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Cohort Study of Oligorecurrent Prostate Cancer Patients: Oncological Outcomes of Patients Treated with Salvage Lymph Node Dissection via Prostate-specific Membrane Antigen–radioguided Surgery

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Abstract

Background: In a subset of patients with recurrent oligometastatic prostate cancer (PCa) salvage surgery with prostate-specific membrane antigen (PSMA)-targeted radioguidance (PSMA-RGS) might be of value.
Objective: To evaluate the oncological outcomes of salvage PSMA-RGS and determine the predictive preoperative factors of improved outcomes.
Design, setting, and participants: A cohort study of oligorecurrent PCa patients with biochemical recurrence (BCR) after radical prostatectomy and imaging with PSMA positron emission tomography (PET), treated with PSMA-RGS in two tertiary care centers (2014–2020), was conducted.
Intervention: PSMA-RGS.
Outcome measurements and statistical analysis: Kaplan-Meier and multivariable Cox regression models were used to assess BCR-free (BFS) and therapy-free (TFS) survival. Postoperative complications were classified according to Clavien-Dindo.
Results and limitations: Overall, 364 patients without concomitant treatment were assessed. At PSMA-RGS, metastatic soft-tissue PCa lesions were removed in 343 (94%) patients. At 2–16 wk after PSMA-RGS, 165 patients reached a prostate-specific antigen (PSA) level of <0.2 ng/ml. Within 3 mo, 24 (6.6%) patients suffered from Clavien-Dindo complications grade III–IV. At 2 yr, BFS and TFS rates were 32% and 58%, respectively. In multivariable analyses, higher preoperative PSA (hazard ratio [HR]: 1.07, 95%

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confidence interval [CI]: 1.02–1.12), higher number of PSMA-avid lesions (HR: 1.23, CI: 1.08–1.40), multiple (pelvic plus retroperitoneal) localizations (HR: 1.90, CI: 1.23–2.95), and retroperitoneal localization (HR: 2.04, CI: 1.31–3.18) of lesions in preoperative imaging were independent predictors of BCR after PSMA-RGS. The main limitation is the lack of a control group.

Conclusions: As salvage surgery in oligorecurrent PCa currently constitutes an experimental treatment approach, careful patient selection is mandatory based on life expectancy, low PSA values, and low number of PSMA PET–avid lesions located in the pelvis.

Patient summary: We looked at the outcomes from prostate cancer patients with recurrent disease after radical prostatectomy. We found that surgery may be an opportunity to prolong treatment-free survival, but patient selection criteria need to be very narrow.

1. Introduction

In recent years, imaging of recurrent prostate cancer (PCa) lesions has changed profoundly. Positron emission tomography (PET) with ligands directed against the prostate-specific membrane antigen (PSMA), a type II transmembrane glycoprotein with overexpression on most PCa cells, significantly influenced the diagnostic pathway [1]. While expression on soft fatty tissue and regular lymph nodes is negligible, PCa lesions within lymph nodes or soft tissue show significant tracer uptake and can be visualized only at a few millimeters in diameter [2–4]. Moreover, PSMA PET imaging can detect metastatic locations at very low prostate-specific antigen (PSA) levels at biochemical recurrence (BCR) [5,6]. Thus, PSMA PET imaging became the recommended imaging modality for biochemically recurring PCa in the last few years [7].

Until now, watchful waiting or beginning of systemic treatment such as androgen deprivation therapy (ADT) is traditionally suggested in biochemically recurrent PCa with evidence of lymph node involvement [7]. However, the imaging evolution led to an increased interest in locally targeted treatment techniques such as targeted salvage radiation or salvage lymph node dissection (SLND). Although these treatments are still deemed experimental, they may delay further systemic palliative treatment and its associated toxicity. Additionally, long-term PSA responses may be seen.

Previous SLND series reported heterogeneous results [8–11]. However, these series suffered from several limitations such as prior conventional or choline-based PET imaging, advanced disease treated with ADT, and up to 20% of negative pathological results at SLND. To improve these outcomes, PSMA-radioguided surgery (PSMA-RGS) has been introduced with promising initial results [4,12,13]. Here, we aimed at evaluating oncological outcomes of PSMA-RGS in patients with early BCR and PSMA PET–avid lesions in a large retrospective cohort.

