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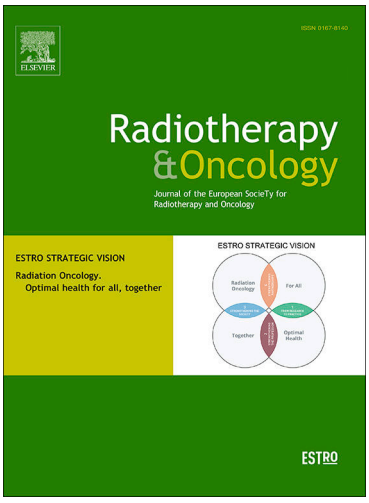

Original Article

Salvage radiotherapy is effective in patients with PSMA-PET-negative biochemical recurrence- results of a retrospective study

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PII: S0167-8140(23)00216-5
DOI: https://doi.org/10.1016/j.radonc.2023.109678
Reference: RADION 109678

To appear in: *Radiotherapy and Oncology*

Received Date: 21 November 2022
Revised Date: 12 April 2023
Accepted Date: 17 April 2023

Please cite this article as: Scharl, S., Zamboglou, C., Strouthos, I., Farolfi, A., Serani, F., Lanzafame, H., Giuseppe Morganti, A., Trapp, C., Koerber, S.A., Debus, J., Peeken, J.C., Vogel, M.M.E., Vrachimis, A., K. B. Spohn, S., Ruf, J., Grosu, A-L., Ceci, F., Fendler, W.P., Bartenstein, P., Kroeze, S.G.C., Guckenberger, M., Krafcsik, M., Klopscheck, C., Fanti, S., Hruby, G., Emmett, L., Belka, C., Stief, C., Schmidt-Hegemann, N-S., Henkenberens, C., Mayer, B., Miksch, J., Shelan, M., Aebersold, D.M., Thamm, R., Wiegel, T., Salvage radiotherapy is effective in patients with PSMA-PET-negative biochemical recurrence- results of a retrospective study, *Radiotherapy and Oncology* (2023), doi: https://doi.org/10.1016/j.radonc.2023.109678

Abstract

Background/Purpose:

The present study aimed to assess whether SRT to the prostatic fossa should be initiated in a timely manner after detecting biochemical recurrence (BR) in patients with prostate cancer, when no correlate was identified with prostate-specific membrane antigen positron emission tomography (PSMA-PET).

Materials and Methods:

This retrospective, multicenter analysis included 1222 patients referred for PSMA-PET after a radical prostatectomy due to BR. Exclusion criteria were: pathological lymph node metastases, prostate-specific antigen (PSA) persistence, distant or lymph node metastases, nodal irradiation, and androgen deprivation therapy (ADT). This led to a cohort of 341 patients. Biochemical progression-free survival (BPFS) was the primary study endpoint.

Results:

The median follow-up was 28.0 months. The 3-year BPFS was 71.6% in PET-negative cases and 80.8% in locally PET-positive cases. This difference was significant in univariate (p=0.019), but not multivariate analyses (p=0.366, HR: 1.46, 95%CI: 0.64-3.32). The 3-year BPFS in PET-negative cases was significantly influenced by age (p=0.005), initial pT3/4 (p<0.001), pathology scores (ISUP) ≥3 (p=0.026), and doses to fossa >70 Gy (p=0.027) in univariate analyses. In multivariate analyses, only age (HR: 1.096, 95%CI: 1.023-1.175, p=0.009) and PSA-doubling time (HR: 0.339, 95%CI: 0.139-0.826, p=0.017) remained significant.

Conclusion:

To our best knowledge, this study provided the largest SRT analysis in patients without ADT that were lymph node-negative on PSMA-PET. A multivariate analysis showed no significant difference in BPFS between locally PET-positive and PET-negative cases.

These results supported the current EAU recommendation to initiate SRT in a timely manner after detecting BR in PET negative patients.

1. Introduction

Salvage radiotherapy (SRT), alone or in combination with androgen deprivation therapy (ADT), is the only curative treatment option for patients with biochemical recurrence (BR) of prostate cancer, after a radical prostatectomy. However, the optimal prostate-specific antigen (PSA) threshold for the initiation of SRT remains to be determined. Retrospective data have indicated that SRT should be initiated as soon as possible [1,2]. The benefits of early SRT have been demonstrated, even at PSA levels below 0.5 ng/ml and especially 0.2 ng/ml [1–3].

