the biochemical progression rate from 40% to 20% at 5 yr after sRT in the PSMA PET-guided sRT arm ($n = 103$) in comparison to the control arm ($n = 90$).

We compared treatment outcomes after PSMA PET-guided sRT versus sRT based on conventional imaging in two well-weighted cohorts. A short-term improvement in BRFS was observed for the PSMA PET-guided approach (HR 0.32–0.51). This effect vanished in the third year after sRT. A potential reason for this effect is more stringent exclusion of patients with metastatic disease (cM1) from the PSMA PET cohort before sRT. Another explanation could be the PET-guided individualization of the treatment strategy. It is essential to mention that patients in the control group received no PLN irradiation or ADT. By contrast, patients in the PSMA PET group underwent personalized RT of PLNs or additional ADT primarily on the basis of PET findings, as patients with high-risk features such as pN1 disease and pre-sRT PSA >0.5 ng/ml were excluded.

As PET-positive PLNs have a prognostic impact on BRFS and MFS following sRT [15], PET-based expansion of the sRT field to cover PLNs and sRT dose escalation to PET-positive PLNs might have let to the short-term improvement in biochemical control. In line with this hypothesis, the PSMA PET group had a lower rate of lymph node relapse after sRT, suggesting sufficient coverage of regional disease within the pelvis. ADT administration in 18.4% of the patients in the PSMA PET cohort with PET-positive findings had only a slight impact on BRFS, as a sensitivity analysis excluding patients who received ADT yielded comparable results. An explanation for this finding might be insufficient ADT duration, as only 22/85 patients (25.9%) received ADT for ≥12 mo.

It is worth mentioning that recurrence patterns revealed comparable occurrence of local relapses in the two groups within 3 yr after sRT, suggesting that local control was independent of focal dose escalation to PET-positive lesions in the fossa. This aligns with a previous study that reported no BRFS benefit for PSMA-guided sRT in patients with cN0 status on imaging before sRT [25]. No positive effect of PSMA PET on MFS was observed. A possible explanation for this finding is the more extensive use of PSMA PET for restaging in the PSMA PET group, as PSMA PET allows detection of distant metastases at earlier time points [10].

The SPORRT randomized controlled trial did not use PSMA PET imaging and reported that 5-yr rates of freedom from progression among 1716 eligible patients were 70.9% for the group with sRT to the fossa, 81.3% for the group with sRT to the fossa plus 6 mo of ADT, and 87.4% for the group with sRT to the fossa and PLNs plus 6 mo of ADT [26]. However, patients in the last group had more acute and chronic grade ≥2 adverse events. The authors stated that expansion of the sRT field to the PLNs was the most plausible cause. According to our results, PSMA PET imaging could be used to identify the most suitable patients for pelvic sRT in the future. However, our study also suggests a relevant effect of this treatment escalation for a maximum of 2 yr. This aligns with current evidence indicating a lack of efficacy for PLN dissection in patients with primary or oligorecurrent prostate cancer [27,28]. Consequently, longer ADT duration, as suggested by the RADICALS-HD trial [29], or addition of other systemic therapies to ADT [30] might lead to a further increase in failure-free survival rates.

Given our results, future prospective studies should incorporate PSMA PET imaging to refine the de-escalation or escalation of sRT treatment strategies. This approach

