

Original Article

Revolutionizing (robot-assisted) laparoscopic gamma tracing using a drop-in gamma probe technology

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Abstract: In complex (robot-assisted) laparoscopic radioguided surgery procedures, or when low activity lesions are located nearby a high activity background, the limited maneuverability of a laparoscopic gamma probe (LGP; 4 degrees of freedom (DOF)) may hinder lesion identification. We investigated a drop-in gamma probe (DIGP) technology to be inserted via a trocar, after which the laparoscopic surgical tool at hand can pick it up and maneuver it. Phantom experiments showed that distinguishing a low objective from a high background source (1:100 ratio) was only possible with the detector faced $>90^\circ$ from the high background source. Signal-low-objective-to-background ratios of 3.77, 2.01 and 1.84 were found for detector angles of 90° , 135° and 180° , respectively, whereas detector angles of 0° and 45° were unable to distinguish the sources. This underlines the critical role probe positioning plays. We then focused on engineering of the gripping part for optimal DIGP pick-up with a conventional laparoscopic forceps (4 DOF) or a robotic forceps (6 DOF). DIGPs with 0° , 45° , 90° , and 135° -grip orientations were designed, and their maneuverability- and scanning direction were evaluated and compared to a conventional LGP. The maneuverability- and scanning direction of the DIGP was found highest when using the robotic forceps, with the largest effective scanning direction range obtained with the 90° -grip design (0 - 180° versus 0 - 111° , 0 - 140° , and 37 - 180° for 0° , 45° and 135° -grip designs, respectively). For the laparoscopic forceps, the scan direction directly translated from the angle of the grip design with the advantage that the 135° -gripped DIGP could be faced backwards (not possible with the conventional LGP). In the ex vivo clinical setup, the surgeon rated DIGP pick-up most convenient for the 45° -grip design. Concluding, the DIGP technology was successfully introduced. Optimization of the grip design and grasping angle of the DIGP increased its utility for (robot-assisted) laparoscopic gamma tracing.

Keywords: Radioguided surgery, gamma probe, urology, interventional molecular imaging, laparoscopic surgery, robot-assisted surgery, sentinel lymph node biopsy

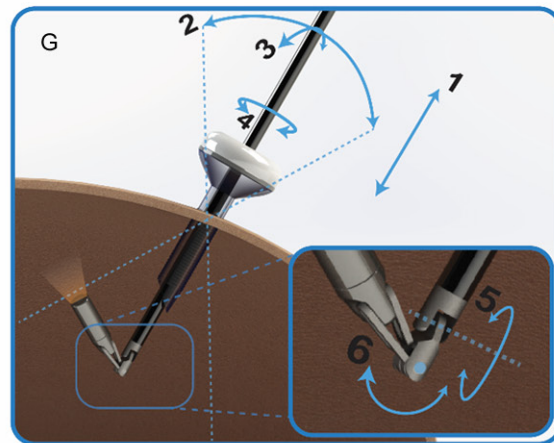
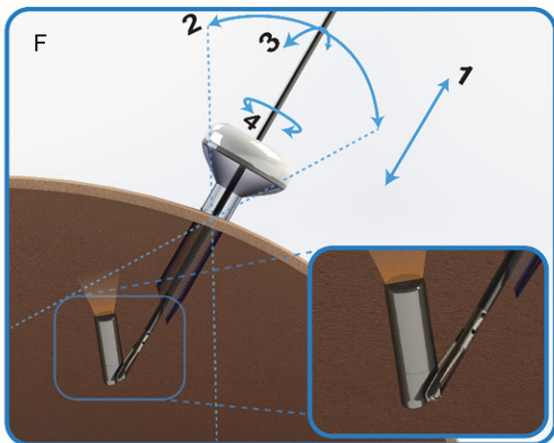
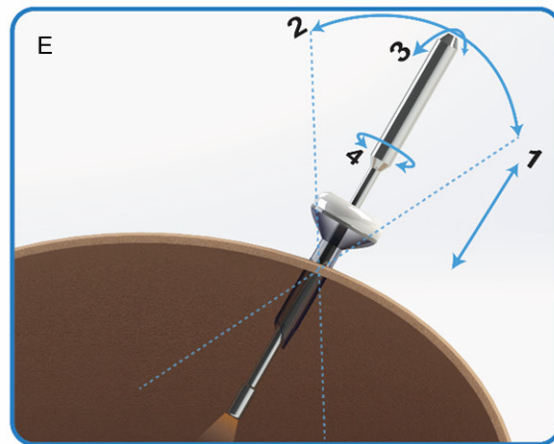
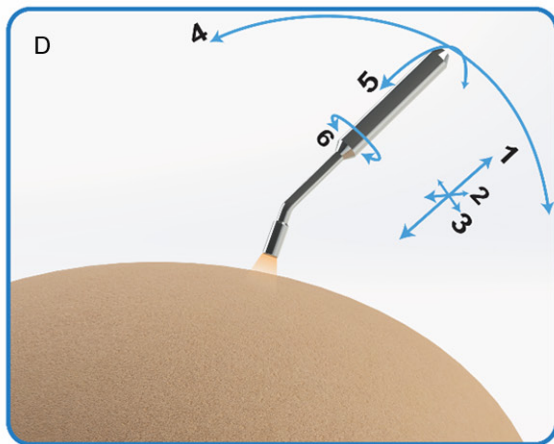
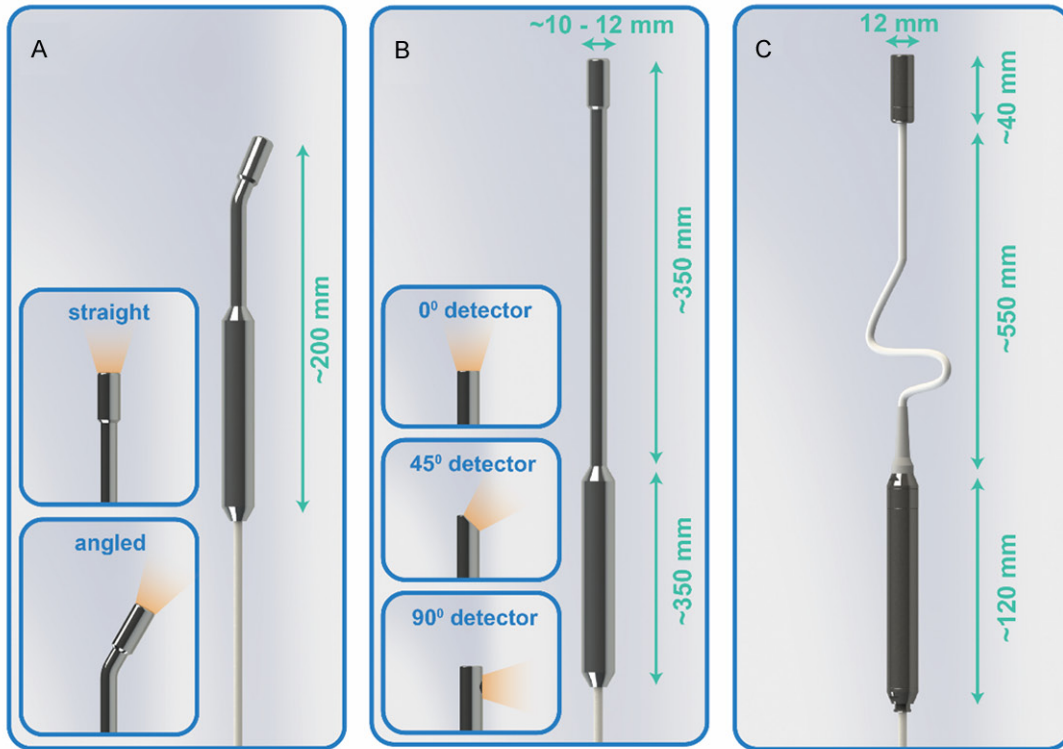
Introduction

A core development in healthcare has been the integration of medical imaging technologies into diagnostic- and therapeutic workflows. Here, the (detailed) information gathered with these imaging technologies can provide preoperative insight into both anatomical (e.g. using computed tomography (CT), magnetic resonance (MR) imaging, or ultrasound (US)) and functional (e.g. using single photon emission computed tomography (SPECT), positron emission tomography (PET), (lympho)scintigraphy, or optical imaging (OI)) patient aspects. Aside from their preoperative use, some imaging

modalities can also be used in an interventional setting (e.g. CT, US, gamma tracing and -imaging, or OI) where they can provide the surgeon with (real-time) information during the procedure.

