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Biochemical Response of <0.1 ng/ml Predicts Therapy-free Survival of Prostate Cancer Patients following Prostate-specific Membrane Antigen–targeted Salvage Surgery

Sophie Knipper[a,b], *Flemming Lischewski*[c], *Daniel Koehler*[d], *Matthias Eiber*[e], *Fijs W.B. van Leeuwen*[f], *Hilda de Barros*[g], *Anne-Claire Berrens*[g], *Lotte Zuur*[g], *Pim J. van Leeuwen*[g], *Henk van der Poel*[g,h], *Francesca Ambrosini*[a,i], *Fabian Falkenbach*[a], *Lars Budäus*[a], *Thomas Steuber*[a,j], *Markus Graefen*[a], *Pierre Tennstedt*[a], *Jürgen E. Gschwend*[c], *Thomas Horn*[c], *Matthias M. Heck*[c,†], *Tobias Maurer*[a,j,†,*]

[a] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [b] *Department of Urology, Vivantes Klinikum am Urban, Berlin, Germany;* [c] *Department of Urology, Technical University of Munich, Munich, Germany;* [d] *Department of Radiology and Nuclear Medicine, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [e] *Department of Nuclear Medicine, Technical University of Munich, Munich, Germany;* [f] *Interventional Molecular Imaging Laboratory, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands;* [g] *Department of Urology, Antoni van Leeuwenhoek Hospital – the Netherlands Cancer Institute, Amsterdam, The Netherlands;* [h] *Department of Urology, Amsterdam University Medical Centers, Amsterdam, The Netherlands;* [i] *IRCCS Ospedale Policlinico San Martino, Genoa, Italy;* [j] *Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany*

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Abstract

Background: In a subset of patients with oligorecurrent prostate cancer (PCa), salvage surgery with prostate-specific membrane antigen (PSMA) radioguided surgery (PSMA-RGS) seems to be of value.
Objective: To evaluate whether a lower level of postoperative prostate-specific antigen (PSA; <0.1 ng/ml) is predictive of therapy-free survival (TFS) following salvage PSMA-RGS.
Design, setting, and participants: This cohort study evaluated patients with biochemical recurrence after radical prostatectomy and oligorecurrent PCa on PSMA positron emission tomography treated with PSMA-RGS in three tertiary care centers (2014–2022).
Intervention: PSMA-RGS.
Outcome measurements and statistical analysis: Postsalvage surgery PSA response was categorized as <0.1, 0.1–<0.2, or >0.2 ng/ml. Kaplan-Meier and multivariable Cox regression models evaluated TFS according to PSA response.
Results and limitations: Among 553 patients assessed, 522 (94%) had metastatic soft tissue lesions removed during PSMA-RGS. At 2–16 wk after PSMA-RGS, 192, 62, and 190 patients achieved PSA levels of <0.1, 0.1–<0.2, and >0.2 ng/ml, respectively. At 2 yr of follow-up, TFS rate was 81.1% versus 56.1% versus 43.1% ($p < 0.001$) for patients with PSA <0.1 versus 0.1–<0.2 versus >0.2 ng/ml. In multivariable analyses, PSA levels of 0.1–0.2 ng/ml (hazard ratio [HR]: 1.9, confidence interval [CI]: 1.1–3.1) and ≥0.2 ng/

† These authors shared senior authorship.
* Corresponding author. Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Martinistraße 52, Hamburg 20246, Germany. Tel. +49 (0)40 7410-51300; Fax: +49 (0)40 7410-51323.
E-mail address: t.maurer@uke.de (T. Maurer).

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ml (HR: 3.2, CI: 2.2–4.6, $p < 0.001$) independently predicted the need for additional therapy after PSMA-RGS. The main limitation is the lack of a control group.

Conclusions: For patients after salvage PSMA-RGS, a lower biochemical response (PSA <0.1 ng/ml) seems to predict longer TFS. This insight may help in counseling patients postoperatively as well as guiding the timely selection of additional therapy.

Patient summary: We studied what happened to prostate cancer patients in three European centers who had salvage surgery using a special method called prostate-specific membrane antigen–targeted radioguidance. We found that patients who had low prostate-specific antigen levels soon after surgery were less likely to need further treatment for a longer time.