2. Patients and methods

2.1. Study population

Overall, 456 consecutive patients were treated with PSMA-RGS in two centers between November 2014 and December 2020. Of these patients, 92 were excluded for further analyses, rendering a final study cohort of 364 patients (Fig. 1). Of the final study cohort, all patients presented with BCR after initial radical prostatectomy (RP) with one or more positive soft tissue or lymph node lesion on PSMA PET imaging.

All patients were informed about the experimental nature of salvage surgery and the additional use of ^{111}In-PSMA-I&T or ^{99m}Tc-PSMA-I&S for radioguided surgery (PSMA-RGS) as described previously [12–15]. 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) and Munich (number 336/18 S), Germany. All men signed an informed consent form on data collection. Questionnaires were used for follow-up. All data were prospectively stored in an institutional database (FileMaker Pro 10; FileMaker, Inc., Santa Clara, CA, USA).

2.2. Procedure of salvage surgery using PSMA-RGS

The PSMA-RGS procedure involves several steps, as previously reported [13,16,17]. In brief, after identification of suitable patients, ^{99m}Tc-PSMA-I&S or ^{111}In-PSMA-I&T is prepared and injected intravenously the day prior to surgery [14,15]. Subsequently, single-photon emission computed tomography/computed tomography (CT) imaging is performed prior to surgery to cross-validate findings of the PSMA PET, document positive tracer uptake within the lesions, and serve as quality control for tracer injection and distribution [14].

The surgical procedure (template-based lymphadenectomy or resection of local recurrence according to the treating physician's discretion) is performed on the following day. Specifically, in case of recurrent tumor within the extended pelvic lymph node dissection template, SLND was performed for the whole template of the respective side and, in some cases, also for the contralateral side (according to the surgeon's discretion). For suspicious lesions located elsewhere (eg, pararectal), resection of the corresponding region with surrounding tissue was performed. For retroperitoneal lesions, the dissection template typically used for testicular cancer patients was resected. In these cases, the pelvic template for an extended pelvic lymph node dissection of at least the respective side was additionally resected.

Prior to its intraoperative use, the gamma probe (Crystal Probe CXS-SG603; Crystal Photonics, Berlin, Germany) is sterile draped. It is then used for in vivo intraoperative measurements of radioactivity caused by specific accumulation of PSMA tracers to facilitate localizing the recurrent lesion. This is particularly helpful as fibrotic alteration of the tissue is often present after previous surgery and radiation treatments. After excision, ex vivo gamma measurements are performed to immediately confirm the successful removal of the metastatic radioactive lesion or to prompt further search in case of a missing signal [13].

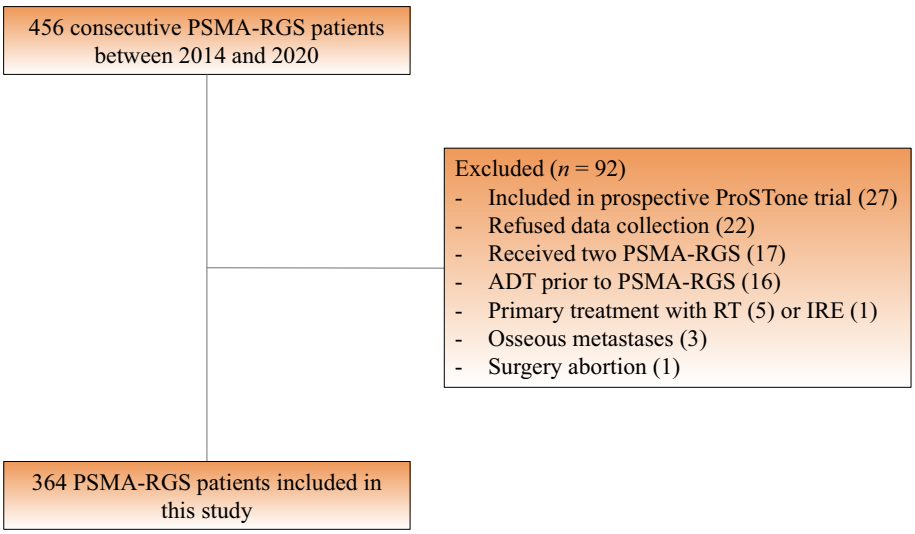

Fig. 1 – Consort diagram of the study cohort treated with prostate-specific membrane antigen–radioguided surgery (PSMA-RGS) between 2014 and 2020 in two tertiary care centers. ADT = androgen deprivation therapy; IRE = irreversible electroporation; RT = radiotherapy.