To date, one of the key surgical guidance tools is the handheld gamma probe. The gamma probe is frequently used in radioguided surgery procedures where it provides the surgeon with feedback with respect to the localization of radioactive isotopes in the surgical field [1, 2]. Using the handheld gamma probe, the intraoperative situation can be directly correlated to preoperative imaging findings (SPECT or (lym-

Drop-in gamma probe evaluation



Drop-in gamma probe evaluation

Figure 1. Degrees of freedom of the various gamma probe setups. The degrees of freedom (DOF) are denoted as numbers for the four different setups (D-G). A. Gamma probe for open surgery (rough dimensions indicated). B. Laparoscopic gamma probe with different detector angles available (rough dimensions indicated). C. Drop-in gamma probe (rough dimensions indicated). D. The open surgery gamma probe can be directly placed in the wound area by the surgeon. The probe has six unrestricted DOF (three translational and three rotational). E. The laparoscopic gamma probe is inserted via a trocar and can then be directed to the area of interest. The probe has four DOF (one translational and three rotational), which are restricted by the movements possible with the trocar. F. The drop-in gamma probe in combination with a non-articulated laparoscopic forceps. After insertion through the trocar, the drop-in gamma probe is picked-up and can be directed to the area of interest. After pick-up, possible over different angles, the probe has four DOF (one translational and three rotational), which are restricted by the movements the non-articulated forceps can make in combination with the trocar through which it was inserted. G. The drop-in gamma probe in combination with an articulated forceps. After insertion through the trocar, the drop-in probe is picked-up and can be directed to the area of interest. After pick-up, possible over different angles, the probe has six DOF (one translational and five rotational) which are restricted by the movements that the articulated forceps can make in combination with the trocar through which this articulated forceps was inserted.

pho) scintigraphy) [3, 4]. Gamma probes have been mainly used for procedures such as sentinel node biopsy (isotope: ^{99m}Tc), radioguided intraoperative margin evaluation (isotopes: ^{99m}Tc and ^{111}In), radioguided seed localization (isotope: ^{125}I) and radioguided occult lesion localization (isotope: ^{99m}Tc) [1, 5-11].

Using different detector materials and different collimator geometries, gamma probes can be tailored to the procedure specific needs like field of view, sensitivity and energy window [1, 2]. The two main types of gamma probe detectors are: 1) scintillation detectors (e.g. (thallium-doped) sodium iodine (NaI(Tl)), (thallium-doped) cesium iodine (CsI(Tl)) or cerium-doped lutetium oxyorthosilicate (LSO)); and 2) semiconductor detectors (e.g. cadmium telluride (CdTe) or cadmium zinc telluride (CdZnTe)). Both types of detectors convert incoming gamma photons into an analog voltage signal that is eventually presented as an acoustic and numerical read-out. The attenuation properties of the collimation materials (e.g. lead, tungsten, gold or platinum), and the collimation thickness and -length can be used to fine-tune the directional specificity of gamma detection [1, 2].

Tissue attenuation of gamma signals like the 140 keV emission of ^{99m}Tc is limited and since there is no native background signal the read-out module provides a very good signal-to-noise ratio. This feature generates a powerful tool enabling the non-invasive identification of small nodules, like sentinel nodes, using imaging technologies such as scintigraphy, SPECT(/CT) and gamma tracing. However, there also is a downside to this sensitivity, namely that the signal coming from small (diseased) nodules can be obscured by background signals coming

from the injection site or nearby anatomies harboring non-specific tracer accumulation (e.g. bladder, kidneys or liver). When these signals reside within the field of view of the detector, it may render the weaker nodules undistinguishable from the background. This effect is particularly limiting in an intraoperative setting when using a gamma probe. Attempts have been made to lower this radiation background, for example by temporary shielding the injection site [12]. Yet the most practical solution to this problem would be to focus the field of view of the detector of the gamma probe on the object of interest solely, whereby the detector is facing the object of interest, but shielded from the background signal. In open surgery procedures this can be accomplished for a great variety of anatomical locations as placement of the gamma probe can occur with six degrees of freedom (DOF; **Figure 1A** and **1D**).

In an attempt to minimize the invasive nature of surgery, there has been a move from open to laparoscopic and, more recently, robot-assisted laparoscopic procedures [13]. To maintain radioguidance for e.g. the sentinel node biopsy procedure under these changed circumstances, extended laparoscopic versions of the traditional gamma probe have been created (**Figure 1B**) and introduced into the clinic [6, 14, 15]. Requirements for this type of laparoscopic gamma probes are that they can be inserted through a single trocar, that their length is sufficient to reach the lesion of interest (distance insertion point-lesion of interest is typically 0-20 cm), and that the resulting maneuverability covers an area with a radius of roughly 15-20 cm. Combined this means that the DOF of the laparoscopic gamma probe is much more restricted than those of its parental version for

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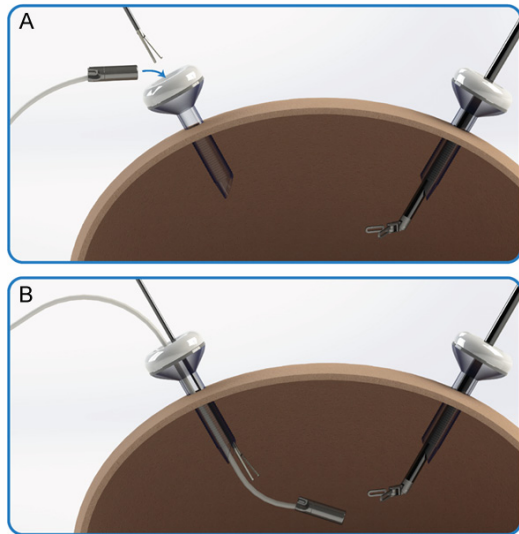


Figure 2. Insertion of the drop-in gamma probe through a trocar. A. The drop-in gamma probe is introduced into the abdominal cavity by the bedside assistant. B. After insertion the operating surgeon grabs the drop-in probe with the available surgical tool.

open surgery (**Figure 1D** and **1E**). More specifically, applying the gamma probe technology in a laparoscopic setting reduces the DOF from six (three translational and three rotational), to four (one translational and three rotational) thereby limiting the detectability of small nodules close to large radioactive background sources [16, 17].

One way to compensate for the reduced maneuverability is to alter the angle of the detector relative to the tip from 0° to 90° [6]. Unfortunately, different anatomical locations may require different angles of detector placement, essentially meaning that in a single procedure with radioactive hotspots at different locations, which is common during sentinel node biopsy procedures in prostate cancer patients [18], detectors with different angles would be required. Another practical disadvantage of a laparoscopic gamma probe is that it temporarily blocks the trocar that could otherwise be used to insert surgical tools that are of value during the resection of these lesions of interest. As a consequence the laparoscopic gamma probe has to be moved in and out of the patient multiple times during the procedure, thereby limiting logistics [6, 7].

In case of robot-assisted laparoscopic procedures, the surgeon is sitting at a distant robot

control console, rather than standing beside the patient in the sterile field. This means that a bedside assistant has to perform laparoscopic gamma tracing under verbal guidance of the surgeon. Next to the above-described limitations for the laparoscopic surgical procedures, this aspect obviously limits the degree of control for the surgeon on the detection process during robot-assisted procedures. This may lead to confusing feedback, especially when using a laparoscopic gamma probe with an angled detector.

Using the drop-in ultrasound technology as an example [19], we reasoned that the use of a small-sized wired gamma probe that can be inserted (“dropped-in”) through a trocar would provide a flexible mode of gamma tracing during (robot-assisted) laparoscopic procedures. Such a modality can be directly manipulated using the available surgical tools (**Figures 1C, 1F, 1G, 2**). Taking general engineering restrictions such as detector surface, shielding, trocar-diameter compatibility, cable thickness, and patient safety into account, we specifically focused on the engineering of the gripping technology for the drop-in gamma probe. Of special interest were the modus of gripping and, in an attempt to reduce the influence of background signals within the probe field of view, the angle of gripping. Subsequently, we evaluated these different approaches in a phantom-, ex vivo clinical- and in vivo animal setting.

Methods and material

Drop-in gamma probe

A schematic outline of the drop-in gamma probe is given in **Figure 1C**. The detection and electronic principles of the drop-in gamma probe are similar to the standard open- and laparoscopic gamma probes of Eurorad S.A. (Eckbolsheim, France).