1. Introduction

Imaging of recurrent prostate cancer (PCa) lesions has seen a significant development in recent years. The diagnostic process was impacted greatly by positron emission tomography (PET) using ligands directed against prostate-specific membrane antigen (PSMA) [1]. With this technology, soft tissue PCa lesions within lymph nodes or connective tissue oftentimes show high tracer uptake and can be detected at only a few millimeters in diameter [2–4]. Moreover, PSMA PET imaging can identify metastatic sites at very low prostate-specific antigen (PSA) levels at biochemical recurrence (BCR) [5,6]. In light of this, PSMA PET imaging has recently been proposed as the preferred imaging technique for biochemically recurrent PCa after radical prostatectomy (RP) [7].

Currently, in biochemically recurrent PCa with evidence of lymph node involvement, watchful waiting or the start of systemic treatment, such as androgen deprivation therapy (ADT), is still recommended [7]. However, the development of imaging has raised awareness of locally targeted therapy approaches including salvage lymph node dissection (SLND) and targeted salvage radiation [8]. While still considered to be experimental, results from these procedures indicate that these may postpone systemic palliative care and its associated toxicity, and may therefore improve quality of life [9]. Long-term PSA responses may also be observed in a minority of patients, as described recently for SLND procedures realized via PSMA radioguided surgery (PSMA-RGS) [10].

However, prediction of long-term outcomes remains difficult, and tools are needed to optimize patient selection and care. To accomplish this, we aimed at evaluating oncological outcomes of PSMA-RGS in patients with early BCR and PSMA PET–avid lesions in a large, multicenter retrospective cohort focusing on early postoperative PSA as a predictor for therapy-free survival (TFS).

2. Patients and methods

2.1. Study population

Overall, 699 consecutive patients were treated with PSMA-RGS in three centers between November 2014 and December 2022. Of these patients, 146 were excluded from further analyses, rendering a final study cohort of 553 patients (Fig. 1). Of the final study cohort, all patients presented with BCR (defined as PSA $\geq$0.2 ng/ml in two controls) after initial RP with one or more positive soft tissue (connective tissue or local recurrence) or lymph node lesion on PSMA PET imaging.

All patients were informed about the experimental nature of salvage surgery and the additional use of PSMA-RGS, as described previously [11–14]. All patients provided their informed consent to the procedure, data collection, as well as data analysis. This permits collection of deidentified patient data at baseline and follow-up, which were entered into a secure, password-protected database for a subsequent analysis. The retrospective analysis was approved by the institutional review boards in Hamburg (2019-PS-09; PV7316), Munich (number 336/18 S), Germany, and Amsterdam (IRBdm21-106, NCT03857113), the Netherlands. All men signed an informed consent form on data collection. Questionnaires concerning PSA values and further treatments were used for follow-up. All data were stored prospectively in an institutional database (FileMaker, Claris, CA, USA).

2.2. Procedure of salvage surgery using PSMA-RGS

The PSMA-RGS procedure involves several steps, as reported previously [11,15,16]. During surgery, a template-based lymphadenectomy for lymph node recurrences or, at the treating physician's discretion, local excision of local recurrence was carried out. Particularly, SLND was performed for the entire template of the affected side and/or (at the surgeon's discretion) for the contralateral side in cases of recurring malignancy inside the extended pelvic lymph node dissection template. Resection of the affected area along with the surrounding tissue was carried out for suspicious lesions found in other locations (such as pararectal lesions). Retroperitoneal lesions were resected using the standard testicular cancer patient dissection template. Additionally, in these cases, the ipsilateral pelvic template was also dissected.

A gamma probe was used for in vivo intraoperative measurements of radioactivity caused by cancer-specific accumulation of PSMA tracers to facilitate localizing the recurrent lesion. After excision, ex vivo gamma measurements were performed to immediately confirm the successful removal of the metastatic radioactive lesion or to prompt further search in case of a missing signal [11].

