Single Lesion on Prostate-specific Membrane Antigen-ligand Positron Emission Tomography and Low Prostate-specific Antigen Are Prognostic Factors for a Favorable Biochemical Response to Prostate-specific Membrane Antigen-targeted Radioguided Surgery in Recurrent Prostate Cancer

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1. Introduction

Serial measurements of prostate-specific antigen (PSA) and subsequent imaging after initial curative treatment of prostate cancer (PC) allow identification of recurrence with limited metastatic burden. However, management of these patients is challenging. Recently, a randomized controlled trial demonstrated a benefit for patients receiving metastasis-directed treatment compared with a control group [1]. A large retrospective study has shown prolonged cancer-specific survival for patients who received metastasis-directed treatment [2]. Several retrospective trials indicate that salvage lymph node dissection (SLND) can yield a long disease-free state for a subset of patients [3–5]. However, high rates of subsequent therapies either without awaiting PSA nadir or without a well-defined trigger yield a substantial interpretation bias. SLND is thus currently regarded as an experimental approach in guidelines, emphasizing that finally most of these patients will experience recurrence [6]. Finally, consensus is lacking regarding which patients benefit from SLND. Nevertheless, such data are missing for cohorts with SLND exclusively based on prostate-specific membrane antigen (PSMA)-ligand positron emission tomography (PET) and for PSMA-targeted radioguided surgery (RGS).

PSMA-ligand PET has emerged as a powerful tool to detect tumor recurrences even at low PSA values [7–11]. The recently introduced PSMA-targeted RGS uses preoperative application of gamma-emitting PSMA-targeting molecules, which radioactively label tumor tissue [12–14]. The subsequent intraoperative use of a gamma probe facilitates the detection of these often small or atypically localized lesions. Early reports state superb rates of intraoperative tumor detection and a substantial PSA decline in a large number of patients [13,15]. Nevertheless, optimal patient selection for PSMA-targeted RGS is unclear. The aim of this study was to describe the outcome of a large patient cohort treated with PSMA-targeted RGS and to explore potential prognostic factors for biochemical recurrence (BCR)-free survival (bRFS).

2. Patients and methods

2.1. Patients

Patients eligible for PSMA-targeted RGS presented with BCR and an anatomical correlate on obligatory PSMA-ligand PET located in lymph nodes (LNs) or the former region of the seminal vesicles. For this retrospective analysis, all patients treated with PSMA-targeted RGS at our institution between April 2014 and May 2017 after primary curatively intended radical prostatectomy (RP) were included. Patient characteristics are summarized in Table 1. The local ethics committee approved retrospective data analysis (number 336/18 S). A part of the patient population included in this manuscript has already been published in other manuscripts [12,13,15].

2.2. PSMA-targeted RGS

PSMA-targeted RGS was performed as described previously [12,13] by two experienced surgeons (T.M. and J.G.). Briefly, patients received an injection of ^{111}In-PSMA I&T [16] or ^{99m}Tc-PSMA I&S [14] 1 d prior to surgery. Either ^{111}In-PSMA I&T or ^{99m}Tc-PSMA I&S was administered in

Table 1 – Characteristics of 121 patients with radical prostatectomy (RP) as their primary treatment

Median patient age (IQR)	70 (63–74)
Median PSA at RP (IQR)	9.5 (6.8–17.9) ng/ml
T stage at RP	
<pT2c	41 (34%)
>pT3a	78 (64%)
NA	2 (2%)
N stage at RP	
pN0	90 (74%)
pN1	25 (21%)
pNX	6 (5%)
Gleason score at RP	
5–6	13 (11%)
7	58 (48%)
8–10	44 (36%)
NA	6 (5%)
Surgical margin status at RP	
R0	78 (65%)
R1	22 (18%)
NA	21 (17%)
Treatment after RP	
No further treatment	38 (31%)
Salvage radiotherapy	77 (64%)
Salvage lymphadenectomy	8 (7%)
Current androgen deprivation before PSMA-targeted RGS	8 (7%)
Median PSA at PSMA-targeted RGS (IQR)	1.13 (0.53–2.16) ng/ml
Location of recurrence	
Seminal vesicle bed	26 (22%)
Pelvic lymph nodes	74 (61%)
Presacral/pararectal lymph nodes	31 (26%)
Retroperitoneal lymph nodes	5 (4%)
Number of tumor lesions	
1	77 (64%)
2	29 (24%)
>2	15 (12%)
Median time from RP to PSMA-targeted RGS (IQR)	4.3 (2.2–9.4) yr