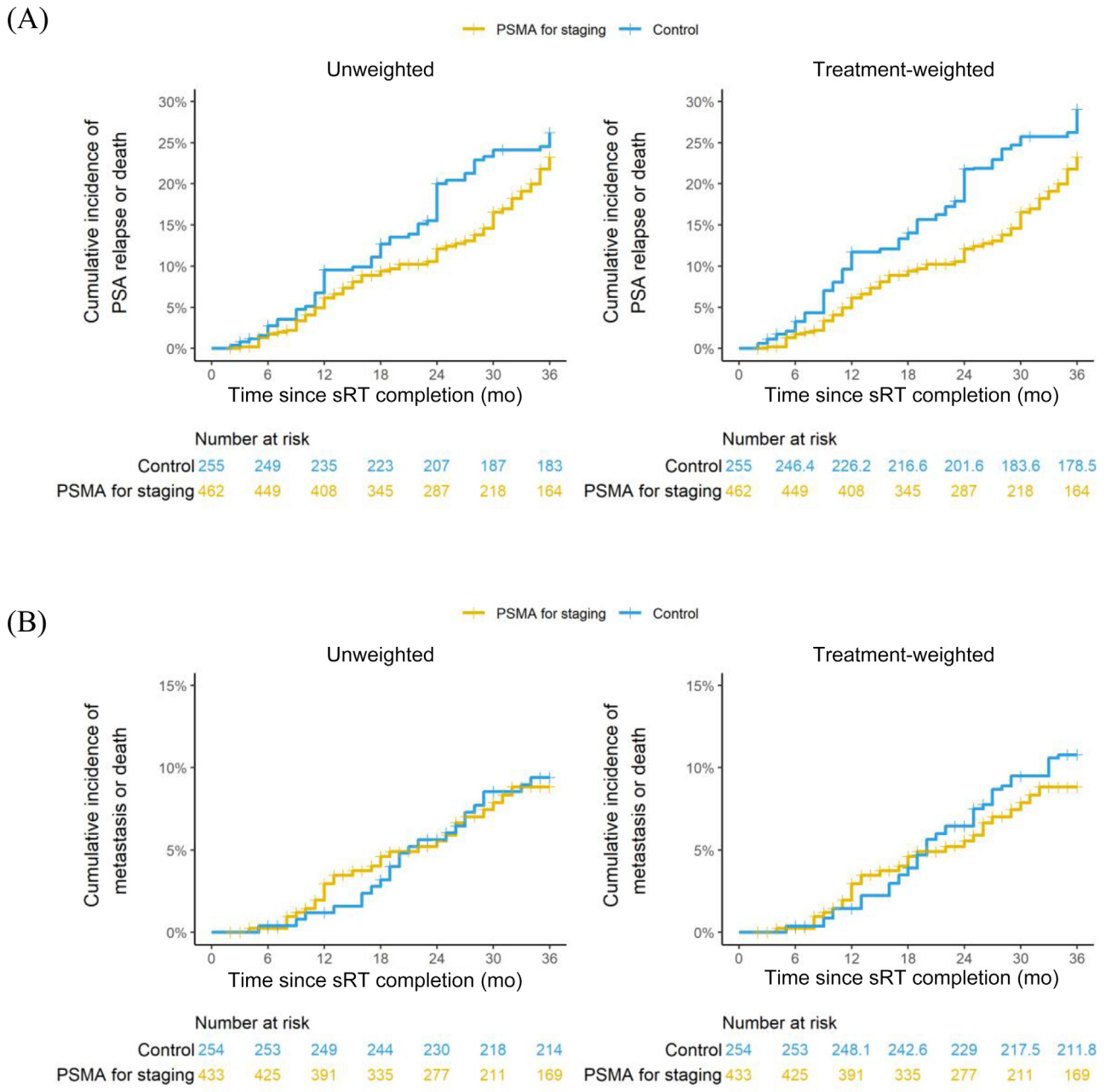

Fig. 1 – Cumulative incidence of PSA relapse or death. (A) Cumulative risk of biochemical relapse or death within the first 3 yr after completion of sRT according to unweighted and treatment-weighted (entropy balancing) analyses . As the curves do not show the same time trends and cross after 3 yr (data not shown), the effect of PSMA PET for staging seems to vary over time. Log-rank tests are not appropriate. We assumed a constant effect of PSMA PET for the first year and each of the following 0.5 yr and estimated the effect of PSMA PET with a Cox model for the period (Fig. 2 and Supplementary Table 4). (B) Cumulative risk of metastasis or death within the first 3 yr after completion of sRT according to unweighted and treatment-weighted (entropy balancing) analyses. Early differences may be attributable to the differential sensitivity of metastasis detection. PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; sRT = salvage radiotherapy.

holds promise for enhancing oncological outcomes or improving patients' quality of life.