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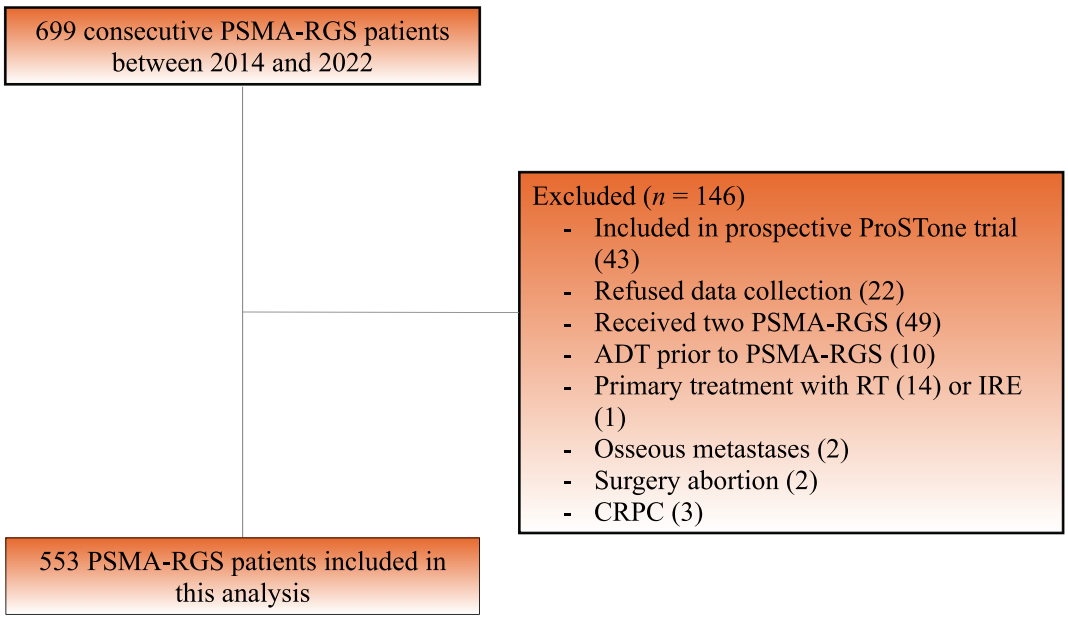

Fig. 1 – Consort diagram of the study cohort treated with prostate-specific membrane antigen radioguided surgery (PSMA-RGS) between 2014 and 2022 in three tertiary care centers. ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; IRE = irreversible electroporation; RT = radiotherapy.

2.3. *Outcomes of interest*

The rate of complete biochemical response (cBR; defined as PSA <0.2 ng/ml) without any additional treatment postoperatively was determined 2–16 wk following PSMA-RGS. A cBR was stratified further according to the depth of PSA response (< 0.1 vs 0.1–<0.2 vs ≥0.2 ng/ml), analogous to different PSA cutoffs for potential reinterventions in other studies [17–19]. BCR following PSMA-RGS was defined as PSA ≥0.2 ng/ml (without the need of a confirmatory value).

Furthermore, BCR-free survival (BFS; defined as survival with PSA <0.2 ng/ml without any further treatment) and TFS (defined as survival without further treatment; initiation of further treatment was at the discretion of the treating physician) after PSMA-RGS were evaluated. Survival was calculated from the time of PSMA-RGS to the time of the event or end of follow-up. Patients were censored on the date of last evidence of freedom from BCR or further treatment.

2.4. *Statistical analyses*

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The statistical significance of differences in medians and proportions was evaluated with the Kruskal-Wallis and Pearson's chi-square tests. Kaplan-Meier plots graphically depicted BFS and TFS following PSMA-RGS. Of note, the Kaplan-Meier estimate provides a statistical method for estimating survival probabilities over time, regardless of the actual follow-up duration. Univariable and multivariable Cox regression models tested the relationship between oncological outcomes (TFS) and several variables, namely, pT stage at RP (pT2 vs pT3a vs pT3b), Gleason grade group at RP (I–II vs III–V), pN stage at RP (pN0/X vs pN1), radiotherapy (RT) after RP (yes vs no), age at PSMA-RGS (continuously coded), time between initial RP and PSMA-RGS (continuously coded), PSA at PSMA-RGS (continuously coded), number of PSMA PET–positive lesions prior to PSMA-RGS (negative vs 1 vs 2 vs ≥3), as well as localizations of PSMA PET–positive lesions prior to PSMA-RGS (pelvic [including pararectal and presacral nodes] vs retrovesical lesions/local recurrences vs retroperitoneal [including common ileac nodes]). Predictors were selected among potential factors previously published and associated with oncological outcomes after SLND [4,10,20]. These potential predictors were included in the multivariable models if significantly associated with the outcome in the univariable analysis. These were tested in independent multivariable Cox regression models for the pre- and postoperative clinical settings. Furthermore, for both clinical settings, two models each were fit, including either the number or the localization of lesions, as these variables may be dependent.