IQR = interquartile range; NA = not available; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.
Location of recurrence is based on preoperative PSMA-ligand PET.

compliance with the German Medicinal Products Act (AMG §13 2b) and in accordance with the responsible regulatory body (Government of Oberbayern). PSMA-targeted RGS was performed with a lower abdominal median laparotomy and a primary transperitoneal approach [13]. A gamma probe (Crystal Probe CXS-SG603; Crystal Photonics, Berlin, Germany) was used to facilitate intraoperative removal of tumor lesions by in vivo and/or ex vivo identification of radioactive tissue.

In case of recurrent tumor within the extended pelvic LN dissection template, SLND was performed for the whole template of the respective side. For suspicious lesions located elsewhere, resection of the corresponding region with surrounding tissue was performed. In case of retroperitoneal lesions, the template of dissection usually performed for testicular cancer patients was resected.

2.3. Follow-up and definition of endpoints

All patients were followed with a postoperative PSA value after 4–8 wk and serial PSA measurements thereafter. The best PSA response and the rate of complete biochemical response (cBR; PSA <0.2 ng/ml) without additional treatment was determined 4–8 wk after PSMA-targeted RGS. BCR was defined as a rise of PSA value from <0.2 to >0.2 ng/ml. BCR-free survival was defined as the time from PSMA-targeted RGS to the first measured PSA value of at least 0.2 ng/ml without further PC-specific therapy. This was also applicable for patients who did not achieve cBR after PSMA-targeted RGS. Patients who received any adjuvant treatment without BCR were censored. Treatment-free survival was defined as the time from PSMA-targeted RGS to the initiation of any further PC-directed treatment. Initiation of any further treatment was up to the treating physicians without a predefined trigger. Patients were regularly contacted to obtain clinical follow-up information. Postoperative complications were classified according to Clavien-Dindo.

2.4. Statistics

Statistical analyses and graphs were made using SPSS (version 23; IBM, Armonk, NY, USA) or R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Mean values, medians, interquartile ranges, and/or ranges are presented for quantitative data as appropriate. Absolute and relative frequencies are given for categorical data. Chi-square tests were used to compare categorical variables between groups. Logistic regression models were fitted to the data to estimate associations of the PSA value (logarithmic scale) and the number of lesions with cBR.

Waterfall plots display the best PSA responses after PSMA-targeted RGS. The distribution of bRFS times after PSMA-targeted RGS was estimated using the Kaplan-Meier method and compared between relevant subgroups using Cox regression. In order to analyze prognostic factors for cBR and bRFS, we investigated the association of different characteristics with outcome: PSA, time from RP, Gleason score, history of prior radiation therapy, and number as well as localization of lesions on PSMA-ligand PET. All statistical tests performed were two sided, and a significance level of 5% was used. To adjust for potential confounders, we calculated multivariable Cox regression analysis with the PSA value, number of lesions in PSMA-ligand PET, and Gleason score. In these models, PSA value before PSMA-targeted RGS was used as a continuous variable. Owing to the nonlinear effect of PSA value on bRFS, PSA value was logarithmized for calculation in multivariable models.

3. Results

3.1. Patient cohort

We identified 121 patients with PSMA-targeted RGS and RP as primary treatment (Table 1). The median age of the patients was 70 yr (interquartile range 63–74 yr) and the mean pre-RGS PSA value was 1.13 ng/ml. During the follow-up period, 71 events of BCR occurred; seven patients were not analyzable for bRFS. Median follow-up in patients without an event was 10.3 mo.

There were 29 patients with Clavien grade I/II complications. Although these complications were mainly lymphedema and hypesthesia, six patients also had new or worsening voiding dysfunction—both incontinence and weak urinary stream/residual urine. We observed 11 patients with Clavien grade III complications; among them seven patients had hydronephrosis due to ureteral strictures, two rectal lesions with the need for temporary colostomy, and one case each of urosepsis and osteomyelitis in the foot due to lymphedema (Table 2). One patient had a fatal pulmonary embolism 6 d after surgery.