The engineering process focused mostly on the mechanical aspects of the drop-in gamma probe. Essentially, with the design of the drop-in gamma probe the standard gamma probe was split in two parts: the general setup remained very similar, though the fixation of the detector section to the rest of the gamma probe was changed from a rigid metal tube to a flexible cable. The head section of the drop-in gamma probe was designed with a diameter of

Drop-in gamma probe evaluation

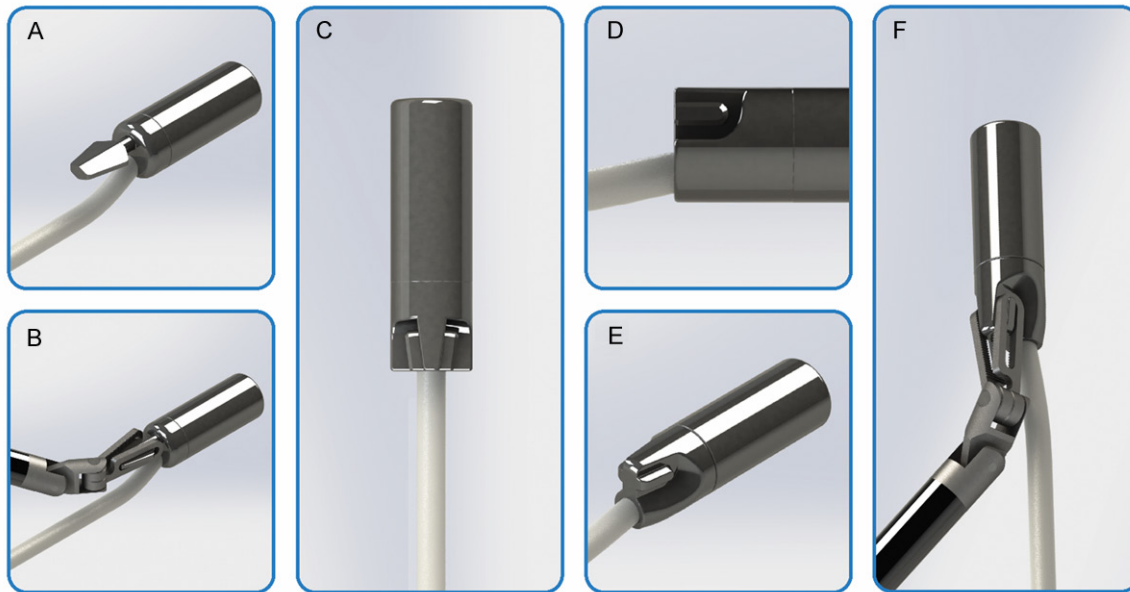


Figure 3. Grip design development steps. A. Off-center gripper and off-center cable exit, facilitating convenient probe pick-up, while maintaining on-center cable origin inside. B. Optimizing the shape of the gripper to the forceps, providing a convenient and reproducible probe pick-up. C. Integration of the design in robust solid block design without sharp edges (view 1). D. Integration of the design in solid block (view 2). E. Modification to the walls surrounding the grip structure, promoting ease and reproducibility of gripping. F. 0° grip structure displayed when grasped by the forceps.

12.0 mm and a length of 39.8 mm. The detector in the head of the drop-in gamma probe consists of a 5.0 mm × 10.0 mm (diameter × length) CsI scintillation crystal coupled to a 25.0 mm² silicon photodiode. The circular collimation applied around the crystal was fabricated out of densimet 176, a tungsten-nickel-iron alloy. A 4.3 mm diameter biocompatible cable was used to connect the head of the drop-in gamma probe to the rest of the probe housing and to connect the total drop-in gamma probe to the control unit Europrobe 3 (Eurorad S.A.). The outer shells of the drop-in gamma probe were constructed of medical grade 316L stainless steel.

Design drop-in gamma probe prototypes

Surgical tool of choice: To ensure accurate, reproducible and intuitive gripping of the drop-in gamma probe, the grip structure was specifically designed to match a surgical tool of choice. From the tools frequently used in (robot-assisted) laparoscopic surgery, it was believed that, for this initial proof-of-concept study, the two below-described models would be most suitable for grasping larger objects like the drop-in gamma probe: 1) An articulated forceps

used in robot-assisted laparoscopic surgery procedures, the da Vinci ProGrasp® forceps from the EndoWrist Graspers series (Intuitive Surgical Inc., Sunnyvale, CA, USA). This tool features a double wrist joint that contributes to a total of six DOF available for maneuverability of the drop-in gamma probe (**Figure 1G**); and 2) A non-articulated forceps that is used during laparoscopic surgical procedures (KARL STORZ Endoskope forceps, #33133 metal handle, #33300 metal outer sheath and #33310 ON forceps insert; KARL STORZ Endoskope GmbH & Co. KG, Tuttlingen, Germany). This laparoscopic tool delivers four DOF for maneuverability of the drop-in gamma probe (**Figure 1F**).

Drop-in gamma probe gripping part design: 3D mechanical computer-aided design (CAD) software SolidWorks (Dassault Systèmes SA, Vélizy-Villacoublay, France) was used to design and optimize the geometries for the gripping process. Limiting these designs were: 1) *The 12 mm trocar inner diameter:* Every structure on top of, or attached to the drop-in gamma probe was bound to a maximal outer diameter of 12 mm; 2) *The <5 mm cable diameter:* Based on availability, we were constrained to a specific biocompatible cable with a 4.3 mm diameter.

Drop-in gamma probe evaluation

Since the maximal diameter of the gripping piece is 12 mm, the current cable occupies approximately 36% (4.3/12 mm) of the total grip diameter. In the future this cable diameter may become smaller; 3) *Cable placement*: Due to the attachment to the electronics inside the drop-in gamma probe, the cable had to originate from the central probe axis, preventing a direct off-center connection; 4) *Matching forceps designs*: The grip design had to be specifically tailored to the two forceps of interest. The grip design had to ensure a reproducible pick-up with an accurate and stable grip with limited translational and rotational movement of the probe with respect to the forceps; 5) *Intuitive and facile probe pick-up by the operating surgeon*: The grip structure had to be designed in such a way that the intraoperative application time was short and the surgeon user-experience was positive for both probe pick-up and control; 6) *Stainless steel processing compatibility*: The grip design had to be fabricated from medical grade 316L stainless steel; 7) *Patient safety*: The grip design has to have a smooth surface without any sharp edges or structures that can potentially lead to unintentional tissue damage during the surgical procedure or when retracting the drop-in gamma probe after its use; 8) *Sterilization procedure*: Both the drop-in gamma probe geometry and the fabrication process used should allow for sufficient probe sterilization and decontamination; 9) The gripping position should allow for flexible detector head placement during surgery covering a scanning range as large as possible.

During the design process we followed specific development steps taking into account the above-mentioned limitations (a schematic overview is shown in **Figure 3**): 1) An off-center gripper position, where the probe cable is directed from an internal center point to an off-center exit, was developed. This allows for an on-center cable attachment to the electronics inside, while providing clearance around the gripping structure facilitating convenient probe pick up (**Figure 3A**); 2) The shape of the gripper was optimized with oblique angles to allow for a stable, reproducible, and conveniently grasped grip (**Figure 3B**); 3) To get a more robust design without any sharp angles, and to promote better probe extraction through the trocar, the optimized gripper conformation was integrated in a solid block (**Figure 3C** and **3D**); 4) To further improve the ease and reproducibility of gripping, the walls surrounding the grip were modi-

fied so that the forceps would lock itself onto the central gripping structure (**Figure 3E**). In addition, these rounded geometries should facilitate probe extraction through the trocar even further; and 5) The grip design was modified so that it could be applied in angles ranging between 0° and 135° with respect to the detector in the head of the drop-in gamma probe.

Drop-in gamma probe gripping part generation: For initial tests of the grip structure, prototypes were 3D printed in either polylactic acid (PLA) or acrylonitrile butadiene styrene (ABS) plastics. The choice of material was simply a matter of 3D printer availability and did not impact the designed structures.

PLA prototypes were printed with a slightly modified 3D Touch 3D printer (Bits from Bytes, 3D Systems Inc., Rock Hill, USA) and the accompanying Axon 2 slicer software (Bits from Bytes, 3D Systems Inc., Rock Hill, USA). Extruder temperatures were set ranging from 195-200°C with print resolution at 0.125 mm for the grip designs.

ABS prototypes were printed on the Dimension Elite 3D printer (Stratasys Ltd., Eden Prairie, MN, USA), with accompanying CatalystEX 4.4 slicer software (Stratasys Ltd., Eden Prairie, MN, USA). Designs were printed at temperatures of 260°C and a print resolution of 0.017 mm. The plastic prototypes were printed in two parts: 1) A generic hollow base, used for all prototypes, where the collimation and detector are normally located; and 2) The specifically designed gripping part.

To further approximate the functioning of a working drop-in gamma probe, the probe cable was put into place and the weight was increased by filling the hollow base with lead. The resulting plastic prototypes weighed approximately 11 g. Note that these plastic prototypes did not house the detection electronics.

After initial plastic prototype evaluation, the most promising designs were fabricated out of stainless steel by Eurorad S.A. to test if the design allowed for metal powder sintering techniques. The real functioning drop-in gamma probe prototypes weighed about 36 g each.