Preoperative models were the following: (1) pT stage at RP, time between RP to PSMA-RGS and PSA prior to PSMA-RGS with the number of PSMA PET–positive lesions, and (2) pT stage at RP, time between RP to PSMA-RGS and PSA prior to PSMA-RGS with localization of PSMA PET–positive lesions.

Postoperative models were the following: (1) cBR with the number of pathologically positive lesions and (2) cBR with localization of pathologically positive lesions.

To address potential biases concerning the categorization of cBR, additional analyses without PSA categorization (postoperative PSA coded continuously) were performed of the last two models.

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For all statistical analyses, R software environment for statistical computing and graphics (version 3.4.3) was used. All tests were two sided, with a level of significance set at $p < 0.05$.

3. Results

Overall, 553 patients without concomitant treatment were assessed (Table 1). As primary treatment, all patients had previously received RP at a median PSA level of 9 ng/ml (interquartile range [IQR]: 6–15 ng/ml) and a median of 49 mo (IQR: 28–93 mo) prior to PSMA-RGS. At RP, pT3a and pT3b disease were found in 144 (26%) and 155 (28%) patients and Gleason grade groups IV and V were found in 63 (11%) and 83 (15%) patients, respectively. Moreover, pN1 disease was found in 98 (18%) patients. Of these patients, 55, 19, and 20 had one, two, and three or more positive nodes, respectively. A positive surgical margin was reported in 112 (20%) patients, and 310 (56%) patients received adjuvant or salvage RT to the prostate bed and/or pelvis after RP (Supplementary Table 1).

At PSMA-RGS, the median age was 67 yr (IQR: 62–72 yr), with a median PSA value of 0.8 ng/ml (IQR: 0.4–1.5 ng/ml) prior to salvage surgery (Table 1). No patient received ADT within the last 6 mo prior to PSMA-RGS. In PSMA PET imaging prior to surgery, 350 (61%), 89 (16%), and 51 (9.2%) patients showed one, two, and three and more PSMA-avid lesions, respectively. Of the patients, 327 (59%) showed pelvic lesions, 85 (15%) showed retrovesical lesions/local recurrences, and 78 (14%) showed retroperitoneal lesions, and in 63 (11%) patients, lesions with questionable PSMA uptake were seen (equivocal findings).

Soft tissue PCa lesions within lymph nodes or connective tissue could be removed in 522 (94%) patients. Of these patients, 233 (42%) had one lesion, and 94 (17%) and 176 (32%) had two and three and more pathologically positive lesions, respectively. In 31 (5.6%) patients, no PCa tissue was found upon a pathological analysis. PCa lesions were located within the pelvis in 299 (54%) patients, were retrovesical in 90 (16%) patients, and were retroperitoneal in 125 (23%) patients (Table 1).

Table 1 – Characteristics of 553 patients treated with salvage surgery between 2014 and 2022 in three centers

Characteristic	*N* = 553
	Median (IQR); *n* ()
Age at PSMA-RGS (yr)	67 (62, 72)
Time between RP and RGS (mo)	49 (25, 97)
PSA prior to PSMA-RGS (ng/ml)	0.81 (0.42, 1.54)
No. of PSMA PET–avid lesions	
1	350 (63)
2	89 (16)
≥3	51 (9.2)
Equivocal findings	63 (11)
PSMA PET localization	
Pelvic	327 (59)
Retrovesical	85 (15)
Retroperitoneal	78 (14)
Equivocal findings	63 (11)
No. of pathologically positive lesions	
Negative pathology	31 (5.6)
1	233 (42)
2	94 (17)
≥3	176 (32)
Unknown	19 (3.4)
Localization of pathologically positive lesions	
Pelvic	299 (54)
Retrovesical	90 (16)
Retroperitoneal	125 (23)
Negative pathology	31 (5.6)
Unknown	8 (1.4)
cBR (ng/ml)	
<0.1	192 (43)
0.1–<0.2	62 (14)
≥0.2	190 (43)
Unknown	109

cBR = complete biochemical response; IQR = interquartile range; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RGS = radioguided surgery.
All patients presented with biochemical recurrence after radical prostatectomy (RP) with positive lesions at PSMA PET imaging.

3.1. Oncological outcomes

At 2–16 wk after PSMA-RGS, 192, 62, and 190 patients reached PSA levels of <0.1, 0.1–<0.2, and ≥0.2 ng/ml, respectively. Within the overall follow-up, 341 patients experienced BCR and 188 received further therapy. The median follow-up period for patients who did not experience BCR was 18.5 mo (IQR: 7.1–36 mo). The median follow-up period for patients who did not receive further therapy was 23.7 mo (IQR: 10–36 mo).