3.2. Clinical impact of PSMA-targeted RGS

At least some metastatic tissue could be removed in 120/121 patients (99%). Any PSA decline was found in 107 of 114 patients with sufficient follow-up information. A PSA decline of at least 50% and 90% was achieved in 88/114 (77%) and 55/114 (48%) patients, respectively (Fig. 1). A cBR was reached for 77/117 (66%) patients. The chance of cBR was highest in patients with both a low preoperative PSA value

Table 2 – Postoperative characteristics after PSMA-targeted RGS of 121 patients with radical prostatectomy (RP) as their primary treatment

Complications from PSMA-targeted RGS	
Clavien grade I/II	29 (24%)
Clavien grade III	11 (9%)
Clavien grade IV	0 (0%)
Clavien grade V	1 (1%)
Transfusion rate	0 (0%)
Median drop in hemoglobin (IQR)	1.6 (1.2–2.6) g/dl
Median duration of PSMA-targeted RGS (IQR)	116 (96–151) min
Number of bRFS events	71 (8 patients unavailable)
Median number of removed LNs (IQR)	11 (6–18)
Median number of metastatic nodes removed (range)	
1 lesion in PSMA-ligand PET	1 (0–6)
2 lesions in PSMA-ligand PET	4 (1–11)
≥3 lesions in PSMA-ligand PET	5 (2–11)
Median number of total lymph nodes removed (range)	
1 lesion in PSMA-ligand PET	8 (0–34)
2 lesions in PSMA-ligand PET	13 (3–30)
≥3 lesions in PSMA-ligand PET	15 (2–34)
Total number of PSMA-ligand PET lesions	175
Total number of PSMA-ligand PET lesions detected by RGS	171
Number of additional lesions detected by PSMA-targeted RGS	9
Number of additional lesions detected only by histology	39

bRFS = biochemical recurrence-free survival; IQR = interquartile range; LN = lymph node; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.
Drop in hemoglobin (Hb) was calculated as follows: Hb the day before surgery – Hb the day after surgery.

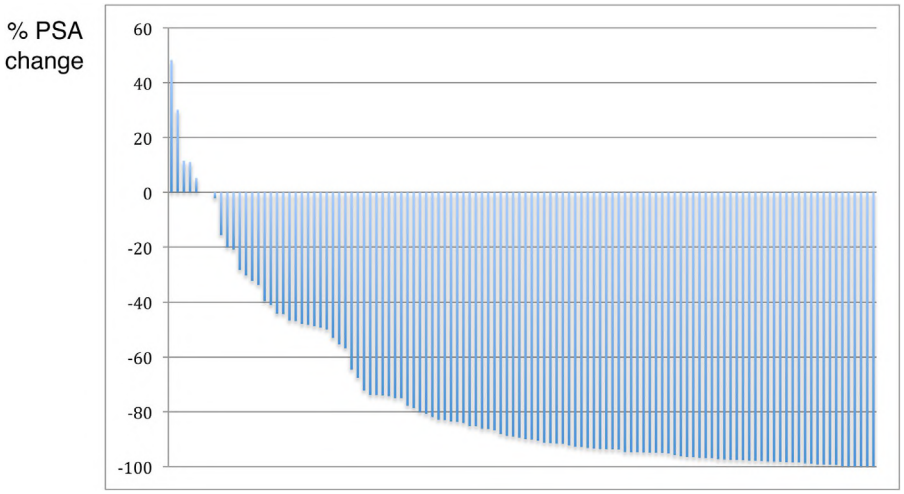


Fig. 1 – PSA responses 4–8 wk after PSMA-targeted RGS without any further treatment in 114 patients with sufficient follow-up information. PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.

and a single lesion (38/45, 84%). Univariate logistic regression showed a significantly higher likelihood of achieving a complete PSA response for lower PSA value ($p = 0.015$, odds ratio [OR] 0.57, 95% confidence interval [CI] 0.37–0.90) and for the presence of a single lesion in PSMA-ligand PET versus multiple lesions ($p = 0.016$, OR 2.7, 95% CI 1.2–5.9).

Median bRFS was 6.4 mo for all patients and 19.8 mo for those who achieved a cBR. At the time of the analysis, the cBR was still ongoing for at least 12 and 18 mo in 19 and nine patients, respectively (Fig. 2).

A total of 39 patients received further treatment after a median of 4.6 mo; 80 patients remained free of any further treatment for a median of 10.2 mo (Fig. 2).