Evaluation process

Gamma probe detection angle evaluation: To evaluate the effect of gamma probe maneuver-

Drop-in gamma probe evaluation

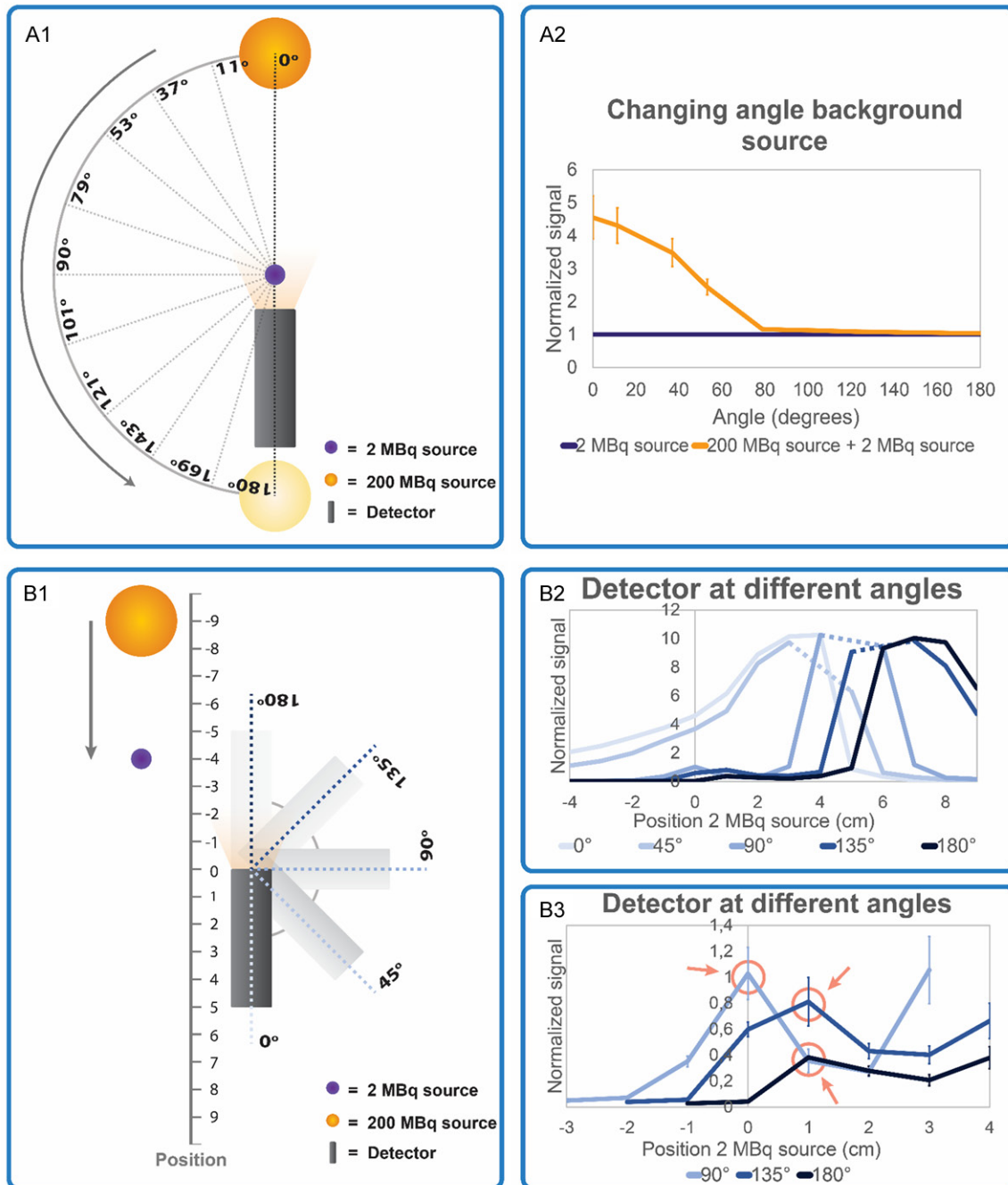


Figure 4. Gamma detector angle evaluation in the background-angle-setup (A) and the detector-angle-setup (B). (A1) Schematic image of phantom measurements setup. The ~ 2 MBq source is at a fixed distance of 1 cm with respect to the front of the detector. The ~ 200 MBq source is at a fixed distance of 5 cm with respect to the ~ 2 MBq source. (A2) Resulting gamma probe signal plotted versus the angle of the ~ 200 MBq source. Error bars plotted with the orange curve indicate ± 1 standard deviation. (B1) Schematic image of phantom measurements setup. The ~ 200 MBq and ~ 2 MBq sources have a fixed distance from the detector to the source path is 1 cm. (B2) Resulting gamma probe signal plotted for five different detector angles (0° , 45° , 90° , 135° and 180°) when the two sources move along the position-axis. (B3) Zoom-in on the additional peak detected (indicated with red circle and arrow) when the detector is placed at 90° , 135° and 180° . Error bars indicate ± 1 standard deviation.

ability on the resolvability of two radioactive sources in close proximity to each other, a “1 cm-grid-phantom” setup was used [20].

Two ^{99m}Tc based radioactive sources were made to resemble a typical injection site and nearby lymph node for a case of prostate can-

Drop-in gamma probe evaluation

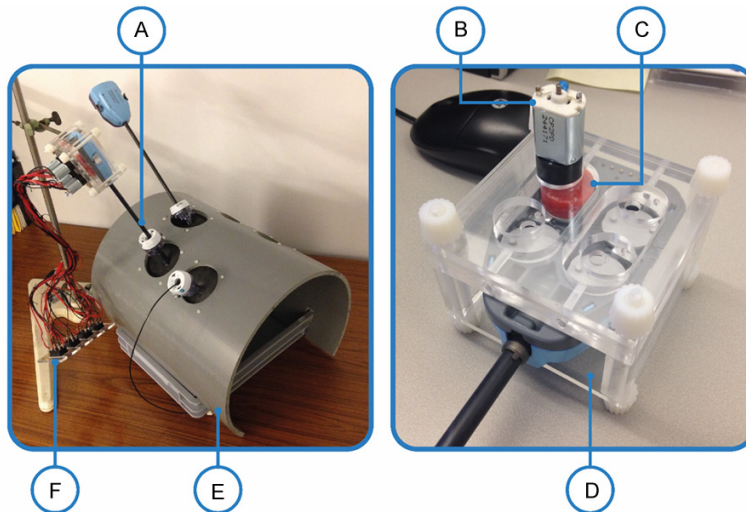


Figure 5. Laparoscopic phantom with motorized articulated forceps. A. Articulated forceps. B. Electro motors. C. Red PLA coupling rings. D. Acrylic housing. E. Laparoscopic phantom. F. Electric control circuit.

cer for which a 100:1 ratio in tracer uptake was chosen. The background source (resembling the injection site) was prepared in an entirely and homogeneously filled 500 μL Eppendorf tube containing ~ 200 MBq of radioactivity calibrated for the time of study. The low intensity objective (resembling the lymph node) was prepared with ~ 2 MBq of radioactivity in a 200 μL Eppendorf tube calibrated for the time of study. To immobilize the height of the radioactivity of this low intensity objective in the tube, the tube was filled 67% with a green colored resin (AG[®] Anion Exchange Resin, Life Science, Bio-Rad Laboratories B.V. Veenendaal, The Netherlands) and subsequently topped with a fitting piece of tissue paper containing the required radioactivity after which a final layer of resin filled the remaining space.

Two different setups were used to investigate the effect of different gamma-ray detection angles. In the first setup both the ~ 2 MBq source and the gamma detector were fixed on the grid with a 1 cm distance between the source and the front of the probe (**Figure 4A1**). The ~ 200 MBq source was then moved in half a circle (0-180 degrees) with a fixed radius of 5 cm with respect to the ~ 2 MBq source. This setup simulated the movement of the gamma probe around a hot nodule hindered by a background signal and is referred to as the “background-angle-setup”.

In the second setup the gamma detector head was fixed at five different angles (0°, 45°, 90°, 135° and 180°) while both

radioactive sources were moved passing the detector with the same 5 cm distance between both sources (**Figure 4B1**). The distance from the gamma probe head to the source path was 1 cm. This setup provided a quantifiable form of feedback on the relation between the angle of detector placement and the influence of a background signal, and what influence this effect has on the resolvability of the two separate sources and is referred to as the “detector-angle-setup”.

The readout for both setups was based on the count rates reported by the Europrobe 3


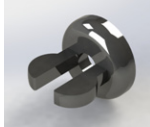

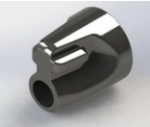
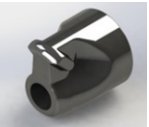
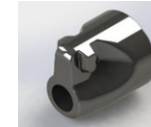
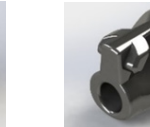
control unit. For every measurement the count scale was set to 10,000 and a counting time of 1 s was selected. For every evaluated point, the mean was taken of three consecutive 1 s measurements. Every complete measurement session was performed in triplicate with three different radioactive source pairs. All signals measured were corrected for radioactive decay with respect to the initial activity. For presenting the data, every separate session was normalized to the signal measured with only the low intensity object present at a 1 cm distance in front of the gamma probe detector head. These resulting signals were used to calculate the mean and standard deviation as shown in the graphs.

