Robotic surgery using a DROP-IN beta probe – feasibility study with 68Ga-PSMA in prostate cancer specimens

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Abstract

Background: Recently, a flexible DROP-IN gamma-probe was introduced for robot-assisted radioguided surgery, using traditional low-energy SPECT-isotopes. This study explores the use of a novel DROP-IN beta-particle (DROP-IN b) detection probe to support the implementation of the large number of PET-tracers available during robot-assisted tumor-receptor-targeted resections.

Methods: Following engineering of the DROP-IN b probe, robotic implementation was investigated using surgical specimens. Seven prostate cancer patients with PSMA-PET positive tumors received an intraoperative injection of ~100 MBq 68 Ga-PSMA-11, followed by prostatectomy and extended pelvic lymph node dissection.

Results: The probe was able to identify the position of the tumor in the prostate specimens: S/B was > 5 when pathology confirmed that the tumor was located <1 mm below the specimen surface. PSMA-PET positive lymph nodes, as found in two patients, could be identified with the DROP-IN b probe (S/B>3).

Conclusions: This ex vivo study underlines the potential to use a DROP-IN b probe for intraoperative tumor identification on the prostate surface and confirmation of PSMA-PET positive lymph nodes.

Background

Radio Guided Surgery (RGS) enables a surgeon to identify preoperatively marked lesions during minimal-invasive surgical resections using a combination of radioactive tracers (i.e. radiopharmaceuticals) and intraoperative detection modalities (1). Unique for radioguided surgery is that non-invasive preoperative imaging can be used to visualize the tracer distribution and provide the surgeon with a 3D roadmap. Furthermore, the confirmation of tracer uptake reduces the probability of false negatives (i.e. lesions missed) during surgery (2) and thus supports the exploration of tumor-receptor targeted excisions. Applications of this approach include the localization of local lymphatic metastases or primary tumor margins (3).

Nowadays, a noticeable amount of commercially available radiopharmaceuticals is used for radioguided surgery (4). Radioguidance based on low-energy (< 150 keV) gamma-ray emitting radiopharmaceuticals is most commonly applied for sentinel lymph node (SN) biopsy procedures
using (indocyanine green-)\textsuperscript{99m}Tc-nanocolloid (5), radioguided occult lesion localization (ROLL) procedures using \textsuperscript{99m}Tc-labeled macro-aggregates (6), radioguided \textsuperscript{125}I-seed localization (RSL) procedures (7) and \textsuperscript{99m}Tc-PSMA-guided resection of lymph node metastases in prostate cancer patients (3). Here the most frequently used detection modality for intraoperative localization is the gamma-detection probe, which provides numerical and acoustical feedback proportional to the amount of radiopharmaceutical localized. Unique for this modality is that it supports relatively “deep” signal detection (i.e. tissue only provides marginal attenuation of gamma-ray emissions). Recently, the introduction of the DROP-IN gamma (DROP-IN\textsubscript{γ}) probe concept made radioguidance compatible with robotic surgery (8–11). However, for many clinical purposes (e.g. prostate cancer) PET radiopharmaceuticals are preferred. These PET isotopes induce both gamma-ray (i.e. 511 keV photon) and β + particle (i.e. positron) emissions, providing two detection routes. Since the intraoperative detection of 511 keV gamma-rays requires heavily collimated approaches, direct detection of β + particle emissions has been explored (4). As a result, a novel β-probe, applicable for both β- (i.e. electron) and β + radioguided surgery, was recently introduced (12–14). As they require a small active area and basically no collimation, such β-probes can be much smaller and lighter than γ-probes, especially when detector materials are chosen that are insensitive to the 511 keV γ-ray background (15). In this case it is possible to exploit the unique spatial resolution achievable with beta emission. In fact, tissue penetration of \textasciitilde 1 MeV β-particles is much less than that of γ-rays (\textasciitilde mm vs \textasciitilde cm) making it a unique “surface scanning” technique, not limited by the ‘shine-through’ of deeper lying tracer uptake (12), and thus a very effective methodology to detect tumors nearby healthy organs characterised by elevated physiological uptake of the radiopharmaceutical.

