available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Surgery in Motion

^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer

Tobias Maurer[a,b,1,*], *Stephanie Robu*[c,1], *Margret Schottelius*[c], *Kristina Schwamborn*[d], *Isabel Rauscher*[e], *Nynke S. van den Berg*[f,g], *Fijs W.B. van Leeuwen*[f], *Bernhard Haller*[h], *Thomas Horn*[a], *Matthias M. Heck*[a], *Jürgen E. Gschwend*[a], *Markus Schwaiger*[e], *Hans-Jürgen Wester*[c], *Matthias Eiber*[e]

[a] *Department of Urology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany;* [b] *Martini-Clinic, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [c] *Pharmaceutical Radiochemistry, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany;* [d] *Institute of Pathology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany;* [e] *Department of Nuclear Medicine, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany;* [f] *Interventional Molecular Imaging Laboratory, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands;* [g] *Department of Otolaryngology, Head and Neck Surgery, School of Medicine, Stanford University, Stanford, CA, USA;* [h] *Institute for Medical Statistics and Epidemiology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany*

Article info

Article history:
Accepted March 14, 2018

Associate Editor:
James Catto

Keywords:
Prostate-specific membrane antigen
Positron emission tomography
Radioguided
Prostate cancer
Salvage lymph node dissection

Please visit www.europeanurology.com and www.urosource.com to view the accompanying video.

Abstract

Background: Prostate-specific membrane antigen (PSMA)–targeted positron emission tomography (PET) can visualize metastatic lesions in recurrent prostate cancer (PC). However, reliable identification of small and/or atypically localized lesions during salvage surgery procedures is challenging.
Objective: To describe the technique, feasibility, and short-term outcomes of ^{99m}Technetium (^{99m}Tc)-based PSMA-radioguided surgery (^{99m}Tc-PSMA-RGS) for removal of recurrent PC lesions.
Design, setting, and participants: Thirty-one consecutive patients with evidence of recurrent PC on ^{68}Ga-PSMA N,N′-bis[2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N′-diacetic acid (^{68}Ga-PSMA-11) PET after radical prostatectomy undergoing ^{99m}Tc-PSMA-RGS were retrospectively analyzed.
Surgical procedure: Salvage surgery with intraoperative radioguidance using a gamma probe was performed after intravenous application of ^{99m}Tc-PSMA investigation and surgery (mean activity 571 MBq, mean time to surgery 19.7 h).
Measurements: Radioactive rating (positive vs negative) of resected tissue was compared with the findings of postoperative histopathological analysis. Best prostate-specific antigen (PSA) response without additional treatment was determined after 8–16 wk postoperatively. Biochemical recurrence- and treatment-free survival was evaluated.
Results and limitations: In total, 132 tissue specimens were removed, of which 58 showed metastatic involvement on histological analysis. On a specimen basis, radioactive rating yielded a sensitivity of 83.6% (confidence interval [CI]: 70.9–91.5%), a specificity of 100%, and an accuracy of 93.0% (CI: 85.5–96.7%). With ^{99m}Tc-PSMA-RGS, all lesions visualized on preoperative ^{68}Ga-PSMA-11 PET could be removed. Moreover, ^{99m}Tc-PSMA-RGS detected additional metastases as small as 3 mm in two patients. Thirteen patients suffered from complications related to surgery (Clavien-Dindo grade 1: 12 patients; grade 3a: one patient). A PSA reduction below 0.2 ng/ml was observed in 20 patients. Thirteen patients remained biochemical recurrence free after a median follow-up of 13.8 (range: 4.6–18.3) mo. Twenty patients continued to be treatment free after a median follow-up of 12.2 (range: 5.5–18.3) mo.
Conclusions: As a new technique for surgical guidance, ^{99m}Tc-PSMA-RGS is feasible, and has been proved to be of high value for successful intraoperative detection and removal of metastatic lesions in PC patients scheduled for salvage surgery. Its long-term impact on outcome has to be evaluated.
Patient summary: In this report, we evaluated a novel technique to identify metastatic lesions intraoperatively in patients with recurrent prostate cancer to facilitate surgical removal. After intravenous injection of radioactive molecules that specifically bind to prostate cancer cells that show increased expression of the prostate-specific membrane antigen, we were able to detect and remove these metastatic lesions during surgery. Following salvage surgery, 41.9% of patients remained biochemical recurrence free (median follow-up of 13.8 mo) and 64.5% continued to be treatment free (median follow-up of 12.2 mo).

[1] These authors shared first authorship.
* Corresponding author. Department of Urology, Technical University of Munich, Klinikum rechts der Isar, Ismaninger Str. 22, München 81671, Germany. Tel. +49 89 4140 2508; Fax: +49 89 4140 4843.
E-mail address: t.maurer@tum.de (T. Maurer).

https://doi.org/10.1016/j.eururo.2018.03.013
0302-2838/

Please cite this article in press as: Maurer T, et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.013

1. Introduction

Prostate cancer (PC) is a global health issue and the most commonly diagnosed cancer in men worldwide [1]. Even after curative-intended primary treatment by radical prostatectomy and/or radiation therapy, a significant number of patients experience biochemical recurrence (BCR) during follow-up. Besides local relapse, PC recurrence within lymph nodes (LNs) is common in early BCR. In some of these patients, salvage LN dissection may be considered as an individual therapeutic option [2]. However, two main challenges for the successful surgical treatment of those patients exist.