Our study has several limitations. One source of bias is the misclassification of the outcome and confounders [31]. Data quality and assurance are often higher in randomized controlled trials, while retrospective trials are based on real-world data of varying quality, including more missing variables and heterogeneous treatment and follow-up protocols. To compensate for the lack of randomization, we used entropy balancing to break the association between confounders and the treatment received. However, unbiased analysis with weighting methods requires assumptions such as overlap of covariate distributions. In addition, unmeasured confounding might exist and only baseline variables were used for balancing.

Time-varying confounders were not included, so there is potential for bias. We used inverse probability of censoring weights to account for the different censoring patterns. Similar assumptions are based on the estimation of these weights. Upweighted patients should be representative of the censored patients. It is assumed that the model is correctly specified, and no residual confounding should be pre-

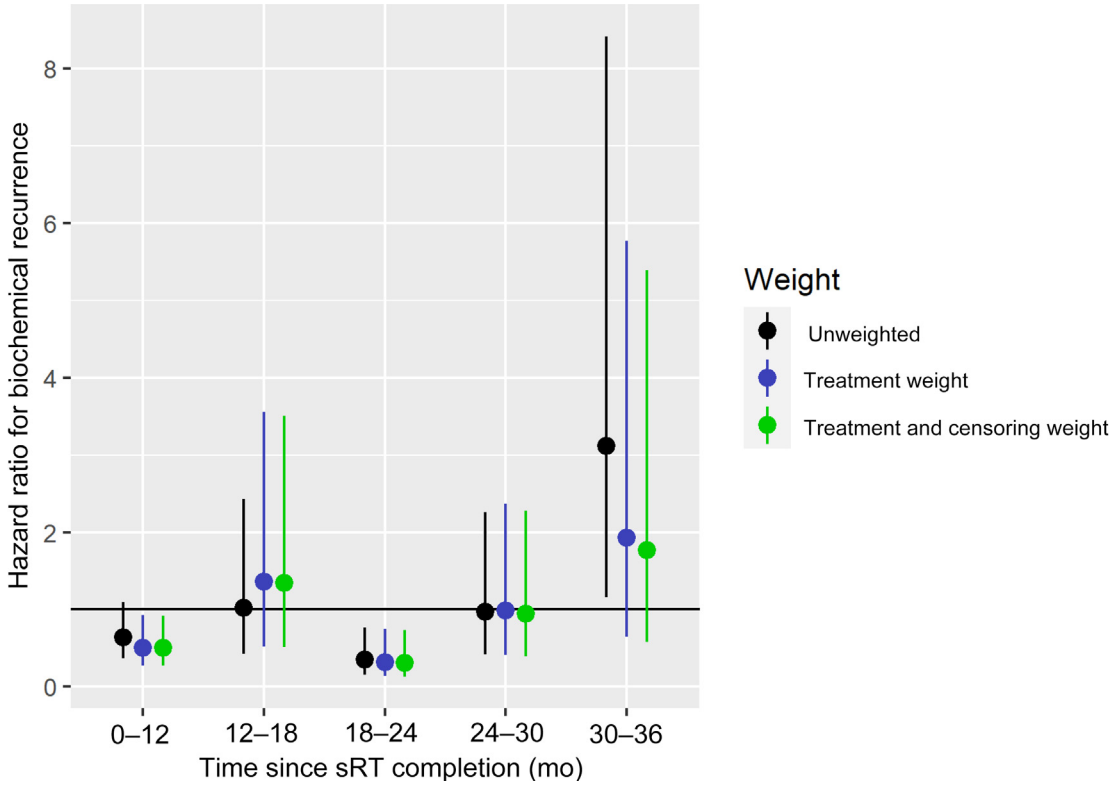

Fig. 2 – Relative effect of PSMA PET on biochemical recurrence-free survival in the first 3 yr after completion of sRT estimated via a Cox model per year. Treatment weight refers to entropy balancing of the two cohorts at baseline. We used treatment and censoring weights to account for imbalance over time due to selective censoring of certain patient groups. A hazard ratio of 1 is interpreted as no effect. A hazard ratio of 0.5 is interpreted as a 50% reduction in the risk of experiencing biochemical recurrence in the PSMA PET cohort in comparison to the control arm. Lines denote the 95% confidence intervals for the hazard ratio and were calculated using the robust standard error. PET = positron emission tomography; PSMA = prostate-specific membrane antigen; sRT = salvage radiotherapy.

sent. Notably, the nonsignificant BRFS difference between the two groups at 12–18 mo after sRT might be attributable to the heterogeneous follow-up protocols in the retrospective cohort. This is evident from the large steps in the cumulative incidence curve for the control group at 12–24 mo (Fig. 2A). Historical controls could introduce bias, but both cohorts in our study showed overlapping patient recruitment times, reducing the impact of this effect.

The multinational composition of the treatment groups means that we anticipate a high degree of generalizability for our results. Nevertheless, it is important to note that the evidence relies on a control cohort from a randomized trial and, given the aforementioned limitations, the effect size observed may vary when applied in real-world settings.

