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Prostate Cancer

Persistent Prostate-Specific Antigen After Radical Prostatectomy and Its Impact on Oncologic Outcomes

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Abstract

Background: Persistent prostate-specific antigen (PSA) represents a poor prognostic factor for recurrence after radical prostatectomy (RP).
Objective: To investigate the impact of persistent PSA at 6 wk after RP on long-term oncologic outcomes and to assess patient characteristics associated with persistent PSA.
Design, setting, and participants: Within a high-volume center database we identified patients who harbored persistent (≥0.1 ng/ml) versus undetectable PSA (<0.1 ng/ml) at 6 wk after RP. Patients with neo- and/or adjuvant androgen-deprivation therapy (ADT) were excluded.
Outcome measurements and statistical analysis: Logistic regression models tested for prediction of persistent PSA. Kaplan–Meier analyses and Cox regression models tested the effect of persistent PSA on metastasis-free survival (MFS), overall survival (OS), and cancer-specific survival (CSS) rates. Propensity score matching (PSM) was performed to test the impact of salvage radiotherapy (SRT) on OS and CSS in patients with persistent PSA.
Results and limitations: Of 11 604 identified patients, 8.8% (n = 1025) harbored persistent PSA. At 15 yr after RP, MFS, OS, and CSS were 53.0% versus 93.2% ($p < 0.001$), 64.7% versus 81.2% ($p < 0.001$), and 75.5% versus 96.2% ($p < 0.001$) for persistent versus undetectable PSA, respectively. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (hazard ratio [HR]: 3.59, $p < 0.001$), death (HR: 1.86, $p < 0.001$), and cancer-specific death (HR: 3.15, $p < 0.001$). SRT was associated with improved OS (HR: 0.37, $p = 0.02$) and CSS (HR: 0.12, $p < 0.01$) after 1:1 PSM. Main limitation is missing data on postoperative PSA and duration of salvage ADT.
Conclusions: Persistent PSA is associated with worse oncologic outcome after RP, namely, metastasis, death, and cancer-specific death. In patients with persistent PSA, SRT resulted in improved OS and CSS.
Patient summary: We assessed the impact of persistent prostate-specific antigen (PSA) at 6 wk after radical prostatectomy on oncologic outcomes. Early persistent PSA was associated with worse metastasis-free survival, overall survival, and cancer-specific survival. Salvage radiotherapy may result in a survival benefit in well-selected patients.

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1. Introduction

Radical prostatectomy (RP) can provide good long-term oncological outcomes in patients with localized and locally advanced prostate cancer (PCa) [1–3]. After RP, prostate-specific antigen (PSA) represents the cornerstone for follow-up of patients. The current European Association of Urology (EAU) PCa guidelines recommend first PSA measurement at 3 mo after RP [4].

However, PSA is expected to be undetectable within 6 wk following RP [5]. Moreover, several investigators focused on persistent PSA after RP and relied on the definition of PSA ≥0.1 ng/ml at 6 wk after RP [6–15].

Some of them reported an association between persistent PSA after RP and biochemical recurrence (BCR) [11,13,15]. Moreover, Ploussard et al. [12] reported that approximately 75% of patients with persistent PSA develop BCR. However, studies investigating the relationship between persistent PSA (≥0.1 ng/ml) at 6 wk and development of metastasis and survival after RP are scant or focus only on subgroups such as pN1 disease or patients with salvage radiotherapy (SRT). Previously, Bianchi et al. [7] reported a higher risk for clinical recurrence and cancer-specific mortality for persistent PSA in RP patients with pN1 disease. In addition, Fossati et al. [6] reported that persistent PSA represents an independent predictor for metastasis. However, the study by Fossati et al. [6] focused only on patients with pN0 who received SRT. Therefore, the impact of persistent PSA on long-term oncologic outcomes and the effect of SRT in patients with persistent PSA following RP need to be clarified.

To address these limitations, we investigated the relationship between persistent PSA at 6 wk after RP and the long-term oncological outcomes, within a large high-volume center database. Specifically, we investigated the relationship between persistent PSA and metastasis-free survival (MFS), overall survival (OS), and cancer-specific survival (CSS). Subgroup analyses focused on patients with persistent PSA. In addition, we tested for risk factors to develop persistent PSA. Finally, the impact of SRT versus no RT on OS and CSS in patients with persistent PSA was studied.

2. Patients and methods

2.1. Study population

After Institutional Review Board approval, patients that underwent RP (1992–2016), from a single-institutional high-volume center database (Martini-Klinik Prostate Cancer Center, Germany), were identified.

Patients were stratified according to persistent (PSA ≥0.1 ng/ml at 6 wk after RP) versus undetectable PSA (PSA <0.1 ng/ml).

RP was performed with the use of an open retropubic or robot-assisted approach, as previously described [16]. Moreover, neurovascular bundle preservation was performed with the intraoperative frozen section technique, as previously described [17,18]. All RP specimen were evaluated by dedicated uropathologists.

