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Salvage Surgery in Patients with Local Recurrence After Radical Prostatectomy

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Abstract

Background: Since the introduction of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging, isolated local recurrence after radical prostatectomy (RP) can be delineated accurately.
Objective: To describe and evaluate surgical technique, biochemical response, and therapy-free survival (TFS) after salvage surgery in patients with local recurrence in the seminal vesicle bed.
Design, setting, and participants: We retrospectively assessed 40 patients treated with open salvage surgery in two centres (11/2014-02/2020). All patients presented with biochemical recurrence (BCR) after RP with a singular local recurrence at PSMA PET imaging. Thirty-three (82.5%) patients received previous salvage radiation therapy.
Surgical procedure: Open salvage surgery with PSMA radioguidance.
Measurements: Prostate-specific antigen (PSA) nadir and percentage of patients with complete biochemical response (cBR) without further treatment (PSA $<$ 0.2 ng/ml) after 6–16 wk were assessed. BCR-free survival and TFS were calculated using Kaplan-Meier estimates. Clavien-Dindo complications were evaluated.
Results and limitations: Prior to salvage surgery, median PSA was 0.9 ng/ml (interquartile range [IQR]: 0.5–1.7 ng/ml). Postoperatively, median PSA nadir was 0.1 ng/ml (IQR: 0–0.4 ng/ml). In 31 (77.5%) patients, cBR was observed. During the median follow-up of 24.4 months, 22 (55.0%) patients experienced BCR and 12 (30.0%) received further therapy. At 1 yr of follow-up, BCR-free survival rate was 62.2% and TFS rate was 88.3%. Three (7.5%) Clavien-Dindo grade III complications were observed. The main limitations are the retrospective design, short follow-up, and lack of a control group.
Conclusions: Salvage surgery of local recurrence within the seminal vesicle bed is feasible. It may present an opportunity in selected, locally recurrent patients to prolong BCR-free survival and increase TFS. Further studies are needed to confirm our findings.

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Patient summary: We looked at the outcomes from prostate cancer patients with locally recurrent disease after radical prostatectomy and radiotherapy. We found that surgery in well-selected patients may be an opportunity to prolong treatment-free survival.

1. Introduction

In prostate cancer (PCa), recurrences are observed frequently even after curatively intended primary treatment such as radical prostatectomy (RP). Primarily, these recurrences are detected via biochemical recurrence (BCR) defined as prostate-specific antigen (PSA) relapse [1]. The diagnostic yield of conventional imaging techniques to localise the area of recurrence is very low in asymptomatic patients since BCR precedes clinical metastases by 7–8 yr on average [1,2]. Therefore, salvage radiation therapy (RT) to the prostatic bed represents the standard option in men with BCR after RP and a suspicion of a local recurrence.

However, since the introduction of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging, recurrences may be delineated accurately, even at very low PSA levels [3]: detection rates of 33%, 45%, 59%, 75%, and 95% have been reported for the respective PSA ranges of 0–0.19, 0.2–0.49, 0.5–0.99, 1–1.99, and $\geq$2 ng/ml [4]. This noninvasive means to assess recurrences creates the opportunity to apply local therapies more accurately. As a consequence, PSMA PET imaging is now recommended prior to treatment decisions in men with BCR if the results influence subsequent treatment decisions [1].

Moreover, in some patients, local recurrence may be observed even after salvage RT after RP. Here, local treatment options are extremely limited. Recently, the results of salvage reirradiation (stereotactic body RT) have been reported [5,6]. However, salvage surgery for local recurrence has not been described in this setting.

In consequence, we aimed at describing and evaluating our technique for open salvage surgery in patients with local recurrence in the area of the former seminal vesicles for the first time. To facilitate successful surgical removal and enable targeting of the local recurrence, we made use of the PSMA overexpression of most PCa tissue by adopting the

Table 1 – Characteristics of 40 consecutive patients treated with salvage surgery between November 2014 and February 2020 in two centres.

