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Surgery in Motion

99mTechnetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer

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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).

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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

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.
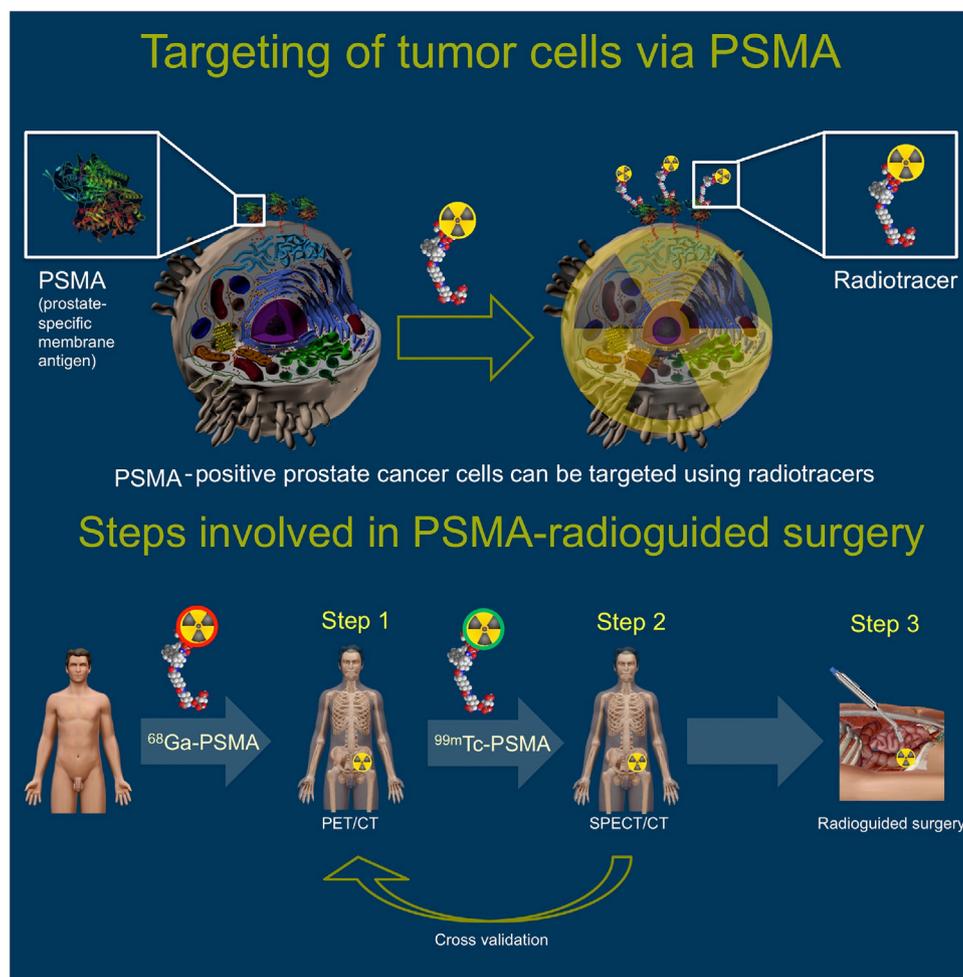
Fig. 1 – Overview of steps for PSMA-radioguided surgery: step 1: selection of patients based on PSMA PET results and clinical history; step 2: injection of ^{99m}Tc-PSMA-I&S and subsequent SPECT/CT imaging to confirm ^{99m}Tc-PSMA-I&S uptake in same lesions of preoperative ^{68}Ga-PSMA-11 findings; step 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

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.
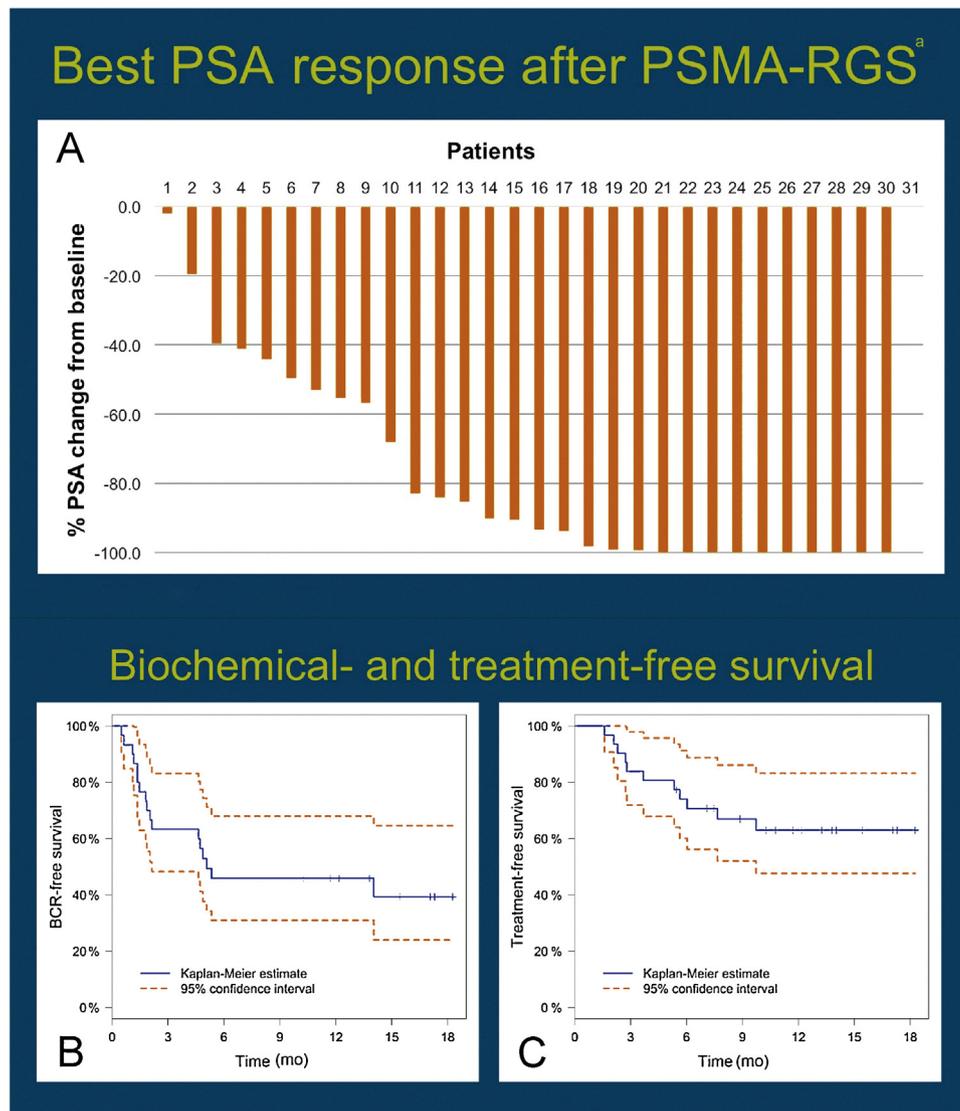
Fig. 2 – (A) Best postoperative PSA response after PSMA-radioguided surgery without additional treatment. In one patient, postoperative salvage-radiation therapy was implemented without prior assessment of PSA value. (B) Biochemical-free survival without additional treatment and (C) treatment-free survival 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

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.

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.

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