First, correct assessment of the true metastatic spread is crucial. Here, the introduction of positron emission tomography (PET) agents targeting the prostate-specific membrane antigen (PSMA) has led to substantial improvements [3]. PSMA represents a cell surface protein that is highly overexpressed on most PC cells. Small-molecular ^{68}Ga-labeled ligands targeting PSMA have successfully been introduced into the clinics for PET imaging of PC [4]. ^{68}Ga-PSMA-ligand PET is able to visualize metastatic lesions both at low prostate-specific antigen (PSA) values and in small subcentimeter metastatic LNs [5–8]. Level 2b evidence based on these superior detection rates after radical prostatectomy led to a grade A recommendation of PSMA PET/computed tomography (CT) by the European Association of Urology [9].

Second, as metastatic LNs can atypically be located and/or are morphologically unremarkable, reliable intraoperative identification and removal of metastatic LNs are still challenging. Most recently, radioactive labeling of PSMA ligands with gamma-emitting radionuclides such as ^{111}Indium (^{111}In-PSMA imaging and therapy [^{111}In-PSMA-I&T]) or ^{99m}Technetium (^{99m}Tc-PSMA investigation and surgery [^{99m}Tc-PSMA-I&S]) was established [10,11]. These agents can be used for preoperative single photon emission computed tomography (SPECT) imaging and, in addition, surgical guidance with conventional gamma probes [12,13]. For routine clinical application, ^{111}In-PSMA-I&T is suboptimal due to its high cost, considerable radiation exposure, and restricted availability of $^{111}InCl_3$ [14,15]. In contrast, ^{99m}Tc-PSMA-I&S represents a valuable alternative based on easy access to ^{99m}Tc from ^{99}Mo/^{99m}Tc generators as routine equipment in a nuclear medicine department at a relatively low cost.

Thus, the aim of this investigation was to describe the technique as well as feasibility of ^{99m}Tc-PSMA-I&S–based radioguided surgery (^{99m}Tc-PSMA-RGS) for removal of recurrent PC lesions and report on short-term outcomes.

2. Patients and methods

2.1. Patients

Thirty-one consecutive patients with BCR after primary radical prostatectomy who underwent ^{99m}Tc-PSMA-RGS between September 2015 and May 2016 were included in this retrospective analysis. The median PSA value at the time of ^{99m}Tc-PSMA-RGS was 1.13 ng/ml (range: 0.29–3.81 ng/ml). Detailed patient characteristics are presented in Table 1.

All patients showed either a single or ≤4 metastatic soft-tissue lesions determined by ^{68}Ga-PSMA N,N′-bis[2-hydroxy-5-(carboxyethyl) benzyl] ethylenediamine-N,N′-diacetic acid (^{68}Ga-PSMA-11) PET imaging (Supplementary Fig. 1). Seventeen (55%) patients showed metastatic lesion(s) within the typical field of an extended LN template (iliaca externa, interna, communis, obturator fossa). Atypically localized lesions were present in a substantial number of patients: retrovesical/seminal vesicle bed in nine patients, presacral/pararectal in nine patients, retroperitoneal in two patients, and inguinal in one patient. All patients were informed about the experimental nature of salvage LN dissection and the use of ^{99m}Tc-PSMA-I&S, and provided their informed consent to the procedure as well as data analysis.

2.2. Procedure of ^{99m}Tc-PSMA-RGS

The ^{99m}Tc-PSMA-RGS procedure involves several steps, which are outlined in Fig. 1. Briefly, suitable patients are identified by ^{68}Ga-PSMA-11 PET imaging and clinical characteristics; ^{99m}Tc-PSMA-I&S was prepared as previously described [11] and intravenously injected the day before surgery. In the presented patient cohort, the mean activity of 571 MBq (range: 221–857 MBq) was administered in compliance with the German Medicinal Products Act (AMG §13 2b) and in accordance with the responsible regulatory body (Government of Oberbayern). Subsequently, SPECT/CT imaging is performed to cross validate findings of the ^{68}Ga-PSMA-11 PET, document positive tracer uptake within the lesions, and serve as quality control for tracer injection and distribution.

This is followed by the surgical procedure. In our patients, salvage surgery was started at a mean time of 19.7 h after injection of ^{99m}Tc-PSMA-I&S (range: 15.8–24.9 h). Patients were placed in a supine position and a urinary catheter was inserted. The latter allows removal of radioactive urine from the bladder, which otherwise may impair gamma probe measurements. Prior to its intraoperative use, the gamma probe (Crystal Probe CXS-SG603; Crystal Photonics, Berlin, Germany) was sterile draped. After preparing the surgical field, a transperitoneal midline incision is performed. This approach allows immediate access to the lower aorta, inferior vena cava, bifurcation, iliac vessels, ureters, as well as the pararectal and presacral area. The gamma probe is then used for in vivo intraoperative measurements to facilitate localizing the metastatic lesion(s). After excision, ex vivo gamma measurements are performed to immediately confirm the successful removal of the metastatic radioactive lesion(s) or to prompt further search in case of a missing signal. After removal of all metastatic lesions depicted on ^{68}Ga-PSMA-11 PET, intraoperative gamma probe measurements are conducted to exclude additional lesions. In case of recurrent tumor within the extended pelvic LN dissection (PLND) template, salvage surgery was performed for the whole extended PLND template of the respective side. For suspicious lesions located elsewhere, resection of the corresponding region with surrounding tissue was performed. The latter approach was chosen due to the lack of standardized templates in these salvage surgery settings. In case of retroperitoneal lesions, the template of dissection usually performed for testicular cancer patients was resected.