Variable		Overall (n = 40)
Age at salvage surgery (yr)	Median (IQR)	67 (63–74)
Year of RP	Median (IQR)	2009 (2006–2012.2)
PSA prior to RP (ng/ml)	Median (IQR)	7.4 (5.3–10.8)
pT at RP, *n* (%)	pT2	18 (45.0)
	pT3a	15 (37.5)
	pT3b	7 (17.5)
pGG at RP, *n* (%)	I	7 (17.5)
	II	12 (30.0)
	III	6 (15.0)
	IV	7 (17.5)
	V	7 (17.5)
	NA	1 (2.5)
pN at RP, *n* (%)	pN0	30 (75.0)
	pN1	6 (15.0)
	pNX	2 (5.0)
	NA	2 (5.0)
Removed lymph nodes at RP	Median (IQR)	13 (6–19)
Surgical margin status at RP, *n* (%)	R0	27 (67.5)
	R1	11 (27.5)
	RX	2 (5)
RT after RP, *n* (%)	Adjuvant RT	12 (30.0)
	Salvage RT	21 (52.5)
	No RT	7 (17.5)
Time from RP to salvage surgery (yr)	Median (IQR)	8.5 (6.0–10.2)
Time since last therapy to salvage surgery (yr)	Median (IQR)	6.4 (3.4–9.6)
PSA prior to salvage surgery (ng/ml)	Median (IQR)	0.9 (0.5–1.7)
First PSA after salvage surgery (ng/ml)	Median (IQR)	0.1 (0–0.4)
Complete biochemical response, *n* (%)	Yes	31 (77.5)
	No	9 (22.5)

IQR = interquartile range; NA = not assigned; pGG = pathological Gleason grade group; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; RT = radiation therapy.
All patients presented with biochemical recurrence after RP with a singular local recurrence at PSMA positron emission tomography imaging.