2.3. Outcomes of interest

The rate of complete biochemical response (defined as PSA <0.2 ng/ml) without any additional treatment was determined 2–16 wk following PSMA-RGS. Furthermore, BCR-free survival (BFS; defined as PSA <0.2 ng/ml without any further treatment) and therapy-free survival (TFS; defined as survival without further treatment) were evaluated. Survival was calculated from the time of PSMA-RGS to the event or end of follow-up. Patients were censored on the date of last evidence of freedom from BCR or further treatment. Postoperative complications were classified according to Clavien-Dindo [18].

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 chi-square tests. Kaplan-Meier plots graphically depicted BFS and TFS after PSMA-RGS. Univariable and multivariable Cox regression models tested the relationship between oncological outcomes (BFS and TFS) and several variables, namely, age at PSMA-RGS (continuously coded), Gleason grade group at RP (I–II vs III–V), pN stage at RP (N0/NX vs N1), radiation therapy (RT) after RP prior to PSMA-RGS (yes vs no), 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 (continuously coded), as well as localizations of PSMA PET–positive lesions prior to PSMA-RGS (pelvic vs retroperitoneal vs both). Predictors were selected among potential factors previously published and associated with oncological outcomes after SLND [4,11]. These were included in the multivariable models if significantly associated with the outcome in the univariable analysis.

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

3.1. Patients' characteristics

Overall, 364 patients were included in this analysis. As primary treatment, all patients received RP at a median PSA value of 9 ng/ml (interquartile range [IQR]: 6–16 ng/ml) and a median of 54 mo (IQR: 28–93 mo) prior to PSMA-RGS (Table 1). At RP, in 105 (29%) and 107 (29%) patients pT3a and pT3b disease were found, and in 40 (11%) and 60 (16%) patients Gleason grade groups IV and V were found, respectively. Moreover, pN1 disease was found in 60 (16%) patients. Of those, 31, 15, nine, three, and two patients had one, two, three, four, and an unknown number of positive nodes, respectively. A positive surgical margin was reported in 72 (20%) patients, and 224 (62%) patients received adjuvant or salvage RT to the prostate bed and/or pelvis after RP.

At PSMA-RGS, the median age was 67 yr (IQR: 62–71 yr) with a median PSA value of 1.0 ng/ml (IQR: 0.5–1.9 ng/ml) prior to salvage surgery (Table 2). No patient received ADT within the last 6 mo prior to PSMA-RGS. In PSMA PET imaging prior to surgery, 241 (66%), 76 (21%), 24 (6.6%), 12 (3.3%), four (1.1%), and one (0.28%) patients showed one, two, three, four, five, and six PSMA-avid lesions, respectively. Of these patients, 154 (42%) showed unilateral pelvic lesions, 12 (3.3%) showed bilateral pelvic lesions, 32 (8.8%) showed pelvic and presacral/pararectal or retrovesical/paravesical lesions, 48 (13%) showed only presacral/pararectal lesions, 54 (15%) showed retrovesical/paravesical lesions, 28 (7.7%) showed retroperitoneal lesions, 27 (7.4%) showed lesions in the retroperitoneum and any of the other localizations, three (0.82%) showed intra-abdominal lesions, and six (1.6%) showed lesions with questionable PSMA uptake only.

Metastatic soft-tissue lesions from PCa metastases could be removed in 343 (94%) patients. Of them, 145 (40%) had one metastasis, and 69 (19%), 34 (9.3%), 24 (6.6%), 15 (4.1%), and 56 (15%) had two, three, four, five, and six or more metastases, respectively. In 21 (5.8%) patients, no metastatic tissue was found in the pathological analysis. Within 3 mo from surgery, 24 (6.6%) patients suffered from Clavien-Dindo complications grade III–IV (Supplementary Table 1).