2.3. Histological correlation of ^{99m}Tc-PSMA-I&S gamma probe measurements

To investigate the reliability of ex vivo gamma probe analyses, we confirmed all measurements prior to sending the tissue specimens for histopathological evaluation. Fatty tissue of each patient served as a background reference for ex vivo measurements. We defined tissue specimens that showed a count rate of at least twice the background reference as radioactive positive. All tissue specimens including reference tissue were collected separately and underwent subsequent

Please cite this article in press as: Maurer T, et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.013

Table 1 – Patients' characteristics

Variables	Value
Median age at ^{99m}Tc-PSMA-RGS (yr)	66.7 (range: 49–79; IQR: 60.5–73.5)
Primary treatment: radical prostatectomy	31 (100%)
Gleason score at primary treatment	GS5: 1; GS6: 3; GS7a: 8; GS7b: 7; GS8: 5; GS9: 7
pT stage at primary treatment	
<pT2c	14 (45.2%)
>pT3a	16 (51.6%)
NA	1 (3.2%)
Resection margin at primary treatment	
R0	22 (71.0%)
R1	5 (16.1%)
NA	(12.9%)
pN stage at primary treatment	
pN0	23 (74.2%)
pN1	5 (16.1%)
pNx/NA	3 (9.7%)
Secondary treatment(s)	20 (64.5%)
Salvage radiation therapy	18 (58.0%)
Salvage lymph node dissection	3 (9.7%)
Androgen deprivation therapy	8 (25.8%)
Median PSA level at ^{99m}Tc-PSMA-RGS (ng/ml)	1.13 (range: 0.29–3.81; IQR: 0.71–2.35)
Localization of lesions on ^{68}Ga-PSMA-11 PET [a]	No. of patients (%)/no. of lesions: median (range)
All patients	31 (100%)/1 (1–4)
Pelvic (iliaca ext., com., int., obturator)	17 (54.8%)/1 (1–3)
Retrovesical and seminal vesicle bed	9 (29.0%)/1 (1–1)
Presacral and pararectal	9 (29.0%)/1 (1–3)
Retroperitoneal	2 (6.5%)/1; 1
Inguinal	1 (3.2%)/2

com. = communis; ext. = externa; ^{68}Ga-PSMA-11 = ^{68}Ga-PSMA N,N′-bis[2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N′-diacetic acid; GS = Gleason score; int. = interna; IQR = interquartile range; NA = not available; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; ^{99m}Tc-PSMA-RGS = ^{99m}Tc-based PSMA-radioguided surgery.
[a] Multiple locations within a patient possible.

histopathological evaluation to allow for exact matching. Routine histopathological evaluation included hematoxylin and eosin staining and PSMA (monoclonal murine PSMA antibody [clone 3E6]; Dako, Hamburg, Germany) if needed. Pathologists were blinded to the results of preoperative imaging and intraoperative gamma probe measurements.

2.4. Follow-up

Patients were contacted on a regular basis to obtain follow-up information. Postoperative complications were classified according to Clavien-Dindo. Best PSA response and rate of complete biochemical response (PSA < 0.2 ng/ml) without additional treatment was determined 6–16 wk following ^{99m}Tc-PSMA-RGS. Furthermore, BCR-free survival (PSA < 0.2 ng/ml without further PC-specific treatment) and PC-specific treatment–free survival were evaluated.

2.5. Statistics

Statistical analyses were performed using SPSS (version 23; IBM, Armonk, N.Y., U.S.A.) or R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Mean values, median, interquartile ranges, and/or ranges are presented for quantitative data as appropriate. Absolute and relative frequencies are given for categorical data. Performance of ex vivo radioactive rating (positive vs negative) for resected tissue specimens is described using sensitivity, specificity, and accuracy.

For estimation of sensitivities and corresponding confidence intervals, an intercept-only logistic generalized estimating equation (GEE) model accounting for multiple measurements in one patient was fit to the data. The result of the dichotomized test was used as a dependent variable, and only patients with a positive histopathological result were considered [16].

To derive estimates for the specificities, a variable indicating whether a negative test result was observed was used as a dependent variable. Here, only patients with a negative histopathological result were included. Accuracy was estimated in an intercept-only model with a dependent variable that indicated whether the test result and the result of the histopathological assessment agreed. For all GEE models, an independent correlation structure was assumed. Waterfall plots were used to show the best PSA responses after ^{99m}Tc-PSMA-RGS. The distribution of biochemical-free survival and PC-specific treatment–free survival times after ^{99m}Tc-PSMA-RGS was estimated using the Kaplan-Meier method.