Within the overall cohort, the median BFS was 9 mo (95% confidence interval [CI]: 6.2–13.9 mo) and median TFS was 43.1 mo (CI: 37.7–59.3 mo). At 2 yr of follow-up, BFS rate was 37.2% (CI: 32.9–41.9%; Supplementary Fig. 1) and TFS rate was 65.2% (CI: 60.7–70%). Seven patients died during follow-up.

In patients reaching PSA levels of <0.1, 0.1–< 0.2, or ≥0.2 ng/ml, the median TFS was not reached, 43.1 mo, and 18 mo, respectively (CI: 48.6– NA vs 19.3–NA vs 11.8–24.7 mo). At 2 yr of follow-up, TFS rate was 81.1% versus 56.1% versus 43.1% (CI: 75.1–87.5% vs 43.6–72.1% vs 35.9–51.7%, $p < 0.001$) in patients reaching a PSA level of < 0.1 versus 0.1–<0.2 versus ≥0.2 ng/ml (Fig. 2).

In univariable analyses predicting TFS, higher pT stage at RP, shorter time from RP to PSMA-RGS, higher PSA prior to PSMA-RGS, a higher number of PSMA-avid lesions on preoperative PSMA PET imaging, retroperitoneal localization of PSMA-avid lesions, a higher number of pathologically positive lesions, as well as worse cBR (PSA 0.1–<0.2 ng/ml, hazard ratio [HR]: 2.2, CI: 1.3–3.5; PSA ≥0.2 ng/ml, HR: 3.6, CI: 2.6–5.2, $p < 0.001$) were all independent predictors of TFS after PSMA-RGS (Supplementary Table 2).

In multivariable analyses predicting TFS, pT stage at RP, time from RP to PSMA-RGS, a higher number of PSMA-avid lesions on preoperative PSMA PET imaging, a higher number of pathologically positive lesions, retroperitoneal localization of pathologically positive lesions, as well as worse cBR (PSA 0.1–<0.2 ng/ml, HR: 1.9, CI: 1.1–3.1; PSA ≥0.2 ng/ml, HR: 3.2, CI: 2.2–4.6, $p < 0.001$) reached independent predictor status (Table 2). This was also true when postoperative PSA was coded continuously (HR: 1.2, CI: 1.1–1.2; $p < 0.001$; Supplementary Table 3).

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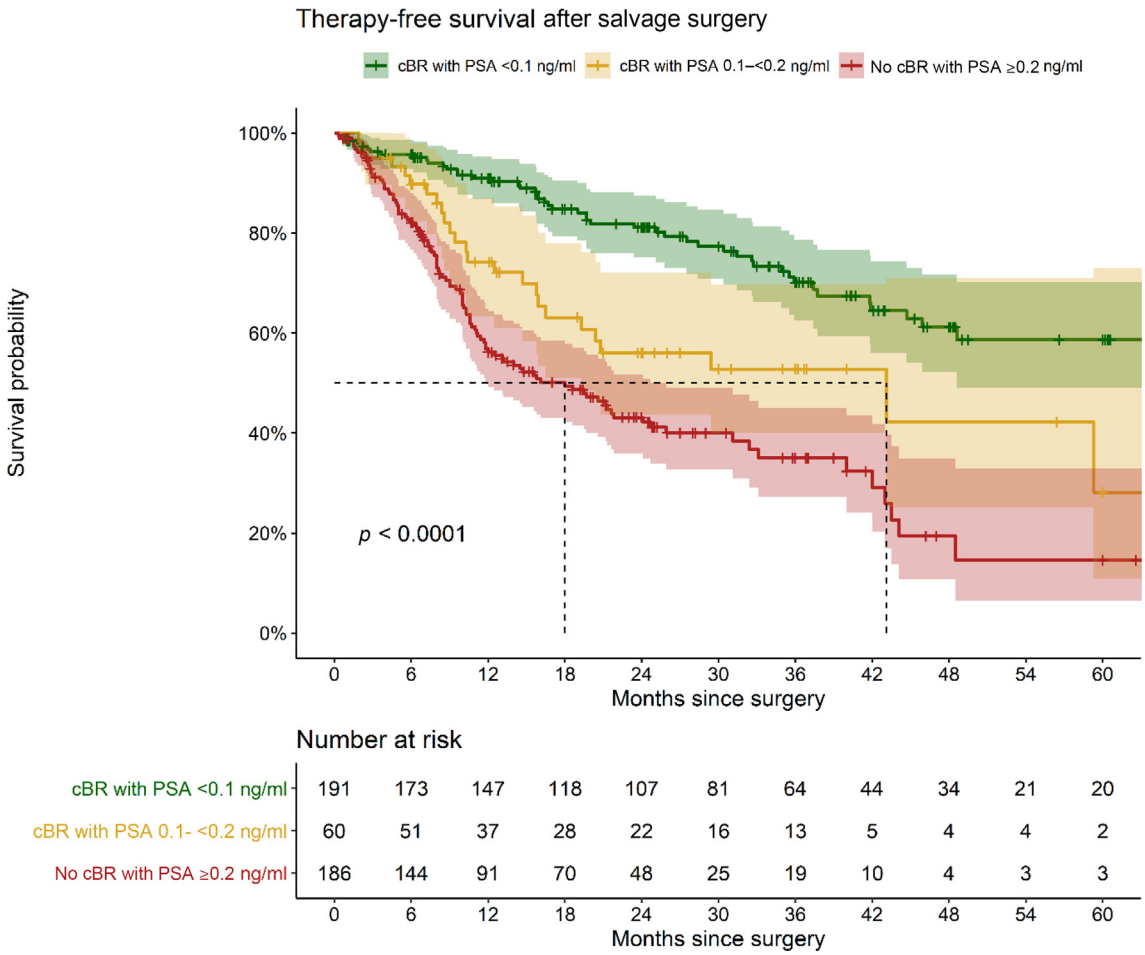