The data in support of early SRT were generated before the wide availability of imaging with positron-emission tomography/computed tomography that targeted prostate-specific membrane antigen (PSMA-PET-CT). PSMA-PET is a highly sensitive diagnostic imaging tool for prostate cancer, and its findings might lead to an adaptation in radiotherapy planning in up to 60% of cases [4]. Even at low pre-SRT PSA values, PSMA-PET has revealed lesions outside the recommended target volume for SRT, at a frequency of approximately 20% [5,6]. Overall, when PSMA-PET-CT was performed before initiating SRT, PSMA-PET correlates were discovered in approximately 50% of patients with a pre-SRT PSA of 0.5 ng/ml [5,6]. This advancement in imaging sensitivity raises the question of whether patients with PET-negative results might equally benefit from a timely SRT at the prostatic fossa, after BR has been detected. Because the detection rate rises with increasing PSA levels [6], a theoretical alternative would be to withhold SRT in patients without detectable lesions in PSMA-PET to provide a more precise treatment after the recurrence can be localized. Currently, most guidelines on prostate cancer, including the 2022 European Association of Urology (EAU) guidelines, strongly recommend early treatment initiation, even when PET results are negative [7]. However,

no prospective study, and only very limited retrospective studies, have provided data to support this recommendation [8,9].

This multicenter, retrospective study aimed to assess whether the benefit of early SRT might extend to patients with negative PET results. To that end, we selected a highly distinctive patient cohort of patients with PSMA-PET-staged BR that received SRT and did not show any sign of recurrence outside the prostatic fossa in pre-SRT PSMA-PET images. The SRT outcome was compared between patients without a PSMA-PET correlate (PET-negative result) and patients with a PSMA-PET correlate confined to the prostatic fossa (PET-positive result).

2. Materials and Methods

2.1 Patients

We retrospectively analyzed data obtained from nine participating centers in Germany (n=6), Italy (n=1), Australia (n=1), Switzerland (n=2), and Cyprus (n=1). The study centers collected data on all patients treated with PSMA-PET-based SRT for PSA recurrence or persistence (defined as PSA ≥0.1 ng/ml) after a radical prostatectomy between August 2013 and June 2020. Patients with distant metastases and patients that received ADT prior to the PSMA-PET scan were excluded. In this database, 1222 patients were identified. We then constrained the cohort to patients without pathological lymph node metastases (pN0) and without lymph node or distant metastases detectable on the PSMA-PET images. Furthermore, we excluded patients with PSA persistence, elective radiotherapy to lymph node regions, macroscopic residual tumor upon surgery (R2), ADT, or inconclusive PET findings. The final cohort included 341 patients with PET-negative or locally PET-positive results (Figure 1).

This study was approved by the local Ethics Committees of the participating centers.

2.2 PSMA-PET scans prior to SRT

Prior to SRT, the following tracers were used for PET-imaging: ^{68}Ga-PSMA-11 (n=252), ^{18}F-PSMA-1007 (n=49) or one of the following: ^{68}Ga-PSMA-I&T, ^{18}F-PSMA-DCFPyL or ^{18}F-PSMA-rhPSMA-7/-7.3 (n=40). Scans were performed according to institutional

protocols. All images were interpreted locally by two experienced readers that employed international recommendations for assessments [10]. The PET protocols were described previously [11]. The time between PSMA-PET and beginning of SRT was less than 3 months in 242 patients (71.0%), 3-6 months in 31 patients (9.1%), > 6 months in 40 patients (11.7%) and not retrievable in 32 patients (9.4%).

2.3 Treatment and follow-up

All patients received intensity-modulated and image-guided SRT. Target volumes were defined and doses were prescribed at the discretion of the treatment center, and according to PSMA-PET findings. Eight out of eleven centers prescribed a boost to local recurrences within the fossa. 3 out of nine venters prescribed higher doses to the fossa in cases of initial miscroscopic residual disease in the fossa irrespective of PET finding. SRT protocols are listed in supplemental Table S1.

Routine follow-ups included PSA testing at regular intervals. The follow-up procedures of the respective centers are summarized in supplemental Table S2. Patients with biological progression after the SRT underwent PSMA-PET (preferably) or conventional imaging to localize the recurrence.[11]

2.4 Statistical analysis

Continuous data are presented as the mean with standard deviation or median with minimum and maximum. Categorical data are described as absolute frequencies and percentages. Statistical comparisons were performed with the t-test for normally distributed continuous data. Pearson's Chi square test was performed for testing the independence of categorical variables. No adjusting for multiple testing was performed, due to the retrospective exploratory approach of this analysis.