In an effort to explore the use of the widely available PET-radiopharmaceutical \textsuperscript{68}Ga-PSMA-11 (\textsuperscript{68}Ga-labeled Glu-urea-Lys (Ahx)-HBED-CC) for robot-assisted radioguided surgery purposes, we have developed a DROP-IN beta (DROP-IN\textsubscript{β}) probe that is compatible with the instruments of the da Vinci surgical robot (Intuitive Surgical Inc., USA; see Fig. 1). Following probe engineering, we have evaluated the feasibility of this technique \textit{ex vivo} in surgical specimens (i.e. prostate and lymph
nodes) of PSMA-PET positive patients that received a dose of ~ 100 MBq $^{68}$Ga-PSMA-11 during surgery.

**Methods**

**DROP-IN$\beta$ Probe Design**

The $\beta$-detection probe used in this study is based on a cylindrical scintillator (6 mm diameter and 3 mm height) made of mono-crystalline para-terphenyl (doped with 0.1% in mass of (E,E)-1,4-Diphenyl-1,3-butadiene) (see Fig. 1A) (15). Being a non-hygroscopic organic scintillator with high light yield ($\sim$140% of anthracene) and low density (1.23 g/cm$^3$), this material provides a high sensitivity to $\beta$ particles and elevated transparency to photons (e.g. the 511 keV $\gamma$ rays as induced by PET-radiopharmaceuticals). To improve light collection, the detector is surrounded with a 2 mm thick white diffusing Delrin ring and covered in front with two 4 µm layers of a reflective aluminized-Mylar film. The light tightness of this assembly is achieved adding an external black poly-vinyl-chloride ring, covered on the front by a 15 µm layer of aluminum. Light-collection efficiency was maximized using a 3 × 3 mm$^2$ silicon photomultiplier (SiPM C-series 30035, SensL Ltd.).

To allow for facile integration with the surgical robot as used in this study (daVinci Si and Xi, Intuitive Surgical Inc.), a housing was designed using computer-aided design software (SolidWorks, Dassault Systèmes SA) allowing to insert the beta probe in the trocar. The design, wherein the grip was placed over an angle of 45° degrees with respect to the longitudinal probe axis, was comparable to the previously optimized DROP-IN$_\gamma$ probe (11). Gripping was optimized for the ProGrasp Forceps (Intuitive Surgical Inc.), an instrument that is often used during a prostatectomy and lymph node dissection and provides great maneuverability for radioguidance. This housing was printed using acrylonitril-butadieen-styreen plastics and a Dimension Elite 3D printer (Stratasys Ltd.).

Finally, portable electronics, based on an Arduino Due (Arduino AG) equipped with a custom analog shield providing signal conditioning and trigger logic, were used for the readout (16). Sampling time was chosen as 1 second. At the end of the chain, the output in terms of counts per second (CPS) was displayed on a tablet, via wireless connection.

**Simulations of the DROP-IN$\beta$ Probe Design**
In order to optimize the design of the \( \beta \)-probe, a dedicated Monte Carlo simulation was performed in Geant4 (17). In the simulation, the whole detector was reconstructed, and all physical processes of interest were taken into account to effectively reproduce particle scattering, absorption, energy deposition and secondary particles generation.

**Patient Selection**

In total 7 patients with primary diagnosed locally (advanced) high-risk prostate cancer were included (see Table 1). Inclusion criteria consisted of a primary tumor \( \geq 2 \) cm (based on MRI) with a minimal average PSMA tracer uptake of 1.7 kBq/mL (based on PSMA PET/CT). These patients were mostly redirected to our clinical institute for prostate cancer treatment, while diagnostics was performed at the referring hospital. Therefore, based on local availability and preferences, diagnostic PSMA-PET/CT was performed with \(^{18}\)F labelled PSMA. This should however provide comparable uptake as \(^{68}\)Ga-PSMA-11 (18). \( \text{SUV}_{\text{mean}} \) measurements were performed using OsiriX medical imaging software (Pixmeo SARL). All patients were scheduled for a radical prostatectomy and extended pelvic lymph node dissection. In order to minimize radioactive exposure to both patient and medical personnel, a limited dose of \( \sim 100 \) MBq \(^{68}\)Ga-PSMA-11 for radioguidance was intravenously administered in the operating room (OR) while the surgeon was preparing the field. The study was approved by the local ethics committee (NL66218.031.18) and all patients provided a written informed consent.