Exclusion criteria consisted of metastasis at time of RP (n = 24), unknown pathologic tumor stage (n = 11), unknown surgical margin status (n = 293), and neoadjuvant (n = 1109) and adjuvant androgen deprivation treatment (n = 356). Finally, patients with unknown PSA at 6 wk after RP (n = 8626) were excluded.

These selection criteria yielded 11 604 patients, which represented the focus of the current analysis.

2.2. Outcomes

Metastasis was diagnosed by positive imaging for persistent PSA or BCR (two consecutive PSA values ≥0.2 ng/ml after surgery). Imaging procedures consisted of bone scan and/or computed tomography (CT) and/or abdominal magnetic resonance imaging and/or ^{11}C-choline positron emission tomography (PET)/CT scan and/or ^{18}F-choline PET/CT and/or ^{68}gallium prostate-specific membrane antigen (^{68}Ga-PSMA) PET/CT. MFS was calculated as time from RP to metastasis or last follow-up. OS was calculated as time from RP to death or last follow-up. Finally, CSS was calculated as time from RP to death attributed to PCa or last follow-up.

2.3. Covariates

Covariates consisted of age, year of surgery, preoperative PSA, biopsy/pathologic Gleason grade group (GG), clinical/pathologic tumor stage, surgical margin status, and pathologic lymph node status. SRT was defined as RT delivered for persistent PSA or BCR. The decision to undergo SRT was at the discretion of the urologist. Information on the SRT field (prostatic bed vs whole pelvis) was unavailable. Median SRT dose was 46 Gy with a median number of 37 fractions and 2 Gy per fraction. However, in 835 SRT patients (46.0%) detailed information on SRT was unavailable. Information about receipt and duration of androgen deprivation during SRT was not available for all patients.

2.4. Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges were reported for continuously coded variables. The chi-square test examined the statistical significance in proportions' differences. The Mann–Whitney U test examined the significance of medians' differences.

Two sets of multivariable logistic regression models tested the relationship between tumor characteristics and persistent PSA. Within the first model adjustment was made for clinical tumor characteristics. Within the second model adjustment was made for pathological tumor characteristics.

Kaplan–Meier analyses depicted MFS, OS, and CSS. Three sets of multivariable Cox regression models were fitted to test the relationship between PSA persistence and the oncologic outcomes. Specifically, the first set tested the relationship between persistent PSA and MFS, the second the relationship between persistent PSA and OS, and the third the relationship between persistent PSA and CSS. All multivariable Cox models were adjusted for pathological tumor characteristics and Charlson Comorbidity Index (CCI). Subsequently, multivariable Cox regression models were repeated in the subgroup of patients with exclusively persistent PSA. Finally, 1:1 propensity score matching (PSM) was performed to test the impact of SRT versus no RT on OS and CSS in patients with persistent PSA. Owing to missing data, PSM was not performed to test the impact of SRT on MFS. Matching was performed for tumor characteristics, namely, pathologic Gleason, surgical margin, pathologic tumor stage, and lymph node status. With the use of a caliper width of 0.4, no significant differences between tumor characteristics were recorded between patients without and with SRT (Supplementary Table 1).

The R software environment for statistical computing and graphics (R Foundation for Statistical Computing, Vienna, Austria, Mac OS X version 3.4.4, http://www.R-project.org) was used for all statistical analyses. All tests were two sided with a level of significance set at p <0.05.

3. Results

3.1. Descriptive statistics

Of 11 604 identified patients, 8.8% ($n = 1025$) versus 91.2% ($n = 10\ 579$) harbored persistent or undetectable PSA, respectively (Table 1). Around 10% ($n = 125$) of patients with persistent PSA at 6 wk had an undetectable PSA in the subsequent PSA testing. The median follow-up was 61.8 versus 46.4 mo for patients with undetectable and persistent PSA. Patients with persistent PSA were older (median age: 64.6 vs 64.2 yr, $p = 0.006$), more frequently had pathologic GG5 (19.6% vs 2.5%, $p < 0.001$), more frequently harbored positive surgical margins (42.9% vs 15.1%, $p < 0.001$), as well as pathologic tumor stage T3b (45.2% vs 8.1%, $p < 0.001$) and lymph node invasion (pN1; 30.2% vs 3.7%, $p < 0.001$) compared to patients with undetectable PSA. Moreover, patients with persistent PSA more frequently received SRT (55.6% vs 11.8%, $p < 0.001$). Approximately 16% ($n = 1694$) of patients with undetectable PSA developed BCR (median time to BCR was 53.0 mo).

3.2. Risk characteristics for persistent PSA

In multivariable models, testing the relationship between clinical tumor characteristics and persistent PSA (Table 2), higher preoperative PSA value, advanced clinical tumor stage, and more aggressive biopsy GG were associated with an increased risk for persistent PSA (all $p < 0.01$). Conversely, more contemporary year of surgery was associated with lower risk for persistent PSA ($p < 0.001$).