The database retrieval was done in January 2022. The primary study endpoint was BPFS, which was defined as the time from completing the SRT to BR (defined as nadir after SRT + 0.2 ng/ml), death from any cause, or the last date recorded alive, whichever came first. Secondary endpoints were overall survival (OS), metastases-free survival (MFS), and local control. OS was defined as the time from completing the SRT to death

from any cause or the last date recorded alive. MFS was defined as the interval between SRT initiation and the date of metastasis or death, whichever occurred first. Local control was defined as the absence of local recurrence.

BPFS, OS, MFS, and local control were estimated with the Kaplan–Meier method (log-rank test) and the Cox regression model. The cohort of PET negative patients served as the reference group. Covariates assessed in a univariate analysis included the International Society of Urological Pathology (ISUP) grade of the surgery specimen, the initial pathological T stage (pT stage), the resection status (R0-R1), PSA serum values before SRT (PSA before SRT), the maximal prescription dose to parts of the prostatic fossa (f.e. boost to the local recurrence) or the complete prostatic fossa (DPF), and the PSA-doubling time. The SRT concepts of the respective centers are described in Supplemental Table S1. Only factors that achieved a p-value <0.1 in the univariate analysis of the complete cohort were included in the multivariate Cox regression analysis.

Hazard ratios (HR) were considered significant, when the corresponding 95% confidence interval (95% CI) excluded 1. All tests were two-sided. P-values <0.05 were considered statistically significant. All calculations were performed with IBM SPSS Statistics Version 28.0 (IBM Corp., Armonk, NY, USA) or R (Version 4.1.2).

3. Results

The median age at diagnosis was 70 years (range: 47-83 years). Among the 341 patients included, 257 (77.6%) had PSA levels ≤0.5 ng/ml before starting SRT, and 166 (48.7%) had a DPF >70 Gray (Gy).

The cohort included 173 patients with negative PET results (50.7%) and 168 (49.3%) with locally positive PET results and only local recurrence. Baseline characteristics and treatments are given in Table 1. The median PSA values before SRT lay between 0.2 to 0.5 ng/ml in both groups. A ≤0.5 ng/ml PSA level before SRT was more common in the PET-negative than in the PET-positive group (p<0.001). An ISUP ≥3 (p=0.003) and a

PSA-doubling time ≤6 months (p=0.036) occurred significantly more frequently in the PET-negative group. Furthermore, the PET-negative group had a lower frequency of DPFs >70 Gy (21.4 vs. 76.8%, p=0.001). The remaining prognostic parameters were distributed equally across the groups.

The median follow-up was 28.0 months (interquartile range 25.7-30.3 months). A Kaplan-Meier analysis showed that the 3-year BPFS was significantly lower in the PET-negative group (71.6%) than in the locally PET-positive group (80.8%, p=0.019, Figure 2). The median time between SRT and BR was 68.0 months (± 4.2 months) in the PET-negative group, but it was not reached in the PET-positive group. Other factors that significantly influenced BPFS in the univariate analysis were age; pT stage 2 vs. 3/4; R stage 0 vs. 1/x; ISUP score 1 or 2 vs. 3-5; PSA-doubling time ≤6 vs. >6 months; and the DPF (Table 3).

Prognostic factors were not equally distributed across the PET-negative and PET-positive groups. Thus, a multivariate Cox-regression analysis was conducted to account for potential confounders. In the multivariate analysis, the difference in BPFS between PET-positive and PET-negative groups was no longer significant. The only factors that remained significant for BPFS were age, R stage, ISUP Score, and the PSA-doubling time (

Table 2).

The groups showed no significant differences in 3-year OS (98.5vs. 100%, p=0.190), 3-year MFS (89.6 vs. 92.5%, p=0.346), or 3-year local control (100vs. 97.8%, p=0.558).

To provide a better understanding of the PET-negative cohort, we investigated potential factors that influenced BPFS in these patients. A univariate analysis identified four significant factors. These factors were age (p=0.005), initial pT stage 2 vs. 3/4 (p=0.002), ISUP 3-5 vs. 1 or 2 (p=0.026), and DPF ≤70 Gy vs. >70 Gy (p=0.027). In a multivariate Cox-regression analysis, only age and PSA-doubling were identified as independent predictive factors for BPFS in this group (Table 3).

The univariate analysis identified two significant predictors of BPFS in the PET-positive group: an ISUP of 3-5 vs. 1 or 2 (p<0.001) and a PSA-doubling time ≤6 months vs. >6 months (p=0.046). In a multivariate Cox-regression analysis, only the ISUP score and the DPF were identified as significant factors in BPFS in this group (Table 4).