**Probe Evaluation and Pathology**

At the end of the surgical procedure, roughly 2.5 hours after injection, the ex vivo prostate (and lymph node packages if positive on PSMA-PET) were rinsed with saline and scanned using the DROP-IN\( \beta \) probe. Rinsing of the ex vivo specimens was performed to remove possible urine contamination, since \(^{68}\)Ga-PSMA-11 is known to undergo renal clearance (19). The highest signal count rate and background count rate were acquired during scanning of the specimen surface. For further investigation, local pathology regulations allowed for cleaving of the prostate through the apex (1 cm), which allowed direct tumor assessment. Thereafter, all specimens were sent to pathology for assessment using standard histopathological procedures (20). Additionally, distances between the tumor and the inked specimen borders were measured at marked locations.
Results

Simulations of the DROP-IN Beta Probe Design

The developed Monte Carlo simulation was used to optimize the \( \beta \)-probe design. These simulations indicated that a cavity behind the \( \beta \)-particle detector would result in a lower noise-background: additional layers of material could in fact promote \( \beta + \) to \( \gamma \) conversion close to the detector, creating noise-background (Fig. 1B). This design concept yielded a light-weight probe construction (Fig. 1A), mostly transparent to 511 keV \( \gamma \)-induced noise.

PET Imaging Findings

The seven included patients displayed clear PSMA-PET positive primary tumors (see Table 1), with a \( \text{SUV}_{\text{mean}} \) in the tumor > 3. Additionally, two patients had PSMA-PET positive lesions, suspected for lymph node metastases (see Fig. 2 and Table 1).

Probe Evaluation in Relation to Pathology

Figure 3 illustrates usage of the DROP-IN beta probe in the OR. Table 2 shows a summary of the data collected. In general, probe background measurements without tissue were in the order of 0–2 CPS, while uncovered tumor areas, cleaved if necessary, provided count rates between 130–250 CPS. Due to its basal (i.e. default) PSMA expression levels, healthy prostate tissue yielded ~ 5–45 CPS. The primary tumor in patients 1, 3, 5, 6 and 7 provided a maximum \( \text{S/B} \) > 5, displaying a maximum count rate of ~ 247 CPS on the surface of the excised prostate specimen. As rated by pathology, only patients 1 and 7 harbored true positive resections margins (i.e. tumor cells were found in the inked borders of the prostate at pathology). However, in patients 3, 5 and 6, tumor was found within 1 mm of the resection margin, confirming a superficial tumor location. The maximum \( \text{S/B} \) measured for the prostate specimens in patients 2 and 4 was much lower: <2.5. In these cases, pathology indicated the tumor was located > 1.5 mm below the specimen margin, limiting the possibility of beta-tracing. Interestingly, patients 3 and 7 both harbored 2 positive lymph nodes on preoperative PSMA-PET. Using the DROP-IN\( \beta \) probe, these lymph nodes also showed elevated tracer uptake ex vivo with respect to the other lymph nodes: \( \text{S/B} \) > 3. At pathology, metastasis was found in 3 of these lymph nodes, suggesting a PSMA false positive signal for 1 lymph node. In this limited group of metastatic lymph nodes, this showed the probe was at least capable of detecting a 7 mm diameter metastasis.
(SUV\textsubscript{\text{mean}} of 5.6 on preoperative PSMA-PET, time between injection of measurement 3 h).