3.3. *Analysis of prognostic factors for bRFS*

There were no statistically significant associations between bRFS and Gleason score (Gleason 5–7 vs 8–10: $p = 0.8$, hazard ratio [HR] 0.93, 95% CI 0.56–1.54), the interval between RP and PSMA-targeted RGS (HR 0.98, 95% CI 0.94–1.03, $p = 0.5$), the tracer used (^{111}In-PSMA I&T [16] or ^{99m}Tc-PSMA I&S [14]; HR 0.9, 95% CI 0.5–1.5, $p = 0.6$), and a history of prior radiation therapy ($p = 0.5$, HR 1.25, 95% CI 0.76–2.05). Interestingly, we saw no significant difference in the likelihood of BCR for different anatomical locations of recurrence (Supplementary Fig. 1).

We found longer bRFS for patients with a pN0 status at RP in comparison with those with pN1 without statistical significance ($p = 0.07$, median bRFS 8.4 vs 2.0 mo, HR 0.51, 95% CI 0.25–1.04).

Patients with a low preoperative PSA value had a significantly lower risk for BCR compared with patients with higher values (PSA used as a continuous variable, $p = 0.004$, HR 1.48, 95% CI 1.13–1.93).

Furthermore, patients with a single lesion of recurrence in preoperative PSMA-ligand PET had longer median bRFS than patients with multiple lesions (bRFS 14.0 vs 2.5 mo, $p = 0.002$, HR 0.47, 95% CI 0.29–0.75; Fig. 3).

In multivariable analysis, both PSA value ($p = 0.014$, HR 1.5, 95% CI 1.08–1.94) and the presence of a single lesion on PSMA-ligand PET ($p = 0.06$, HR 0.57, 95% CI 0.27–0.8), remained statistically significant prognosticators of longer bRFS.

4. Discussion

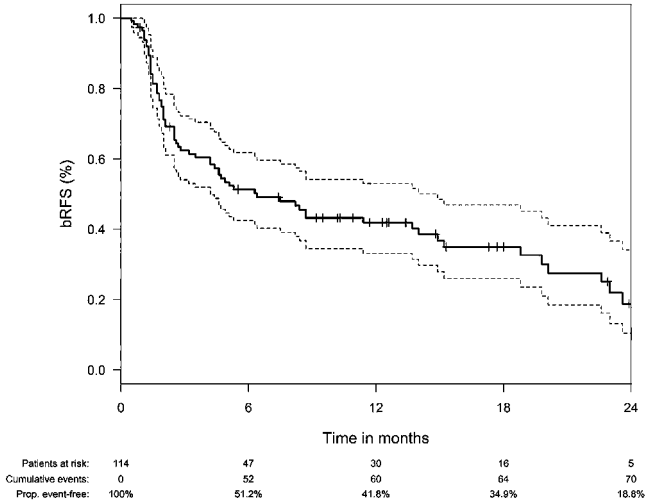
The oncological value of SLND in PC is unknown. Therapeutic alternatives are the initiation of hormonal treatment upon further progression associated with a potential negative impact on the patients' quality of life or radiotherapeutic concepts.

Several series on SLND exist that mainly rely on choline PET [17–20]. The series with the longest follow-up reports 59 patients, and describes an intraoperative detection rate of 80% and a rate of cBR of 60% [3]. A recent multicentric analysis with 654 patients (70% choline and 30% PSMA-ligand PET) reports a detection rate of 91% and a cBR of 44%. In addition, a high PSA value at SLND, Gleason grade group 5, more than two PET lesions, retroperitoneal location, and hormonal treatment at the time of PET scan were identified as negative prognostic factors [21].

We recently introduced PSMA-targeted RGS [12,13,15]. Now, we have substantially expanded our cohort, including longer follow-up, compared with previously published cohorts [13,15]. We now present analyses exploring potential preoperative prognostic factors.

Of note, our patient cohort had a lower median PSA value of 1.13 ng/ml compared with PSA values of 2 [3] and 2.1 ng/ml [21] in the studies mentioned above. Nevertheless, we were able to remove PC lesions in nearly all patients (99.2%) compared with 80% [3] and 91% [21] of patients. This can be attributed to both the high specificity of PSMA-ligand PET and the use of radioguidance.