3. Results

3.1. ^{99m}Tc-PSMA-RGS and comparison of gamma probe measurements with histopathology

^{99m}Tc-PSMA-RGS was able to identify and remove all lesions detected on preoperative ^{68}Ga-PSMA-11 PET in all patients. In total, 132 surgical specimens were removed (median specimens per patient: 4; range: 1–10). Forty-six specimens were classified as positive and 86 were considered negative.

The count rate of the background reference ranged between 0 and 4 counts/s. For positive specimens, the median count rate during ex vivo gamma probe measurements was 21.5 (range: 4–246) counts/s, while negative specimens showed a median count rate of 0.5 (range: 0–4) counts/s.

Please cite this article in press as: Maurer T, et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.013

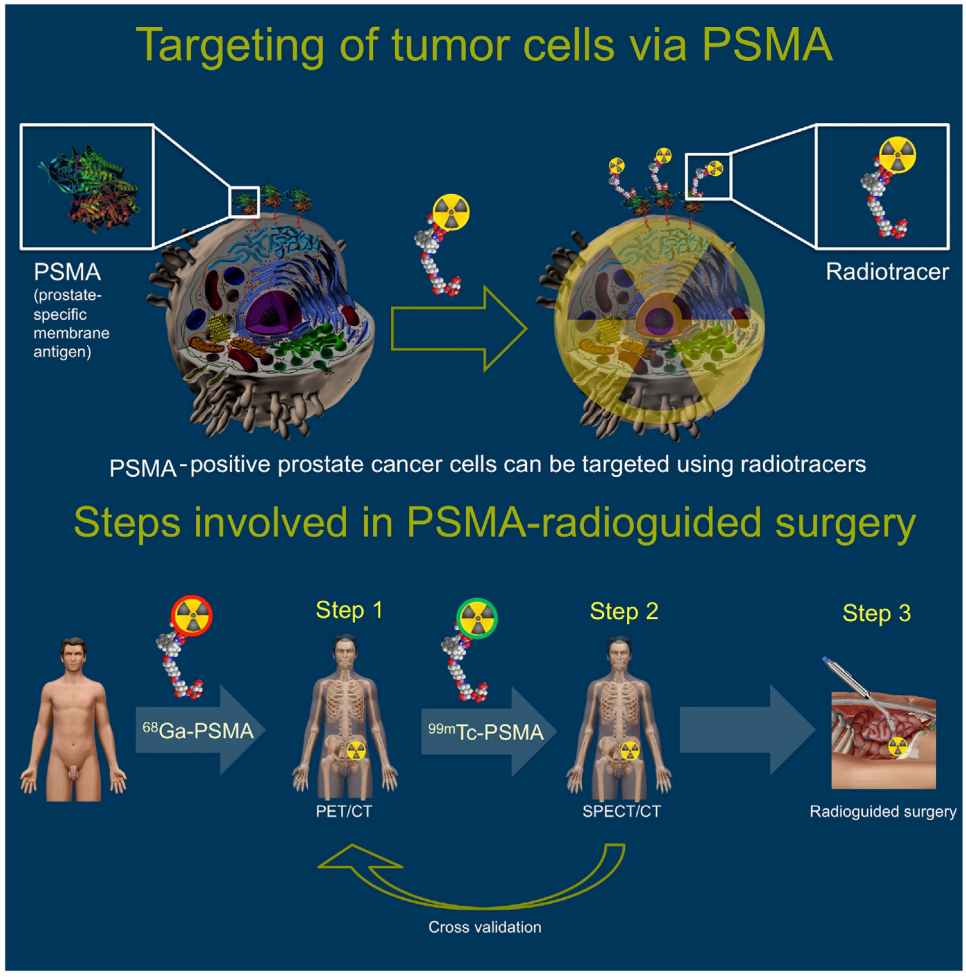

Fig. 1 – Overview of steps for PSMA-radioguided surgery: step 1: selection of patients based on PSMA PET results and clinical history; step 2: injection of ^{99m}Tc-PSMA-I&S and subsequent SPECT/CT imaging to confirm ^{99m}Tc-PSMA-I&S uptake in same lesions of preoperative ^{68}Ga-PSMA-11 findings; step 3: PSMA-radioguided surgery is performed with in vivo and ex vivo gamma probe measurements to reliably identify metastatic prostate cancer lesions. CT = computed tomography; ^{68}Ga-PSMA-11 = ^{68}Ga-PSMA N,N′-bis[2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N′-diacetic acid; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SPECT = single photon emission computed tomography; ^{99m}Tc-PSMA-I&S = ^{99m}Tc-PSMA investigation and surgery.

Fifty-eight of 132 (43.9%) specimens showed metastatic involvement at histological analysis. According to gamma probe measurements, 46 specimens were correctly classified as metastatic and 74 as cancer free. No specimen was false positive, but 12 specimens were false negative. Combined, this resulted in a sensitivity of 83.6% (95% confidence interval: 70.9–91.5%), a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 89.2% (78.0–95.0%), and an accuracy of 93.0% (85.8–96.7%; Table 2).

