Robot-assisted prostate-specific membrane antigen-radioguided salvage surgery in recurrent prostate cancer using a DROP-IN gamma probe: the first prospective feasibility study

Barros, H.A. de; Oosterom, M.N. van; Donswijk, M.L.; Hendrikx, J.J.M.A.; Vis, A.N.; Maurer, T.; ... ; Leeuwen, P.J. van

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

European Association of Urology

Surgery in Motion

Robot-assisted Prostate-specific Membrane Antigen–radioguided Salvage Surgery in Recurrent Prostate Cancer Using a DROP-IN Gamma Probe: The First Prospective Feasibility Study

Hilda A. de Barros[a,b,*], *Matthias N. van Oosterom*[a,c], *Maarten L. Donswijk*[d], *Jeroen J.M.A. Hendrikx*[d,e], *André N. Vis*[b,f], *Tobias Maurer*[g,h], *Fijs W.B. van Leeuwen*[a,c], *Henk G. van der Poel*[a,b,f], *Pim J. van Leeuwen*[a,b]

[a] *Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [b] *Netherlands Prostate Cancer Network, Amsterdam, The Netherlands;* [c] *Interventional Molecular Imaging Laboratory, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands;* [d] *Department of Nuclear Medicine, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [e] *Department of Pharmacy & Pharmacology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [f] *Department of Urology, Amsterdam University Medical Center, VU University, Amsterdam, The Netherlands;* [g] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [h] *Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany*

Article info

Article history:
Accepted March 4, 2022

Associate Editor:
James Catto

Keywords:
Prostate cancer
Prostate-specific membrane antigen
Image-guided surgery
Radioguided surgery
Robot-assisted surgery

Abstract

Background: It has been proven that intraoperative prostate-specific membrane antigen (PSMA)-targeted radioguidance is valuable for the detection of prostate cancer (PCa) lesions during open surgery. Rapid extension of robot-assisted, minimally invasive surgery has increased the need to make PSMA-radioguided surgery (RGS) robot-compliant.
Objective: To evaluate whether the miniaturized DROP-IN gamma probe facilitates translation of PSMA-RGS to robotic surgery in men with recurrent PCa.
Design, setting, and participants: This prospective feasibility study included 20 patients with up to three pelvic PCa recurrences (nodal or local) on staging PSMA positron emission tomography (PET) after previous curative-intent therapy.
Surgical procedure: Robot-assisted PSMA-RGS using the DROP-IN gamma probe was carried out 19–23 h after intravenous injection of ^{99m}technetium PSMA-Investigation & Surgery (^{99m}Tc-PSMA-I&S).
Measurements: The primary endpoint was the feasibility of robot-assisted PSMA-RGS. Secondary endpoints were a comparison of the radioactive status (positive or negative) of resected specimens and final histopathology results, prostate-specific antigen (PSA) response following PSMA-RGS, and complications according to the Clavien-Dindo classification.
Results and limitations: Using the DROP-IN probe, 19/21 (90%) PSMA-avid lesions could be resected robotically. On a per-lesion basis, the sensitivity and specificity of robot-assisted PSMA-RGS was 86% and 100%, respectively. A prostate-specific antigen (PSA) reduction of >50% and a complete biochemical response (PSA <0.2 ng/ml) were seen in 12/18 (67%) and 4/18 (22%) patients, respectively. During follow-up of up to 15 mo,

* Corresponding author. Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, Amsterdam 1066 CX, The Netherlands. Tel. +31 205126988.
E-mail address: h.d.barros@nki.nl (H.A. de Barros) .

https://doi.org/10.1016/j.eururo.2022.03.002

4/18 patients (22%) remained free of biochemical recurrence (PSA ≤0.2 ng/ml). One patient suffered from a Clavien-Dindo grade >III complication.
Conclusions: The DROP-IN probe helps in realizing robot-assisted PSMA-RGS. The procedure is technically feasible for intraoperative detection of nodal or local PSMA-avid PCa recurrences.
Patient summary: A device called the DROP-IN probe facilitates minimally invasive, robot-assisted surgery guided by radioactive tracers in patients with recurrent prostate cancer. This procedure holds promise for improving the intraoperative identification and removal of prostate cancer lesions.

1. Introduction

The introduction of positron emission tomography (PET) agents targeting prostate-specific membrane antigen (PSMA), a cell-surface glycoprotein highly overexpressed on prostate cancer (PCa) cells, has significantly improved the accuracy for detection of PCa metastases in comparison to conventional imaging [1–3]. The availability of PSMA imaging has led to a paradigm shift in the treatment of PCa in patients with a limited metastatic burden, moving from systemic therapy towards metastasis-directed therapy such as stereotactic body radiotherapy (SBRT) and salvage lymph node dissection (SLND) [4,5]. Unfortunately, a considerable percentage of patients still demonstrate a persistently elevated prostate-specific antigen (PSA) level following SLND [6–8], which may be a result of an incomplete resection of metastatic lesions [6,7,9].

To improve the intraoperative localization of PCa recurrences, radioguided surgery (RGS) has been introduced using γ-emitting radionuclide-labeled PSMA ligands. After intravenous injection, radioactive tracers bind to and accumulate in PSMA-expressing PCa lesions. The first generation of PSMA tracers for surgical use were labeled with ^{111}indium (^{111}In-PSMA-617) [5,10]. However, the more favorable characteristics of ^{99m}technetium (^{99m}Tc)-labeled ligands, including lower isotope costs, lower radiation burden, better compatibility with detectors, and wide availability, have resulted in a general preference for ^{99m}Tc-labeled ligands for intraoperative radioguidance [4,5,11,12]. During open PCa surgery, PSMA targeting has allowed for efficient resection of both nodal [4,5,13] and local recurrences [11]. Recent studies have even shown that PSMA-RGS could positively impact oncological outcomes [13]. In parallel to tracer development, the field of image-guided surgery is advancing via developments in detector engineering. One such improvement is the recent clinical introduction of tethered DROP-IN gamma probes that facilitate implementation of radioguidance in the robotic setting [14–16]. Unlike traditional laparoscopic gamma probes, the DROP-IN probe allows the surgeon to autonomously position the probe using the robot console with enhanced maneuverability.