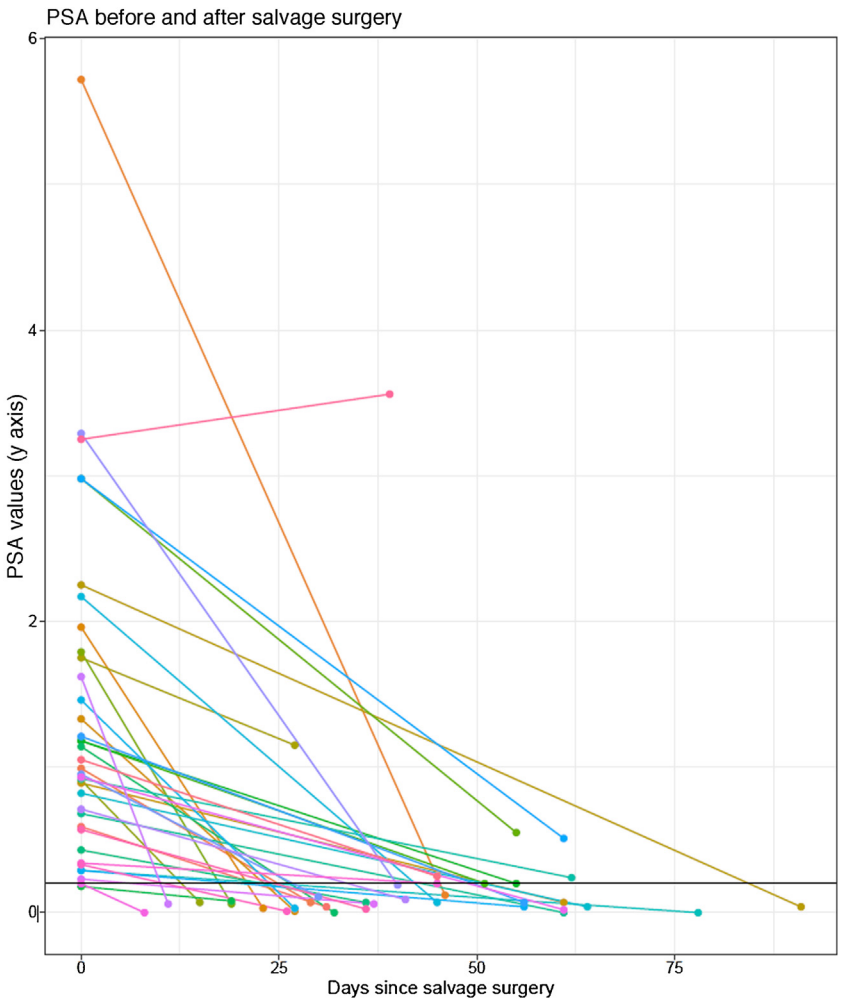

Fig. 1 – Spaghetti plot graphically depicting PSA decline within 3 mo after salvage surgery in 37 patients treated with salvage surgery between November 2014 and February 2020 in two centres. In three patients, the first PSA was determined >3 mo after salvage surgery. Of those, two patients had PSA below 0.2 ng/ml (complete biochemical response) and one patient had a PSA of 0.3 ng/ml (1.7 ng/ml prior surgery) after 4 mo without further prostate cancer–specific treatment. Each line represents the PSA values of one patient without further prostate cancer–specific treatment. PSA = prostate-specific antigen.

PSMA radioguided surgery approach, which until now had only been described in salvage lymph node surgery [7,8]. We examined biochemical response, therapy-free survival, as well as complication rates after this procedure.

2. Patients and methods

2.1. Study population

Overall, 40 consecutive patients treated with salvage surgery in two centres between November 2014 and February 2020 were included in this retrospective analysis. All patients presented with BCR after initial RP, with a singular local recurrence (retrovesical/seminal vesicles bed) at 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 [7,9–11]. All patients provided their informed consent to the procedure, as well as data analysis. The retrospective analysis was approved by the institutional review boards in Hamburg and Munich, Germany. In accordance with federal and institutional guidelines, all men signed an institutional review board–approved, protocol-specific informed consent form before study entry. This permits collection of deidentified patient data at baseline and follow-up, which were entered into a secure, password-protected database for subsequent analysis. Questionnaires were used for follow-up. All data were stored prospectively 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 reported previously [7,12]. In brief, after the 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 [10,11]. Subsequently, single-photon emission computed tomography/computed tomography imaging is performed prior to surgery to cross-validate findings of the PSMA PET, document positive tracer uptake within the lesions, and serve as a quality control for tracer injection and distribution [10]. The surgical procedure is performed on the following day.

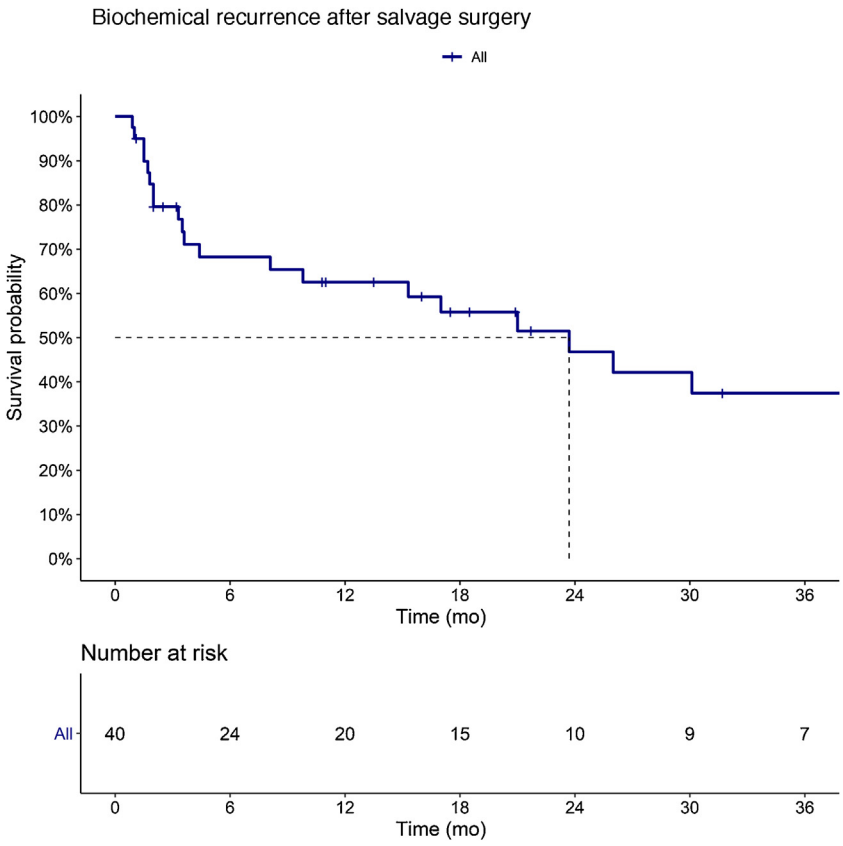

Fig. 2 – Kaplan-Meier analyses depicting biochemical recurrence–free survival rates in 40 patients treated with salvage surgery between November 2014 and February 2020 in two centres.