Discussion

With high signal to background (> 5) for tumors located < 1 mm from the resected surface, our study clearly indicates that the DROP-IN\textsubscript{\text{\beta}} probe concept has the potential to support robotic surface scanning of primary tumor margins. In fact, future optimization of the detection software algorithms might provide even more precise characterization of the possible lesion depth with respect to the surgical margin. Additionally, the DROP-IN\textsubscript{\text{\beta}} probe concept can support the identification of PSMA-positive lymph nodes (S/B > 3). Using the DROP-IN concept, the surgeon has full control of probe placement, yielding autonomy and great maneuverability during radioguidance (8–11).

Compared to the previously reported use of a DROP-IN\textsubscript{\text{\gamma}} probe in combination with the tracer $^{99m}\text{Tc}$-PSMA-I&S (10), the use of a DROP-IN\textsubscript{\text{\beta}} probe in combination with $^{68}$Ga-PSMA-11 possesses some unique advantages. Not only does this approach support the use of more widely available PET tracers, but the limited tissue penetration of $\beta$-particles (only a few mm’s) also allows for accurate surface scanning of the primary tumor margins (12). This effect is clearly observed in the current study, where beta radiation was severely attenuated when > 1.5 mm of (healthy) tissue was located between the surface of the prostate specimen and the pathological tumor margins. In this sense, $\beta$-tracing benefits from similar positive features as fluorescence imaging (21): i.e. no ‘shine-through’ of neighboring or deeper lying tracer-uptake and a superior spatial resolution (12, 22). These features are essential when the extracapsular spread of PSMA-overexpressing tumor lesions is pursued in a prostate with (significant) basal PSMA-expression (23). This means $\beta$-tracing could provide a superior means for margin assessment during e.g. nerve sparing surgery (24, 25). Alternative to investigated beta-radiation detection for tumor margin assessment, fully matured ex vivo technologies are available (e.g. NeuroSAFE (26)), while experimental imaging technologies are currently being explored (e.g. Cerenkov (27)). Future research, and in particular randomized trials, will have to show which technology is superior, or if different technologies can work in synergy.

Potential limitations of the proposed $^{68}$Ga-PSMA-11 guided surgery concept are the radiation dose for
the surgical staff and the contamination of the prostate margins by tracer containing urine. Current results suggest the DROP-IN$_{\beta}$ probe would even function with < 100 MBq doses of radiopharmaceutical. As stated previously, the accumulation of PSMA tracers in healthy organs and in particular urine may yield background signals that make intraoperative margin detection challenging (19). However, the direct detection of beta particles, as suggested in this paper, performed with a detector substantially transparent to gamma rays, should drastically reduce the impact of such a background. In fact, when detecting beta radiation, only particles originating from few millimeters around the detector can give a signal, and thus only a very small urine layer must be considered (28–29). Nonetheless, acknowledgement of this effect by radiochemists (30–31) and the reduced renal clearance of for example $^{18}$F-PSMA tracers (32–34) may in the future help to further minimize this potential limitation. In addition, the influence of renal clearance might also be overcome by using $\beta$-emitting isotopes that have a longer half-life, allowing the tumor resection to take place after all renal clearance of non-bound tracer is realized, e.g. using alternative PET isotopes such as $^{64}$Cu ($t_{1/2} = 12.7$ hours), or even theranostic isotopes such as $^{67}$Cu ($t_{1/2} = 2.5$ days), $^{90}$Y ($t_{1/2} = 2.66$ days) or $^{177}$Lu ($t_{1/2} = 6.6$ days) (35-37).

**Conclusion**

In this study we investigated a novel DROP-IN$_{\beta}$ probe for robot-assisted radioguided surgery based on beta-emitting radiopharmaceuticals, with the aim to exploit at the same time the unique spatial sensitivity and background rejection achievable with direct beta detection and the amount of available PET tracers. After optimization of the design, evaluation on surgical specimens of patients receiving $^{68}$Ga-PSMA-11 in the OR underlined the potential to use this probe for tumor detection on the prostate surface and possible confirmation of PSMA-PET positive lymph nodes. Further *in vivo* evaluation is required to strengthen these results.

**Abbreviations**

RGS
Radio Guided Surgery
PSMA
Declarations

**Ethics approval and consent to participate**

The study was approved by the local ethics committee (NL66218.031.18) and all patients provided a written informed consent.

