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EUO Priority Article – Prostate Cancer

Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Is Associated with Improved Oncological Outcome in Men Treated with Salvage Radiation Therapy for Biochemically Recurrent Prostate Cancer

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Abstract

Background: Radiolabeled prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has shown superior diagnostic accuracy to conventional imaging for the detection of prostate cancer deposits . Consequently, clinical management changes have been reported in patients with biochemical recurrence (BCR) of disease after robot-assisted radical prostatectomy (RARP). We hypothesized that, due to the exclusion of patients with metastatic disease on PSMA-PET/CT, those who underwent local salvage radiation therapy (SRT) after restaging PSMA-PET/CT for BCR may have better oncological outcomes than patients who underwent "blind" SRT.

Objective: To compare the oncological outcome of a patient cohort that underwent PSMA-PET imaging prior to SRT with that of a patient cohort that did not have PSMA-PET imaging before SRT.

Design, setting, and participants: We included 610 patients who underwent SRT, of whom 298 underwent PSMA-PET/CT prior to SRT and 312 did not. No additional hormonal therapy was prescribed.

Outcome measurements and statistical analysis: To compare both cohorts, case-control matching was performed, using the prostate-specific antigen (PSA) value at the initiation of SRT, pathological grade group, pathological T stage, surgical margin status, and

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Case-control matching

biochemical persistence after RARP as matching variables. The outcome variable was biochemical progression at 1 yr after SRT, defined as either a rise of PSA ≥0.2 ng/ml above the nadir after SRT or the start of additional treatment.

Results and limitations: After case-control matching, 216 patients were matched in both cohorts (108 patients per cohort). In the patient cohort without PSMA-PET/CT prior to SRT, of 108 patients, 23 (21%) had biochemical progression of disease at 1 yr after SRT, compared with nine (8%) who underwent restaging PSMA-PET/CT prior to SRT ($p = 0.007$).

Conclusions: PSMA-PET/CT is found to be associated with an improved oncological outcome in patients who undergo SRT for BCR after RARP.

Patient summary: Performing prostate-specific membrane antigen positron emission tomography/computed tomography imaging in patients with biochemical recurrence of disease after robot-assisted radical prostatectomy, before initiating salvage radiation therapy, resulted in improved short-term oncological outcomes.

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1. Introduction

In 2018, prostate cancer (PCa) accounted for 7.1% of all cancer cases, which made it the second most common type of cancer in men [1]. One of the main curative treatment options for patients with localized PCa is robot-assisted radical prostatectomy (RARP). Despite good long-term outcomes of RARP, approximately 20–40% of patients experience biochemical recurrence (BCR) of disease, measured by rising prostate-specific antigen (PSA) values (ie, PSA ≥0.2 ng/ml) after RARP [2–4]. For these patients, salvage radiation therapy (SRT) to the prostatic fossa is the only potentially curative treatment option. Therefore, the European Association of Urology (EAU) guidelines strongly recommend early SRT to men with two consecutive PSA rises after RARP [5].

Historically, patients with BCR after RARP underwent immediate "blind" SRT on the first evidence of BCR. Siegmann et al [6] found that 51% of patients undergoing SRT for BCR reached a PSA nadir of <0.1 ng/ml. Besides, Stephenson et al [7] showed that in patients who did not receive androgen deprivation therapy (ADT), 55% had a PSA value of ≤0.1 ng/ml after SRT. These studies thus showed that SRT resulted in long-term PSA-free survival in only about 50% of patients with BCR, meaning that half of patients might not be cured by SRT alone. It is likely that these patients might be metastasized at the time of SRT and potentially underwent SRT unnecessarily, with all the risks of complications, such as losses in health-related quality of life in the domains of urinary, bowel, and sexual functions [8].

Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has shown superior diagnostic accuracy to conventional imaging for the detection of PCa-deposits in men with BCR after RARP [9]. In their study, van Leeuwen et al [10] showed that in 20/70 patients (29%) staged by ^{68}Ga-PSMA-PET/CT for BCR after RARP, lesions outside of the prostatic fossa were detected. It is assumed that in these patients, local salvage treatment would probably result in early treatment failure. Furthermore, Calais et al [11] and Meijer et al [12] showed that restaging data retrieved from PSMA-PET/CT lead to a change of management in 40–50% of patients with BCR. Therefore, hypothetically, patients who undergo PSMA-PET/CT imaging prior to SRT may have improved oncological outcomes after SRT compared with patients who underwent blind SRT, due to the exclusion of patients with metastatic disease on PSMA-PET/CT. The aim of the present study was to compare the biochemical progression rate at 1 yr after SRT in patients within a case-control matching study, who underwent SRT either with or without restaging PSMA-PET/CT for BCR after RARP.

2. Patients and methods

2.1. Study design and data collection

In the present study, we evaluated patients with BCR after RARP who subsequently underwent SRT to the prostatic fossa. Four reference centers in the Netherlands for PCa radiation therapy, that is, Amsterdam UMC (Amsterdam), Netherlands Cancer Institute (Amsterdam), University Medical Center Utrecht, and MAASTRO clinic (Maastricht), collaborated in this study. To assess the oncological outcome of patients who underwent PSMA-PET imaging prior to SRT versus patients without PSMA-PET imaging before SRT, a PSMA cohort (2016–2020) was compared with a historical cohort (2010–2015) undergoing SRT. In all patients, biochemical progression after SRT was assessed and defined as a PSA value of ≥0.2 ng/ml above the nadir after SRT or the start of additional treatment.

The study was approved by the institutional review board of the participating centers (VUmc2019.275; IRBd19182; UMCU21-049; MAASTRO-W-21-02-00060). Patients were excluded from analyses when they had lymph-node or distant metastases found either during extended pelvic lymph-node dissection (pN1) or at restaging PSMA-PET/CT imaging. Moreover, we excluded patients who received ADT or antiandrogen therapy during or prior to SRT, patients who underwent more extensive radiation therapy such as elective pelvic nodal radiation, and patients for whom insufficient biochemical follow-up after SRT was available (<1 yr).

2.2. PSMA-PET imaging

All PSMA-PET scans were either performed according to local protocol or clinically revised in one of the four participating high-volume PCa radiation centers. All scans were reviewed independently at each institution and discussed in a multidisciplinary meeting. No centralized review was

Table 1 – Baseline characteristics of all included patients who underwent salvage radiation therapy (SRT) for biochemically recurrent prostate cancer after radical prostatectomy.

	All patients (*n* = 610)	Historical cohort (*n* = 312)	PSMA cohort (*n* = 298)	*p* value
Age at SRT (yr), median (IQR)	67 (62–71)	65 (61–70)	68 (64–72)	**<0.001**
PSA value at initiation of SRT (ng/ml), median (IQR)	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.3 (0.2–0.5)	**<0.001**
Total administered dose (Gy), median (IQR)	70 (66–70)	70 (66–70)	70 (66–70)	0.44
Equivalent dose in 2 Gy fractions (Gy), median (IQR)	70 (68–70)	70 (66–70)	70 (70–70)	**<0.001**
Interval between RARP and SRT (mo), median (IQR)	24 (11–49)	25 (11–47)	22 (10–56)	0.62
PSA doubling time (mo), median (IQR)	7.0 (3.7–13.2)	6.1 (3.0–11.9)	8.0 (4.1–14.7)	**0.029**
Pathological grade group according to ISUP, *n* (%)				
1	95 (15)	63 (20)	32 (11)	**0.003**
2	218 (36)	102 (33)	116 (39)	
3	132 (21)	57 (18)	75 (25)	
4	85 (14)	49 (16)	36 (12)	
5	65 (11)	30 (10)	35 (12)	
Missing	15 (3)	11 (3)	4 (1)	
Pathological T stage, *n* (%)				
≤pT2	312 (51)	161 (52)	151 (51)	0.34
pT3a	190 (31)	90 (29)	100 (34)	
≥pT3b	105 (17)	59 (19)	46 (15)	
Missing	3 (1)	2 (<1)	1 (<1)	
Surgical margin status, *n* (%)				
Negative	254 (41)	115 (37)	139 (47)	**0.023**
Positive	340 (56)	186 (60)	154 (52)	
Missing	16 (3)	11 (3)	5 (1)	
Biochemical persistence after RARP, *n* (%)				
No	437 (72)	212 (68)	225 (76)	0.11
Yes	159 (26)	89 (29)	70 (23)	
Missing	14 (2)	11 (3)	3 (1)	