Fig. 2 – Kaplan-Meier analyses depicting therapy-free survival rates in 553 patients (109 with missing cBR data) treated with prostate-specific membrane antigen radioguided surgery (PSMA-RGS) between 2014 and 2022 in three tertiary care centers. cBR = complete biochemical response; PSA = prostate-specific antigen.

4. Discussion

With evolving PSMA PET imaging in biochemically recurrent PCa, an increased interest in metastasis-targeted treatment techniques such as salvage surgery can be observed.

In the context of eliminating the source of further metastatic spread, PSMA-RGS is a promising method to improve surgical identification of metastatic lesions in PCa [4,10,21]. In a subset of patients with PCa recurrence, it may offer a chance to prolong TFS for several years [16]. However, oncological outcomes may vary depending on several disease characteristics as well as follow-up management. Additionally, the worry of potentially missing a window of opportunity for early additional adjuvant therapy was discussed [20]. As a PSA response was already proved to be predictive of survival outcomes in later-stage PCa [22], we aimed at evaluating the early biochemical response and the depth of the biochemical response after PSMA-RGS as additional prognostic factors.

Our analyses demonstrated several noteworthy observations. In our cohort, >40% of patients reached a PSA level of <0.1 ng/ml postoperatively, with another roughly 15% of patients reaching a PSA level between 0.1 and ≤0.2 ng/ml. These patients seem to have a significantly better long-term outcome. Specifically, patients with a very low PSA response (≤0.1 ng/ml) seem to have median TFS of <5 yr. Moreover, this factor was also confirmed as an independent predictor in uni- and multivariable analyses.

With more and more data emerging about the potential efficacy of early intensified treatment approaches in aggressive disease, the early postoperative PSA response may help guide additional treatment in patients treated by PSMA-RGS. Moreover, early counseling for the use of adjuvant therapy may be facilitated.

Our study has several strengths. First, it is the largest multicenter series of patients undergoing salvage surgery based on PSMA PET imaging. Second, it also comprises the largest series of PSMA-RGS, underlining the efficacy of PSMA-RGS. Moreover, no patients received ADT within 6 mo prior to PSMA-RGS, which may otherwise have masked further metastatic spread, thus rendering the biochemical response rates in our analysis highly reliable.