**Consent for publication**

Not applicable

**Availability of data and material**

The Monte Carlo simulation datasets used during the current study are available from the corresponding author on reasonable request.

All data gained on patients samples during this study are included in this published article

**Competing interests**

F.C. and R.F are listed as inventors on an Italian patent application (RM2013A000053) entitled “Utilizzo di radiazione beta- per la identificazione intraoperatoria di residui tumorali e la corrispondente sonda di rivelazione” dealing with the implementation of an intra-operative beta-probe for radio-guided surgery according to the results presented in this paper. The same authors are also inventors in the PCT patent application (PCT/IT2014/000025) entitled “Intraoperative detection of tumor residues using beta- radiation and corresponding probes” covering the method and the instruments described in this paper.

FWB van Leeuwen is a consultant for Hamamatsu Photonics and is Chief Innovation Officer at ORSI Academy. The authors would like to thank Sven van Leeuwen (IMI-Lab, Department of Radiology, LUMC, the Netherlands) and Michael Boonekamp (Department of Technical Services subsection Development, LUMC, the Netherlands) for their assistance with the illustrations and prototyping of the probe housing. This study was supported in part by an NWO-TTW-VICI grant (no. TTW 16141).

No other potential conflicts of interest relevant to this article exist.

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Authors’ contributions

C., M. F., C. M. T. and R M developed and tuned the Monte Carlo simulation, and analysed its output
D S, R. F., R. M., E. S. C. and Silvio M. took care of the hardware development of the detector including
its testing
N. van O., J. o H., F. v B., H. G. v d P., R. A. V. O., P. J. v. L. and F. W.B. v. L. organized and performed the
medical part of the experimentation, from the nuclear medicine and surgical point of view.

References

1. Herrmann K, Nieweg OE, Povoski SP. Radioguided surgery: current applications and
innovative directions in clinical practice. 2016. 503 p.

2. Meershoek P, Buckle T, van Oosterom MN, KleinJan GH, van der Poel HG, van
Leeuwen F. Can fluorescence-guided surgery help identify all lesions in unknown
locations or is the integrated use of a roadmap created by preoperative imaging
mandatory? A blinded study in prostate cancer patients. J Nucl Med. 2019, ahead of
print;

3. Horn T, Krönke M, Rauscher I, Haller B, Robu S, Wester HJ, 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 Oct 1;76(4):517–23.

4. Van Oosterom MN, Rietbergen DDD, Welling MM, Van Der Poel HG, Maurer T, Van
Leeuwen FWB. Recent advances in nuclear and hybrid detection modalities for image-
guided surgery. Vol. 16, Expert Review of Medical Devices. Taylor and Francis Ltd;
2019. p. 711–34.

5. KleinJan GH, van Werkhoven E, van den Berg NS, Karakullukcu MB, Zijlmans HJMAA,
vander Hage JA, et al. The best of both worlds: a hybrid approach for optimal pre-
and intraoperative identification of sentinel lymph nodes. Eur J Nucl Med Mol Imaging. 2018 Oct 1;45(11):1915–25.

6. Bowles H, Sánchez N, Tapias A, Paredes P, Campos F, Bluemel C, et al. Radioguided surgery and the GOSTT concept: From pre-operative image and intraoperative navigation to image-assisted excision. Rev Española Med Nucl e Imagen Mol (English Ed. 2017 May;36(3):175–84.

7. Pouw B, De W-VD Veen, Stokkel LJ, Loo MPM, Vrancken Peeters CE, Valdés Olmos MJTFD RA. Heading toward radioactive seed localization in non-palpable breast cancer surgery? A meta-analysis. Vol. 111, Journal of Surgical Oncology. John Wiley and Sons Inc.; 2015. p. 185–91.

8. Fuerst B, Sprung J, Pinto F, Frisch B, Wendler T, Simon H, et al. First Robotic SPECT for Minimally Invasive Sentinel Lymph Node Mapping. IEEE Trans Med Imaging. 2016 Mar 1;35(3):830–8.