The aim of this prospective study was to evaluate whether the DROP-IN gamma probe facilitates minimally invasive, robot-assisted, PSMA-targeted surgery in patients with recurrent PCa.

2. Patients and methods

2.1. Study design and patient population

This single-institution, investigator-initiated, prospective, single-arm feasibility study was approved by the local ethics committee at the Netherlands Cancer Institute (NCI), Amsterdam, The Netherlands (ClinicalTrials.gov NCT03857113). All patients provided written informed consent and underwent surgery between June 2020 and May 2021.

Patients with biochemical recurrence (BCR, defined as PSA ≥0.2 ng/ml at two consecutive measurements) of PCa after previous curative-intent treatment (radical prostatectomy or local radiotherapy) were selected. Patients needed to have a maximum of three soft-tissue lesions within the pelvis suspicious for lymph node metastases (LNMs) or local residual disease on preoperative PSMA PET/computed tomography (CT). Exclusion criteria were a coexistent malignancy within 5 yr before study participation, recurrent PCa in the prostatic fossa that was not amenable to surgical treatment, nonregional lymphadenopathy or distant metastases, and PSA ≥4 ng/ml [17]. Androgen deprivation therapy within 6 mo before surgery was not allowed.

2.2. Preoperative imaging

All men underwent a ^{68}Ga-PSMA-11 or ^{18}F-DCFPyl PET/CT according the local protocol [18,19] within 60 d before salvage surgery. ^{99m}Tc-PSMA-I&S was prepared as previously described [20]. At 1 d before surgery, a single dose of ^{99m}Tc-PSMA-I&S was injected intravenously (median activity 541 MBq, interquartile range [IQR] 526–578). At approximately 17 h after injection, single-photon emission CT (SPECT)/CT was performed as quality control for tracer injection and distribution. Nuclear medicine physicians at the NCI evaluated all preoperative images to determine the location and number of suspect lesions.

2.3. Surgical procedure

All procedures were performed using a da Vinci Si surgical robotic system (Intuitive Surgical, Sunnyvale, CA, USA) via a six-port transperitoneal approach [21]. Radioguidance was achieved using a prototype DROP-IN probe (Eurorad S.A., Eckbolsheim, France) [16] inserted into the abdominal peritoneal cavity either through or next to a 12-mm trocar within the Alexis port (Alexis laparoscopic system, Applied Medical Corp., Rancho Santa Margarita, CA, USA) [4,15,16,22]. The probe provides both acoustic and numerical feedback as a response to ^{99m}Tc activity and can be autonomously grasped and maneuvered by the urologist using the surgical console and da Vinci ProGrasp forceps (Fig. 1).

First, radioactivity was measured for anatomical landmarks near target PCa lesions (ureter, iliac artery, iliac vein, bladder, intestines and psoas muscle) to assess the amount of nonspecific tracer activity. Second, suspected PCa lesion locations were scanned in vivo using the