In multivariable models, testing the relationship between pathological tumor characteristics and persistent PSA (Table 2), higher preoperative PSA, more advanced pathologic tumor stage, pathologic GG3–5, positive surgical margins, and pN1 were associated with an increased risk for persistent PSA (all $p < 0.01$). Conversely, older age was associated with lower risk for persistent PSA ($p = 0.04$).

Table 2 – Multivariable logistic regression models predicting persistent PSA (≥0.1 ng/ml) at 6 wk after radical prostatectomy

	OR	95% CI	p value
Clinical model			
Year of surgery	1.04	1.02–1.05	<0.001
Age	0.99	0.99–1.01	0.8
Preoperative PSA	1.05	1.04–1.05	<0.001
Clinical tumor stage T1c (referent)	1.00	–	–
Clinical tumor stage T2a	1.50	1.24–1.8	<0.001
Clinical tumor stage T2b	2.43	1.93–3.03	<0.001
Clinical tumor stage ≥T2c	3.50	2.50–4.88	<0.001
Biopsy GG1 (referent)	1.00	–	–
Biopsy GG2	1.52	1.25–1.85	<0.001
Biopsy GG3	2.73	2.19–3.39	<0.001
Biopsy GG4	3.96	3.12–5.03	<0.001
Biopsy GG5	5.06	3.85–6.64	<0.001
Pathological model			
Year of surgery	1.01	0.99–1.03	0.1
Age	0.99	0.98–0.99	0.04
Preoperative PSA	1.02	1.02–1.03	<0.001
Pathologic stage ≤T2c (referent)	1.00	–	–
Pathologic stage T3a	1.96	1.61–2.38	<0.001
Pathologic stage T3b	3.76	3.02–4.7	<0.001
Pathologic GG1 (referent)	1.00	–	–
Pathologic GG2	1.25	0.95–1.66	0.1
Pathologic GG3	3.51	2.58–4.82	<0.001
Pathologic GG4	3.96	2.16–7.0	<0.01
Pathologic GG5	4.95	3.41–7.24	<0.001
Negative surgical margin (referent)	1.00	–	–
Positive surgical margin	1.66	1.40–1.95	<0.001
Pathologic lymph node status N0 (referent)	1.00	–	–
Pathologic lymph node status N1	2.32	1.88–2.85	<0.001
Pathologic lymph node status Nx	1.04	0.84–1.28	0.7

CI = confidence interval; GG = Gleason grade group; OR = odds ratio; PSA = prostate-specific antigen.

Table 1 – Descriptive characteristics of patients treated with radical prostatectomy, stratified according to postoperative PSA (persistent PSA vs undetectable PSA)

	Persistent PSA ($n = 1025$, 8.8%)	Undetectable PSA ($n = 10\ 579$, 91.2%)	p value
Age (yr), median (IQR)	64.6 (59.9–69.1)	64.2 (59.2–68.3)	<0.01
Preoperative PSA (ng/ml), median (IQR)	11.2 (6.8–19.8)	6.6 (4.7–9.7)	<0.001
Year of surgery, median (IQR)	2011 (2007–2013)	2009 (2005–2012)	<0.001
Pathologic Gleason grade group, *n* (%)			
1	75 (7.3)	2748 (26.0)	<0.001
2	309 (30.2)	6042 (57.2)	
3	419 (40.9)	1433 (13.5)	
4	21 (2.0)	82 (0.8)	
5	201 (19.6)	265 (2.5)	
Pathologic tumor stage, *n* (%)			
≤pT2c	275 (26.8)	7565 (71.5)	<0.001
pT3a	287 (28.0)	2156 (20.4)	
pT3b	463 (45.2)	858 (8.1)	
Surgical margin status, *n* (%)			
Negative	585 (57.1)	8977 (84.9)	<0.001
Positive	440 (42.9)	1602 (15.1)	
Pathologic lymph node status, *n* (%)			
pN0	566 (55.2)	6516 (61.6)	<0.001
pNx	150 (14.6)	3673 (34.7)	
pN1	309 (30.2)	390 (3.7)	
Salvage radiotherapy performed, *n* (%)	570 (55.6)	1245 (11.8)	<0.001

IQR = interquartile range; PSA = prostate-specific antigen.

3.3. Effect of PSA persistence on MFS

Overall, 221 (21.6%) and 250 (2.4%) patients with persistent and undetectable PSA, respectively, developed metastasis ($p < 0.001$). Patients with persistent PSA who developed metastasis most frequently harbored M1a disease ($n = 102$). Conversely, patients with undetectable PSA at 6 wk who developed metastasis most frequently harbored M1b disease ($n = 118$) (Supplementary Table 2).