9. Meershoek P, van Oosterom MN, Simon H, Mengus L, Maurer T, van Leeuwen PJ, et al. Robot-assisted laparoscopic surgery using DROP-IN radioguidance: first-in-human translation. Eur J Nucl Med Mol Imaging. 2019 Jan;46(1):49–53.

10. Van Leeuwen FWB, Van Oosterom MN, Meershoek P, Van Leeuwen PJ, Berliner C, Van Der Poel HG, 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 Jul;1(7):580–1. 44(.

11. van Oosterom MN, Simon H, Mengus L, Welling MM, Van der Poel HG, van den Berg NS, et al. Revolutionizing (robot-assisted) laparoscopic gamma tracing using a drop-in gamma probe technology. Am J Nucl Med Mol Imaging. 2016.

12. Camillocci ES, Baroni G, Bellini F, Bocci V, Collamati F, Cremonesi M, et al. A novel radioguided surgery technique exploiting β – decays. Sci Rep. 2015 May;20(1):4401.
13. Solfaroli Camillocci E, Schiariti M, Bocci V, Carollo A, Chiodi G, Colandrea M, et al. First ex vivo validation of a radioguided surgery technique with $\beta$-radiation. Phys Medica. 2016;32(9).

14. Mancini-Terracciano C, Donnarumma R, Bencivenga G, Bocci V, Cartoni A, Collamati F, et al. Feasibility of beta-particle radioguided surgery for a variety of “nuclear medicine” radionuclides. Phys Medica. 2017;43.

15. Angelone M, Battistoni G, Bellini F, Bocci V, Collamati F, De Lucia E, et al. Properties of para-terphenyl as a detector for $\alpha$, $\beta$ and $\gamma$ radiation. IEEE Trans Nucl Sci. 2014;61(3):1483–7.

16. Bocci V, Chiodi G, Iacoangeli F, Nuccetelli M, Recchia L. The ardisipm a compact trasportable software/hardware data acquisition system for sipm detector. Paper presented at: 2014 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2014.

17. Allison J, Amako K, Apostolakis J, Arce P, Asai M, Aso T, et al. Recent developments in GEANT4. Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip. 2016 Nov 1;835:186–225.

18. Ferreira G, Iravani A, Hofman MS, Hicks RJ. Intra-individual comparison of 68 Ga-PSMA-11 and 18F-DCFPyL normal-organ biodistribution. Cancer Imaging. 2019 Dec 15; 19(1):23.

19. Van Leeuwen FWB, Van Der Poel HG. Surgical guidance in prostate cancer: “from molecule to man” translations. Clin Cancer Res. 2016 Mar 15;22(6):1304–6.

20. Wang M, Tulman DB, Sholl AB, Kimbrell HZ, Mandava SH, Elfer KN, et al. Gigapixel surface imaging of radical prostatectomy specimens for comprehensive detection of cancer-positive surgical margins using structured illumination microscopy. Sci Rep.
van Oosterom MN, van der Poel HG, van Leeuwen FWB, Meershoek P, Welling MM, Pinto F, et al. Extending the Hybrid Surgical Guidance Concept With Freehand Fluorescence Tomography. IEEE Trans Med Imaging. 2020;39(1):226–35.

Bluemel C, Rubello D, Colletti PM, de Bree R, Herrmann K. Sentinel lymph node biopsy in oral and oropharyngeal squamous cell carcinoma: current status and unresolved challenges. Vol. 42, European Journal of Nuclear Medicine and Molecular Imaging. Springer Berlin; 2015. p. 1469–80.

Fendler WP, Calais J, Allen-Auerbach M, Bluemel C, Eberhardt N, Emmett L, et al. 68Ga-PSMA-11 PET/CT interobserver agreement for prostate cancer assessments: An international multicenter prospective study. J Nucl Med. 2017 Oct 1;58(10):1617–23.

van Leeuwen FWB, Winter A, van Der Poel HG, Eiber M, Suardi N, Graefen M, et al. Technologies for image-guided surgery for managing lymphatic metastases in prostate cancer. Vol. 16, Nature Reviews Urology. Nature Publishing Group; 2019. p. 159–71.