Drop-in gamma probe prototype evaluation: A basic laparoscopic phantom was fabricated to simulate the setup of a (robot-assisted) laparoscopic prostatectomy procedure (**Figure 5A**). The phantom consisted of a 38.7 cm diameter, 46.0 cm long PVC tube with a wall thickness of 1.1 cm. The bottom was removed to create a level surface inside the phantom, resulting in a phantom height of 31.0 cm. Five pieces of ~ 3 mm thick rubber were fitted to mimic the stretch nature of skin and subsequently, holes were punctured and five 12 mm trocars were put in to place.

Initial evaluation of the designed and printed plastic drop-in gamma probe prototypes was performed with the laparoscopic phantom

Drop-in gamma probe evaluation

Table 1. Overview of drop-in gamma probe grip design evaluation

Criteria	Reference	Prototype					
							
	Rigid laparoscopic gamma probe	Drop-in grip design 0	Drop-in grip design 1	Drop-in grip design 2	Drop-in grip design 3	Drop-in grip design 4	Drop-in grip design 5
Cable exit	Center	Center	Off-center	Off-center	Off-center	Off-center	Off-center
Rounded edges	Yes	Yes	No	Yes	Yes	Yes	Yes
Grip location	N/A	Center	Off-center	Off-center	Off-center	Off-center	Off-center
Grip orientation (degrees)	N/A	0	0	0	45	90	135 (<i>potential for additional 45</i>)
Convenience of pickup with forceps	N/A	-	+	+	++	+	+
Scanning direction with rigid probe (degrees)	0, 45 or 90	N/A	N/A	N/A	N/A	N/A	N/A
Scanning direction with non-articulated forceps (degrees)	N/A	0	0	0	45	90	135 (<i>potential for additional 45</i>)
Scanning direction with articulated forceps (range, degrees)	N/A	0-125	0-111	0-111	0-140	0-186 (<i>effective range: 0-180</i>)	37-235 (<i>effective range: 37-180</i>)

Drop-in gamma probe evaluation

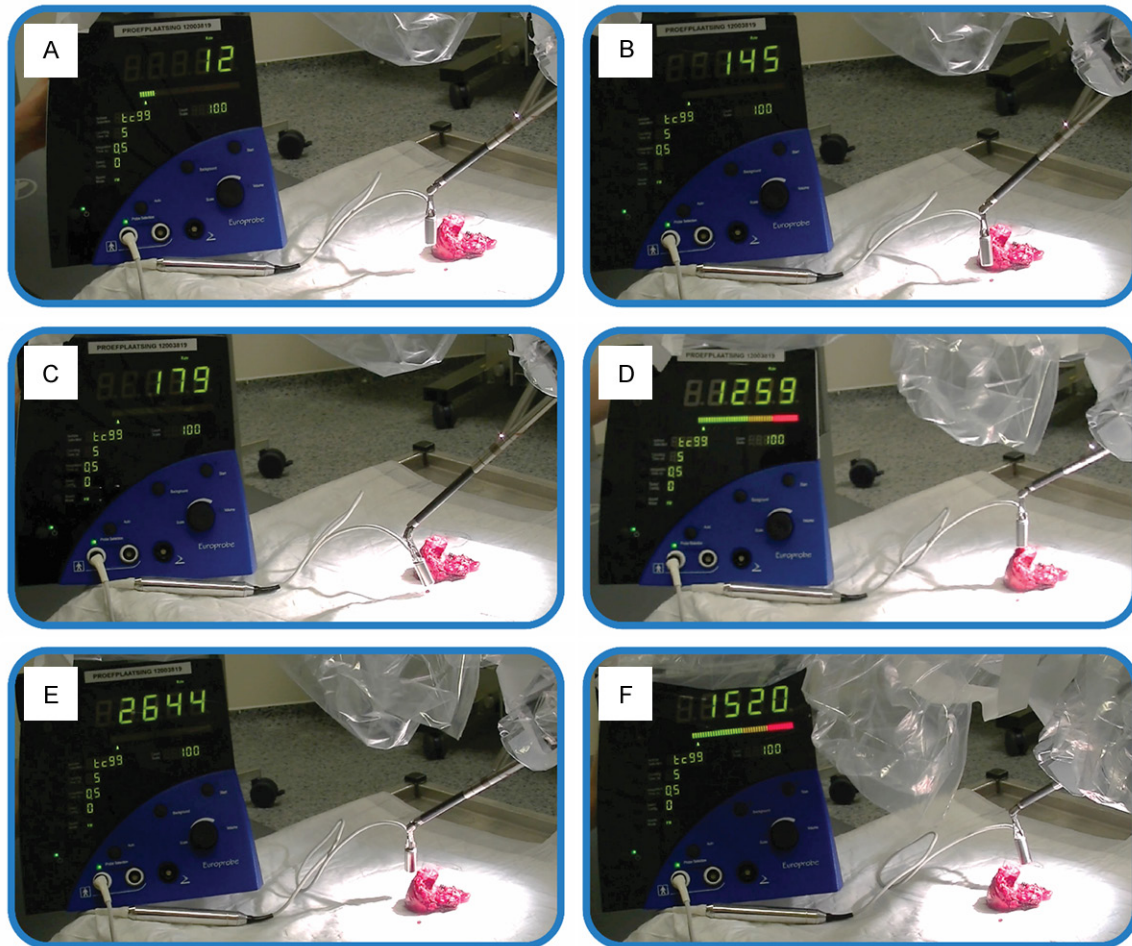


Figure 6. Maneuverability of the drop-in gamma probe evaluated in ex vivo tissue setup with prototype design 0. A-C. Drop-in gamma probe gamma tracing of a tiny sentinel node that is lying directly next to the prostate. D-F. Drop-in gamma probe gamma tracing of the prostate. By changing the angle under which the drop-in gamma probe looks at the radioactive sources, these can be discriminated from each other.

using a motorized articulated forceps (**Figure 5**). The generated motorized forceps setup was similar as described before (Integration of force feedback into minimally invasive robotic surgery 2007, <https://www.youtube.com/watch?v=OtFy1AF8SbQ>) and consisted of: 1) A ProGrasp® forceps (Intuitive Surgical Inc.); 2) Four 12 V direct current (DC) transmission electro motors (20G-150, Igarashi Motoren GmbH, Burghann-Ezelsdorf, Germany); 3) Four 3D printed coupling rings to couple the torque of the motor shaft to the four forceps wheels; 4) An acrylic plastic housing to mount all components together; and 5) A small electric circuit build to control all four forceps wheels in two directions.

After the phantom evaluation, the plastic prototypes were evaluated by a surgeon (HGvdP)

who is specialized in (robot-assisted) laparoscopic radioguided surgery procedures. Evaluation of the designed prototypes was performed ex vivo with the ProGrasp® forceps in combination with the da Vinci Si surgical robot system (Intuitive Surgical Inc.) and the KARL STORZ Endoskope laparoscopic forceps (KARL STORZ Endoskope GmbH & Co KG) in a typical operation room setup.

In both the phantom and ex vivo surgical setting, the grip structure of every designed prototype- in combination with the respective forceps- was evaluated for: 1) *Convenience of the probe pick-up*: This was rated from 'very poor' (--), to 'poor' (-), to 'medium' (o), to 'convenient' (+), to 'very convenient' (++); 2) *Scanning range available for gamma ray detection*: Multiple orientations of probe pick-up were evaluated. The

Drop-in gamma probe evaluation

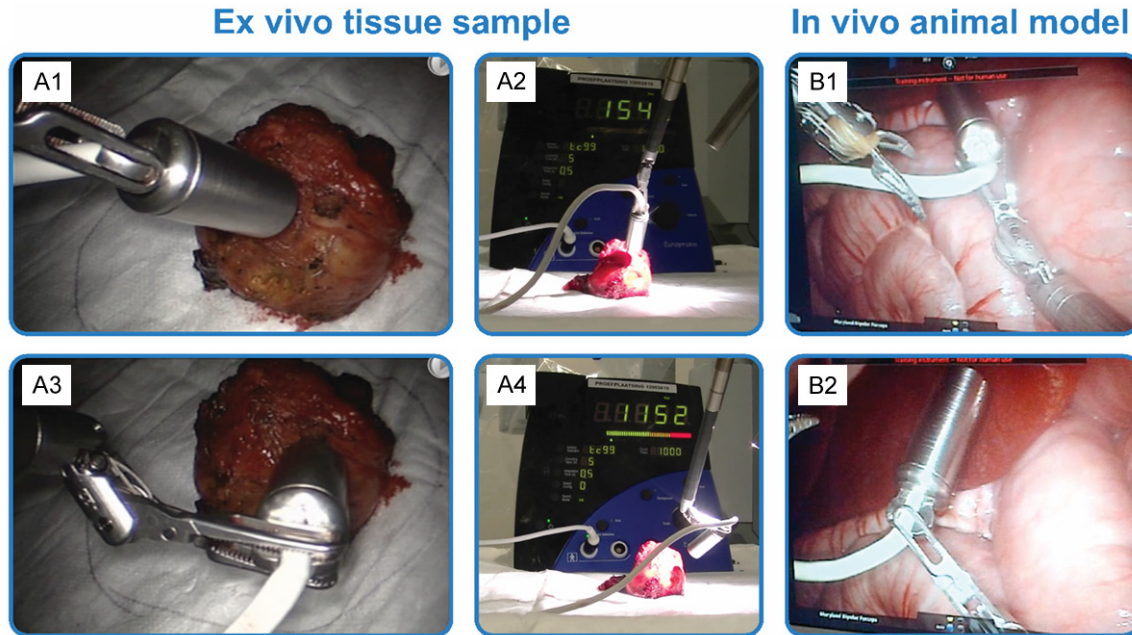


Figure 7. Ex vivo and in vivo gripping of drop-in gamma probe design 0. A1-A2. 0° grip facing the radioactive prostate using the articulated forceps as seen when looking through the surgical goggles (surgeon view; A1) or when looked at from the side (filmed by camera; A2). A3-A4. 90° grip facing the radioactive prostate using the articulated forceps as seen when looking through the surgical goggles (surgeon view; A3) or when looked at from the side (filmed by camera; A4). B1-B2. In vivo (porcine model), gripping and maneuverability of prototype design 0 were evaluated using an articulated forceps (surgeon view).