IQR = interquartile range; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RARP = robot-assisted radical prostatectomy; SRT = salvage radiation therapy.

Table 2 – Baseline characteristics after case-control matching.

	All patients (*n* = 216)	Historical cohort (*n* = 108)	PSMA cohort (*n* = 108)	*p* value
Age at SRT (yr), median (IQR)	66 (62–71)	65 (61–69)	67 (64–71)	**0.027**
PSA value at initiation of SRT (ng/ml), median (IQR)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	1.0
Total administered dose (Gy), median (IQR)	70 (66–70)	66 (66–70)	70 (66–70)	**0.001**
Equivalent dose in 2 Gy fractions (Gy), median (IQR)	70 (66–70)	66 (66–70)	70 (70–70)	**<0.001**
Interval between RARP and SRT (mo), median (IQR)	26 (14–53)	22 (12–49)	30 (16–57)	0.052
PSA doubling time (mo), median (IQR)	7.8 (4.0–13.3)	6.8 (3.4–13.3)	8.6 (4.7–13.6)	0.35
Pathological grade group according to ISUP, *n* (%)				
1	28 (13)	14 (13)	14 (13)	1.0
2	102 (47)	51 (47)	51 (47)	
3	44 (21)	22 (21)	22 (21)	
4	24 (11)	12 (11)	12 (11)	
5	18 (8)	9 (8)	9 (8)	
Pathological T stage, *n* (%)				
≤pT2	130 (60)	65 (60)	65 (60)	1.0
pT3a	66 (31)	33 (31)	33 (31)	
≥pT3b	20 (9)	10 (9)	10 (9)	
Surgical margin status, *n* (%)				
Negative	94 (44)	47 (44)	47 (44)	1.0
Positive	122 (56)	61 (56)	61 (56)	
Biochemical persistence after RARP, *n* (%)				
No	178 (82)	89 (82)	89 (82)	1.0
Yes	38 (18)	19 (18)	19 (18)	
Biochemical progression 1 yr after SRT, *n* (%)				
No	184 (85)	85 (79)	99 (92)	**0.007**
Yes	32 (15)	23 (21)	9 (8)	

IQR = interquartile range; ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RARP = robot-assisted radical prostatectomy; SRT = salvage radiation therapy.

performed. Indication to perform PSMA-PET imaging was a PSA value of ≥0.2 ng/ml. Synthesis of ^{18}F-DCFPyL and ^{18}F-PSMA-1007 was carried out via direct radiofluorination at an on-site cyclotron facility, whereas ^{68}Ga-PSMA-11 was produced on site, compliant to the Good Manufacturing Practices guidelines [13–15]. PET images were made from midthigh to skull base, approximately 120 min after injection following a median dose of 293 MBq (interquartile range [IQR] 202–320) for ^{18}F-DCFPyL, approximately 60 min after injection following a median dose of 120 MBq (IQR 101–148) for ^{68}Ga-PSMA-11, and approximately 90 min after injection following a median dose of 250 MBq (IQR 211–286) for