5. Conclusion

Our comparison of two well-balanced cohorts (one prospective and one retrospective) suggests that PSMA PET for sRT planning has an effect on short-term biochemical control in prostate cancer. This effect might be caused by individualized expansion of the sRT field to the PLNs or selective exclusion of patients with cM1 disease before sRT. Increasing the ADT duration or addition of an androgen receptor signaling inhibitor for patients with cN1 disease identified via PET might lead to a further and more durable biochemical response. PSMA PET use did not improve MFS. This effect might be explained by early detection of distant metastases via repeat PSMA PET imaging in cases with relapse after sRT. Prospective studies with longer follow-up are warranted to validate our findings and assess the impact of PSMA guidance for sRT on overall survival.

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Author contributions: Mohamed Shelan 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.

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Table 3 – Weighted recurrence patterns following salvage radiotherapy [a]

Parameter	Number (%)		SMD [b]
	Control cohort	PSMA PET cohort	
Number	26.5	27.0	
Local recurrence			0.025
No	25.4 (95.8)	26.0 (96.3)	
Yes	1.1 (4.2)	1.0 (3.7)	
Any lymph node recurrence			0.603
No	3.9 (14.9)	11.0 (40.7)	
Yes	22.6 (85.1)	16.0 (59.3)	
Bone metastasis			0.202
No	19.2 (72.4)	17.0 (63.0)	
Yes	7.3 (27.6)	10.0 (37.0)	
Visceral metastasis			0.342
No	25.0 (94.5)	27.0 (100.0)	
Yes	1.5 (5.5)	0.0 (0.0)	
Recurrence status known	26.5 (100.0)	27.0 (100.0)	<0.001
More than one recurrence type			0.204
No	21.7 (81.7)	24.0 (88.9)	
Yes	4.8 (18.3)	3.0 (11.1)	0.502
Mean time to metastasis, mo (SD) [c]	20.79 (7.74)	16.78 (8.22)	
Median time to metastasis, mo (IQR) [c]	20.00 (15.01–27.00)	13.00 (10.75–23.00)	

SD = standard deviation; SMD = standardized mean difference IQR: interquartile range; PSMA = prostate-specific membrane antigen; PET = positron emission tomography.
[a] Entropy balancing weighted recurrence pattern for patients with metastases within 3 yr after salvage radiotherapy.
[b] SMD = 0.1 indicates balance.
[c] Median follow-up was 36 mo (IQR 36–36) for the control cohort and 29 mo (IQR 18–36) for the PSMA PET cohort.

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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.2024.11.006.

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