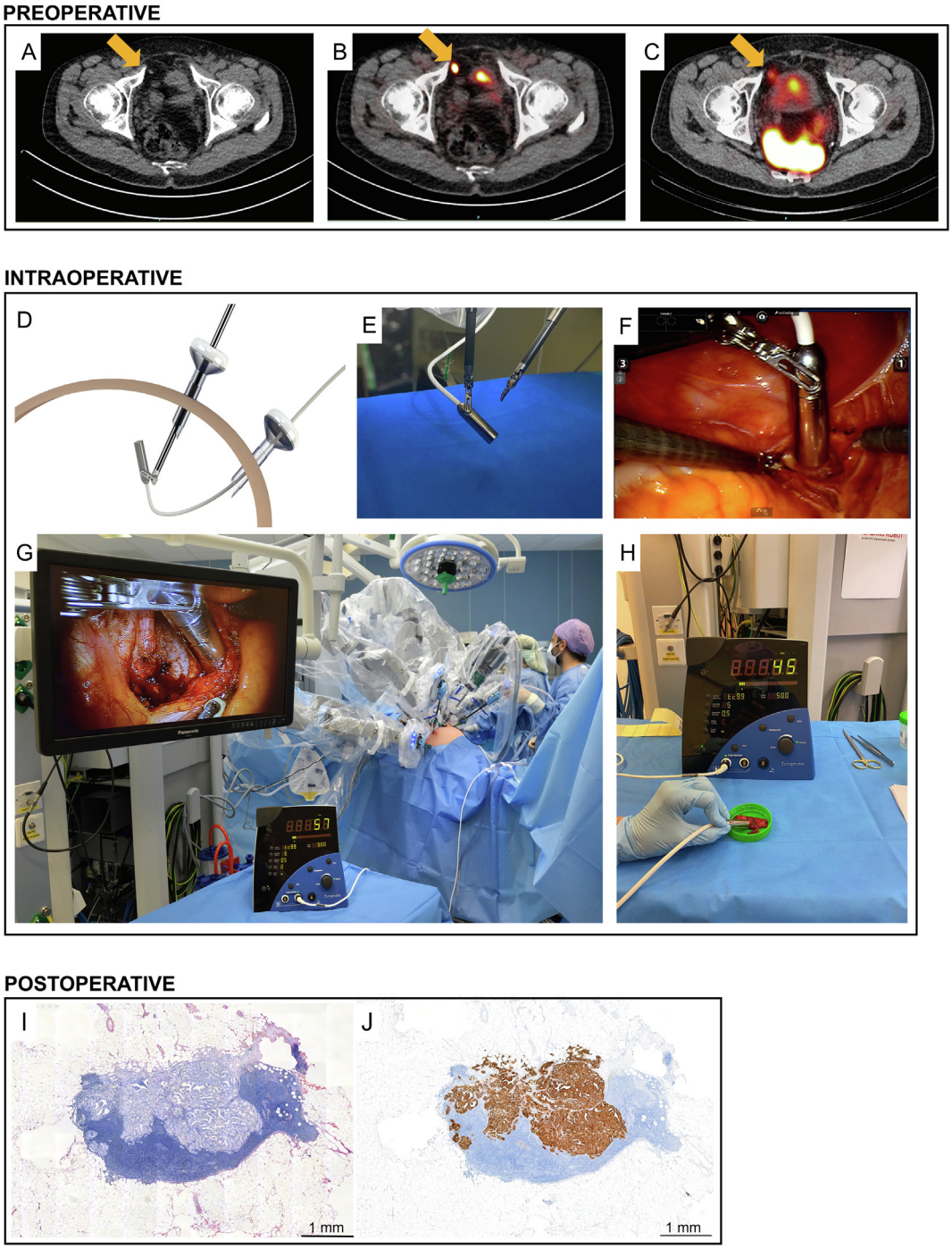

Fig. 1 – Robot-assisted ^{99m}Tc-PSMA radioguided surgery procedure. Preoperative (A) CT, (B) PSMA PET/CT, and (C) ^{99m}Tc-PSMA-I&S SPECT/CT imaging demonstrate a prevesical lesion (indicated with an arrow) in a patient with biochemical recurrence after primary treatment for prostate cancer. (D) During the surgery, the DROP-IN probe is inserted in the abdomen through a trocar (E) and is autonomously maneuvered by the surgeon using a Da Vinci surgical console. (F,G) In vivo radioactivity measurement of a suspected prostate cancer recurrence. (H) Ex vivo radioactivity measurement of the resected specimen. Histological analysis revealed a lymph node metastasis on (I) hematoxylin and eosin staining and (J) PSMA immunohistochemistry. CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SPECT = single-photon emission CT.

DROP-IN probe. Ex vivo validations were performed with the DROP-IN probe to confirm successful removal of radioactive tissue or to guide further examination of the surgical field in cases with no elevated signal. Specimens were considered radioactive when the count rate was at least twice that of the local background (ie, lymphatic or soft tissue) count rate. In the absence of consensus on the best template for SLND [23], we recommended a SLND extent on the basis of previous pelvic LN treatment. Unilateral SLND was recommended for patients who had previously been treated with an extended pelvic LND (ePLND) or whole-pelvis radiotherapy. Patients without previous pelvic LN therapy underwent bilateral SLND. When lesions were located outside the ePLND template or in the case of a local recurrence, targeted resection of the suspicious lesion and the directly surrounding tissue (potentially bearing micrometastases) was recommended.

2.4. Histopathological evaluation

All dissected specimens were sent for histopathological examination with hematoxylin and eosin staining and, if needed, immunohistochemical pancytokeratin AE13 (CK AE1/3) staining. When histopathologically confirmed PCa metastases were not considered radioactive using gamma probe readings (ie, false-negative), immunohistochemical PSMA staining was performed (Clone 3E6; Dako, Carpinteria, CA, USA). Dedicated uropathologists microscopically evaluated all slides and were blinded to the results of preoperative imaging and perioperative radioactivity measurements with the DROP-IN probe.

2.5. Follow-up

Follow-up consisted of clinical examination and serum PSA measurements at 6 wk after surgery and every 3 mo thereafter. All adverse events reported by the patient or observed by the investigator within 24 h after ^{99m}Tc-PSMA-I&S administration were recorded using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Surgical complications were assessed at 30 d postoperatively according to the Clavien-Dindo classification.

2.6. Study endpoints

The primary outcome was the feasibility of resecting PSMA-avid lesions suspicious for recurrent PCa during minimally invasive robot-assisted ^{99m}Tc-PSMA-RGS with the assistance of a DROP-IN gamma probe. Secondary outcomes included the diagnostic accuracy of preoperative PSMA PET/CT compared to histologic evaluation, the accuracy of SPECT/CT compared to PSMA PET/CT, agreement between the radioactive status (ie, positive or negative) of specimens removed and final pathology results (ie, benign or malignant), tumor-to-background ratios (TBRs; defined in vivo as the radioactive count for metastatic tissue divided by the radioactive count for surrounding background and ex vivo as the radioactive count for excised metastatic specimens divided by the count for excised benign specimens), and the frequency of PSA reduction >50% and complete biochemical response (cBR; PSA <0.2 ng/ml) at 6 wk after surgery. In addition, the rate of biochemical recurrence (BCR; PSA $\geq$0.2 ng/ml at two consecutive measurements) was recorded at last follow-up.

2.7. Statistical analysis

Descriptive statistics are reported as the median and IQR or the frequency and proportion, as appropriate [24]. The diagnostic accuracy of ^{99m}Tc-PSMA-RGS and preoperative imaging was described on a lesion basis in terms of the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Radioactive count rates for resected specimens (benign vs malignant) were compared with a two-sided Wilcoxon signed-rank test. A waterfall plot was used to graphically depict the PSA change after ^{99m}Tc-PSMA-RGS. All statistical analyses were performed using SPSS v25 (IBM, Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad, La Jolla, CA, USA). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Feasibility of robot-assisted ^{99m}Tc-PSMA-RGS

Twenty patients with a suspicion of nodal disease (n = 15) or local recurrent PCa (n = 5) on staging PSMA PET were included (Table 1 and Fig. 2). Initially, 15 patients (75%) had been treated with radical prostatectomy and five (25%) with radiotherapy. The median time from the last therapy to salvage surgery was 26 mo (IQR 11–47).

Table 1 – Characteristics of the 20 patients before salvage ^{99m}Tc-PSMA radioguided surgery

Parameter	Result
Median age at radioguided surgery, yr (IQR)	68 (66–72)
Median prostate-specific antigen at radioguided surgery, ng/ml (IQR)	1.02 (0.46–2.43)
Primary treatment, *n* (%)	
Radical prostatectomy	3 (15)
Radical prostatectomy + lymph node dissection	12 (60)
Radiotherapy	5 (25)
Secondary treatment before radioguided surgery, *n* (%)	
Adjuvant radiotherapy	5 (25)
Salvage radiotherapy	4 (20)
Salvage radical prostatectomy	1 (5)
Salvage lymph node dissection	1 (5)
No secondary treatment	9 (45)
Tertiary treatment before radioguided surgery, *n* (%)	
Salvage lymph node dissection	1 (5)
Salvage radiotherapy	1 (5)
Lutetium-PSMA	1 (5)
No tertiary treatment	17 (85)
Median time from last treatment to radioguided surgery, mo (IQR)	25.5 (11.3–46.7)
Number of lesions on PSMA PET/CT, *n* (%)	
One lesion	18 (90)
Two lesions	2 (10)
Localization of lesions on PSMA PET/CT, *n* (%)	
Pelvic (iliaca externa, interna, communis, obturator)	12 (60)
Prevesical	1 (5)
Pararectal and presacral	2 (10)
Local recurrence (vas deferens, pararectal local recurrence)	5 (25)

IQR = interquartile range; PSMA = prostate-specific membrane antigen; PET/CT = positron emission tomography/computed tomography.