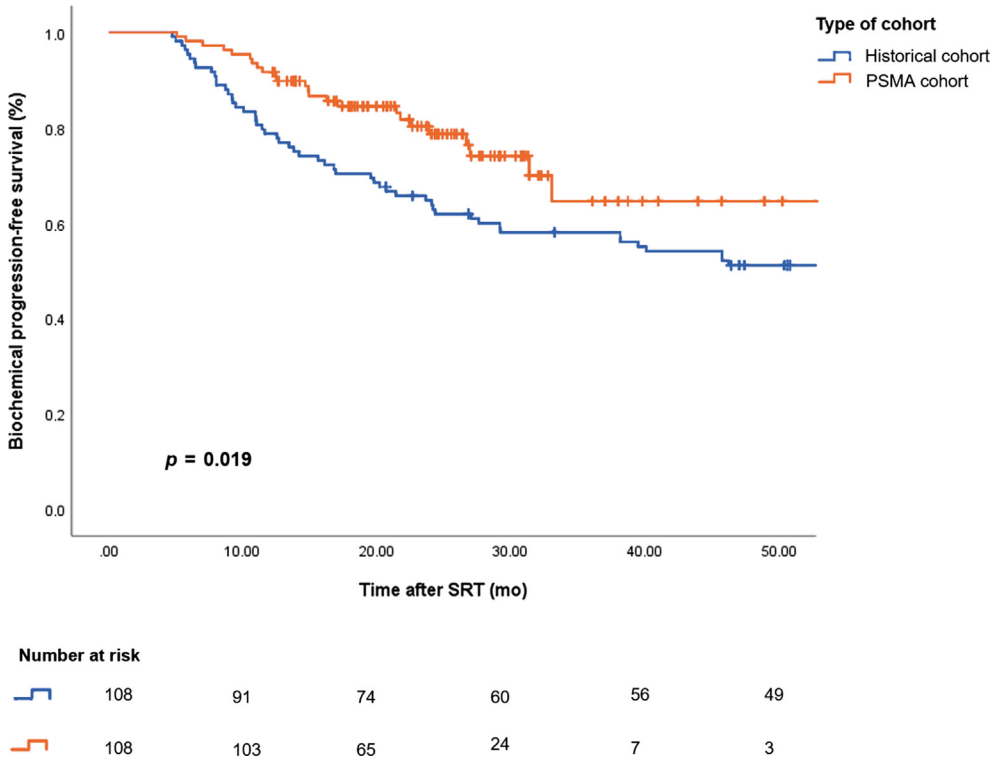

Fig. 1 – Kaplan-Meier curve of the case-control matched population (n = 216) assessing biochemical progression-free survival after salvage radiation therapy. PSMA = prostate-specific membrane antigen; SRT = salvage radiation therapy.

^{18}F-PSMA-1007. PET images were combined with either a low-dose CT scan (120–140 kV, 40–80 mAs with dose modulation) or a diagnostic CT scan (130 kV, 110 mAs) for anatomical correlation. All PET images were corrected for scatter, decay, and random coincidences; attenuation correction was performed using CT images.

2.3. Salvage radiation therapy

All patients who underwent SRT received a range of 60–78 Gy in 20–35 sessions of image-guided radiation 3D-conformal or volumetric modulated arc radiation therapy to the prostatic fossa. In some cases, if macroscopic local recurrence was suspected on PSMA-PET/CT, a simultaneous integrated boost was given to the PET-positive lesion. The prostate bed (clinical target volume) was contoured according to the European Organisation for Research and Treatment of Cancer guidelines [16].