axial axis, in-line with the gamma probe scanning direction, was defined as the 0° axis (see also **Figure 4A1**). The orthogonal axis, perpendicular with the gamma probe scanning direction, was defined as the 90° axis (see also **Figure 4A1**). The orientation of pick-up influences the resulting scanning range available for gamma ray detection. This was measured in degrees with respect to the axial axis; and 3) *Probe fixation in forceps grip*: Both the fixation of the grasped drop-in probe in the forceps and the reproducibility of this grip was evaluated.

First ex vivo and in vivo evaluation of a fully functioning drop-in gamma probe prototype: In addition to the evaluations as described above, a functioning drop-in gamma probe prototype was fabricated and used for a first ex vivo human tissue- and in vivo animal model evaluation. This drop-in gamma probe incorporated the first grip design prototype and was labeled as design 0 (**Table 1**).

Design 0 was firstly evaluated in an ex vivo clinical setup (**Figures 6 and 7A**). This setup consisted of a radioactive prostate and a radioactive sentinel node at an approximate distance

of 2 cm (approximate radioactivity ratio: 100:1). These human tissue samples were obtained from a patient that underwent a robot-assisted radical prostatectomy combined with sentinel node biopsy and an extended lymph node dissection as previously described [13]. Next to a gamma tracing evaluation in this setup, the surgeon evaluated the above-described three criteria (convenience of probe pick-up, scanning range, and probe fixation in the forceps grip).

Secondly, design 0 was evaluated in an in vivo porcine animal model (**Figure 7B**). Due to the facility-restricted use of radioactive sources in animals, evaluation of the drop-in gamma probe purely focused on evaluation of the convenience of probe pick-up, probe maneuverability and probe fixation in the forceps.

Results

Gamma probe detection angle evaluation

In **Figure 4A2** the results are shown for the measurements of the background-angle-setup, where a high-background source was moved around a fixed detector head-objective setup.

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The orange line was obtained when both the background and the objective sources were present in the setup. These measurements clearly underline how background signal positions in a $<75^\circ$ angle relative to the gamma probe detector head can lead to background counts that significantly exceed those emitted by the objective alone (blue line). In **Figure 4B2** the measurements performed in the detector-angle-setup are presented. In the areas presented by the dashed line the detector was saturated. Only with the $>90^\circ$ positioning of the detector (90° , 135° , and 180°) a distinct peak of the ~ 2 MBq objective could be differentiated from the background signal (**Figure 4B3**). Calculating the ratio between the low objective peak and the lowest signal in-between the low objective peak and high background peak, the signal-low-objective-to-background ratio, resulted in 3.77, 2.01 and 1.84 for detector angles of 90° , 135° and 180° , respectively. This result further underlines the influence the angle of the detector-placement has on the diagnostic accuracy of gamma detection. Combined these results suggest that being able to turn the gamma probe detector head away from a high activity background source in an angle exceeding 90° improves the detection of a low activity objective.

Drop-in gamma probe prototype evaluation

Table 1 provides an overview of the evaluated drop-in gamma probe prototype designs. During the evaluation process a 0° laparoscopic gamma probe served as reference.

Since the gamma photon scanning section is located at the front end of the probe head, and the most commonly used (laparoscopic) gamma probes have a 0° scanning configuration, we designed and fabricated the initial drop-in gamma probe with an axial grip design: design number 0. From the ex vivo and in vivo experiments of this drop-in gamma probe, we found that gripping could be challenging. As can be seen in **Figure 7**, this was due to the central location of the connector cable, partly obstructing facile forceps placement over the grip design. Therefore, the resulting drop-in gamma probe prototype was rated 'poor' (-) for probe pick-up. When picked-up with the non-articulated forceps, this drop-in probe design gave the same maneuverability as the rigid laparoscopic gamma probe. However, in combi-

nation with the articulated forceps, maneuverability was largely extended due to the extra DOFs available (see **Figure 6**). While both the rigid laparoscopic gamma probe and the non-articulated forceps drop-in probe combination had a fixed scanning direction of 0° , the extra DOF with the articulated forceps allowed for a variable scanning direction of 0 - 125° with respect to the axial axis. Moreover, the fixation and reproducible gripping of this drop-in gamma probe were found challenging due to the round shapes of the grip design. The fixation and reproducibility errors were found to be $\sim 8^\circ$ and ~ 1 mm, respectively.

The main focus of grip design 1, compared to design 0, was to optimize the central gripping structure for convenience of probe pick-up (see **Figure 3A** and **3B**). This was done using a (double sided) pyramid shaped geometry that allowed the forceps to slide to a fixed end-position. To maintain a diameter <12 mm the cable had to be directed from the central probe axis to an off-center exit point at the probe back end. The resulting drop-in gamma probe prototype was rated 'convenient' (+) for probe pick-up. The scanning range delivered with the non-articulated forceps setup was equal to that of design number 0 (0° with respect to the axial axis). The scanning range delivered with the articulated forceps setup was found to be 0 - 111° with respect to the axial axis. The fixation and reproducibility errors were found to be $\sim 5^\circ$ and ~ 1.5 mm, respectively. During probe retraction through the trocar, this grip design could act as a small hook on the trocar, hindering the extraction process.

Grip number 2 was designed to further reduce the fixation and reproducibility errors, while improving the retraction process and maintaining usability (see **Figure 3C-E**). This was achieved using tightly fitted oblique walls surrounding the grip structure, which allowed the forceps to always slide back to a fixed end-position. To better place these oblique walls, and at the same time increase the mechanical durability of the grip structure, the design was integrated into a solid block. The resulting drop-in gamma probe prototype was still rated 'convenient' (+) for probe pick-up by the surgeon. The scanning range delivered with both the non-articulated forceps and the articulated forceps setup was equal to that of design number 1 (0° and 0 - 111° with respect to the axial axis,