In our cohort, cBR could be achieved in 66% of patients, which is higher than in the other studies (59% [3] and 44% [21]). Another study with a higher median PSA value at



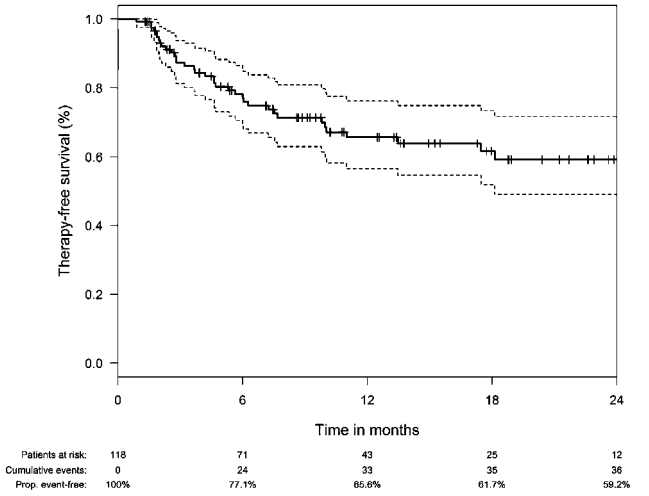


Fig. 2 – Biochemical recurrence-free survival and therapy-free survival of all patients undergoing PSMA-targeted RGS (bRFS; time interval between PSMA-targeted RGS and first PSA measurement >0.2 ng/ml; therapy-free survival: time interval between PSMA-targeted RGS and initiation of the first PC-directed treatment thereafter). Kaplan-Meier estimates of bRFS and 95% confidence intervals are shown.
bRFS = biochemical recurrence-free survival; PC = prostate cancer; Prop. = proportion; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.

SLND reports an even lower cBR rate of 27.5% [22]. Although high rates of detection and cBR were achieved, we removed fewer LNs (median numbers 11 in our study vs 26 in other studies [3,21]) than reported in other studies. Having a rather low rate (9% in final pathology) of retroperitoneal LN involvement (18% in Fossati et al.'s study [21] and 39% in Suardi et al.'s study [3]), which is a previously published adverse factor [21], could have contributed to the relatively high cBR rate in our patients. Although the added value by the use of radioguidance is hard to establish, these rates can be seen as a hint for a benefit. In support of an advantage for intraoperative radioguidance, an SLND data collection report demonstrated superior removal of affected LNs and a more pronounced PSA decline for PSMA-targeted RGS [23] compared with standard SLND.

SLND yields better results if based on PSMA-ligand PET [24]. Only few studies exclusively include patients with PSMA-ligand PET. One study reports a rate of cBR of 43% and a fraction without BCR at 12 mo of 23% (our cohort 42%) [20]. Reasons for the better outcome in our study may be the lower median PSA value (1.3 vs 2.2 ng/ml), a slightly higher fraction of patients with a singular lesion (64% vs 57%), and the use of radioguidance.

Of course, PSMA-targeted RGS does not detect very small metastatic lesions. In 32 patients (26.4%), a histological analysis revealed 48 regions (median size 3 mm) negative on previous PSMA-ligand PET that harbored metastatic tissue. Only 18.8% of those could be identified on intraoperative measurements during PSMA-targeted RGS. We see this as a confirmation of not limiting the resection to the PET-positive lesions, as well as dissect not only a tissue that can be identified during PSMA-targeted RGS, but also surrounding tissue [4,25].

Long-term bRFS results in our study are immature. A relevant fraction (41.8%) of patients without any further treatment has bRFS of at least 12 mo.

BCR-free survival is the most objective endpoint in the early postsurgical phase. We also provided information about treatment-free survival—64% of our patients remained without any PC-directed treatment in the 1st year after SLND. Despite being highly relevant for individual patients, it is prone to large variation as patients were subsequently treated in clinical routine and no predefined trigger for the initiation of further treatment was used.

As SLND for PC is not likely to become a "one-size-fits-all" approach, patient selection is the key to optimize outcome. Concerning preoperative parameters, we were able to show that a low PSA value and single localization of recurrence in PSMA-ligand PET are associated with longer bRFS. On the contrary, Gleason score at RP, prior radiation treatment, time from RP, and localization of recurrence had no significant impact on bRFS. This is in line with the study by Suardi et al. [3], where also PSA value and up to a maximum of two positive LNs on postoperative histology were associated with a better outcome. Nevertheless, Fossati et al. [21] found Gleason grade group 5 in the RP specimen to be the strongest predictor of bRFS, which we could not observe to have an impact.