In the seven patients with false-negative findings, histopathology revealed a total of 12 metastatic lesions that were detected neither on preoperative ^{68}Ga-PSMA-11 PET nor during ^{99m}Tc-PSMA-RGS. In one of these patients harboring three undetected lesions (maximum diameter 5 mm), this might be attributed to a low amount of tracer injected (221 MBq, 2.3 MBq/kg) and a long time interval between injection and surgery (22.2 h). In the other six patients, lesions had a median size of 2 mm (range: 1–4 mm). The median size of correctly identified metastatic lesions during ^{99m}Tc-PSMA-RGS was 12 mm (range: 3–25 mm). Moreover, compared with preoperative ^{68}Ga-PSMA-11 PET, ^{99m}Tc-PSMA-RGS detected additional metastases as small as 3 mm in two patients. Of note, due to inherent limitations of SPECT/CT, imaging with ^{99m}Tc-PSMA-I&S was able to detect only 25 (56.8%) of the 44 lesions observed on ^{68}Ga-PSMA-11 PET.

3.2. Complications

Thirteen patients suffered from surgery-related complications during follow-up. Most of them were grade 1 according to Clavien-Dindo: lymphedema ($n = 7$), paresthesia at the upper thigh ($n = 3$), wound healing disorder ($n = 1$), and bladder leakage with conservative management ($n = 1$). One patient developed hydronephrosis with urosepsis that

Please cite this article in press as: Maurer T, et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.013

Table 2 – Intraoperative parameters, pathological results, and complication rates

Variables		Value
Intraoperative parameters		
Surgical time (min)		116 (range: 63–195; IQR: 93–134)
Estimated blood loss (ml)		150 (range: 50–1300; IQR: 75–200)
Transfusion rate		0
	Histology positive	Histology negative
Pathological results [a]		
PSMA-RGS positive	46	0
PSMA-RGS negative	12	74
Statistical performance of PSMA-RGS ex vivo measurements in correlation with histopathology [b]		
Sensitivity		83.6% (95% CI: 70.9–91.5%)
Specificity		100% (–)
Positive predictive value		100% (–)
Negative predictive value		89.2% (95% CI: 78.0–95.0%)
Accuracy		93.0% (95% CI: 85.8–96.7%)
Clavien-Dindo grade	Patients (%)	Complication
Complication rates		
0	18 (58.1%)	
1	12 (38.7%)	7 pts: lymphedema (conservative management) 3 pts: paresthesia (upper thigh) 1 pt: wound healing disorder (conservative management) 1 pt: bladder leakage (conservative management with catheterization)
3a	1 (3.2%)	Urosepsis and hydronephrosis (DJ catheter insertion, antibiotic treatment)

95% CI = 95%-confidence interval; GEE = generalized estimating equation; IQR = interquartile range; PSMA-RGS = prostate-specific membrane antigen–radioguided surgery, rating by ex vivo gamma probe measurements; pt(s) = patient(s).
[a] Of separate tissue specimens.
[b] GEE model to account for multiple measurements within one patient.

required DJ catheter insertion and antibiotic therapy. No adverse events related to the ^{99m}Tc-PSMA-I&S injection were observed.

3.3. *Short-term outcome*

PSA follow-up was available in 30 patients. One patient received postoperative salvage-radiation therapy without prior PSA measurement. Compared with preoperative baseline, 24 (80%) and 17 (57%) patients showed 50% and 90% PSA decline, respectively (Fig. 2A). In 20 (67%) patients, a PSA decline below 0.2 ng/ml after ^{99m}Tc-PSMA-RGS was achieved. Seventeen of 30 (57%) patients showed an incomplete PSA response (PSA > 0.2 ng/ml) or rising PSA values >0.2 ng/ml during follow-up after a median of 1.9 mo. PSA value remained below 0.2 ng/ml without additional PC-specific treatment in 13 (43%) patients after a median follow-up of 13.8 mo (Fig. 2B). Eleven of 31 (35%) patients received additional PC-specific therapies after a median of 3.7 mo. The remaining 20 (65%) patients continued to be treatment free after a median of 12.2 mo (Fig. 2C). Median time for treatment-free survival was not reached yet.

4. Discussion

The introduction of PSMA-targeting PET imaging has led to substantially improved visualization of small tumor deposits in patients with biochemically recurrent PC [7,8,17]. In parallel, salvage surgery has gained increasing interest in patients with locoregional oligometastatic disease to positively influence disease progression and delay the need for further systemic treatment [18–20]. However, no consensus about the extent of LN dissection and the templates that need to be dissected during salvage procedures could yet be reached. Difficulties are the varying and often altered lymphatic drainage patterns after previous therapy, and the different extent of prior surgeries. Besides careful selection of suitable patients potentially profiting from salvage surgery approaches, reliable detection and removal of metastatic soft tissue lesions are of utmost importance.

Here, we demonstrate the feasibility of ^{99m}Tc-PSMA-RGS to guide the intraoperative identification and surgical removal of metastatic LNs in PC patients scheduled for salvage surgery. The surgical technique proved especially useful to identify and excise small and/or atypically localized lesions, as depicted on preoperative PSMA PET. However, as patient selection is based on individual tumor-specific history and PSMA PET, the limited performance of PSMA PET for small metastatic lesions has to be acknowledged. As the detection rate is clearly size dependent (eg, >50% and >90% if short axis diameter equals or exceeds 2.3 and 4.5 mm, respectively [17]), careful dissection of surrounding tissue is mandatory to remove possible adjacent micrometastatic disease during RGS. Here, the sensitivity of 83.6% in our analysis reflects that even a negative gamma probe measurement cannot exclude small metastatic lesions completely.