At salvage surgery, the median patient age was 68 yr (IQR 66–72) and the median PSA was 1.02 ng/ml (IQR 0.46–2.43). One patient did not undergo intraperitoneal probe insertion as the surgical procedure was discontinued after unexpected intraoperative detection of peritonitis carcinomatosa, and this patient was therefore excluded from further analysis. A total of 21 PSMA-avid lesions were pursued in 19 patients (Fig. 2). Owing to the inferior spatial resolution of SPECT/CT, only 13 out of 21 (62%) suspicious lesions on PSMA PET/CT could be imaged using ^{99m}Tc-PSMA-I&S. Nevertheless, intraoperatively the DROP-IN probe was able to identify 19 out of 21 (90%) PSMA-avid PCa lesions detected on PSMA PET/CT. One suspicious LN could not be localized because of extensive intestinal adhesions, and one LN (2 mm on PSMA PET/CT) located in the pararectal fat could not be detected owing to a high background signal in the rectum as a result of hepatobiliary tracer clearance [25]. In these patients, subsequent PCa treatment will be left at the discretion of the treating urologist. No conversion to open surgery was necessary. The probe was used without malfunction and was inserted into and extracted from the intraperitoneal cavity uneventfully.

3.2. Diagnostic accuracy of preoperative PSMA PET/CT compared to histopathology

A total of 75 specimens were excised, of which 22 (29%) contained PCa at pathology (median metastasis size 8.4 mm, IQR 3.9–15.0; Fig. 2). PSMA PET/CT was able to detect

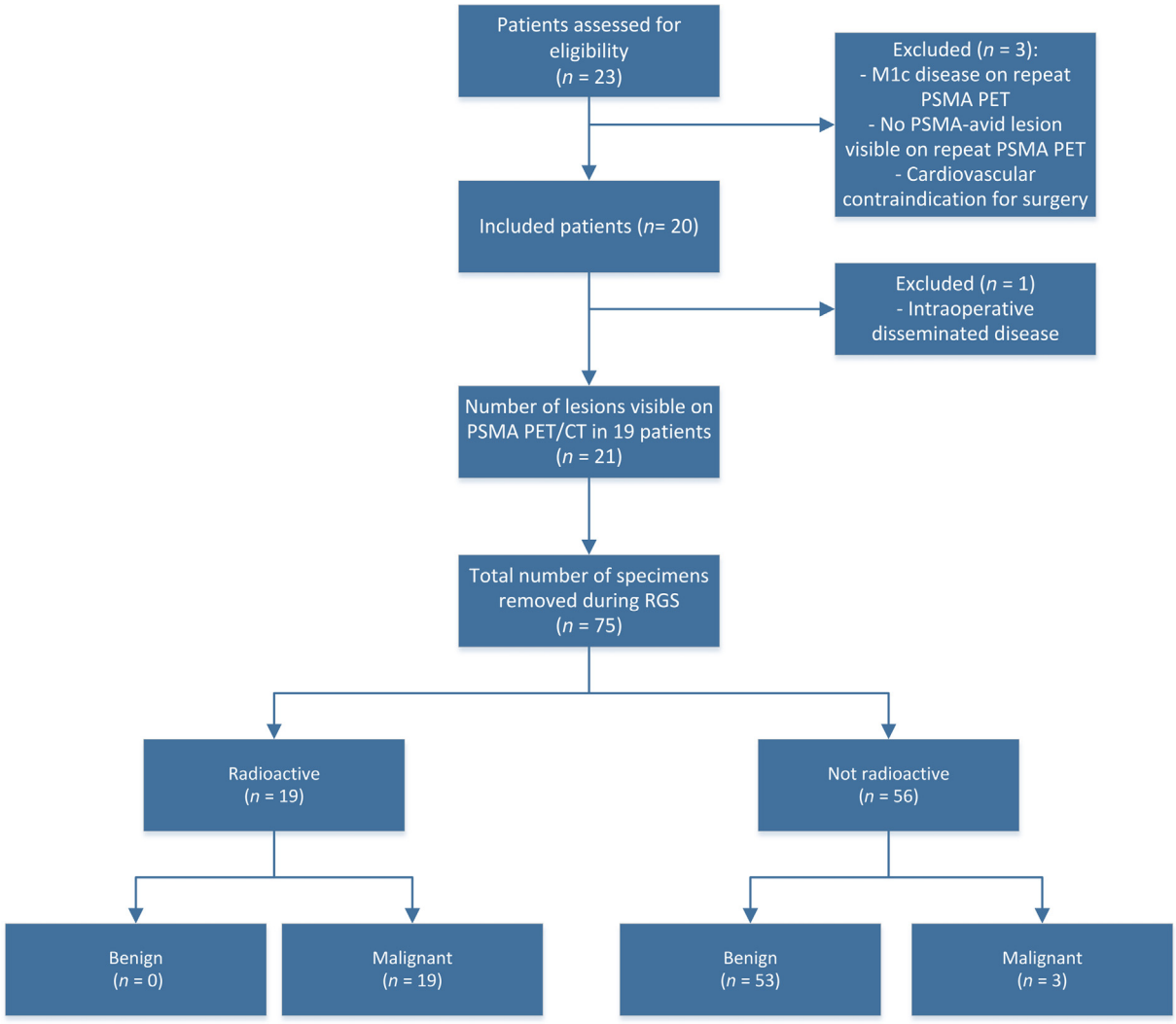

Fig. 2 – Flowchart of the study design showing the inclusion of patients up to histology results for resected specimens. M1c = distant metastases with/without bone involvement; PSMA = prostate-specific membrane antigen; PET/CT = positron emission tomography/computed tomography; RGS = radioguided surgery.