Information on a PSA nadir <0.1 ng/ml could be obtained in 82 (24.0%) patients in the complete cohort. Of these, only 58 patients (70.7%) attained an undetectable PSA after SRT. 30 out of 44 PET negative patients (68.2%) and 28 out of 38 PET positive patients (73.7 %) achieved an undetectable PSA after SRT (p=0.633). An undetectable PSA was highly predictive of the outcome. BPFS (HR: 0.026, 95%-CI: 0.006-0.117, p<0.001) and MFS (HR: 0.041, 95%-CI: 0.005-0.327, p=0.003) were significantly superior among patients that achieved undetectable PSA (log-rank <0.001 for both). This superiority was observed in both the PET-negative (BPFS:HR 0.019, 95%-CI: 0.002-0.147, p=0.012, MFS: HR 0.06, 95%-CI: 0.007-0.492, p=0.009) and the PET-positive groups (BPFS: HR 0.068, 95%-CI: 0.007- 0.545, p<0.001, MFS: HR 0.009, 95%-CI: 0.00-12078.45, p=0.457).

In the entire cohort, BR was observed in 71 patients (20.8%). Of these patients, 64 (90.1%) were restaged with PSMA-PET. The recurrence could be localized in 34 patients (47.9%). Most patients experienced a pelvic lymph node recurrence alone (n=15, 44.1%), distant metastases (n=10, 29.4%), or a combination of distant metastases and pelvic recurrence (n=7, 20.6%). Local recurrence within the prostatic fossa was rare. Only one patient experienced a local recurrence and one patient experienced a local recurrence combined with a pelvic lymph node recurrence (2.9% for both).

Among the patients with initially negative PET results (n=49), the recurrence location was recorded in 23 (46.9%). No recurrences were observed within the prostatic fossa; 11 (48%) recurrences were observed within the pelvic lymph nodes; and 12 (52%) recurrences involved distant metastases, either alone (n=7, 30%) or in combination with a pelvic recurrence (n=5, 22%). There were no significant differences in metastatic patterns between the PET-negative and PET-positive groups (p=0.484).

4. Discussion

In this study, we compared the outcome of biological progression after SRT in patients with negative and locally positive PET results. We chose a highly select, homogenous cohort of patients with negative primary lymph nodes and solely local recurrences that had not undergone ADT treatment. The key finding of our study was that SRT provided an excellent outcome in both the PET-negative and the locally PET-positive groups. The 3-year BPFS rate in the PET-negative group was 71.6%, which was comparable to the 60 to 75% 3-year BPFS rates reported in previous studies of cohorts without pre-SRT PSMA-PET [2,12–14]. We also found a 3-year MFS of 89.6% for the PET-negative group, and no significant difference in the PET-positive group. Hence, our results supported the current EAU guideline recommendation to initiate SRT (+/-ADT) in a timely manner after detecting BR in PET-negative cases, without waiting until the recurrence can be localized with PSMA-PET.

Our univariate analysis indicated a significant (roughly 10%) difference in 3-year BPFS rates, in favor of patients with a local PSMA-PET correlate. This difference might be explained by a number of factors. One concern -particularly in the PET negative group- is the potential presence of micro-metastases outside the radiation field. However, after adjusting for confounding factors, this difference did not remain significant. Therefore, we assumed that the difference in 3-year BPFS was due to the presence of higher risk prognostic factors in the PET-negative group. Furthermore, the PET-positive group was three-fold more likely to have received a maximal dose >70 Gy to parts or the whole fossa. The randomized SAKK 09/10 trial did not show a benefit for dose escalation in SRT [12]. Nevertheless, a number of retrospective studies and a subgroup analysis of a prospective study suggested otherwise [14–16]. However, all the previous studies were conducted without PSMA-PET-CT. Therefore, it remains unresolved whether dose escalation might provide a benefit in patients staged with PSMA-PET. In our study, eight out of eleven centers prescribed a higher dose to patients with a local PSMA-PET correlate. Dose escalations above 70 Gy were associated with a favorable BPFS in the univariate, but not the multivariate analysis in the complete cohort. However, the multivariate analysis might have included insufficient patient numbers for adequate

statistical power. In the PET positive cohort, we found a statistically significant effect of dose escalation on BPFS.