Please cite this article in press as: Maurer T, et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.013

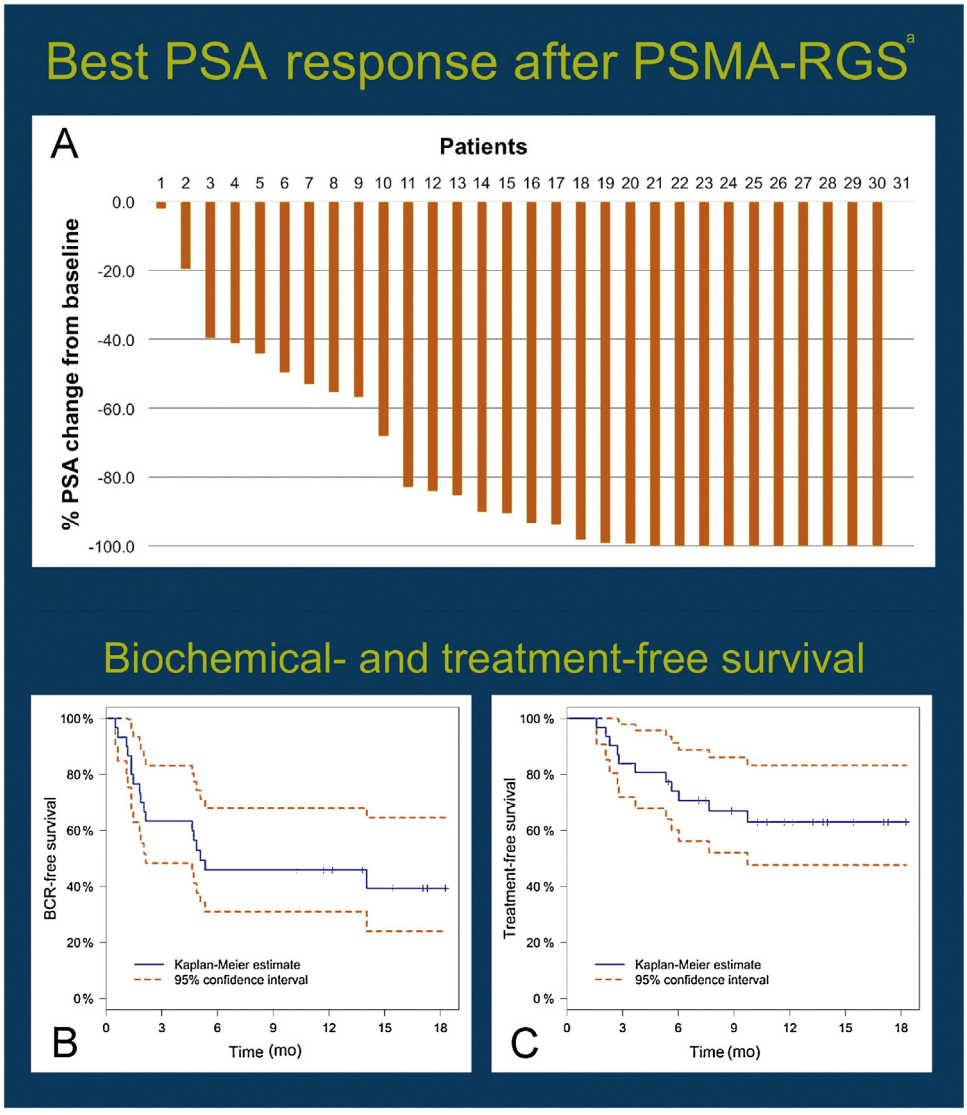

Fig. 2 – (A) Best postoperative PSA response after PSMA-radioguided surgery without additional treatment. In one patient, postoperative salvage-radiation therapy was implemented without prior assessment of PSA value. (B) Biochemical-free survival without additional treatment and (C) treatment-free survival after ^{99m}Tc-PSMA-RGS. Kaplan-Meier estimates and 95% confidence intervals are shown. PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; ^{99m}Tc-PSMA-RGS = ^{99m}Tc-based PSMA-radioguided surgery. [a] No additional treatment given.

One of the main advantages of RGS in general is the possibility of immediate confirmation of successful removal of metastatic lesions by ex vivo gamma probe measurements. Although it cannot replace histopathological analysis, these measurements may guide dissections and prompt the surgeon to further explore the surgical field in case of missing positive signals of resected tissue specimens. Results from the current study support this theory: in our series, all lesions identified on preoperative ^{68}Ga-PSMA-11 PET were also detected by positive gamma probe measurements. All positive tissue specimens on gamma probe measurements contained metastatic PC tissue. In fact, even additional lesions not seen on ^{68}Ga-PSMA-11 PET were detected in two patients, which were proved to be metastatic. However, low-volume small-sized PC lesions might be detected neither by preoperative ^{68}Ga-PSMA-11 PET nor by intraoperative gamma probe measurements; thus, dissection of immediate neighboring tissue seems advisable. Of note, preoperative ^{99m}Tc-PSMA-I&S SPECT can also help anticipate the signal intensity from intraoperative gamma probe measurements. However, missing visualization on SPECT (compared with prior PSMA PET) does not imply negative gamma probe measurements, as in vivo and ex vivo measurements with low distance yield higher sensitivity compared with whole-body SPECT imaging. In addition, the lower efficacy of PSMA-targeted SPECT compared with PET has already been described for ^{111}In-PSMA-I&T SPECT/CT [21].