Table 1 – Characteristics of 364 patients treated with salvage surgery between 2014 and 2020 in two centers

Characteristic	*N* = 364
Year of initial RP, median (IQR)	2014 (2010, 2016)
PSA at RP (ng/ml), median (IQR)	9 (6, 16)
pT stage at RP, *n* (%)	
pT2	145 (40)
pT3a	105 (29)
pT3b	107 (29)
NA	7 (1.9)
Gleason grade group, *n* (%)	
I	27 (7.4)
II	96 (26)
III	127 (35)
IV	40 (11)
V	60 (16)
NA	14 (3.8)
pN stage at RP, *n* (%)	
pN0	276 (76)
pN1	60 (16)
pNX	18 (4.9)
NA	10 (2.7)
Lymph node yield at RP, median (IQR)	13 (7, 20)
No. of positive lymph nodes at RP, *n* (%)	
0	276 (76)
1	31 (8.5)
2	15 (4.1)
3	9 (2.5)
4	3 (0.82)
Unknown	30 (8.3)
Surgical margin status, *n* (%)	
R0	266 (73)
R1	72 (20)
RX	11 (3.0)
NA	15 (4.1)
RT after RP, *n* (%)	
No RT	140 (38)
RT after RP	224 (62)

IQR= interquartile range; NA= not assigned; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy.
All patients presented with biochemical recurrence after RP with positive lesions at prostate-specific membrane antigen positron emission tomography imaging.

Table 2 – Characteristics of 364 patients treated with salvage surgery between 2014 and 2020 in two centers

Characteristic	*N* = 364
Age at PSMA-RGS (yr), median (IQR)	67 (62, 71)
Time between RP and PSMA-RGS (mo), median (IQR)	54 (28, 93)
PSA prior to PSMA-RGS (ng/ml), median (IQR)	1.0 (0.5, 1.9)
No. of PSMA PET–avid lesions, *n* (%)	
0	6 (1.6)
1	241 (66)
2	76 (21)
3	24 (6.6)
4	12 (3.3)
5	4 (1.1)
6	1 (0.28)
PSMA PET localization, *n* (%)	
Pelvic unilateral	154 (42)
Pelvic bilateral	12 (3.3)
Pelvic plus presacral or retrovesical	32 (8.8)
Presacral/pararectal	48 (13)
Retrovesical/paravesical	54 (15)
Retroperitoneal	28 (7.7)
Retroperitoneal plus other localization	27 (7.4)
Intra-abdominal	3 (0.82)
None	6 (1.6)
No. of pathologically positive lesions, *n* (%)	
0	21 (5.8)
1	145 (40)
2	69 (19)
3	34 (9.3)
4	24 (6.6)
5	15 (4.1)
≥6	56 (15)
Postoperative complications (Clavien-Dindo), *n* (%)	
I	81 (22)
II	13 (3.6)
IIIa	8 (2.2)
IIIb	15 (4.1)
IVa	0
IVb	1 (0.28)
V	0

IQR = interquartile range; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; PSMA-RGS = PSMA-targeted radioguidance; RP = radical prostatectomy.
All patients presented with biochemical recurrence after RP with positive lesions at PSMA PET imaging.

3.2. Oncological outcomes

At 2–16 wk after PSMA-RGS, 165 patients reached complete biochemical response (defined as PSA <0.2 ng/ml; Fig. 2). Within the overall follow-up, 225 patients experienced BCR and 121 patients received further therapy during follow-up. The median follow-up for patients who did not experience BCR was 10.8 mo (IQR: 1.2–25.1 mo). The median follow-up for patients who did not receive further therapy was 10.3 mo (IQR: 2.3–24.0 mo).

Within the overall cohort, the median BFS was 7.8 mo (95% confidence interval [CI]: 5.4–10.5 mo) and the median TFS was 35.5 mo (CI: 25.9–45.9 mo). At 2 yr of follow-up, BFS rate was 32% (CI: 27–38%) and TFS rate was 58% (CI: 52–65%; Fig. 3A and 3B). Three patients died during follow-up (one due to an accident, one with septic complications after transurethral resection of a bladder cancer, and one for unknown reasons).

In patients with one versus two and more lesions in preoperative PSMA PET imaging, the median BFS was 10.9 versus 4.8 mo (CI: 6.0–17.8 vs 2.7–8.9 mo) and the median TFS was 40.0 versus 19.7 mo (CI: 32.6–48.6 vs 16 mo–not reached). At 2wo yr of follow-up, BFS rate was 38% versus 22% (CI: 31–46% vs 15–33%, $p = 0.001$) and TFS rate was 64% versus 44% (CI: 57–72 vs 33–58%, $p = 0.06$) in patients with one versus two and more lesions in preoperative PSMA PET imaging (Supplementary Fig. 1A and 1B).