Few other studies have compared the SRT outcome between patients with PET-negative and PET-positive results [8,9,17,18]. However, the cohorts of those studies contrasted with our cohort, because the patient selection was less restrictive and they included fewer patients with PSMA-PET scans that showed no lymph node involvement or distant metastases.

Wenzel et al. analyzed a subgroup of 90 patients with PET-negative results and 48 patients with presumably locally PET-positive results from a cohort of 1599 patients receiving SRT for BR [8]. They observed a significantly worse MFS in the PET-positive group. However, they did not have access to PSMA-PET-CT reports; thus, they could not accurately differentiate between patients with only locally PET-positive results and those with lymph-node recurrences. Consequently, the worse MFS might have been due to the inclusion of patients in higher disease stages before SRT in the PET-positive group. Moreover, other confounding factors were present in that cohort: approximately 15% had lymph node metastases at surgery and 50% had received ADT [8].

Emmet et al conducted a study with 186 patients that underwent PSMA-PET-CT and received SRT with or without ADT for BR. In that cohort, 43 patients had locally PET-positive results and 57 patients had negative PSMA-PET-CT results. Similar to our results, their failure-free survival rates were comparable between the groups [9]. However, ADT was not excluded in that study. Therefore, their results cannot be directly compared to our results.

Three large retrospective studies in patients without pre-SRT PSMA-PET-CT demonstrated that higher pre-SRT PSA values were correlated with higher rates of distant metastases and lower BPFS rates [1,2,19]. In contrast, we did not find a significant correlation between pre-SRT PSA values and BPFS. However, it must be pointed out that, in our database, PSA was recorded as a range, not as the actual value. Furthermore, our cohort included few patients that were treated at PSA levels above 0.5 ng/ml. In an previous analysis of the same consortium with less restrictive patient

selection, and consequently higher patient numbers, a significant correlation was observed between a low pre-SRT PSA and MFS [11].

In around 50% of patients in the initially PET-negative group that relapsed after SRT, we detected a PET correlate during the recurrence. This finding confirmed the suspicion that, in some patients with PET-negative results, a PSMA-PET correlate could be detected at a later stage. Indeed, the main problem with an SRT for patients with PET-negative results is that micro-metastases outside the typical SRT-target volume might be missed. However, postponing SRT in favor of follow-up imaging may deprive those patients of the only curative treatment option. This situation is particularly problematic, because approximately 50% of patients remain PET-negative after they surpass the therapeutic window of 0.5 ng/ml [20,21]. Moreover, BR has been shown to impact OS in patients with low PSA-doubling times (<12 months) and/or high ISUP scores (4+5) [22]. We found that both these risk factors occurred more frequently in the PET-negative group. These results indicated that we need a better means of selecting patients that might benefit from elective nodal irradiation, because approximately 50% of recurrences were detected in pelvic lymph nodes. The randomized SPPORT trial demonstrated a benefit of adding pelvic nodal RT and short-term ADT to SRT in high risk patients [23].

Based on current knowledge that was not available at the time of treatment, a substantial proportion of patients in our cohort could have been candidates for additional ADT [24,25]. Thus, future research should focus on identifying prognostic markers for predicting a benefit from additional ADT in patients with PET-negative results. In our cohort, the PSA-doubling time had a significant effect on BPFS in the PET-negative group. Undetectable PSA might serve as a predictor for the outcome after SRT [3,13]. Although the PSA-doubling time was recorded in only 24% of patients in our cohort, it was significantly associated with BPFS and MFS.

Our study had some limitations. First, it had the limitations inherent to retrospective studies. The risk factors were not distributed equally, and a selection bias is always a concern in retrospective analyses. Second, SRT concepts differed between treatment centers and for PSMA-PET institutional protocols and a variety of different PET tracers were used, because they were not predefined. Moreover, the pre-SRT PSA was not recorded as a value in our database; instead it was categorized as: 0.01-0.2 ng/ml, 0.2-

0.5 ng/ml, 0.5-1 ng/ml, and >1 ng/ml. Therefore, the multivariate analysis could not be accurately adjusted for this covariate. Another major limitation is the fact that the year of treatment was not recorded in the database. Adjustments in multivariate analysis therefore do not account for this parameter. Since the total number of patients per center over a treatment period of 8 years seems low, we assume that in the earlier years starting from 2012 only a fraction of patients treated for SRT received PET-CTs and were included in the database. This would also explain why the follow-up time is only 28 months. Unfortunately, we cannot retrieve information on how many patients received SRT without PET-CT in the respective centers as these patients were not considered for the database.