Compared with our previous report on the use of ^{111}In-PSMA-I&T [12,13], the application of ^{99m}Tc-PSMA-I&S–based RGS offers substantial advantages. ^{99m}Tc is cheap, has been utilized since decades in nuclear medicine, and is readily available in most nuclear medicine departments. Although not specifically proved for ^{99m}Tc-PSMA-I&S

Please cite this article in press as: Maurer T, et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.013

compared with ^{111}In-PSMA-I&T, the more favorable radiation profile of ^{99m}Tc (lower gamma energy and shorter half-life compared with ^{111}In) leads to less radiation exposure for patients and medical personnel [14,15]. Finally, the use of ^{99m}Tc in the operation theater has a long history based on sentinel LN surgery in PC [22], making the adaption of ^{99m}Tc-PSMA-RGS a straightforward process (eg, permit from radiation safety, postprocedural measurements, etc.) with a low learning curve.

Within the literature, there are several reports on outcomes of salvage surgery in recurrent PC. Suardi et al [18] published one of the largest series including 59 patients with a median follow-up of 81.1 mo. In their study, Suardi et al report a biochemical response rate (PSA $<$ 0.2 ng/ml) of 59.3% versus 66.7% in our study (which dropped to 43% during follow-up). Despite similar results, several differences between the studies hamper a direct comparison. In the study by Suardi et al [18], inclusion of patients was based on ^{11}C-choline PET showing up to two pelvic or retroperitoneal LN metastases. Median PSA at salvage surgery was 2.0 ng/ml (higher than in our study), and salvage surgery dissections were carried out bilaterally. Furthermore, several patients with biochemical response were treated with androgen deprivation therapy. Thus, the comparison of both patient collectives is limited. However, the study by Suardi et al [18] with long follow-up highlights that only a limited number of patients experience long-term biochemical-free survival (23% after 8 yr). Thus, salvage surgery represents a therapeutic option only for selected patients with PC recurrence.

Besides the limited number of patients included and the rather short follow-up, our study is also limited by the fact that the administered dose of ^{99m}Tc-PSMA-I&S, and the time interval between application and surgery have been chosen empirically and were not evaluated in detail.

However, the clinical introduction of PSMA-targeted RGS approaches might open the field for further innovations and technical refinements. The recent development of small drop-in gamma probes that can be utilized during robotic surgery could enable minimally invasive targeted salvage surgery procedures in PC patients [23]. Modifications of PSMA-targeted agents employing optical-dye conjugates for fluorescence imaging [24,25] as well as development of specialized camera systems [26] might enable multifunctional image guidance during surgical procedures and thus improve the efficacy of salvage dissections. In general, complete follow-up of patients undergoing these individual salvage surgery procedures, preferentially in registries, is mandatory to identify clinical predictors of favorable outcome to further define the role of salvage surgery or intraoperative guidance by labeled PSMA ligands.

5. Conclusions

We demonstrate the feasibility of ^{99m}Tc-PSMA-RGS to guide intraoperative identification and surgical removal of metastatic LN in PC patients scheduled for salvage surgery. The surgical technique complemented by ex vivo gamma probe measurement with immediate feedback about successful removal of tumor deposits is highly useful to identify and excise small or atypically localized lesions, as seen on preoperative PSMA PET. However, caution is advised as both the procedure of ^{99m}Tc-PSMA-RGS and PSMA PET as an initial tool to stratify patients for salvage lymphadenectomy are not capable of detecting microscopic disease. Our short-term follow-up data indicate a high potential to positively influence disease progression and delay further systemic treatment, which has to be validated in prospective clinical trials.

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: Maurer, Robu, Schottelius, van den Berg, van Leeuwen, Gschwend, Schwaiger, Wester, Eiber.
Acquisition of data: Maurer, Robu, Schwamborn, Rauscher, van den Berg, Horn, Heck, Eiber.
Analysis and interpretation of data: Maurer, Robu, Schwamborn, Rauscher, van den Berg, van Leeuwen, Haller, Horn, Eiber.
Drafting of the manuscript: Maurer, Robu, van den Berg, van Leeuwen, Eiber.
Critical revision of the manuscript for important intellectual content: Schottelius, Rauscher, Horn, Heck, Gschwend, Schwaiger, Wester.
Statistical analysis: Maurer, Haller.
Obtaining funding: None.
Administrative, technical, or material support: Maurer, Robu, Schottelius, van den Berg, van Leeuwen, Gschwend, Schwaiger, Wester, Eiber.
Supervision: Gschwend, Schwaiger, Wester.
Other: None.

Financial disclosures: Tobias Maurer certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: H.-J. Wester is CEO of Scintomics GmbH and owns stock or options at the company. Scintomics is the distributor of the automated module used for the synthesis of the ^{68}Ga-PSMA HBED-CC ligand.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

The Surgery in Motion video accompanying this article can be found in the online version at https://doi.org/10.1016/j.eururo.2018.03.013 and via www.europeanurology.com.