Patients are placed in the supine position and a urinary catheter is inserted. This allows removal of the tracer containing urine from the bladder as well as facilitates access to the retrovesical space during surgery. After sterile draping, a midline incision below the umbilicus is performed. A transperitoneal approach is prepared with adhesiolysis if necessary. This approach allows immediate access to the vessels, ureters, as well as pararectal and retrovesical space. The bowel is retracted cranially; the ductus deferens (landmark) and the ureter (crossing below the ductus deferens) of the respective side are identified. In this area, careful preparation with limited use of cautery is necessary to avoid damage or necrosis leading to subsequent stricture of the ureter. After careful lateral mobilisation of the bladder, an incision of the peritoneum ventrally to the rectum is performed. Here, careful preparation is necessary to avoid damage to the rectum (caveat: preirradiated field). In some cases, a ventral stitch of the dorsal bladder wall to elevate the bladder is performed, which facilitates access to the retrovesical space.

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 localisation of the recurrent lesion. This is particularly helpful as fibrotic alteration of the tissue is often present after previous surgery and radiation treatments. Moreover, the distal margin of the lesion may be identified. After excision, ex vivo gamma measurements are performed to confirm immediately the successful removal of the metastatic radioactive lesion or to prompt further search in case of a missing signal [7].

2.3. *Outcomes of interest*

The rate of complete biochemical response (cBR, defined as PSA < 0.2 ng/ml) without additional treatment was determined at 6–16 wk following salvage surgery. Furthermore, BCR-free survival (defined as PSA < 0.2 ng/ml without further treatment) and therapy-free survival (TFS, defined as survival without further treatment) were evaluated. Postoperative complications were classified according to Clavien-Dindo [13].

2.4. *Statistical analyses*

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. A spaghetti plot graphically depicted PSA decline after salvage surgery. Kaplan-Meier plots graphically depicted BCR-free survival and TFS after salvage surgery.

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, 40 consecutive patients were included (Table 1). The median follow-up was 24.4 mo (interquartile range [IQR]: 11.8–41.9 mo).