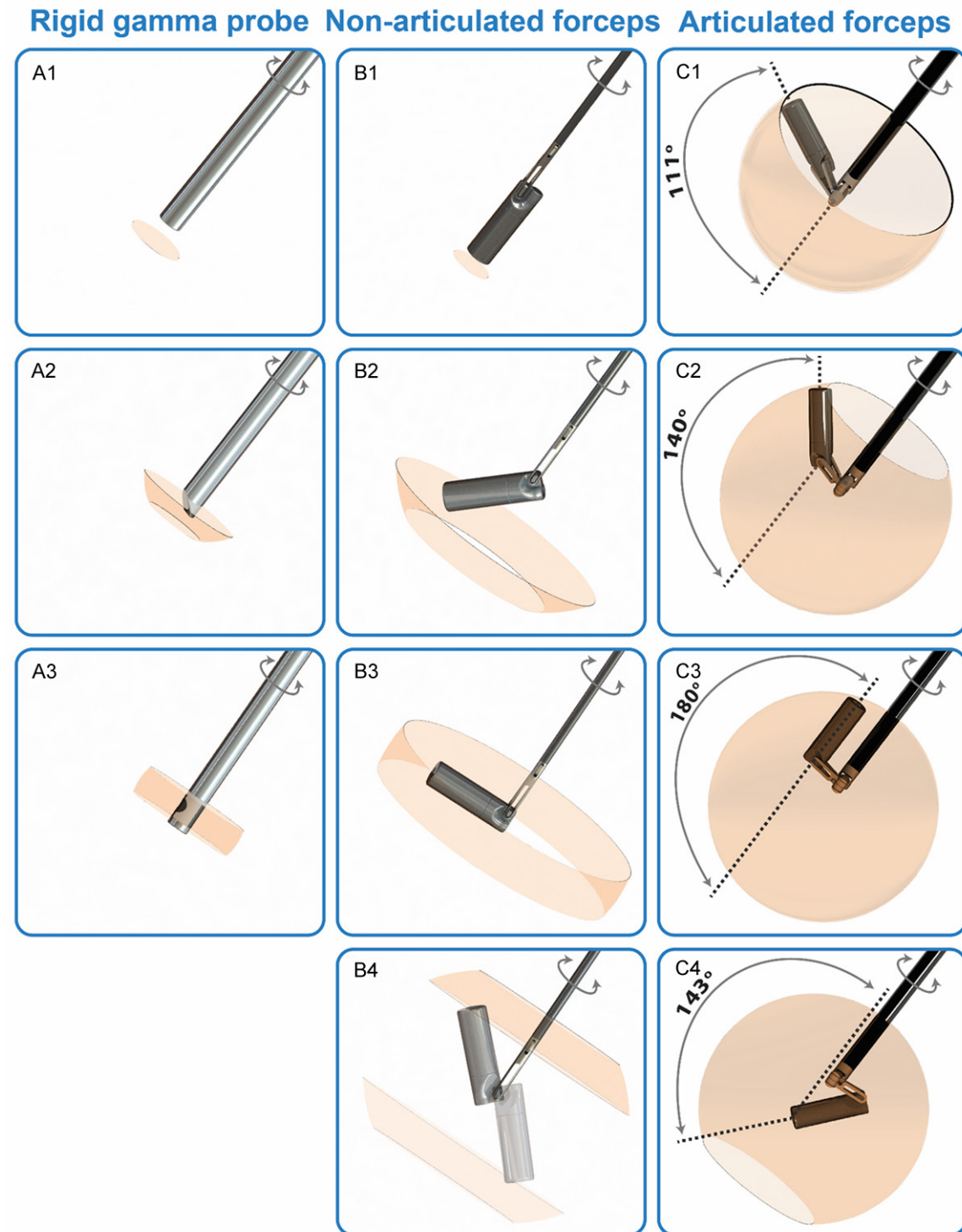


Figure 8. Effective scanning range available with the rigid laparoscopic gamma probe versions (A) and the different drop-in gamma probe designs in combination with the laparoscopic non-articulated forceps (B) and the robotic articulated forceps (C). A1, A2 and A3 illustrate the 0°, 45° and 90° laparoscopic gamma probe versions respectively. B1, B2, B3 and B4 illustrate design number 2 (0° grip), 3 (45° grip), 4 (90° grip) and 5 (135° grip) in combination with the non-articulated forceps, respectively. For design number 5, an additional 45° application is shown in transparent. C1, C2, C3, and C4 illustrate design number 2 (0° grip), 3 (45° grip), 4 (90° grip) and 5 (135° grip) in combination with the articulated forceps, respectively. In all these articulated forceps combinations the effective scanning range was found to comprise 0-111°, 0-140°, 0-180° and 37-180° respectively.

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respectively; **Figure 8B1** and **8C1**). With this design the fixation and reproducibility errors were reduced to a negligible amount of $\sim 0^\circ$ and ~ 0 mm respectively. Probe retraction through the trocar was found to be more convenient compared to design number 1.

After optimization of the grip convenience, fixation and reproducibility, the goal of design number 3, 4, and 5 was to optimize the scanning range obtained with the drop-in gamma probe. By changing the grip orientation with respect to the axial axis, the three designs delivered 45° (design 3), 90° (design 4) and 135° (design 5) versions of the drop-in gamma probe. For all three designs the grip structure and the oblique walls had to be tailored to the specific forceps orientation and openings-angle, resulting in minor variations of the design. Prototype number 3 was rated 'very convenient' (++) for probe pick-up, due to the easiest approach. Prototypes 4 and 5 were rated 'convenient' (+) for probe pick-up. Grasped with the non-articulated forceps, design number 3 and 4 showed a scan direction of 45° and 90° , respectively. Design number 5 allowed for a 135° scan direction, allowing to position the gamma probe detector head in a backwards direction (**Figure 8B4**). Although the grip structure of design number 5 was not specifically designed for two-way grasping, it was also possible to grasp this drop-in gamma probe prototype in a second direction of 45° . If further developed, this may add an extra functionality to this design: The ability to look in both a forward and backwards direction. In combination with the articulated forceps, the scanning range for these three designs was found to cover 0 - 140° , 0 - 186° , and 37 - 235° with respect to the axial axis (**Figure 8C2-C4**), respectively. With the 135° grip orientation it was thus no longer possible to scan in a straight forward 0° direction. **Figure 8A** displays the obtained scanning ranges made possible with the different rigid laparoscopic gamma probe versions.

As designed, all drop-in gamma probe prototypes fitted through the 12 mm trocar. The use of the biocompatible cable and the medical grade stainless steel housing allowed the drop-in probe to be sterilized with ethylene oxide (ETO) sterilization methods. Complete sterilization results in overcoming the need for e.g. sterile draping which can interfere with reproducible and facile gripping of the probe.

Discussion

The application of the current rigid laparoscopic gamma probes has proven to be challenging during complex surgical procedures such as sentinel node biopsy for prostate cancer [13] and gastrointestinal cancer [16, 17] or radioguided localization of ^{111}In -prostate specific membrane antigen (PSMA) positive lesions [21]. One of the main limitations are the limited DOF that the current laparoscopic gamma probe setup has, rendering it difficult to accurately place the gamma detector. In this paper, the phantom experiments with the background-angle-setup and the detector-angle-setup clearly illustrate the diagnostic benefit of detector maneuverability with respect to a high and low radiation source. Being able to turn the detector away from the high activity background source (typically produced by the injection site) allowed us to distinguish the low activity objective. Based on these results we therefore hypothesize that a small sized drop-in gamma probe, in combination with the right laparoscopic surgical tools can have great benefits in laparoscopic radioguided surgery applications.

Similar to the small sized drop-in ultrasound probe presented in the field of intra-abdominal ultrasound [19], the drop-in gamma probe was designed to be inserted through a trocar, after which it can be picked-up and manipulated by the (robotic) tools of the operating surgeon, as was illustrated in the porcine animal model. The two laparoscopic tools used for this proof-of-concept showed a clear difference in the drop-in probe maneuverability. The greatest DOF, and therefore maneuverability, was found with the articulated ProGrasp® forceps, allowing to scan (with grip design number 4) in both a forward 0° direction (for scanning while approaching the surgical site) and a backwards 180° direction (for placing the drop-in gamma probe in between the high background objective and low objectives), while also allowing the directional scanning angles in between (1 - 179°).

Although instruments with more DOF will give higher flexibility, the drop-in gamma probe can also be of value in combination with more conventional non-articulated laparoscopic tools. For example, the combination of grip design number 5 and the non-articulated KARL STORZ Endoskope laparoscopic forceps allowed back-

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wards directed scanning (135°), which is impossible with current rigid laparoscopic gamma probes. This 135° scanning direction facilitates the placement of the drop-in gamma probe in-between high activity background signals and low activity objectives, while possibly allowing forward facing detection (45°) when using the reversed gripping modus.

In the ideal situation gamma probes have no limitations on maneuverability, harboring the freedom to scan in every direction of the abdominal cavity, focusing on (low) objective radiation while avoiding (high) background radiation. In this study, only the angle of the grip was changed with respect to the drop-in gamma probe, grasping the entire probe over different angles and so creating an as-large-as-possible scan direction range. Just as with the rigid laparoscopic gamma probe, it would also be possible to place the detector itself at different angles in the gamma probe [1, 2]. Adjusting this element of the probe could open up additional interesting possibilities; for example: if a 45° detector placement would be combined with the 135° probe grip, that could also be grasped over 45° , it would be possible with the non-articulated laparoscopic forceps used in this study, to scan in a direction of 0° and 180° with the same drop-in gamma probe. The drop-in gamma probe technique as described in this study, is therefore not limited to the tools used in this study. Slight adaptations to the grasping part will allow versions of the drop-in gamma probe to complement other dedicated surgical tools.

Because the drop-in gamma probe technology is controlled with the surgical tools the surgeon has at hand during the procedure, positioning should be intuitive directly following the movement of the surgical tools. The impact of this feature will be most prominent in robot-assisted laparoscopic procedures where the surgeon is positioned away from the operating table. Additionally, during robot-assisted laparoscopic procedures, the surgeon has often three robot arms available with which can be worked. With these three arms, the arm holding the drop-in gamma probe can be positioned in such a way that the surgeon can monitor the removal of the target lesion in real-time as performed by the two other arms. The latter is similar to that used during open surgery [22]. Contrary to the rigid laparoscopic gamma probe, with the <5

mm diameter cable of the drop-in probe it will be possible to share a trocar (typically 12-14 mm) with different laparoscopic tools (typical diameter: 6 mm). This avoids the need of an extra trocar, and allows the probe to stay in the abdominal cavity during the entire procedure. This particular feature helps to further minimize the impact on the surgical procedure.