At 15 yr after RP, MFS (Fig. 1) was 53.0% versus 93.2% ($p < 0.001$) for persistent versus undetectable PSA, respectively. In multivariable Cox regression models, testing the relationship between PSA persistence and metastasis (Table 3), persistent PSA achieved an independent predictor status of metastasis (hazard ratio [HR]: 3.59, 95% confidence interval [CI]: 2.83–4.57, $p < 0.001$), after adjustment for all covariates.

In subgroup analyses, focusing exclusively on patients with PSA persistence (Table 4), pathologic tumor stage T3b (HR: 2.01, 95% CI: 1.21–3.35, $p < 0.01$), pathologic GG3–5 (HR: 3.17, 95% CI: 1.92–5.24, $p < 0.001$), year of surgery (HR: 1.23, 95% CI: 1.17–1.30, $p < 0.001$), and age (HR: 0.97, 95% CI: 0.95–0.99, $p = 0.02$) were all associated with higher metastasis risk.

3.4. Effect of PSA persistence on OS

During the study period, 106 (10.3%) versus 531 (5.0%) patients with persistent and undetectable PSA ($p < 0.001$) died. At 15 yr after RP, OS (Fig. 2) was 64.7% versus 81.2% ($p < 0.001$) for persistent versus undetectable PSA, respectively. In multivariable Cox regression models, testing the relationship between PSA persistence and OS (Table 3), persistent PSA achieved independent predictor status of death (HR: 1.86, 95% CI: 1.41–2.45, $p < 0.001$).

Finally, in subgroup analyses, focusing exclusively on patients with PSA persistence (Table 4), pathologic tumor stage T3b (HR: 2.92, 95% CI: 1.16–7.33, $p = 0.02$), GG3–5 (HR: 2.49, 95% CI: 1.30–4.77, $p < 0.01$), and CCI ≥1 (HR: 1.82, 95% CI: 1.07–3.13, $p = 0.03$) represented independent predictors for death.

3.5. Effect of PSA persistence on CSS

Of all death that occurred during the study period, 64 (6.2%) and 84 (0.8%) were attributed to PCa ($p < 0.001$), respectively. At 15 yr after RP, CSS (Fig. 3) was 75.5% versus 96.2% ($p < 0.001$) for persistent versus undetectable PSA, respectively. In multivariable Cox regression models, testing the relationship between PSA persistence and CSS (Table 3), persistent PSA achieved independent predictor status of cancer-specific death (HR: 3.15, 95% CI: 1.92–5.18, $p < 0.001$).

Finally, in subgroup analyses, focusing exclusively on patients with PSA persistence (Table 4), GG3–5 (HR: 5.05, 95% CI: 1.76–14.46, $p < 0.01$) and year of surgery (HR: 0.91, 95% CI: 0.85–0.98, $p < 0.01$) represented independent predictors for cancer-specific death.

3.6. Effect of SRT on OS and CSS

In the subgroup of patients with persistent PSA, after 1:1 PSM between patients with SRT and those with no RT, OS at 10 yr after RP was 86.6% versus 72.6% in the entire cohort ($p < 0.01$; Fig. 4), 86.3% versus 60.0% in patients with positive surgical margin ($p = 0.02$; Supplementary Fig. 1), 77.8% versus 49.0% in pT3b disease ($p < 0.001$; Supplementary Fig. 2), 79.3% versus