2.4. Outcome variables and statistical analysis

All analyses were performed in the Statistical Package of Social Sciences (SPSS, v-26; IBM). To compare the outcomes of the historical and PSMA cohorts, case-control matching was performed using the two cohorts (historical cohort = 0; PSMA cohort = 1) as a grouping variable. PSA value at the initiation of SRT (continuous), pathological grade group (GG [categorical; 1/2/3/4/5]), pathological T stage (categorical; ≤pT2/pT3a/≥pT3b), surgical margin status (categorical; negative/positive), and biochemical persistence after RARP (ie, PSA value ≥0.1 ng/ml [categorical; no/yes]) were used as matching variables. In the matched dataset, patients were included when a patient from the historical cohort had an exact match of all selected matching variables with a patient from the PSMA cohort. Consequently, the biochemical progression rate at 1 yr after SRT was compared in patients with and without PSMA-PET/CT for restaging purposes using the chi-square test.

To obtain predicted risks for patients with missing variables, a Bayesian stochastic regression imputation procedure was conducted. The imputation model consisted of the PSA value at the initiation of SRT, pathological GG, pathological T stage, surgical margin status, presence of biochemical persistence after RARP, and outcome variable (biochemical progression 1 yr after SRT).

3. Results

3.1. Baseline characteristics

In total, 610 patients were included, of whom 298 underwent PSMA-PET imaging prior to SRT (49%) and 312 did not (51%; Table 1). Patients had a median age of 67 yr (IQR 62–71) at SRT and a median PSA value at the initiation of SRT of 0.3 ng/ml (IQR 0.2–0.5). Both age (median 65 and 68 yr, respectively; $p < 0.001$) and the PSA value at SRT (median 0.2 and 0.3 ng/ml, respectively; $p < 0.001$) differed significantly between the historical and PSMA cohorts.

Patients with local recurrent disease on PSMA-PET (n = 61) underwent SRT at a median PSA value of 0.5 ng/ml (IQR 0.3–1.2), compared with 0.3 ng/ml (IQR 0.2–0.5) in patients with "negative for cancer" PSMA-PET (n = 237).

3.2. Final histopathological evaluation

Pathological GG, pT stage, and surgical margin status are listed in Table 1. Both GG (p = 0.003) and surgical margin status (p = 0.023) differed significantly between the cohorts, while pT stage (p = 0.34) did not.

3.3. Case-control matching

After case-control matching, 216 patients were matched in both cohorts (108 identical patients in both cohorts; Table 2). The age of patients differed significantly between the historical and PSMA cohorts, with a median age of 65 yr (IQR 61–69) in the historical cohort and 67 yr (IQR 64–71) in the PSMA cohort ($p = 0.027$). The median biologically effective dose (ie, equivalent dose in 2 Gy fractions) in the historical cohort was 66 Gy (IQR 66–70) compared with 70 Gy (IQR 70–70) in the PSMA cohort ($p < 0.001$). The median time between RARP and SRT was 22 mo in the historical cohort (IQR 12–49), compared with 30 mo (IQR 16–57) in the PSMA cohort ($p = 0.052$). No difference was found for PSA doubling time between the historical and PSMA cohorts (median 6.8 vs 8.6 mo; $p = 0.35$). Since the remaining variables were used as matching variables, no differences were noted ($p = 1.0$). A subgroup analysis between patients with BCR or biochemical progression after RARP is displayed in Supplementary Table 1.

3.4. Outcome after SRT

In the historical cohort, without PSMA-PET/CT prior to SRT, 23/108 patients (21%) had biochemical progression at 1 yr after SRT, compared with 9/108 patients (8%) who underwent PSMA-PET/CT imaging for restaging purposes prior to SRT (chi-square test; $p = 0.007$). In other words, selecting patients via PSMA-PET/CT imaging for restaging purposes prior to SRT leads to a relative risk reduction of 62% of developing biochemical progression at 1 yr after SRT.

In Fig. 1, a Kaplan-Meier curve was constructed, showing the biochemical progression-free survival of patients with and without PSMA-PET for restaging prior to SRT. Patients who underwent PSMA-PET imaging for restaging had significantly improved biochemical progression-free survival, in comparison with patients who did not undergo PSMA-PET imaging (hazard ratio 1.79, 95% confidence interval 1.09–2.05; $p = 0.019$).