Yossepowitch O, Briganti A, Eastham JA, Epstein J, Graefen M, Montironi R, et al. Positive surgical margins after radical prostatectomy: A systematic review and contemporary update. Eur Urol. 2014;Vol. 65:303–13.

Beyer B, Schlommm T, Tennstedt P, Boehm K, Adam M, Schiffmann J, et al. A feasible and time-efficient adaptation of NeuroSAFE for da Vinci robot-assisted radical prostatectomy. Eur Urol. 2014;66(1):138–44.

Fragoso Costa P, Darr C, Binse I, Grootendorst, Maarten & ken, & Hadaschik B, Harke, Nina. (2019). Early Results of Intraoperative68Ga-PSMA Cerenkov Luminescence Imaging in Radical Prostatectomy. J Nucl Med. 2019;60:658.

Collamati F, Maccora D, Alfieri S, Bocci V, Cartoni A, Collarino A, et al. Radioguided
surgery with β - radiation in pancreatic Neuroendocrine Tumors: a feasibility study. Sci Rep. 2020 Dec 1;10(1):1-10.

29. Morganti S, et al. Tumor-non-tumordiscriminatiorbyaβ-
detectorforRadioGuidedSurgeryonex-vivo neuroendocrine tumors samples, Physica Medica, accepted for publication, 2020.

30. Hensbergen AW, Buckle T, van Willigen DM, Schottelius M, Welling MM, van der Wijk FA, et al. Hybrid Tracers Based on Cyanine Backbones Targeting Prostate-Specific Membrane Antigen – Tuning Pharmacokinetic Properties and Exploring Dye–Protein Interaction. J Nucl Med. 2019 Sep 3;jnumed.119.233064.

31. Hensbergen AW, van Willigen DM, van Beurden F, van Leeuwen PJ, Buckle T, Schottelius M, et al. Image-Guided Surgery: Are We Getting the Most Out of Small-Molecule Prostate-Specific-Membrane-Antigen-Targeted Tracers? Bioconjug Chem. 2020 Jan 6;acs.bioconjchem.9b00758.

32. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging. 2017 Apr 1;44(4):678-88.

33. Rahbar K, Weckesser M, Ahmadzadehfar H, Schäfers M, Stegger L, Bögemann M. Advantage of 18F-PSMA-1007 over 68 Ga-PSMA-11 PET imaging for differentiation of local recurrence vs. urinary tracer excretion. Eur J Nucl Med Mol Imaging. 2018 Jun 1;45(6):1076–7.

34. Collamati F, Bellini F, Bocci V, De Lucia E, Ferri V, Fioroni F, et al. Time evolution of DOTATOC uptake in neuroendocrine tumors in view of a possible application of radioguided surgery with b2 decay. J Nucl Med. 2015;56(10):1501–6.

35. Zia NA, Cullinane C, Van Zuylekom JK, Waldeck K, McInnes LE, Buncic G, et al. A
Bivalent Inhibitor of Prostate Specific Membrane Antigen Radiolabeled with Copper-64 with High Tumor Uptake and Retention. Angew Chemie Int Ed. 2019 Oct 14, 58(42):14991-4.

36. Baur B, Solbach C, Andreolli E, Winter G, Machulla HJ, Reske SN. Synthesis, radiolabelling and in vitro characterization of the gallium-68-, yttrium-90- and lutetium-177-labelled PSMA Ligand, CHX-A"-DTPA-DUPA-Pep. Pharmaceuticals. 2014 Apr;29(5):517–29. 7.

37. Collamati F, Moretti R, Alunni-Solestizi L, Bocci V, Cartoni A, Collarino A, et al. Characterisation of a β detector on positron emitters for medical applications. Phys Medica. 2019 Nov 1;67:85–90.