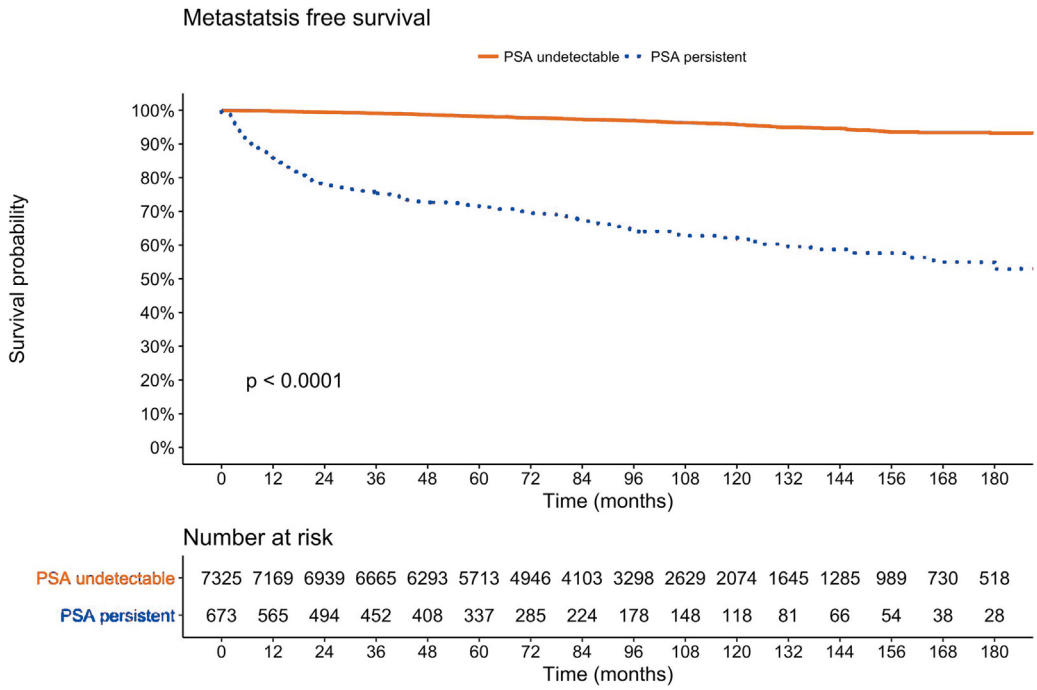

Fig. 1 – Kaplan–Meier plot depicting metastasis-free survival rates in patients with prostate cancer treated with radical prostatectomy stratified according to persistent versus undetectable prostate-specific antigen (PSA).

Table 3 – Multivariable Cox regression models predicting metastasis, death, and cancer-specific death in the entire study cohort

	Predicting metastasis			Predicting death			Predicting cancer-specific death		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Undetectable PSA postoperative	1.00	–	–	–	–	–	–	–	–
Persistent PSA postoperative	3.59	2.83–4.57	<0.001	1.86	1.41–2.45	<0.001	3.15	1.92–5.18	<0.001
Year of surgery	1.23	1.19–1.28	<0.001	0.99	0.96–1.01	0.3	0.92	0.87–0.97	<0.01
Age	0.98	0.96–0.99	0.02	1.08	1.06–1.09	<0.001	1.02	0.99–1.06	0.2
Preoperative PSA	1.00	0.99–1.01	0.7	0.99	0.98–1.01	0.3	0.99	0.98–1.01	0.6
Pathologic stage ≤T2c (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic stage T3a	2.14	1.56–2.93	<0.001	1.03	0.81–1.31	0.8	1.16	0.60–2.25	0.6
Pathologic stage T3b	3.87	2.77–5.41	<0.001	1.63	1.22–2.16	<0.001	4.00	2.16–7.38	<0.001
Pathologic GG1–2 (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic GG3–5	3.60	2.71–4.79	<0.001	1.56	1.22–1.99	<0.001	3.36	2.01–5.63	<0.001
Negative surgical margin (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Positive surgical margin	1.05	0.84–1.33	0.7	1.26	1.02–1.57	0.03	1.72	1.10–2.68	0.02
Pathologic lymph node status N0 (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic lymph node status N1	1.48	1.14–1.92	<0.01	1.38	0.95–1.99	0.1	1.38	0.78–2.46	0.3
Pathologic lymph node status Nx	0.44	0.30–0.64	<0.001	1.02	0.83–1.26	0.8	0.90	0.52–1.56	0.7
CCI 0 (reference)	1.00	–	–	1.00	–	–	1.00	–	–
CCI 1	0.80	0.59–1.08	0.1	1.62	1.28–2.07	<0.001	1.35	0.80–2.28	0.3
CCI ≥2	0.85	0.60–1.21	0.4	2.38	1.91–2.98	<0.001	0.47	0.20–1.11	0.1

CCI = Charlson Comorbidity Index; CI = confidence interval; GG = Gleason grade group; HR = hazard ratio; PSA = prostate-specific antigen.

Table 4 – Multivariable Cox regression models predicting metastasis, death, and cancer-specific death in the subgroup with postoperative persistent PSA (≥0.1 ng/ml at 6 wk after RP)

	Predicting metastasis			Predicting death			Predicting cancer-specific death		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Year of surgery	1.23	1.17–1.30	<0.001	0.96	0.91–1.02	0.2	0.91	0.85–0.98	<0.01
Age	0.97	0.95–0.99	0.02	1.03	0.99–1.07	0.2	1.03	0.98–1.10	0.3
Preoperative PSA	1.01	0.99–1.01	0.4	0.98	0.97–1.01	0.1	0.99	0.97–1.01	0.3
Pathologic stage ≤T2c (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic stage T3a	1.59	0.95–2.66	0.1	1.77	0.70–4.49	0.2	1.95	0.38–10.03	0.4
Pathologic stage T3b	2.01	1.21–3.35	<0.01	2.92	1.16–7.33	0.02	4.48	0.93–21.72	0.1
Pathologic GG1–2 (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic GG3–5	3.17	1.92–5.24	<0.001	2.49	1.30–4.77	<0.01	5.05	1.76–14.46	<0.01
Negative surgical margin (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Positive surgical margin	0.93	0.67–1.27	0.6	1.60	0.98–2.62	0.1	1.50	0.77–2.93	0.2
Pathologic lymph node status N0 (referent)	1.00	–	–	1.00	–	–	1.00	–	–
Pathologic lymph node status N1	1.32	0.96–1.83	0.1	1.49	0.87–2.54	0.1	1.46	0.71–2.99	0.3
Pathologic lymph node status Nx	0.68	0.35–1.30	0.2	0.79	0.39–1.63	0.5	1.09	0.41–2.86	0.9
CCI 0	1.00	–	–	1.00	–	–	1.00	–	–
CCI ≥1	0.89	0.63–1.25	0.5	1.82	1.07–3.13	0.03	1.06	0.51–2.21	0.9

CCI = Charlson Comorbidity Index; CI = confidence interval; GG = Gleason grade group; HR = hazard ratio; PSA = prostate-specific antigen.