References

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
[2] Boorjian SA, Thompson RH, Tollefson MK, et al. Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. Eur Urol 2011;59:893–9.

[3] Eder M, Schafer M, Bauder-Wust U, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem 2012;23:688–97.
[4] Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. Nat Rev Urol 2016;13:226–35.
[5] Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42:197–209.
[6] Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid (6)(8) Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 2015;56:668–74.
[7] Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70:926–37.
[8] Rauscher I, Duewel C, Haller B, et al. Efficacy, predictive factors, and prediction nomograms for 68Ga-labeled prostate-specific membrane antigen-ligand positron-emission tomography/computed tomography in early biochemical recurrent prostate cancer after radical prostatectomy. Eur Urol. In press. doi:10.1016/j.eururo.2018.01.006.
[9] Guideline EAU. Prostate cancer: guidelines for imaging in patients with biochemical recurrence. 2017 In: http://uroweb.org/guideline/prostate-cancer/?type=summary-of-changes
[10] Schottelius M, Wirtz M, Eiber M, Maurer T, Wester HJ. [(111)In] PSMA-I&T: expanding the spectrum of PSMA-I&T applications towards SPECT and radioguided surgery. EJNMMI Res 2015;5:68.
[11] Robu S, Schottelius M, Eiber M, et al. Preclinical evaluation and first patient application of 99mTc-PSMA-I&S for SPECT imaging and radioguided surgery in prostate cancer. J Nucl Med 2017;58:235–42.
[12] Maurer T, Weirich G, Schottelius M, et al. Prostate-specific membrane antigen-radioguided surgery for metastatic lymph nodes in prostate cancer. Eur Urol 2015;68:530–4.
[13] Rauscher I, Duwel C, Wirtz M, et al. Value of 111 In-prostate-specific membrane antigen (PSMA)-radioguided surgery for salvage lymphadenectomy in recurrent prostate cancer: correlation with histopathology and clinical follow-up. BJU Int 2017;120:40–7.
[14] Benz P, Oberhausen E, Berberich R. Monoclonal antibody BW431/26 labelled with technetium 99m and indium 111: an investigation of the biodistribution and the dosimetry in patients. Eur J Nucl Med 1991;18:813–6.
[15] Bunschoten A, van den Berg NS, Valdés Olmos RA, Blokland JAK, van Leeuwen FWB. Tracers applied in radioguided surgery. In: Hermann K, Nieweg OE, Povosiki SP, editors. Radioguided surgery—current applications and innovation directions in clinical practice.. Heidelberg, Germany: Springer International Publishing; 2016.
[16] Genders TS, Spronk S, Stijnen T, Steyerberg EW, Lesaffre E, Hunink MG. Methods for calculating sensitivity and specificity of clustered data: a tutorial. Radiology 2012;265:910–6.
[17] Jilg CA, Drendel V, Rischke HC, et al. Diagnostic accuracy of Ga-68-HBED-CC-PSMA-Ligand-PET/CT before salvage lymph node dissection for recurrent prostate cancer. Theranostics 2017;7:1770–80.
[18] Suardi N, Gandaglia G, Gallina A, et al. Long-term outcomes of salvage lymph node dissection for clinically recurrent prostate cancer: results of a single-institution series with a minimum follow-up of 5 years. Eur Urol 2015;67:299–309.
[19] Rauscher I, Maurer T, Beer AJ, et al. Value of 68Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. J Nucl Med 2016;57:1713–9.
[20] Bandini M, Fossati N, Briganti A. Salvage surgery for nodal recurrent prostate cancer. Curr Opin Urol 2017;27:604–11.
[21] Rauscher I, Maurer T, Souvatzoglou M, et al. Intrapatient comparison of 111In-PSMA I&T SPECT/CT and hybrid 68Ga-HBED-CC PSMA PET in patients with early recurrent prostate cancer. Clin Nucl Med 2016;41:e397–402.
[22] van der Poel HG, Wit EM, Acar C, et al. Sentinel node biopsy for prostate cancer: report from a consensus panel meeting. BJU Int 2017;120:204–11.
[23] van Oosterom MN, Simon H, Mengus L, et al. Revolutionizing (robot-assisted) laparoscopic gamma tracing using a drop-in gamma probe technology. Am J Nucl Med Mol Imaging 2016;6:1–17.
[24] Baranski AC, Schafer M, Bauder-Wust U, et al. PSMA-11 derived dual-labeled PSMA-inhibitors for preoperative PET imaging and precise fluorescence-guided surgery of prostate cancer. J Nucl Med. In press. doi:10.2967/jnumed.117.201293.
[25] Banerjee SR, Foss CA, Horhota A, et al. (111)In- and IRDye800CW-labeled PLA-PEG nanoparticle for imaging prostate-specific membrane antigen-expressing tissues. Biomacromolecules 2017;18:201–9.
[26] Neuman BP, Eifler JB, Castanares M, et al. Real-time, near-infrared fluorescence imaging with an optimized dye/light source/camera combination for surgical guidance of prostate cancer. Clin Cancer Res 2015;21:771–80.

Please cite this article in press as: Maurer T, et al. ^{99m}Technetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.013