In patients with pelvic-only versus retroperitoneal/multiple (pelvic plus retroperitoneal) localizations in preoperative PSMA PET imaging, the median BFS was 9.8 versus 3.0 mo (CI: 6.1–14.7 vs 1.4–7.2 mo) and the median TFS was 40.0 versus 18.6 mo (CI: 31.4–59.3 vs 11.7–37.8 mo). At 3 yr of follow-up, BFS rate was 36% versus 15% (CI: 30–43% vs 7.2–30%, $p < 0.001$) and TFS rate was 62% versus 30% (CI: 55–69% vs 17–54%, $p < 0.001$) in patients with pelvic-only versus retroperitoneal/multiple (pelvic plus retroperitoneal) localizations in preoperative PSMA PET imaging (Supplementary Fig. 2A and 2B).

In univariable analyses predicting BFS, higher preoperative PSA (hazard ratio [HR]: 1.06, CI: 1.02–1.11, $p = 0.009$), higher number of PSMA-avid lesions on preoperative imaging (HR: 1.24, CI: 1.09–1.42, $p = 0.001$), and multiple (pelvic plus retroperitoneal) localizations (HR: 2.02, CI: 1.30–3.13, $p = 0.002$) as well as retroperitoneal localizations (HR: 2.02, CI: 1.30–3.16, $p = 0.002$) of lesions in PSMA PET imaging were independent predictors of BCR after PSMA-RGS. Conversely, age at surgery, Gleason grade group at RP, pN

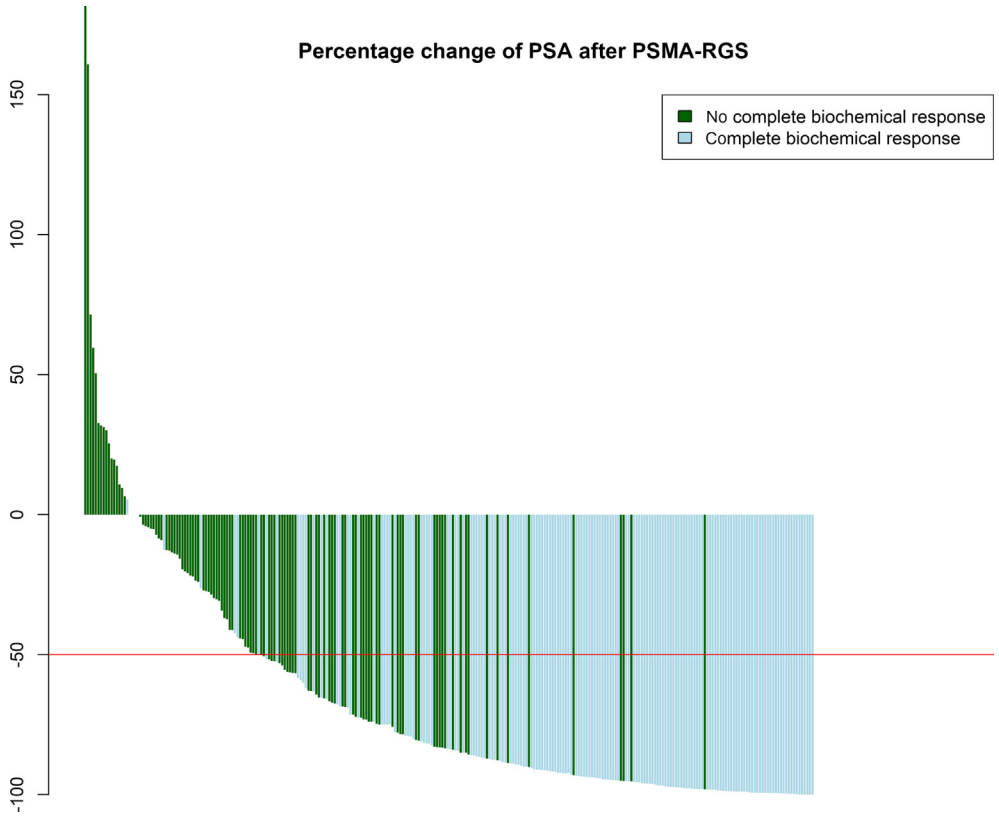

Fig. 2 – Waterfall plot graphically depicting the depicting the percentage of PSA change from before to after prostate-specific membrane antigen–radioguided surgery (PSMA-RGS). PSA = prostate-specific antigen.