55.8% in GG3–5 disease ($p < 0.01$; Supplementary Fig. 3), and 87.4% versus 50.5% in pN1 disease ($p < 0.01$; Supplementary Fig. 4) for SRT and no RT, respectively. Moreover, CSS at 10 yr after RP was 93.7% versus 81.6% in the entire cohort ($p < 0.01$; Fig. 4), 90.8% versus 69.7% in patients with positive surgical margin ($p = 0.04$; Supplementary Fig. 1), 82.7% versus 55.3% in pT3b disease ($p < 0.01$; Supplementary Fig. 2), 85.4% versus 69.7% in GG3–5 disease ($p < 0.01$; Supplementary Fig. 3), and 96.2% versus 55.8% in pN1 disease ($p < 0.01$; Supplementary Fig. 4) for SRT and no RT, respectively. The median time to SRT was 5.4 mo.

In multivariable Cox regression models, after PSM, SRT was associated with lower risk for death (HR: 0.37, 95% CI: 0.16–0.83, $p = 0.02$) and cancer-specific death (HR: 0.12, 95% CI: 0.03–0.47, $p < 0.01$; Supplementary Table 3).

4. Discussion

PSA after RP represents the cornerstone in follow-up of patients with PCa. Specifically, early PSA values after RP could help to identify patients at risk for worse oncologic outcome. Moreover, early PSA after RP could help to identify patients who benefit from further treatment. However, few previous studies tested the impact of persistent PSA on long-term oncologic outcomes. To address this void, we investigated the relationship between persistent PSA at 6 wk and the long-term oncologic outcomes after RP. In addition, we focused on the subgroup of patients with persistent PSA to identify candidates who may benefit from SRT. Our analyses revealed several noteworthy findings.

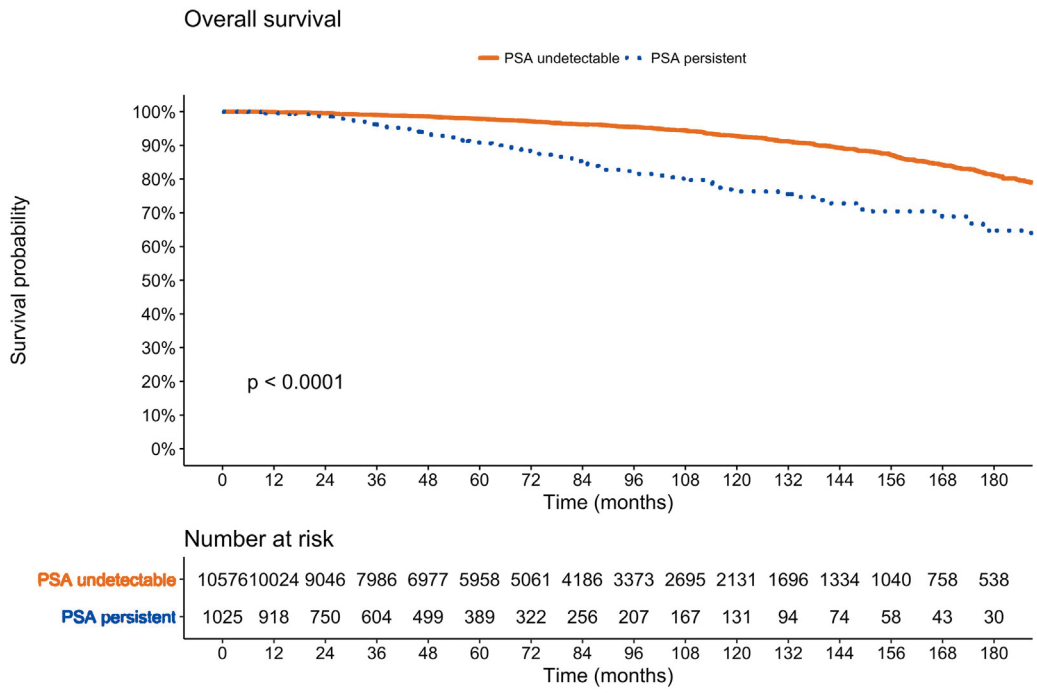

Fig. 2 – Kaplan–Meier plot depicting overall survival rates in patients with prostate cancer treated with radical prostatectomy stratified according to persistent versus undetectable prostate-specific antigen (PSA).

