Robotic surgery using a DROP-IN beta probe – feasibility study with ^{68}Ga -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-)^{99m}Tc-nanocolloid (5), radioguided occult lesion localization (ROLL) procedures using ^{99m}Tc-labeled macro-aggregates (6), radioguided ¹²⁵I-seed localization (RSL) procedures (7) and ^{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_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 ~ 1 MeV β -particles is much less than that of γ -rays ($\sim$ mm vs $\sim$ 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 ^{68}Ga -PSMA-11 (^{68}Ga -labeled Glu-urea-Lys (Ahx)-HBED-CC) for robot-assisted radioguided surgery purposes, we have developed a DROP-IN β (DROP-IN $_{\beta}$) 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 *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 β -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 β particles and elevated transparency to photons (e.g. the 511 keV γ 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 $3 \times 3\text{ mm}^2$ 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-butadiene-styrene 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_β Probe Design

In order to optimize the design of the β -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 ≥ 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). SUV_{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 ~ 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_β 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 β -probe design. These simulations indicated that a cavity behind the β -particle detector would result in a lower noise-background: additional layers of material could in fact promote β + to γ 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 γ -induced noise.

PET Imaging Findings

The seven included patients displayed clear PSMA-PET positive primary tumors (see Table 1), with a SUV_{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 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 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: 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_{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 $_{\beta}$ 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 $_{\beta}$ 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_γ probe in combination with the tracer ^{99m}Tc-PSMA-I&S (10), the use of a DROP-IN_β probe in combination with ⁹⁸Ga-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 β-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, β-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 β-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 ⁶⁸Ga-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_β 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 ¹⁸F-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 β-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 ⁶⁴Cu (t_{1/2} = 12.7 hours), or even theranostic isotopes such as ⁶⁷Cu (t_{1/2} = 2.5 days), ⁹⁰Y (t_{1/2} = 2.66 days) or ¹⁷⁷Lu (t_{1/2} = 6.6 days) (35–37).

Conclusion

In this study we investigated a novel DROP-IN_β 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

Prostatic Specific Membrane Antigen

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.

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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.

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Tables

Table 1. Preoperative patient characteristics

t	Age	PSA (ng/mL)	Gleason score	Prostate volume MRI (cc)	on	Tumor stage	SUV _{mean} in primary tumor focus on PET	SUV _{mean} positive LNs on PET
	71	4.4	4+4=8	30		cT2aN0M0	13.8	N.A.
	57	5	4+4=8	55		cT1cN0M0	3.3	N.A.
	73	8.3	4+5=9	76		cT3aN1M0	17.8	- 5.6 (ExR) - 3.1 (ObR)
	66	2.7	4+4=8	47		cT3bN0M0	4.1	N.A.
	63	6.4	4+5=9	41		cT2cN0M0	11.7	N.A.
	55	9.3	4+4=8	28		cT2bN0M1	14.7	N.A.
	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

<i>Probe evaluation</i>				<i>Pathologic evaluation</i>				
ected ivity Bq)	Total activity left at time of scanning (MBq)	S/B prostate tumor*	S/B PET positive LNs	Extra- capsular tumor spread	Positive resection margins	Shortest- Tumor- border distance (mm)	Tumor in PET Positive LNs	Tumor stage
	11	107/14 = 7.6	N.A.	Yes	Yes	0	N.A.	pT3aN0 R1
	15	40/16 = 2.5	N.A.	No	No	>3	N.A.	pT2N0 R0
	13	108/15 = 7.2	- 50/8 = 6.3 (ExR) - 34/10 = 3.4 (ObR)	Yes	No	<1	- yes (ExR) - no (ObR)	pT3bN1 R0
3	48	88/40= 2.2	N.A.	Yes	No	>1.5	N.A.	pT3bN0 R0
	14	108/15= 7.2	N.A.	No	No	<0.5	N.A.	pT2N0 R0
	18	247/45= 5.5	N.A.	Yes	No	<0.5	N.A.	pT3aN1 R0
	7	35/7 = 5.0	- 20/3 = 6.7 (ObL) - 9/3 = 3.0 (ExR)	Yes	Yes	0	- yes(ObL) - yes (ExR)	pT3bN1 R1

*Pt # = patient number, S/B = signal to background, N.A. = not applicable, ExR = external iliac right, ObR = obturator right, ObL = obturator left. *As measured on the surface of the resected specimen.*

Figures

Figure 1

DROP-IN β 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.

Figure 2

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).

Figure 3

DROP-IN β probe evaluation in relation to pathology. (A) Overview of the robot-assisted OR setup. (B) Example of beta-tracing with the DROP-IN β 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.