4. Discussion

In patients with BCR after RARP, SRT to the prostatic fossa is a potential curative salvage treatment option. However, approximately 50% of patients undergoing SRT do not respond to SRT, probably due to either metastatic disease at the time of SRT or persisting local recurrent disease [17]. As PSMA-PET has increased sensitivity for the detection of metastatic disease compared with conventional imaging [9,18], it has a substantial influence on management decisions made by clinicians for patients with BCR. However, it remains largely unknown whether improved staging by modern imaging techniques such as PSMA-PET/CT is followed by improved oncological outcomes.

In the present study, we evaluated 610 patients who underwent SRT after RARP in four reference centers for PCa radiation therapy. Of these patients, 298 received PSMA-PET imaging prior to SRT, whereas 312 did not. After case-control matching, patients who underwent PSMA-PET/CT for restaging purposes had a significantly lower biochemical progression rate at 1 yr after SRT than those who did not undergo restaging PSMA-PET/CT (ie, 8% vs 21%; $p = 0.007$). In other words, patients who underwent restaging PSMA-PET/CT imaging on BCR had a relative risk reduction of 62% of developing biochemical progression of disease after SRT compared with patients in the historical cohort who underwent blind SRT. With these findings, we demonstrated that selecting patients for local salvage treatment, without metastatic disease on restaging PSMA-PET/CT, improves oncological outcomes in this selected series of patients.

The BCR rates after SRT in our historical cohort are comparable with those found in the study of Stephenson et al [19], who studied the oncological outcome of 501 patients who underwent SRT to the prostatic fossa for BCR after radical prostatectomy. They reported biochemical progression of disease in 25% of patients at 1 yr after SRT. After 4 yr, this percentage increased to 50%. It needs to be mentioned that the definitions of biochemical progression differed between their study group and that of ours. In the study performed by Stephenson et al [19], biochemical progression was defined as a PSA value of $\geq$0.1 ng/ml above the post-SRT nadir, which is a somewhat different definition from that used in the present study. As the definition of biochemical progression was stricter in the study by Stephenson et al [19], a somewhat higher percentage of patients with recurrent disease are expected.

Several recent studies that evaluated the oncological outcome after SRT in patients staged by PSMA-PET/CT on BCR after RARP demonstrated that the biochemical progression rates were comparable with those of ours. Emmett et al [20] showed that in 100 patients with either negative PSMA-PET or local recurrent disease on PSMA-PET, approximately 10% of patients experienced biochemical progression of disease at 1 yr after SRT. Besides, Meijer et al [21] and Schmidt-Hegemann et al [22] showed an overall treatment response, defined as a PSA value of $\leq$0.1 ng/ml after PSMA-PET/CT-guided SRT, rate of 75–78%.

However, the outcome of the abovementioned studies may not be completely comparable with the outcome of those performed before the introduction of PSMA-PET imaging. First, in the studies performed by Emmett et al [20] and Schmidt-Hegemann et al [22], patients underwent more extensive SRT to both the prostatic fossa and the pelvis, whereas patients with known (lymph-node) metastases at lymph-node dissection were not excluded. Besides, Meijer et al [21] performed their analyses on patients who underwent SRT at a median PSA value of 0.4 ng/ml, compared with 0.7 ng/ml in the study performed by Stephenson et al [19]. Furthermore, the use of ADT was no reason for exclusion in most of these studies, making biochemical endpoints difficult to interpret.