5. Conclusion

To our best knowledge, this study represented the largest analysis of the SRT outcome after a radical prostatectomy in patients without hormonal treatment that were staged with negative lymph-node involvement, based on a PSMA-PET. Early salvage radiotherapy in patients with negative PSMA-PET-CT results was associated with high rates of biochemical control. Approximately 70% of the PET-negative group achieved a 3-year BPFS without ADT. In a multivariate analysis, we found no significant difference in BPFS between PET-positive and PET-negative groups. Consequently, these findings supported the current EAU guideline recommendation to initiate SRT in a timely manner after detecting BR. These results need to be confirmed prospectively.

Figures

Figure 1: Flowchart shows selection of patients treated with SRT for prostate cancer. PET: positron emission tomography; PSA: prostate-specific antigen; SRT: salvage radiotherapy; ADT: Androgen deprivation therapy; pN0: no pathologic lymph nodes observed in surgical specimen, pN1: pathologic lymph nodes observed in surgical specimen, pNx: no information on : pathologic lymph nodes observed in surgical specimen; R0, R1, R2: degrees of microscopic or macroscopic residual tumor after resection

Figure 2: Biochemical progression-free survival (BPFS) in patients with PET-negative and locally PET-positive results after salvage radiotherapy for prostate cancer. Cum: cumulative PET: positron emission tomography; No: number

Tables

Table 1: Characteristics of patients treated with salvage radiotherapy for prostate cancer, grouped by positive or negative results from PET scans

Table 2: Univariate and multivariate Cox-regression results for factors that influence BPFS in the complete cohort

Table 3: Univariate and multivariate Cox-regression results for factors that influence BPFS in the PET-negative cohort

Table 4: Univariate and multivariate Cox-regression results for factors that influence BPFS in the PET-positive cohort

Supplemental Table S1: Dose concepts and delineation guidelines for salvage RT in the participating centers.

Supplemental Table S2: Follow-up schedule of the respective centers.

Acknowledgments:

We thank Kilian Schiller, Stephanie E.Combs, Joerg Sahlmann, Simon Kirste, Christian Gratzke, Federica Medici, Leticia Cavallini and Konstantinos Ferentinos for their role in building the database.

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Table 5: Characteristics of patients treated with salvage radiotherapy for prostate cancer, grouped by positive or negative results from PET scans

Characteristic	Category	PET negative n=173 (50.7%)	PET positive n=168 (49.3%)	P-value
Age, years		68.0±7.4	70.0 ± 6.3	0.008*
Initial PSA (ng/ml)	0-10	85 (49.1%)	92 (54.8%)	0.819
	10.1-20	46 (26.6%)	45 (27.8%)	
	>20	13 (7.5%)	11 (6.5%)	
	Unknown	29 (16.8%)	20 (11.9%)	
Initial pT stage	2	98 (56.7%)	103 (61.3%)	0.369
	3a/3b/4	75 (43.3%)	64 (38.1%)	
	unknown	0	1 (0.6%)	
R stage	R0	120 (69.4%)	113 (67.3%)	0.160
	R1	51 (29.4%)	46 (27.3%)	
	unknown	2 (1.2%)	9 (5.4%)	
Time between surgery and BR	≤ 1 year	74 (42.8%)	70 (41.7%)	0.825
	> 1 year	95 (54.9%)	96 (57.1%)	
	unknown	4 (2.3%)	2 (1.2%)	
ISUP Score	1+2	71 (41.0%)	96 (57.1%)	0.003*
	3+4+5	100 (57.8%)	70 (41.7%)	
	unknown	2 (1.2%)	2 (1.2%)	
PSA-doubling time (months)	0-6	53 (30.6%)	27 (16.1%)	0.036*
	6.1-12	27 (15.6%)	29 (17.3%)	
	>12	37 (21.4%)	40 (23.8%)	
	unknown	56 (32.4%)	72 (42.8%)	
PSA before SRT (ng/ml)	0.01-0.2	65 (37.6%)	33 (19.6%)	<0.001*
	0.2-0.5	82 (47.4%)	77 (45.8%)	
	0.5-1.0	19 (10.9%)	24 (14.3%)	
	>1.0	7 (4.1%)	24 (14.3%)	
	unknown	0	10 (6.0%)	
Dose to fossa (Gy)	≤70	134 (77.5%)	35 (20.8%)	<0.001*
	>70	37 (21.3%)	129 (76.8%)	
	unknown	2 (1.2%)	4 (2.4%)	