20 out of 22 (91%) PCa recurrences; the two undetected lesions (both <3 mm) can be attributed to the limited intrinsic spatial resolution of PET imaging. This resulted in PSMA PET/CT sensitivity of 91% (95% confidence interval [CI] 71–99%), specificity of 100%, PPV of 100%, and NPV of 96% (95% CI 88–99%).

3.3. Agreement between ^{99m}Tc-PSMA-I&S accumulation and histopathology

In vivo and ex vivo radioactivity measurements for resected specimens and surrounding vital structures are presented in Table 2 and Figure 3A–C. The median TBR was 2.3 (IQR 1.3–4.0) in vivo and 15.3 (IQR 10.2–30.9) ex vivo. The DROP-IN probe correctly classified all benign specimens as negative on ex vivo measurements. Three resected LNMs (2.0–2.6 mm) were falsely deemed negative both in vivo and ex vivo. PSMA expression in false-negative LNMs was confirmed via immunohistochemical PSMA staining. Overall, this resulted in sensitivity of 86% (95% CI 65–97%), specificity of 100%, PPV of 100%, and NPV of 95% (95% CI 86–98%).

3.4. Oncological outcomes and complications

Short-term oncological outcomes for 18 patients are presented in Figure 3D. A PSA reduction >50% was seen in 12 patients (67%) and cBR in four (22%). In the subgroup of patients who had previously undergone radical prostatectomy (n = 14), a PSA reduction >50% was observed in ten patients (71%) and cBR in four (29%). No cBR was achieved in patients who still had a prostate in situ after previous radiotherapy. During maximum follow-up of 15 mo, 4/18 patients (22%) remained BCR-free. Postsurgical PSMA PET/CT was performed in 12 patients with a detectable PSA level and confirmed successful resection of preoperatively defined lesions in 11 out of 12 patients. One postoperative PSMA PET/CT scan showed a remnant pararectal LN that was already seen on preoperative imaging and could not be detected during surgery owing to a high radioactivity signal from the rectum (see above).

No complications directly related to administration of ^{99m}Tc-PSMA-I&S or use of the DROP-IN gamma probe occurred (Table 2). Overall, five patients experienced a

Table 2 – Surgical characteristics, radioactivity, and complications of salvage ^{99m}Tc-PSMA radioguided surgery

Parameter	Result
Median surgical time, min (IQR)	128 (105–157)
Median hospital stay, d (IQR)	2 (2–2)
Median in vivo radioactivity in vital structures, counts/s (IQR)	
Intestines	230 (81–460)
Bladder	175 (163–191)
Ureter	77 (58–98)
Iliac artery	60 (45–77)
Iliac vein	48 (37–55)
Psoas muscle	50 (30–59)
Median in vivo radioactivity, counts/s (IQR)	
Prostate cancer–positive tissue	108 (77–167)
Local background	38 (32–83)
Median in vivo tumor-to-background ratio (IQR)	2.3 (1.3–4.0)
Median ex vivo radioactivity, counts/s (IQR)	
Prostate cancer–positive tissue	97 (71–197)
Prostate cancer–negative tissue	6 (4–7)
Median ex vivo tumor-to-background ratio (IQR)	15.3 (10.2–30.9)
Complications related to ^{99m}Tc-PSMA-I&S administration according to CTCAE, *n* (%)	
No complications	19 (100)
Complications related to surgery by Clavien-Dindo grade, *n* (%)	
No complications	13 (68.4)
Clavien-Dindo grade I	5 (26.3)
Paresthesia of the upper thighs	1
Lymphedema	1
Painful leg requiring analgesics	1
Abdominal pain requiring analgesics	1
Serosal injury to the bladder requiring an indwelling urinary catheter for 1 wk	1
Clavien-Dindo grade V	1 (5.3)

IQR = interquartile range; ^{99m}Tc-PSMA = ^{99m}technetium prostate-specific membrane antigen; ^{99m}Tc-PSMA-I&S = ^{99m}Tc-PSMA-Investigation & Surgery; CTCAE = Common Terminology Criteria for Adverse Events.

surgery-related Clavien-Dindo grade I complication, and one patient with a medical history of multiple myocardial infarctions and significant coronary sclerosis died of congestive heart failure 4 wk after surgery (Clavien-Dindo grade V). There were no clinical signs of postoperative thromboembolic events in this patient.

4. Discussion

This—to our knowledge—first prospective feasibility study indicates that the DROP-IN gamma probe allows translation of PSMA-RGS to minimally invasive robotic surgery for men with recurrent PCa. As a result, 19 out of 21 (90%) preoperatively identified lesions suspicious for recurrent PCa on staging PSMA PET/CT were successfully removed, which is in line with results obtained in open PSMA-RGS [5]. The sensitivity and specificity of PSMA-RGS was 86% and 100%, respectively. All false-negative LNs were smaller than 3 mm, which corresponds to the detection limit of the gamma probe in previous PSMA-RGS series [4,5,26]. No conversion to open surgery was necessary and we demonstrated that the surgical technique is safe. During short-term follow-up, no complications directly related to administration of ^{99m}Tc-PSMA-I&S or the use of intraoperative PSMA-targeted radioguidance occurred. However, careful patient selection remains warranted, as even minimally invasive, robot-assisted salvage surgery might lead to severe complications in patients with significant comorbidity. In this study, one patient with an extensive cardiovascular medical history died of congestive heart failure 4 wk after surgery.