To our knowledge, only one study directly compared the outcome of SRT in patients who underwent modern PET imaging for restaging purposes at BCR with that in patients who underwent conventional imaging techniques [23]. In a single-center randomized controlled trial, Jani et al [23] showed that patients who underwent ^{18}F-Fluciclovine-PET at BCR had significantly improved 3-yr event-free survival in comparison with patients who underwent conventional imaging for restaging purposes. An event in this study was

defined as a PSA rise of 0.2 ng/ml above the nadir after SRT, persistent PSA, an imaging or digital examination failure, or initiation of systemic treatment. However, it needs to be addressed that the diagnostic accuracy of ^{18}F-Fluciclovine has been investigated poorly in patients with PSA <1.0 ng/ml on BCR, whereas the EAU guidelines recommend any PSMA-based tracer in patients with PSA >0.2 ng/ml [5].

Several alternative explanations may rise for the reported improved oncological outcomes in those who underwent staging PSMA-PET/CT in our case-control matching study compared with those who did not undergo staging. First, it was observed that the median biologically effective radiation dose administered in the PSMA cohort (70 Gy) was significantly higher than that in the historical cohort (66 Gy). This might suggest that local control may be gained by more robust radiation schemes. However, Ghadjar et al [24] recently showed that the biochemical progression rate after SRT between patients who underwent 64 or 70 Gy to the prostate bed without hormonal therapy for BCR PCa did not differ significantly. Second, it is known that PSA doubling time is significantly associated with impaired oncological outcome after SRT [25]. In our study, however, we were not able to include PSA doubling time as a variable in the case-control matching study due to too many missing cases (231/610 patients [38%]). Nevertheless, the median PSA doubling time did not differ between the historical and PSMA cohorts (6.8 vs 8.6 mo; $p = 0.35$).

Despite the finding that the diagnostic accuracy of PSMA-PET/CT for the detection of metastatic disease is higher than that of conventional imaging [9], it does not necessarily translate into improved oncological outcomes. Through the earlier detection of recurrences and metastases, the Will Rogers phenomenon, that is, the improvement of clinical outcome in separate staging groups due to stage migration, is likely to occur, whereas the prognosis in the entire group is not changed [26]. Eventually, only well-performed randomized clinical trials with more robust endpoints such as overall survival will or will not prove that modern diagnostic imaging modalities lead to improvement of oncological outcomes.

In the present study, patients with metastatic disease on PSMA-PET outside the prostatic fossa were excluded from this analysis, as they usually do not undergo local SRT with curative intent. It is however not unlikely that patients with one metastasis on PSMA-PET might benefit from local salvage treatment, besides eventual metastasis-directed therapy. Future trials should answer the question whether SRT has a role in patients with (oligo-)metastatic disease on PSMA-PET.

Our study is not devoid of limitations. First, it should be noted that PSMA-PET scans were reported in routine clinical settings and were not part of a prospective clinical trial, possibly leading to interobserver variability. Furthermore, different scan protocols, PSMA-targeting radiotracers, and PET scanners were used. Second, regarding SRT, both the total dose and the number of fractions differed between participating PCa radiation therapy centers. Third, as BCR after SRT is not associated with overall survival, it might not be a reliable surrogate for long-term oncological outcome, such as disease-free survival and overall survival. On the contrary, BCR is often used as a surrogate endpoint for robust endpoints in clinical trials [27]. Fourth, all patients in the control group did not undergo conventional imaging modalities prior to SRT. Possibly, in some cases, macrometastatic disease might have been visualized on conventional imaging, and these patients would therefore not undergo SRT. Last, due to the retrospective nature of this analysis, a bias may have occurred, which is not accounted for in the case-control analysis.

5. Conclusions

Patients who underwent restaging PSMA-PET/CT for BCR after RARP had better short-term oncological outcomes after SRT than those who underwent blind SRT. Thus, PSMA-PET/CT is associated with an improved oncological outcome in a selected series of patients. Prospective trials are required to further confirm these findings.

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Drafting of the manuscript: D. Meijer, van den Bergh, van Leeuwen, Vis.
Critical revision of the manuscript for important intellectual content: Eppinga, Vanneste, Meijnen, Daniels, Donswijk, Oprea-Lager, Schaake.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2022.01.001.

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