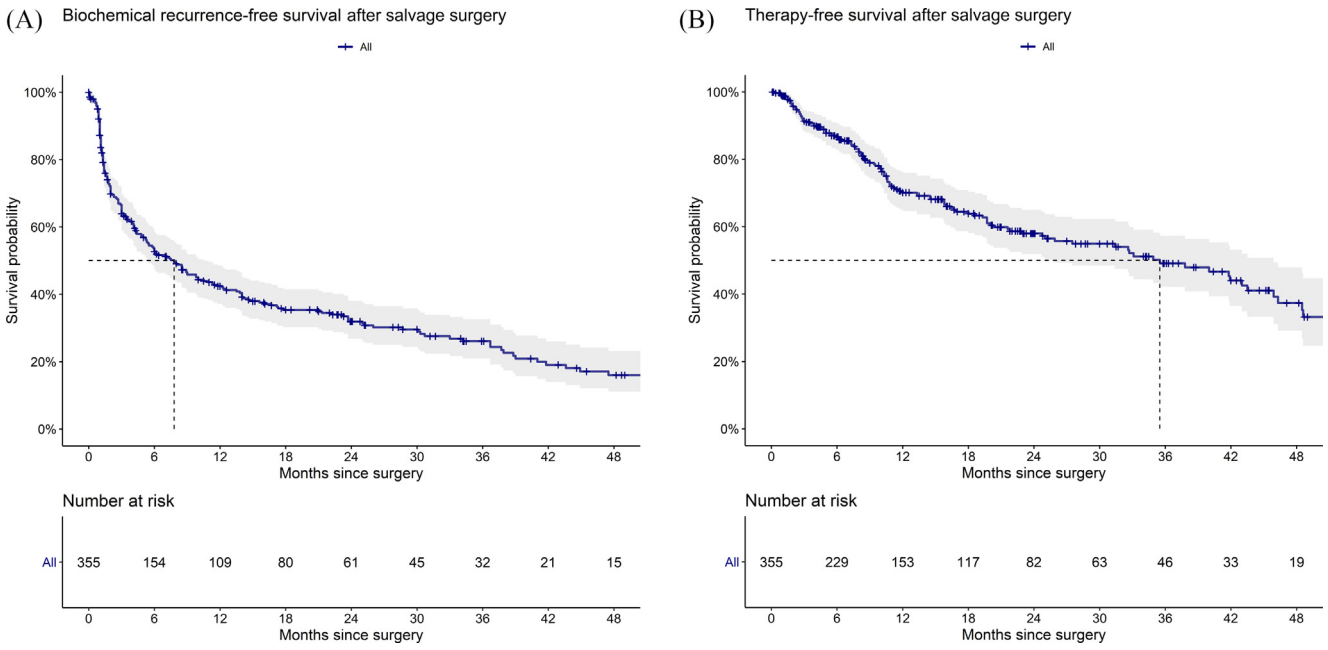

Fig. 3 – Kaplan-Meier analyses depicting (A) biochemical recurrence–free survival rates and (B) therapy-free survival rates in 364 patients (nine with missing follow-up) treated with prostate-specific membrane antigen–radioguided surgery between 2014 and 2020 in two tertiary care centers.

stage at RP, RT after RP, and time between RP and PSMA-RGS did not reach independent predictor status in univariable analyses and were thus not included into the multivariable models (Table 3).

In multivariable analyses predicting BFS, higher preoperative PSA (HR: 1.07, CI: 1.02–1.12, $p = 0.009$), higher number of PSMA-avid lesions on preoperative imaging (HR: 1.23, CI: 1.08–1.40, $p = 0.002$), and multiple (pelvic plus retroperi-

Table 3 – Uni- and multivariable Cox regression models predicting biochemical recurrence–free survival