Values are the number (%) or mean ±SD, unless otherwise indicated. *Significant difference; PSA: prostate-specific antigen, pT: Size and extend of primary tumor in surgical specimen, R stage: degrees of

microscopic or macroscopic residual tumor after resection, ISUP Score: International Society of Urological Pathology Score

Factor	Category	Cox-Regression							
		univariate				multivariate			
				95% CI				95% CI	
		p	HR	Lower	Upper	*p*	HR	Lower	Upper
PET correlate	No	.020*	1.000			.526	1.000		
	Yes		.555	.337	.913		1.291	.586	2.845
Age (years)	continuous	.004	1.056	1.017	1.097	.004*	1.081	1.025	1.140
Initial PSA (ng/ml)	≤10		1.000						
	10.1-20	.527	.822	.449	1.507				
	>20	.414	1.378	.638	2.977				
pT Stage	2	<.001*	1.000			.239	1.000		
	3a/3b/4		2.284	1.425	3.661		1.468	.775	2.780
R stage	0		1.000				1.000		
	1/x	.016*	.502	.288	0.877	.045*	.467	.221	.985
ISUP Score	1+2	<.001	1.000			.001*	1.000		
	3-5		3.510	2.008	6.137		4.225	1.748	10.212
PSA-doubling time (months)	≤6	.008*	1.000			.007*	1.000		
	>6		.441	.240	.810		.409	.212	0.789
PSA before SRT (ng/ml)	0.01-0.2		1.000						
	0.21-0.5	.304	1.357	.759	2.426				
	>0.5	.228	1.512	.772	2.964				
RT dose (Gy)	≤70	.001*	1.000			.389	1.000		
	>70		.437	.263	.726		.714	.331	1.537

Table 6: Univariate and multivariate Cox-regression results for factors that influence BPFS in the complete cohort

*Significant difference; PET: positron emission tomography; PSA: prostate-specific antigen; SRT: salvage radiotherapy; pT: Size and extend of primary tumor in surgical specimen, R stage: degrees of microscopic or macroscopic residual tumor after resection, ISUP Score: International Society of Urological Pathology Score;

Table 7: Univariate and multivariate Cox-regression results for factors that influence BPFS in the PET-negative cohort

Factor	Category	Cox-Regression							
		univariate				multivariate			
				95% CI				95% CI	
		p	HR	Lower	Upper	*p*	HR	Lower	Upper
Age (years)	continuous	.005	1.067	1.020	1.117	.009*	1.096	1.023	1.175
Initial PSA (ng/ml)	≤10		1.000						
	10.1-20	.875	.941	.442	2.004				
	>20	.211	1.790	.719	4.454				
pT Stage	2	.002*	1.000			.254	1.000		
	3a/3b/4		2.506	1.392	4.514		1.680	.689	4.095
R stage	0	.125	1.000			.164			
	1/x		.590	.301	1.159		.504	.192	1.322
ISUP Score	1+2	.026*	1.000			.120	1.000		
	3-5		2.108	1.092	4.068		2.471	.790	7.727
PSA-doubling time (months)	≤6	.085	1.000			.017*	1.000		
	>6		.504	.232	1.099		.339	.139	.826
PSA before SRT (ng/ml)	0.01-0.2		1.000						
	0.21-0.5	.421	1.307	.680	2.511				
	>0.5	.294	1.594	.668	3.807				
RT dose (Gy)	≤70	.027*	1.000			.563	1.000		

	>70		.376	.158	.896	.729	.261	2.124

*Significant difference; PET: positron emission tomography; PSA: prostate-specific antigen; SRT: salvage radiotherapy; pT: Size and extend of primary tumor in surgical specimen, R stage: degrees of microscopic or macroscopic residual tumor after resection, ISUP Score: International Society of Urological Pathology Score;

Table 8: Univariate and multivariate Cox-regression results for factors that influence BPFS in the PET-positive cohort

Factor	Category	Cox-Regression							
		univariate				multivariate			
				95% CI				95% CI	
		p	HR	Lower	Upper	*p*	HR	Lower	Upper
Age (years)	continuous	.247	1.041	0.9725	1.114	.757	1.015	.925	1.113
Initial PSA (ng/ml)	≤10		1.000						
	10.1-20	.551	.730	.260	2.052				
	>20	.828	.848	.190	3.778				
pT Stage	2	.091	1.000			.291	1.000		
	3a/3b/4		2.040	.894	4.655		1.756	.617	5.001
R stage	0		1.000				1.000		
	1/x	.083	.412	.151	1.122	.096	.302	.074	1.236
ISUP Score	1+2	<.001*	1.000			.002*	1.000		
	3-5		10.020	2.974	33.750		11.004	2.276	53.205
PSA-doubling time (months)	≤6	.046*	1.000			.189	1.000		
	>6		.368	.138	.982		.511	.188	1.392
PSA before SRT (ng/ml)	0.01-0.2		1.000						
	0.21-0.5	.249	2.446	.535	11.180				
	>0.5	.109	3.508	.757	16.250				
RT dose (Gy)	≤70	.169	1.000			.040*	1.000		