The rate of Clavien grade III complications (9.1%) is in the range of what has been reported [26]. The most frequent grade III complication was hydronephrosis due to ureteral strictures. Six of those seven lesions occurred after previous radiation therapy. Six patients had a new or worsened voiding dysfunction among grade I/II complications. This may result from damage of autonomic nerves or blood supply to the bladder. Patients should be counseled about this side effect that is dependent on the location of recurrence.

Strengths of our study include, first, the use of PSMA-ligand PET for patient selection in all cases. Second, the observed bRFS time is only due to the effects of PSMA-targeted RGS as patients who initiated any treatment after

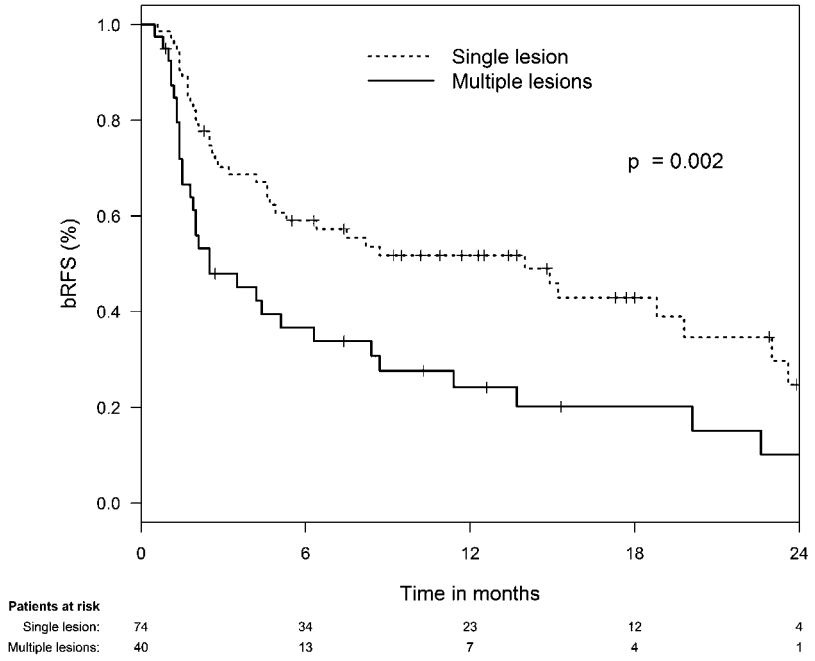


Fig. 3 – Kaplan-Meier analysis of biochemical recurrence-free survival dependent on the number of suspected metastatic lesions in preoperative PSMA-ligand PET. Patients with a single lesion were statistically compared with all patients with more than one lesion. bRFS = biochemical recurrence-free survival; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

PSMA-targeted RGS were censored for the event of BCR. Third, this is the largest cohort with PSMA-targeted RGS reported so far and the first to report prognostic factors. Fourth, all patients had RP as their primary treatment.

Limitations of our study are its retrospective nonrandomized design without a uniform resection template, relatively short follow-up period without sufficient data for clinical recurrence, and lack of information about hormonal treatment between RP and 6 mo prior to PSMA-targeted RGS.

5. Conclusions

PSMA-targeted RGS in recurrent PC facilitates removal of lesions, resulting in cBR in two-thirds of patients. A subset of patients experiences a remarkable interval of bRFS and treatment-free survival. Our data indicate that the outcome of PSMA-targeted RGS in terms of cBR and bRFS is most favorable in patients with a low preoperative PSA value and a single anatomical site of recurrence as defined on PSMA-ligand PET.

Author contributions: Tobias Maurer 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: Horn, Wester, Gschwend, Weber, Eiber, Maurer.
Acquisition of data: Horn, Krönke, Rauscher, Heck, Eiber, Maurer.
Analysis and interpretation of data: Horn, Krönke, Rauscher, van Leeuwen, van der Poel, Heck, Eiber, Maurer.
Drafting of the manuscript: Horn, Maurer.
Critical revision of the manuscript for important intellectual content: Robu, Wester, Schottelius, van Leeuwen, van der Poel, Weber, Eiber.
Statistical analysis: Haller.
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Appendix A. Supplementary data

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