Nonetheless, several limitations of our study need to be mentioned. First and foremost is the lack of a control group

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Table 2 – Multivariable Cox regression models predicting therapy-free survival, first tested in two preoperative independent multivariable Cox regression models: (1) pT stage at RP, time between RP to PSMA-RGS and PSA prior to PSMA-RGS with the number of PSMA PET–positive lesions, and (2) pT stage at RP, time between RP to PSMA-RGS and PSA prior to PSMA-RGS with localization of PSMA PET–positive lesions), and second tested in two postoperative independent multivariable Cox regression models: (1) cBR with number of pathologically positive lesions and (2) cBR with localization of pathologically positive lesions)

Variables	Multivariable Cox regression model			
	HR	CI 2.5%	CI 97.5%	*p* value
Preoperative model: (1)				
pT stage at RP				
pT2	Ref.			
pT3a	1.1	0.7	1.5	0.7
pT3b	1.5	1.1	2.2	0.02
Time between RP and PSMA-RGS (in years, continuous)	0.9	0.9	1.0	<0.01
PSA prior to PSMA-RGS (continuous)	1.1	1.1	1.2	<0.001
No. of PSMA PET–positive lesions				
1	Ref.			
2	1.7	1.2	2.5	<0.01
≥3	2.1	1.3	3.3	<0.01
Equivocal findings	1.0	0.6	1.6	0.9
Preoperative model: (2)				
pT stage at RP				
pT2	Ref.			
pT3a	1.1	0.7	1.6	0.7
pT3b	1.5	1.1	2.2	0.02
Time between RP and PSMA-RGS (in years, continuous)	0.9	0.9	1.0	<0.01
PSA prior to PSMA-RGS (continuous)	1.1	1.1	1.2	<0.001
Localization of PSMA PET–positive lesions				
Pelvic	Ref.			
Retrovesical	0.8	0.5	1.2	0.3
Retroperitoneal	1.4	0.9	2.1	0.09
Equivocal findings	0.9	0.5	1.4	0.5
Postoperative model: (1)				
cBR (ng/ml)				
<0.1	Ref.			
0.1–<0.2	1.9	1.1	3.1	0.02
≥0.2	3.2	2.2	4.6	<0.001
No. of pathologically positive lesions				
1	Ref.			
2	1.6	1.0	2.5	0.07
≥3	2.8	2.0	4.0	<0.001
Negative pathology	1.9	1.0	3.7	0.05
Postoperative model: (2)				
cBR (ng/ml)				
<0.1	Ref.			
0.1–<0.2	1.9	1.2	3.1	0.01
≥0.2	3.3	2.3	4.7	<0.001
Localization of pathologically positive lesions				
Pelvic	Ref.			
Retrovesical	0.7	0.4	1.1	0.1
Retroperitoneal	2.1	1.5	2.9	<0.001
Negative pathology	1.4	0.7	2.6	0.3

cBR = complete biochemical response 2–16 wk after PSMA-RGS; CI = confidence interval; HR = hazard ratio; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA-RGS = prostate-specific membrane antigen radioguided surgery; Ref. = reference; RP = radical prostatectomy.

including men managed with either observation or systemic treatment. Arguably, relevant data demonstrating benefit exist also for pelvic nodal RT in combination with salvage RT after post-RP BCR (RTOG 0534) [23], for comprehensive nodal RT in selected PET-defined oligonodal recurrent PCa [24], and for stereotactic body RT to defer the need for ADT in oligometastatic PCa [25,26]. Ideally, a randomized controlled trial or at least a prospective register would compare all four treatment modalities (observation vs systemic treatment vs RT vs surgery) to better guide future treatment decisions. Second, patient selection was not standardized, probably differing between institutions and throughout the study period. In addition, details regarding prior radiation treatment, use and length of ADT, or trigger for PSMA-RGS were not available. The same accounted for PSA-doubling time; therefore, the incorporation of European Association of Urology risk groups were impossible. Additionally, follow-up was only intermediate term without a standardized trigger for next treatment, and the initial PSA follow-up was not uniform, possibly leading to biased results. Here, standardized evaluations including triggers for next treatment are needed in order to compare future study results. Moreover, as all surgeries were performed in three tertiary referral centers with highly experienced surgeons, results may not be generalizable.

5. Conclusions

A cBR with a PSA value below 0.1 ng/ml seems to predict longer TFS for patients treated with SLND via PSMA-RGS.

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This insight may help in counseling patients postoperatively as well as guiding the timely selection of additional therapy.

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: Knipper, van der Poel, Maurer.
Acquisition of data: Knipper, Lischewski, de Barros, Berrens, Ambrosini, Heck, Maurer.
Analysis and interpretation of data: Knipper, Maurer.
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Appendix A. Supplementary data

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