Retrospective series on open PSMA-RGS have demonstrated its feasibility for guiding intraoperative resection of PCa lesions in both primary and recurrent disease [4,5,11,27]. In more than 90% of patients, suspicious lesions on preoperative PSMA PET/CT were also detected with the gamma probe. Radioguided SLND even seemed to be superior to conventional SLND in a small series [11]. However, with the increasing implementation of minimally invasive surgery, it is thought that the robot-assisted approach will play a major role in the future for perioperative detection and subsequent resection of residual or recurrent PCa in patients after treatment with curative intent. Two features of PSMA-RGS were crucial for identification of metastatic tissue during robot-assisted surgery in this study: (1) the maneuverability of the DROP-IN probe, which helped to minimize the influence of background signals in tissues with nonspecific tracer uptake, in line with results obtained using the DROP-IN probe for sentinel LN detection [14]; and (2) immediate confirmation via ex vivo gamma probe measurements of the radioactive status of specimens removed, which thereby guided RGS. However, particularly in patients with pararectal and paravesical lesions, high background radioactivity as a result of hepatic and renal tracer clearance complicated the intraoperative detection of adjacent suspicious lesions. This suggests that a learning curve is required for optimal execution of PSMA-RGS. Optimal use of the DROP-IN maneuverability to actively scan under multiple angles seems to be an important feature in this learning process.

Oncological outcomes for patients with recurrent PCa are heterogeneous. While some patients truly only have pelvic recurrent PCa amenable to surgical resection, others are already affected by (PET-undetectable) systemic disease at the time of salvage surgery. In our short-term follow-up data, we observed heterogeneity in the biochemical response to PSMA-RGS. Retrospective studies with long-term follow-up demonstrate that only a minority of patients experience a long-lasting response after salvage surgery [6,28]. Salvage surgery thus seems to represent a durable therapeutic strategy for a select group of patients and requires adequate patient selection to avoid overtreatment. In previous series, lower PSA and a lower number of PSMA-avid lesions located solely in the pelvis were associated with a lower risk of clinical recurrence after SLND [7].

Given the current lack of specific biomarkers, identification of suitable candidates for salvage surgery predominantly relies on technological advances in diagnostic procedures. Currently, PSMA PET/CT is the most sensitive imaging technique for detection of metastases at low PSA values [2]. Better selection of suitable candidates for PSMA-RGS may be achieved via advances in PSMA PET diagnostic accuracy—the use of PET tracers with lower positron energy [29,30], addition of early PSMA PET imaging to standard imaging protocols [31], and deep learning methods [32] may improve the sensitivity of PSMA PET/CT for detection of PSMA-avid lesions—and identification of (un)favorable biomarkers (currently under investigation in the BioPoP trial, NCT04324983). Our study revealed a minor discrepancy between preoperative and intraoperative detection of PCa recurrences. Future research aimed at

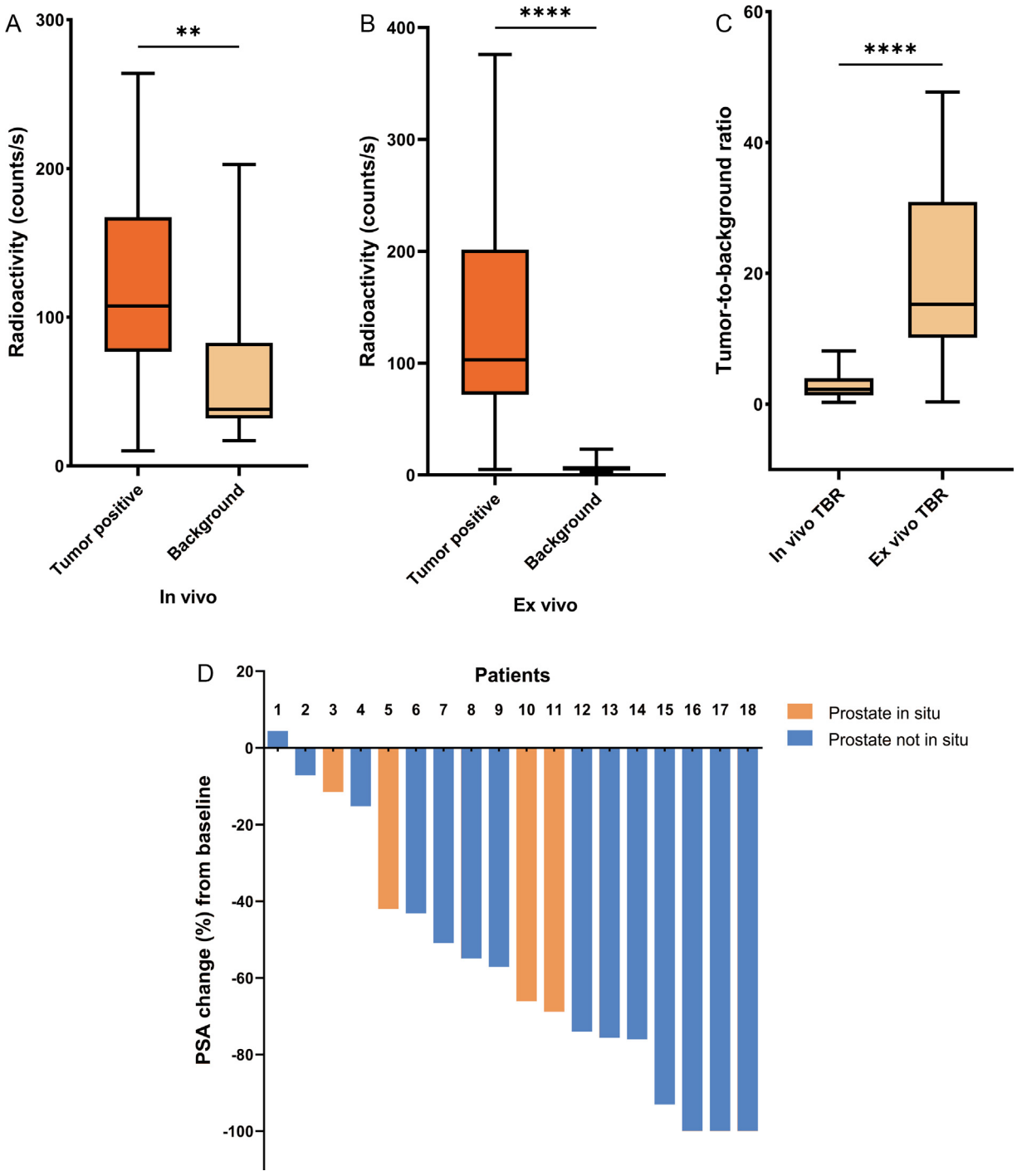

Fig. 3 – (A) In vivo and (B) ex vivo quantification of the radioactivity of tumor-positive specimens versus background using the DROP-IN gamma probe. Horizontal lines denote the median values with the interquartile range. (C) Comparison of in vivo and ex vivo tumor-to-background ratio (TBR). **** $p \leq 0.0001$, ** $p \leq 0.01$. (D) Waterfall plot demonstrating the prostate-specific antigen (PSA) response 6 wk after robot-assisted ^{99m}Tc-PSMA radioguided salvage surgery. Each bar represents the PSA change (%) between the last preoperative PSA value and the first postoperative PSA value.