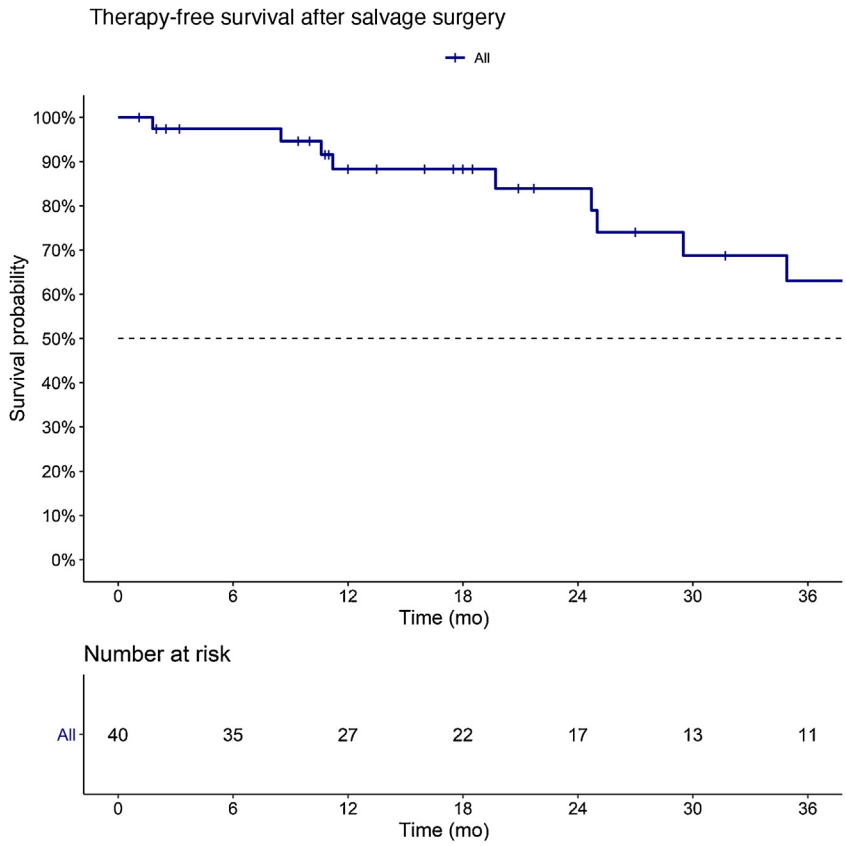

Fig. 3 – Kaplan-Meier analyses depicting therapy-free survival rates in 40 patients treated with salvage surgery between November 2014 and February 2020 in two centres.

Initially, all patients were treated with RP at a median PSA of 7.4 ng/ml (IQR: 5.3–10.8 ng/ml). Of those, 18 (45.0%) patients presented with organ-confined tumours (pT2), while 22 (55.0%) had non–organ-confined tumours (37.5% pT3a, 17.5% pT3b). In 11 (27.5%) patients, a positive surgical margin was present. The median time from RP to salvage surgery was 8.5 yr (6.0–10.2 yr). Previous RT was administered in 33 (82.5%) patients. Of these patients, 12 (30%) received adjuvant RT, while 21 (52.5%) received salvage RT. The median time from last treatment (RT) to salvage surgery was 6.4 yr (IQR: 3.4–9.6 yr).

At salvage surgery, the median age was 67 yr (IQR: 63–74 yr). Prior to salvage surgery, the median PSA was 0.9 ng/ml (IQR: 0.5–1.7 ng/ml). No patient received hormonal therapy within 6 mo prior to salvage surgery. All removed specimens showed PCa tissue. After salvage surgery, the median PSA nadir was 0.1 ng/ml (IQR: 0–0.4 ng/ml; Fig. 1). In 31 (77.5%) patients, cBR was observed. During the median follow-up of 24.4 mo (IQR: 11.8–41.9 mo), 22 (55.0%) patients experienced BCR and 12 (30.0%) received further therapy. Of these patients, six received hormonal therapy, three received RT, two were treated with salvage lymphadenectomy, and one received combined chemohormonal therapy.

In Kaplan-Meier analyses, the median BCR-free survival was 23.7 mo (95% confidence interval [95% CI]: 9.8–not reached). At 1 yr of follow-up, BCR-free survival rate was 62.2% (95% CI: 48.3–80.1%; Fig. 2). Median TFS was 46.3 mo (95% CI: 34.9–not reached). At 1 yr of follow-up, TFS rate was 88.3% (95% CI: 78.0–99.8%; Fig. 3).

Overall, seven complications (17.5%) were observed. All these patients were preirradiated. Of these complications, four (10%) were of Clavien-Dindo grade I (obstipation, neuropathy, haematoma, and residual urine). Three (7.5%) Clavien-Dindo grade III complications were observed. One patient needed a suprapubic catheter due to a urethral stricture (IIIa). In one patient, a secondary rectal injury occurred with subsequent colostomy (IIIb). In one patient, a ureteral injury occurred with subsequent ureteral implantation (IIIb). No grade IV or V complications were observed.

4. Discussion

In patients with local recurrence after salvage RT following RP, local treatment options are extremely limited. Several small series with heterogeneous retrospective cohorts reported interesting results of salvage reirradiation [5,6]. However, to the best of our knowledge, salvage surgery for local recurrence after RP has not been assessed. In consequence, we evaluated PSMA-directed salvage surgery and examined oncological outcomes, as well as