Variables	Univariable Cox regression model				Multivariable Cox regression model			
	HR	CI 2.5%	CI 97.5%	*p* value	HR	CI 2.5%	CI 97.5%	*p* value
Age at surgery (continuous)	1.0	0.98	1.01	0.5				
Gleason grade group at RP								
I–II	Ref.							
III–V	1.08	0.81	1.43	0.6				
pN stage at RP								
pN0/X	Ref.							
pN1	1.39	0.99	1.97	0.06				
RT after RP								
No	Ref.							
Yes	1.17	0.89	1.54	0.3				
Time RP to PSMA-RGS (continuous), yr	1.0	0.97	1.02	0.7				
PSA prior to PSMA-RGS (continuous)[a]	1.06	1.02	1.11	0.009	1.07	1.02	1.12	0.009
No. of PSMA PET–positive lesions (continuous)[a]	1.24	1.09	1.42	0.001	1.23	1.08	1.40	0.002
Localization of PSMA PET–positive lesions [a]								
Pelvic only	Ref.							
Pelvic and retroperitoneal	2.02	1.30	3.13	0.002	1.90	1.23	2.95	0.004
Retroperitoneal only	2.02	1.30	3.16	0.002	2.04	1.31	3.18	0.002

CI = confidence interval; HR = hazard ratio; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; PSMA-RGS = PSMA-radioguided surgery; Ref. = reference; RP = radical prostatectomy; RT = radiotherapy.
[a] Tested in two independent multivariable Cox regression models: PSA with the number of PSMA PET–positive lesions, and PSA with localization of PSMA PET–positive lesions.

toneal) localizations (HR: 1.90, CI: 1.23–2.95, $p = 0.004$) as well as retroperitoneal localization (HR: 2.04, CI: 1.31–3.18, $p = 0.002$) of lesions in PSMA PET imaging were independent predictors of BCR after PSMA-RGS (Table 3).

In univariable analyses predicting TFS, pN stage at RP (HR: 1.72, CI: 1.01–2.70, $p = 0.02$), time between RP and PSMA-RGS (HR: 0.93, CI: 0.88–0.97, $p = 0.001$), higher preoperative PSA (HR: 1.11, CI: 1.04–1.19, $p = 0.003$), higher number of PSMA-avid lesions on preoperative imaging (HR: 1.33, CI: 1.11–1.60, $p = 0.003$), and multiple (pelvic plus retroperitoneal) localizations (HR: 2.36, CI: 1.39–4.04, $p = 0.002$) of lesions in PSMA PET imaging were independent predictors of next treatment after PSMA-RGS. Conversely, age at surgery, Gleason grade group at RP, and RT after RP did not reach independent predictor status in univariable analyses and were thus not included in the multivariable models.

In multivariable analyses predicting TFS and adjusted for pN stage at RP and time between RP and PSMA-RGS, higher preoperative PSA (HR: 1.09, CI: 1.02–1.17, $p < 0.001$), higher number of PSMA-avid lesions on preoperative imaging (HR: 1.43, CI: 1.17–1.74, $p < 0.001$), and multiple (pelvic plus retroperitoneal) localizations (HR: 2.47, CI: 1.44–4.24, $p = 0.001$) of lesions in PSMA PET imaging were independent predictors of next treatment after PSMA-RGS (Supplementary Table 2).

4. Discussion

As PSMA PET imaging evolved, increased interest in locally targeted treatment techniques such as SLND can be observed. However, previous SLND series, albeit mostly based on outdated choline-based PET or conventional cross-sectional imaging, reported mixed results. After initial encouraging reports [8–10,19,20], rather critical views have been published more recently. In these, either oncological long-term outcomes were unclear or favorable outcomes were observed only in a minority of men [11,21,22]. In consequence, to further improve SLND outcomes in patients with early BCR after RP and with PSMA PET–avid lesions, PSMA-RGS has been introduced with promising initial results [4,12,13,23]. In this report, we evaluated medium-term oncological outcomes of PSMA-RGS in this patient cohort. Additionally, as SLND is still considered an individual experimental therapy, we aimed at determining predictive preoperative factors of favorable outcomes with PSMA-RGS.