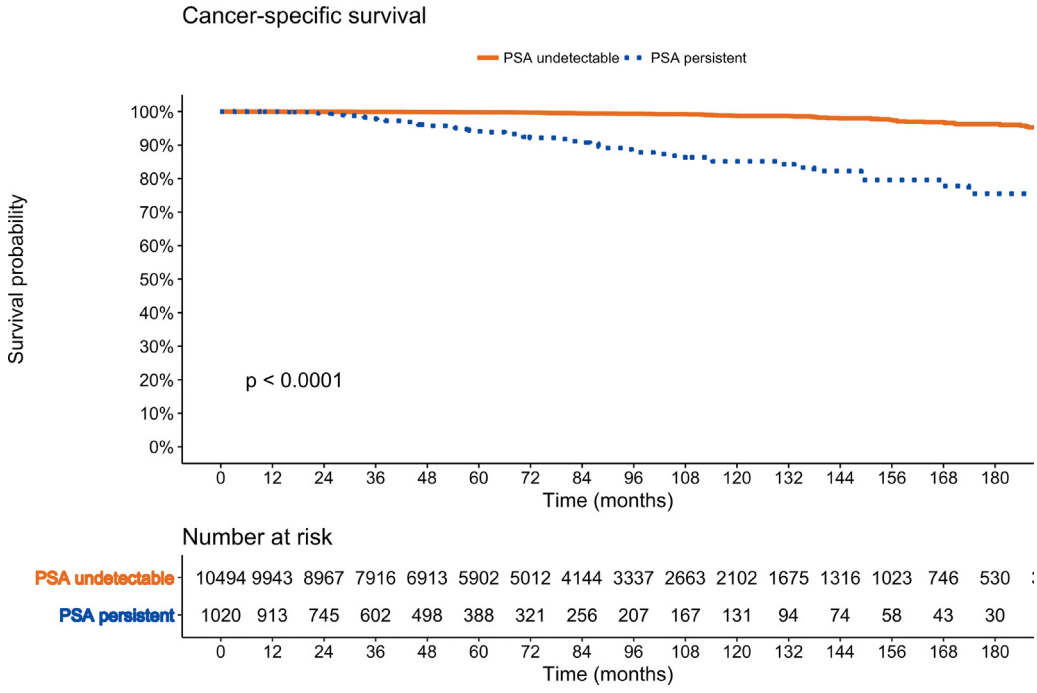

Fig. 3 – Kaplan–Meier plot depicting cancer-specific survival rates in patients with prostate cancer treated with radical prostatectomy stratified according to persistent versus undetectable prostate-specific antigen (PSA).

First, of 11 604 identified patients, 8.8% ($n = 1025$) harbored persistent PSA. This result demonstrates that persistent PSA represents a common finding early after RP. This result is different from previous studies. Our proportion of patients with persistent PSA is lower than the one reported by Bianchi et al. [7] (26.0%). However, Bianchi et al. [7] relied on a cohort that exclusively consisted of pN1 cases, which have a higher risk for persistent PSA as reported by Sengupta et al. [19]. One reason for the lower proportion of patients with persistent PSA in our study may be the rate of

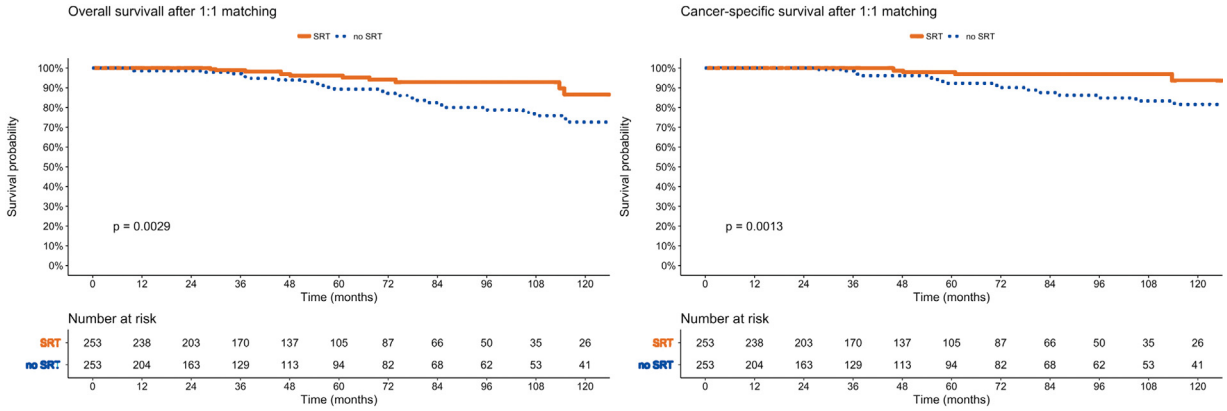

Fig. 4 – Kaplan–Meier plots depicting overall survival and cancer-specific survival rates in patients with prostate cancer treated with radical prostatectomy and persistent prostate-specific antigen after radical prostatectomy, stratified according to salvage radiotherapy (SRT) versus no radiotherapy, after 1:1 propensity score matching.

patients with missing information. However, our results corroborate the findings by McDonald et al. [20], who reported a proportion of 9.2% with persistent PSA, which is similar to our rate. Moreover, 10% (n = 125) of patients with persistent PSA at 6 wk had an undetectable PSA in the subsequent PSA testing. One explanation could be related to receipt of androgen deprivation in these patients.