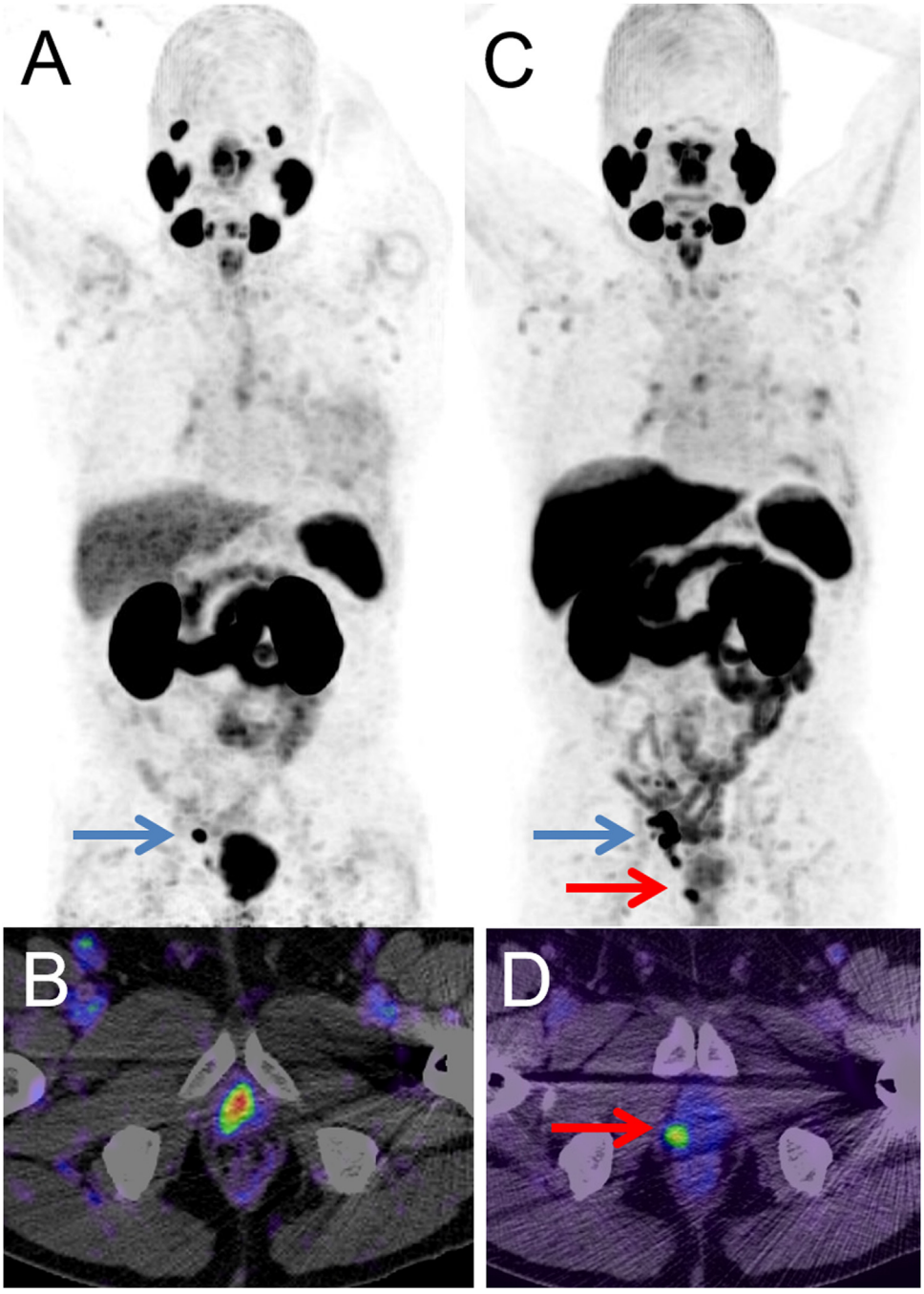

Fig. 4 – (A and B) Patient with BCR presenting with a PSMA PET–positive LN metastasis on ^{68}Ga-PSMA-11 PET (blue arrow) without evidence of a local recurrent tumour in the prostate bed due to urinary excretion of ^{68}Ga-PSMA-11 and subsequent tracer activity within the bladder. (C and D) A PSMA PET scan 3 mo later using ^{18}F-PSMA-1007 revealed, in addition to the LN metastasis (blue arrow), a local recurrence that was not obscured due to lack of urinary excretion of the tracer (red arrow). (A and C) PSMA PET maximum-intensity images and (B and D) axial PSMA PET/CT fusion images are shown. BCR = biochemical recurrence; LN = lymph node; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

complication rates after this procedure for the first time. Our analyses demonstrated several noteworthy observations.