improving the relation between preoperative and intraoperative imaging could also directly benefit the procedure. Such integration could be realized via, for example, PSMA PET/SPECT-guided positioning of the DROP-IN probe using a navigation workflow [33] and/or the use of hybrid (fluorescent and radioactive) PSMA-specific tracers that complement RGS with fluorescence imaging [34].

The present study is not devoid of limitations. This was a single-center study with a small sample size. In addition, only moderate follow-up is available in a very heterogeneous patient population that includes patients with local or nodal PCa recurrences. Hence, the oncological impact of robot-assisted PSMA-RGS remains to be assessed. Nevertheless, our preliminary results underscore the feasibility of robot-assisted PSMA-RGS using the DROP-IN gamma probe. The recent introduction of CE-marked DROP-IN gamma probes should facilitate the initiation of such extended studies.

5. Conclusions

Robot-assisted PSMA-targeted RGS using the DROP-IN probe appears to be feasible, safe, and valuable for intraoperative detection of nodal or local PSMA-avid PCa recurrences in clinical practice. To the best of our knowledge, this is the first prospective study to show the feasibility of minimally invasive, robot-assisted, salvage PSMA-RGS, and these results justify a phase 3 trial.

Author contributions: Hilda A. de Barros 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: van Oosterom, P.J. van Leeuwen, van der Poel, F. W.B. van Leeuwen.
Acquisition of data: de Barros, P.J. van Leeuwen, van der Poel.
Analysis and interpretation of data: de Barros, van Oosterom, Maurer, F.W. B. van Leeuwen, van der Poel, P.J. van Leeuwen.
Drafting of the manuscript: de Barros, van Oosterom, F.W.B. van Leeuwen, van der Poel, P.J. van Leeuwen.
Critical revision of the manuscript for important intellectual content: de Barros, van Oosterom, Donswijk, Hendrikx, Vis, Maurer, F.W.B. van Leeuwen, van der Poel, P.J. van Leeuwen.
Statistical analysis: de Barros, P.J. van Leeuwen.
Obtaining funding: F.W.B. van Leeuwen, van der Poel.
Administrative, technical, or material support: Hendrikx, Donswijk, de Barros, P.J. van Leeuwen.
Supervision: P.J. van Leeuwen, F.W.B. van Leeuwen, van der Poel.
Other: None.

Financial disclosures: Hilda A. de Barros 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: None.

Funding/Support and role of the sponsor: This study was partly supported by an NWO-TTW-VICI grant (TTW 16141) and Eurorad S.A. provided a prototype DROP-IN gamma probe. The sponsors played no direct role in the study.

Acknowledgments: The authors would like to thank the nuclear medicine staff and surgical staff of the Netherlands Cancer Institute. They would also like to thank Sue Young for providing the voiceover narration for the surgery in the accompanying video.

Peer Review Summary

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2022.03.002.

References

[1] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16. 10.1016/S0140-6736(20)30314-7.
[2] Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol 2020;77:403–17. 10.1016/j.eururo.2019.01.049.
[3] Morigi JJ, Stricker PD, Van Leeuwen PJ, et al. Prospective comparison of ^{18}F-fluoromethylcholine versus 68Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. J Nucl Med 2015;56:1185–90. 10.2967/jnumed.115.160382.
[4] Maurer T, Robu S, Schottelius M, et al. ^{99m}Technetium-based prostate-specific membrane antigen–radioguided surgery in recurrent prostate cancer. Eur Urol 2019;75:659–66. 10.1016/j.eururo.2018.03.013.
[5] Jilg CA, Reichel K, Stoykow C, et al. Results from extended lymphadenectomies with ^{111}InPSMA-617 for intraoperative detection of PSMA-PET/CT-positive nodal metastatic prostate cancer. EJNMMI Res 2020;10:17. 10.1186/s13550-020-0598-2.
[6] Bravi CA, Fossati N, Gandaglia G, et al. Long-term outcomes of salvage lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy: not as good as previously thought. Eur Urol 2020;78:661–9. 10.1016/j.eururo.2020.06.043.
[7] Fossati N, Suardi N, Gandaglia G, et al. Identifying the optimal candidate for salvage lymph node dissection for nodal recurrence of prostate cancer: results from a large, multi-institutional analysis. Eur Urol 2019;75:176–83. 10.1016/j.eururo.2018.09.009.
[8] Ploussard G, Gandaglia G, Borgmann H, et al. Salvage lymph node dissection for nodal recurrent prostate cancer: a systematic review. Eur Urol 2019;76:493–504. 10.1016/j.eururo.2018.10.041.
[9] Farolfi A, Ilhan H, Gafita A, et al. Mapping prostate cancer lesions before and after unsuccessful salvage lymph node dissection using repeat PSMA PET. J Nucl Med 2020;61:1037–42. 10.2967/jnumed.119.235374.
[10] Schottelius M, Wirtz M, Eiber M, Maurer T, Wester HJ. ^{111}InPSMA-I&T: expanding the spectrum of PSMA-I&T applications towards SPECT and radioguided surgery. EJNMMI Res 2015;5:68. 10.1186/s13550-015-0147-6.
[11] Knipper S, Ascalone L, Ziegler B, et al. Salvage surgery in patients with local recurrence after radical prostatectomy. Eur Urol 2020;79:537–44. 10.1016/j.eururo.2020.11.012.
[12] Bunschoten A, van den Berg NS, Valdés Olmos RA, Blokland JAK. Tracers applied in radioguided surgery. In: Herrmann K, Nieweg OE, Povoski SP, editors. Radioguided surgery: current applications and innovative directions in clinical practice. Cham, Switzerland: Springer International; 2016. p. 75–101.
[13] Horn T, Krönke M, Rauscher I, et al. Single lesion on prostate-specific membrane antigen-ligand positron emission tomography and low prostate-specific antigen are prognostic factors for a favorable biochemical response to prostate-specific membrane antigen-targeted radioguided surgery in recurrent prostate cancer. Eur Urol 2019;76:517–23. 10.1016/j.eururo.2019.03.045.
[14] Dell'Oglio P, Meershoek P, Maurer T, et al. A DROP-IN gamma probe for robot-assisted radioguided surgery of lymph nodes during radical prostatectomy. Eur Urol 2020;79:124–32. 10.1016/j.eururo.2020.10.031.
[15] Meershoek P, van Oosterom MN, Simon H, et al. Robot-assisted laparoscopic surgery using DROP-IN radioguidance: first-in-human translation. Eur J Nucl Med Mol Imaging 2019;46:49–53. 10.1007/s00259-018-4095-z.
[16] 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.
[17] Rigatti P, Suardi N, Briganti A, et al. Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by ^{11}C-choline positron emission tomography/computed tomography. Eur Urol 2011;60:935–43. 10.1016/j.eururo.2011.07. 060.
[18] Hinsenveld FJ, Wit EMK, van Leeuwen PJ, et al. Prostate-specific membrane antigen PET/CT combined with sentinel node biopsy for primary lymph node staging in prostate cancer. J Nucl Med 2020;61:540–5. 10.2967/jnumed.119.232199.
[19] Donswijk ML, Van Leeuwen PJ, Vegt E, et al. Clinical impact of PSMA PET/CT in primary prostate cancer compared to conventional nodal