Our analyses demonstrated several noteworthy observations. In almost 95% of patients, metastatic soft-tissue lesions from PCa metastases could be removed. This is in contrast to conventional SLND, where pathological examination reveals no metastatic PCa tissue within the removed tissue specimens in at least 20% of patients [11]. These increased intraoperative detection rates translated into a complete early biochemical response (PSA <0.2 ng/ml without any further treatment) in about 60% of cases and median BFS of about 8 mo. At 2 yr of follow-up, a third of patients did not experienced BCR and the median TFS was almost 3 yr. In consequence, our data highlight previous findings that patient selection is key for beneficial outcomes. Previously, PSA at the time of salvage treatment and the number and localization of PET-positive lesions have been reported as predictive factors [21]. Moreover, Gleason grade group at primary treatment, as well as time between RP and SLND was found to be predictive of outcomes after SLND [21]. This was only partly confirmed by our multivariable results, showing an increased risk of BCR with higher PSA at PSMA-RGS, higher number of positive imaging lesions, and retroperitoneal localization of lesions, but not for any further variables. Our results reiterate the importance of risk assessment and patient selection depending on the imaging status prior to salvage surgery.

Our study has several strengths. First, to the best of our knowledge, it is the largest series of salvage surgery patients based on PSMA PET imaging. Second, it also comprises the largest series of PSMA-RGS, underlining the safety

and efficacy of PSMA-RGS. Moreover, no patients received ADT within 6 mo prior to PSMA-RGS, which otherwise may have masked further metastatic spread, thus rendering the biochemical response rate highly reliable.

Nonetheless, several limitations of our study need to be mentioned. First and foremost is the lack of a control group including men managed with either observation or systemic treatment. Arguably, relevant data exist also for pelvic nodal RT benefit with salvage RT after post-RP BCR (RTOG 0534) [24], for comprehensive nodal RT benefit in selected PET-defined oligonodal recurrent PCa [25] and for stereotactic body RT to defer ADT need in oligometastatic PCa [26,27]. Ideally, a randomized-controlled trial would compare all four treatment modalities (observation vs systemic treatment vs RT vs surgery). Second, follow-up was only intermediate term without standardized trigger for next treatment, possibly leading to biased results. Moreover, as all surgeries were performed in two tertiary referral centers with highly experienced surgeons, results may not be generalizable.

In general, there are two important questions in oncological practice: do patients live longer and do they live better when a suggested novel treatment is applied? Unfortunately, the question of prolonged survival still remains unanswered with our study. However, increased TFS may translate into higher quality of life due to the absence of side effects associated with ADT [28,29]. Moreover, toxicities of novel treatments need to be weighed carefully against potential benefits. In our cohort, <7% of patients experienced higher-grade complications, resulting in an acceptable toxicity profile.

In conclusion, patient selection remains key when discussing experimental treatment approaches with patients and their relatives. Ideally, all patients should be included in prospective trials or registries such as "PEACE V: Salvage Treatment of OligoRecurrent Nodal Prostate Cancer Metastases" (NCT03569241), "ProSTone: Early Prostate Cancer Recurrence With PSMA PET Positive Unilateral Pelvic Lesion(s): is One-sided Salvage Extended Lymph Node Dissection Enough?" (NCT04271579), "Salvage Lymph Node Dissection in Prostate Cancer Patients With Recurrence After Radical Prostatectomy" (NCT02974075), "BioPoP: Identification of Predictive Biomarkers" (NCT04324983), "TRACE: Technetium Based Radioguided Surgery for Prostate Cancer Study" (NCT03857113), "DETECT: Radio Guided Lymph Node Dissection in Oligometastatic Prostate Cancer Patients" (NCT04300673), "Imaging Guided Surgery to Improve the Detection of Lymph Node Metastases in Prostate Cancer Patients" (NCT04832958), or "99mTc-PSMA-I&S Biodistribution in Patients With Prostate Cancer" (NCT04857502), in order to advance treatment approaches in oligorecurrent PCa patients.

5. Conclusions

PSMA-RGS is a promising tool to enhance intraoperative detection of metastatic lesions in PCa during salvage surgery with an acceptable rate of high-grade complications. It presents an opportunity to prolong BFS and increase TFS in highly selected patients with PCa recurrence. However, as salvage surgery in oligorecurrent PCa currently constitutes an experimental treatment approach, careful patient selection is mandatory based on life expectancy, low PSA values, and low number of PSMA PET–avid lesions, ideally located in the pelvis. Further studies are needed to confirm our findings and define the oncological value of salvage surgical procedures in oligorecurrent PCa.

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Analysis and interpretation of data: Knipper, Tennstedt, Maurer.
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Peer Review Summary

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