First, in 77.5% of patients, a cBR was observed. This translated into a BCR-free survival rate of 62.2% and a TFS rate of 88.3% at 1 yr of follow-up. With a median BCR-free survival of 23.7 mo and a median TFS of 46.3 mo, our short-term oncological outcomes show promising results. This is particularly important, since most patients did not have any other local treatment option. In this setting, hormonal treatment with its known side effects will most commonly be the next step [1]. Nonetheless, even if short-term results are encouraging, long-term oncological outcomes are necessary to further evaluate the benefit for patients.

Second, complication rates were acceptable. Overall, seven complications were observed. Of these, three were

Clavien-Dindo grade III complications, namely, one suprapubic catheterisation (IIIa), one rectal injury (IIIb), and one ureteral injury (IIIb). No grade IV or V complications were observed. All these patients were preirradiated.

Exact localisation of the recurrent lesion is important when considering salvage surgery: only cranial lesions in the area of the seminal vesicle bed are safely accessible for surgery. However, lesions at the anastomotic area should not be approached by surgery, since the risks of rectal or sphincter injuries are too high and functional outcomes (especially continence) might be impaired. Additionally, reliable intraoperative identification of the recurrent tissue is often challenging. It may be small, morphologically unrecognisable, or hidden in fibrotic tissue. Here, intraoperative guidance with PSMA-RGS is of great value [7]. PSMA-RGS provides further security during the salvage procedure, as it is used for intraoperative measurements to facilitate localisation of the recurrent lesion [14]. Moreover, successful removal can be verified immediately after dissection by ex vivo measurements rendering frozen section dispensable. Furthermore, the addition of radioguidance seems to increase the efficacy of salvage surgery when compared with a conventional unguided surgical approach in salvage lymph node dissection [15].

Future prospects are aiming at improved diagnostic detection of the recurrent lesion using ^{18}F-labelled PSMA tracers for PSMA PET imaging that are not excreted renally. These tracers show only limited bladder accumulation, thus allowing optimal detection of perivesical lesions (Fig. 4) [16,17]. In a review focussed on PSMA-specific tracers for image-guided surgery purposes suggested that reduced renal clearance is also observed for certain hybrid (radioactive and fluorescent) PSMA tracers [18]. When such hybrid tracers are used, the process of radioguidance may be complemented using real-time fluorescence imaging, a feature that may help further refine the surgeon's approach of the target [19]. The recent availability of DROP-IN gamma probes now also allows for the implementation of radioguidance surgery during robotic-assisted procedures [20,21]. This may be particularly helpful in lesions with retrovesical localisations that could easily be accessed by a robotic approach in a similar fashion to retrovesical (Retzius-sparing) robotic-assisted RP procedures [22].

Several limitations of our study need to be mentioned. First and foremost are the limitations inherent to retrospective analyses, including a significant risk of bias and the lack of a control group, as well as the lack of data supporting an overall survival benefit. Second, our cohort included only 40 patients. Thus, it was impossible to perform a univariable and a multivariable analysis of potential factors predicting relapse. However, to the best of our knowledge, we are the first to describe this procedure in the salvage setting. Additionally, as radiation planning was historically based on conventional imaging, outcome improvements in salvage RT may also be observed when irradiation is planned according to PSMA PET imaging. Moreover, our follow-up period was moderate concerning the long natural history of PCa. Thus, information on the further course, such as localisation of next recurrence, is unfortunately unavailable yet. In addition, functional data have not been assessed yet. Since the cohort represents a highly selected patient population with single focus of recurrence and low PSA, there needs to be caution in interpretation of efficacy results. Thus, further studies with longer follow-up are needed to confirm our findings, ideally including control groups with watchful waiting and salvage reirradiation cohorts.

5. Conclusions

Salvage surgery of PSMA PET–positive local recurrence within the seminal vesicle bed is feasible. It may present an opportunity in highly selected patients with local recurrence to prolong BCR-free survival and therefore increase TFS.

Author contributions: Sophie Knipper 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: Maurer, Knipper.
Acquisition of data: Ascalone, Ziegler, Simon.
Analysis and interpretation of data: Knipper, Maurer.
Drafting of the manuscript: Knipper, Maurer.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Knipper.
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Appendix A. Supplementary data

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