and distant staging: a retrospective single center study. BMC Cancer 2020;20:723. 10.1186/s12885-020-07192-7.
[20] Aalbersberg EA, van Andel L, Geluk-Jonker MM, Beijnen JH, Stokkel MPM, Hendrikx JJMA. Automated synthesis and quality control of [^{99m}Tc]Tc-PSMA for radioguided surgery (in a [^{68}Ga]Ga-PSMA workflow). EJNMMI Radiopharm Chem 2020;5:10. 10.1186/s41181-020-00095-9.
[21] Montorsi F, Gandaglia G, Fossati N, et al. Robot-assisted salvage lymph node dissection for clinically recurrent prostate cancer. Eur Urol 2017;72:432–8. 10.1016/j.eururo.2016.08.051.
[22] Van Leeuwen FWB, Van Oosterom MN, Meershoek P, et al. Minimal-invasive robot-assisted image-guided resection of prostate-specific membrane antigen-positive lymph nodes in recurrent prostate cancer. Clin Nucl Med 2019;44:580–1. 10.1097/RLU.0000000000002600.
[23] Bravi CA, Fossati N, Gandaglia G, et al. Assessing the best surgical template at salvage pelvic lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy: when can bilateral dissection be omitted? Results from a multi-institutional series. Eur Urol 2020;78:7–10. 10.1016/j.eururo.2020.06.047.
[24] Assel M, Sjoberg D, Elders A, et al. Guidelines for reporting of statistics for clinical research in urology. Eur Urol 2019;75:358–67. 10.1016/j.eururo.2018.12.014.
[25] Robu S, Schottelius M, Eiber M, et al. Preclinical evaluation and first patient application of ^{99m}Tc-PSMA-I&S for SPECT imaging and radioguided surgery in prostate cancer. J Nucl Med 2017;58:235–42. 10.2967/jnumed.116.178939.
[26] van Leeuwen FWB, Winter A, van Der Poel HG, et al. Technologies for image-guided surgery for managing lymphatic metastases in prostate cancer. Nat Rev Urol 2019;16:159–71. 10.1038/s41585-018-0140-8.
[27] Rauscher I, Maurer T, Souvatzoglou M, et al. Intrapatient comparison of ^{111}In-PSMA I&T SPECT/CT and hybrid ^{68}Ga-HBED-CC PSMA PET in patients with early recurrent prostate cancer. Clin Nucl Med 2016;41:e397–402. 10.1097/RLU.0000000000001273.
[28] 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. 10.1016/j.eururo.2014.02.011.
[29] Giesel FL, Knorr K, Spohn F, et al. Detection efficacy of ^{18}F-PSMA-1007 PET/CT in 251 patients with biochemical recurrence of prostate cancer after radical prostatectomy. J Nucl Med 2019;60:362–8. 10.2967/jnumed.118.212233.
[30] Pattison DA, Debowski M, Gulhane B, et al. Prospective intra-individual blinded comparison of [^{18}F]PSMA-1007 and [^{68}Ga] Ga-PSMA-11 PET/CT imaging in patients with confirmed prostate cancer. Eur J Nucl Med Mol Imaging 2021;49:763–76. 10.1007/s00259-021-05520-y.
[31] Wen J, Zhu Y, Li L, Liu J, Chen Y, Chen R. Determination of optimal ^{68}Ga-PSMA PET/CT imaging time in prostate cancers by total-body dynamic PET/CT. Eur J Nucl Med Mol Imaging. In press. https://doi.org/10.1007/s00259-021-05659-8.
[32] Zhao Y, Gafita A, Vollnberg B, et al. Deep neural network for automatic characterization of lesions on ^{68}Ga-PSMA-11 PET/CT. Eur J Nucl Med Mol Imaging 2020;47:603–13. 10.1007/s00259-019-04606-y.
[33] Azargoshasb S, Houwing KHM, Roos PR, et al. Optical navigation of a DROP-IN gamma probe as a means to strengthen the connection between robot-assisted and radioguided surgery. J Nucl Med 2021;62:1314–7. 10.2967/jnumed.120.259796.
[34] Schottelius M, Wurzer A, Wissmiller K, et al. Synthesis and preclinical characterization of the PSMA-targeted hybrid tracer PSMA-I&F for nuclear and fluorescence imaging of prostate cancer. J Nucl Med 2019;60:71–8. 10.2967/jnumed.118.212720.