Tables

**Table 1. Preoperative patient characteristics**

| Pt # | Age | PSA (ng/mL) | Gleason score | Prostate volume on MRI (cc) | Tumor stage | SUVmean in primary tumor focus on PET | SUVmean pos LNs on PET |
|------|-----|-------------|---------------|----------------------------|-------------|--------------------------------------|-----------------------|
| 1    | 71  | 4.4         | 4+4=8         | 30                         | cT2aN0M0    | 13.8                                 | N.A.                  |
| 2    | 57  | 5           | 4+4=8         | 55                         | cT1cN0M0    | 3.3                                  | N.A.                  |
| 3    | 73  | 8.3         | 4+5=9         | 76                         | cT3aN1M0    | 17.8                                 | - 5.6 (ExR)           |
|      |     |             |               |                            |             |                                      | - 3.1 (ObR)           |
| 4    | 66  | 2.7         | 4+4=8         | 47                         | cT3bN0M0    | 4.1                                  | N.A.                  |
| 5    | 63  | 6.4         | 4+5=9         | 41                         | cT2cN0M0    | 11.7                                 | N.A.                  |
| 6    | 55  | 9.3         | 4+4=8         | 28                         | cT2bN0M1    | 14.7                                 | N.A.                  |
| 7    | 48  | 4.4         | 4+5=9         | 62                         | cT3bN1M0    | 13.3                                 | - 4.8 (ObL)           |
|      |     |             |               |                            |             |                                      | - 3.5 (ExR)           |

Pt # = patient number, N.A. = not applicable, LNs = lymph nodes, ExR = external iliac Right, ObR = Obturator right, ObL = Obturator left.

**Table 2. Probe evaluation in relation to pathology**
| Pt # | Injected activity (MBq) | Total activity left at time of scanning (MBq) | S/B prostate tumor* | S/B PET positive LNs | Extraprostatic tumor spread | Positive resection margins | Shortest tumor-border distance (mm) |
|------|------------------------|-----------------------------------------------|--------------------|---------------------|-----------------------------|--------------------------|----------------------------------|
| 1    | 68                     | 11                                           | 107/14 = 7.6       | N.A.                | No                          | Yes                      | 0                                |
| 2    | 88                     | 15                                           | 40/16 = 2.5        | N.A.                | No                          | No                       | >3                               |
| 3    | 76                     | 13                                           | 108/15 = 7.2       | - 50/8 = 6.3 (ExR)  | Yes                         | No                       | <1                               |
| 4    | 143                    | 48                                           | 88/40 = 2.2        | N.A.                | Yes                         | No                       | >1.5                             |
| 5    | 65                     | 14                                           | 108/15 = 7.2       | N.A.                | No                          | No                       | <0.5                             |
| 6    | 62                     | 18                                           | 247/45 = 5.5       | N.A.                | Yes                         | No                       | <0.5                             |
| 7    | 23                     | 7                                            | 35/7 = 5.0         | - 20/3 = 6.7 (ObL)  | Yes                         | Yes                      | 0                                |

*As measured on the surface of the resected specimen.

Pt # = patient number, S/B = signal to background, N.A. = not applicable, ExR = external iliac right, ObR = obturator right, ObL = obturator left.

Figures
Figure 1

DROP-INβ probe design. (A) Schematic representation of the probe components. (B) Example of one of the Monte Carlo simulations optimizing β-particle detection and γ-photon transparency. (C) Overview of the probe application setup, showing its high maneuverability.
Preoperative tumor mapping using PSMA-PET. (A) Example of total body PET maximum intensity projection with tumor focus in prostate (blue-upwards arrow) and lymph node metastasis (green-downwards arrow). (B) PET/CT slice of the same patient illustrating a clear tumor focus within the prostate (blue arrow; SUVmean= 17.8). (C) PET/CT slice of the same patient displaying a lymph node metastasis (green arrow; SUVmean= 5.6).
DROP-INβ probe evaluation in relation to pathology. (A) Overview of the robot-assisted OR setup. (B) Example of beta-tracing with the DROP-INβ probe on the surface of a resected prostate sample. (C) Histopathology slide displaying tumor spread within the prostate with respect to the specimen surface. (D) Example of beta-tracing on the surface of a resected lymph node package. (E) Histopathology slide showing tumor spread within a PSMA-PET positive lymph node.