	>70		.531	.216	1.308	.232	.058	0.935

*Significant difference; PET: positron emission tomography; PSA: prostate-specific antigen; SRT: salvage radiotherapy; pT: Size and extend of primary tumor in surgical specimen, R stage: degrees of microscopic or macroscopic residual tumor after resection, ISUP Score: International Society of Urological Pathology Score;

Figure

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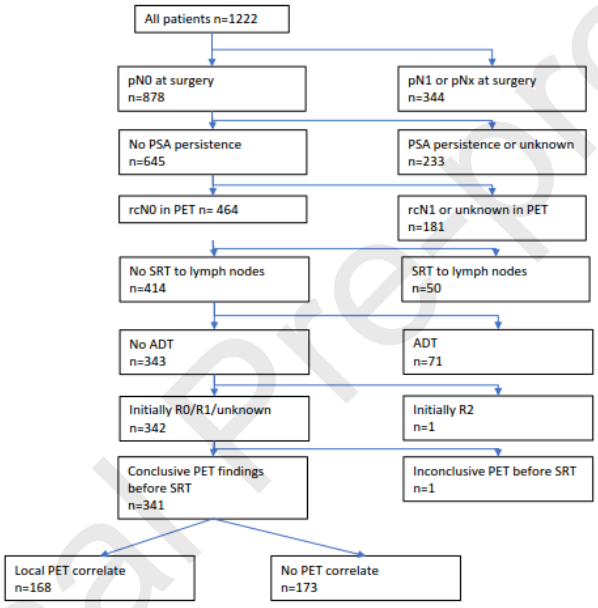

Figure

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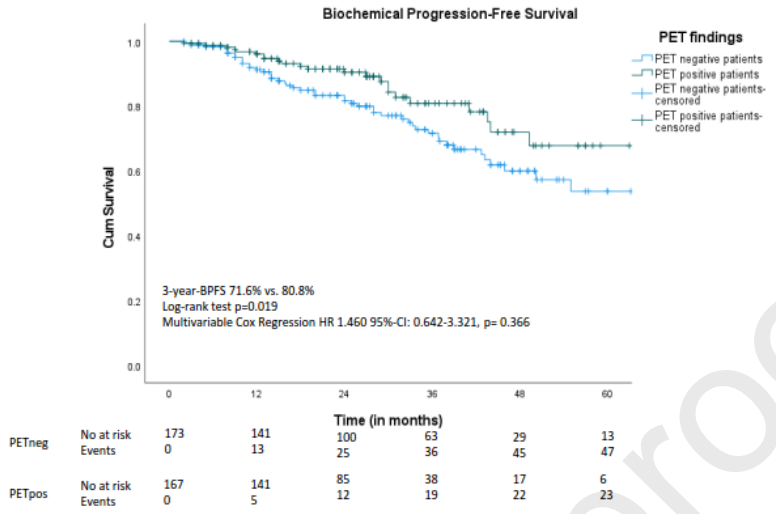

Salvage radiotherapy is effective in patients with PSMA-PET-negative biochemical recurrence- results of a retrospective study

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Short title:

Salvage radiotherapy in patients with PET-negative biochemical recurrence

Highlights:

- Salvage radiotherapy effectively treats biochemical recurrence of prostate cancer regardless of PET imaging result
- Salvage radiotherapy should be initiated in a timely manner in patients without PET correlate
- Biochemical progression-free survival significantly depended on age and prostate-specific antigen-doubling time
- In patients with locally positive lesions, pathology and dose to the fossa influenced biochemical progression-free survival

Conflicts of interest

Wolfgang P. Fendler reports fees from SOFIE Bioscience (research funding), Janssen (consultant, speaker bureau), Calyx (consultant), Bayer (consultant, speaker bureau, research funding), Parexel (image review), and AAA (speaker bureau), all outside the purview of the submitted study.

All other authors declare no conflicts of interests, in terms of employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, grants, or any funding.