Second, in multivariable logistic regression several pre- and postoperative tumor characteristics represented independent predictors for persistent PSA. These results demonstrate the direct relationship between more advanced pre- and postoperative tumor characteristics and persistent PSA and can help to identify those with an increased risk.

Third, patients with persistent PSA had worse oncological outcomes compared to patients with undetectable PSA. Specifically, at 15 yr after RP, MFS, OS, and CSS were better for persistent versus undetectable PSA, respectively. Moreover, in multivariable models, persistent PSA remained an independent predictor for metastasis (HR: 3.59, $p < 0.001$), death (HR: 1.86, $p < 0.001$), and cancer-specific death (HR: 3.15, $p < 0.001$). These findings corroborate the report by Fossati et al. [6] within pN0 patients treated with SRT, who reported a HR of 4.64 for persistent PSA cases to develop metastasis. Moreover, our findings corroborate the study by Bianchi et al. [7], who reported higher risk for development of metastasis and cancer-specific mortality in pN1 patients with persistent PSA.

Fourth, in analyses focusing on patients with persistent PSA, after PSM between patients with SRT and no RT, SRT was associated with better OS and CSS at 10 yr after RP, in the entire cohort, in patients with positive surgical margin, pT3b disease, GG3–5 disease, and pN1 disease. Moreover, in multivariable models, SRT was associated with lower risk for death (HR: 0.37, p = 0.02) and cancer-specific death (HR: 0.12, $p < 0.01$). These results are important in clinical decision-making to select best candidates for SRT. Therefore, patients with persistent PSA after RP and additional risk factors, such as pT3b, GG3–5, positive surgical margin, or pN1 disease, appear to have a survival benefit by SRT. Moreover, to the best of our knowledge, our study, including 1025 patients with persistent PSA after RP, is the largest study which addressed this topic.

Taken together, our results demonstrated that persistent PSA at 6 wk is an independent predictor for death and development of metastasis. Current EAU guidelines recommend first PSA value after RP at 3 mo. However, earlier PSA measurement can help in clinical practice to identify patients with unfavorable outcome. Moreover, earlier PSA measurement can help identify candidates who may benefit from SRT and result in a shorter delay to salvage treatment. Because the half-life of PSA is approximately 3.15 d, serum PSA values of $\leq$50 ng/ml should be undetectable within 4 wk after RP [21]. PSA testing at 6 wk following RP should be considered to identify patients with persistent PSA after RP and worse oncologic outcome. Moreover, future prospective studies testing the impact of SRT after RP should consider persistent PSA, as it can provide important information.

Our study is not devoid of limitations. First and foremost, PSA testing after RP was performed with multiple methods, which could have influenced our results. Ideally, ultrasensitive PSA testing should be performed. With regard to MFS, differences in imaging modalities performed might have influenced our results. It is reasonable that in patients with persistent PSA more advanced imaging modalities were used. However, detailed information on the imaging performed for each patient was unavailable. Moreover, despite relying on multivariable adjustments and PSM, a selection bias may still exist. In addition, detailed information on SRT regimens was not available for all patients. With a median dose of 46 Gy in our cohort, the dose was lower than SRT regimens from contemporary reports, which could have influenced our results [22]. Moreover, androgen-deprivation therapy (ADT) duration during SRT was unavailable, which could have biased our findings, because short- as well as long-term ADT during SRT has been shown to result in a survival benefit [22,23]. Finally, toxicity related to SRT was not covered by our database. It is of note that although SRT resulted in improved OS and CSS, quality of life

may have been negatively influenced by SRT-related toxicity and needs to be considered in decision-making.

5. Conclusion

Persistent PSA at 6 wk after RP represents a strong prognostic predictor for development of metastasis and death after RP. Therefore, early measurement of PSA can be useful in clinical practice to identify patients with high risk for worse oncologic outcome. Moreover, SRT was associated with improved OS and CSS in patients with persistent PSA. In those with persistent PSA and additional risk factors, such as pT3b, GG3–5, positive surgical margin, or pN1, SRT should be considered.

Author contributions: Derya Tilki 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: Tilki, Preisser.
Acquisition of data: Preisser, Chun, Pompe, Heinze, Salomon, Graefen, Huland, Tilki.
Analysis and interpretation of data: Preisser, Tilki.
Drafting of the manuscript: Preisser, Tilki.
Critical revision of the manuscript for important intellectual content: Preisser, Chun, Pompe, Heinze, Salomon, Graefen, Huland, Tilki.
Statistical analysis: Preisser, Pompe.
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Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.01.048.

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