Besides providing acoustic radioguidance, (laparoscopic) gamma probes have also been used to produce a freehand SPECT scan in the operating room for example during parathyroidectomy and sentinel node biopsy procedures for breast and head and neck cancer [23-27]. In this technique a surgical navigation or tracking system is used to record every position of the gamma probe (or small handheld gamma camera) during scanning, thereby linking the measurements found to the corresponding location in space. To perform a freehand SPECT scan, it is important that sufficient information is acquired from different positions and orientations with respect to the tissue of interest [28]. For this reason, we imagine that the availability of drop-in gamma probes may enable a superior form of intra-abdominal freehand SPECT [29].

The drop-in probe technology isn't restricted to gamma radiation only, but can possibly also be extended to other forms of molecular imaging. With the proper adjustments, drop-in probes might be applied to the fields of for example beta radiation [2, 30], Cherenkov [31], (lifetime) luminescence [32] and even optoacoustic imaging [33].

Conclusion

The drop-in gamma probe technology increases the degrees of freedom with which laparoscopic gamma tracing can be performed. Herein the angle of gripping has proven to be the most critical engineering feature. Tailoring the grip design and angle helped in improving reproducible and easy grasping, while increasing the detection range and reducing the negative influence that background signals can have during gamma tracing procedures.

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Hervé Simon and Laurent Mengus, both co-authors of this paper, are employees of Eurorad S.A.

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References

- [1] Povoski SP, Neff RL, Mojzisek CM, O'Malley DM, Hinkle GH, Hall NC, Murrey DA, Knopp MV and Martin EW. A comprehensive overview of radioguided surgery using gamma detection probe technology. *World J Surg Oncol* 2009; 7: 11-74.
- [2] Heller S and Zanzonico P. Nuclear probes and intraoperative gamma cameras. *Semin Nucl Med* 2011; 41: 166-181.
- [3] Valdés Olmos RA, Vidal-Sicart S and Nieweg OE. SPECT-CT and real-time intraoperative imaging: new tools for sentinel node localization and radioguided surgery? *Eur J Nucl Med Mol Imaging* 2009; 36: 1-5.
- [4] Jeschke S, Beri A, Grull M, Ziegerhofer J, Prammer P, Leeb K, Sega W and Janetschek G. Laparoscopic radioisotope-guided sentinel lymph node dissection in staging of prostate cancer. *Eur Urol* 2008; 53: 126-132.
- [5] Alex JC, Weaver DL, Fairbank JT, Rankin BS and Krag DN. Gamma-probe-guided lymph node localization in malignant melanoma. *Surg Oncol* 1993; 2: 303-308.
- [6] Beri A and Janetschek G. Technology insight: radioguided sentinel lymph node dissection in the staging of prostate cancer. *Nat Clin Pract Urol* 2006; 3: 602-610.
- [7] Winter A and Wawroschek F. Lymphadenectomy in prostate cancer. Radio-guided lymph node mapping: an adequate staging method. *Front Radiat Ther Oncol* 2008; 41: 58-67.
- [8] van den Berg NS, Valdes-Olmos RA, van der Poel HG and van Leeuwen FW. Sentinel lymph node biopsy for prostate cancer: a hybrid approach. *J Nucl Med* 2013; 54: 493-496.
- [9] KleinJan GH, Bunschoten A, Brouwer OR, Van den Berg NS, Valdes-Olmos RA and Van Leeuwen FW. Multimodal imaging in radioguided surgery. *Clin Transl Imaging* 2013; 1: 433-444.
- [10] van der Poel HG, Buckle T, Brouwer OR, Olmos RAV and van Leeuwen FW. Intraoperative Laparoscopic Fluorescence Guidance to the Sentinel Lymph Node in Prostate Cancer Patients: Clinical Proof of Concept of an Integrated Functional Imaging Approach Using a Multimodal Tracer. *Eur Urol* 2011; 60: 826-833.
- [11] Bunschoten A, Van den Berg NS, Valdes-Olmos RA, Blokland JA and Van Leeuwen FW. Tracers applied in radioguided surgery. In: Herrmann K, Nieweg OE, Povoski SP, editors. *Radioguided Surgery - Current Applications and Innovation Directions in Clinical Practice*. Springer; 2015. pp. (in press).
- [12] Warncke SH, Mattei A, Fuechsel FG, Z'Brun S, Krause T and Studer UE. Detection rate and operating time required for gamma probe-guided sentinel lymph node resection after injection of technetium-99m nanocolloid into the prostate with and without preoperative imaging. *Eur Urol* 2007; 52: 126-132.
- [13] KleinJan GH, van den Berg NS, Brouwer OR, de Jong J, Acar C, Wit EM, Vegt E, van der Noort V, Olmos RA, van Leeuwen FW and van der Poel HG. Optimisation of Fluorescence Guidance During Robot-assisted Laparoscopic Sentinel Node Biopsy for Prostate Cancer. *Eur Urol* 2014; 66: 991-998.
- [14] Meinhardt W, Valdes Olmos RA, van der Poel HG, Bex A and Horenblas S. Laparoscopic sentinel node dissection for prostate carcinoma: technical and anatomical observations. *BJU Int* 2008; 102: 714-717.
- [15] Pijpers R, Buist MR, van Lingen A, Dijkstra J, van Diest PJ, Teule GJ, Kenemans P and Verheijen RH. The sentinel node in cervical cancer: scintigraphy and laparoscopic gamma probe-guided biopsy. *Eur J Nucl Med Mol Imaging* 2004; 31: 1479-1486.
- [16] Kitagawa Y and Kitajima M. Gastrointestinal cancer and sentinel node navigation surgery. *J Surg Oncol* 2002; 79: 188-193.
- [17] Kitagawa Y, Kitano S, Kubota T, Kumai K, Otani Y, Saikawa Y, Yoshida M and Kitajima M. Minimally invasive surgery for gastric cancer-toward a confluence of two major streams: a review. *Gastric Cancer* 2005; 8: 103-110.
- [18] Meinhardt W, van der Poel HG, Valdes Olmos RA, Bex A, Brouwer OR and Horenblas S. Laparoscopic sentinel lymph node biopsy for prostate cancer: the relevance of locations outside the extended dissection area. *Prostate Cancer* 2012; 2012: 751753.
- [19] Schneider C, Guerrero J, Nguan C, Rohling R and Salcudean S. Intra-operative "Pick-Up" Ultrasound for Robot Assisted Surgery with Vessel Extraction and Registration: A Feasibility Study. In: Taylor RH, Yang G, editors. *Informa-*

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- tion Processing in Computer-Assisted Interventions- Second International Conference, IPCAI 2011, Berlin, Germany, June 22, 2011. Proceedings. Springer Berlin Heidelberg; 2011. pp. 122-132.
- [20] Engelen T, Winkel BM, Rietbergen DD, Klein-Jan GH, Vidal-Sicart S, Olmos RA, van den Berg NS and van Leeuwen FW. The next evolution in radioguided surgery: breast cancer related sentinel node localization using a freehand-SPECT-mobile gamma camera combination. *Am J Nucl Med Mol Imaging* 2015; 5: 233-245.
- [21] Maurer T, Weirich G, Schottelius M, Weineisen M, Frisch B, Okur A, Kubler H, Thalgot M, Navab N, Schwaiger M, Wester HJ, Gschwend JE and Eiber M. Prostate-specific Membrane Antigen-radioguided Surgery for Metastatic Lymph Nodes in Prostate Cancer. *Eur Urol* 2015; 68: 530-4.
- [22] Vermeeren L, Meinhardt W, Bex A, van der Poel HG, Vogel WV, Hoefnagel CA, Horenblas S and Olmos RA. Para-aortic Sentinel Lymph Nodes: Toward Optimal Detection and Intraoperative Localization Using SPECT/CT and Intraoperative Real-Time Imaging. *J Nucl Med* 2010; 51: 376-382.
- [23] Bluemel C, Schnelzer A, Okur A, Ehlerding A, Paepke S, Scheidhauer K and Kiechle M. Freehand SPECT for image-guided sentinel lymph node biopsy in breast cancer. *Eur J Nucl Med Mol Imaging* 2013; 40: 1656-1661.
- [24] Heuveling DA, van Weert S, Karagozoglu KH and de Bree R. Evaluation of the use of freehand SPECT for sentinel node biopsy in early stage oral carcinoma. *Oral Oncol* 2015; 51: 287-290.
- [25] Rahbar K, Colombo-Benkmann M, Haane C, Wenning C, Vrachimis A, Weckesser M and Schober O. Intraoperative 3-D mapping of parathyroid adenoma using freehand SPECT. *EJNMMI Res* 2012; 2: 51-54.
- [26] van den Berg NS, KleinJan GH, Brouwer OR, Wendler T, Valdes-Olmos RA, Van der Poel HG and Van Leeuwen FW. SPECT/CT mixed-reality combined with freehand SPECT augmented-reality for intraoperative navigation in sentinel node biopsy during laparoscopic procedures. *Eur J Nucl Med Mol Imaging* 2013; 40: S215.
- [27] Wendler T, Herrmann K, Schnelzer A, Lasser T, Traub J, Kutter O, Ehlerding A, Scheidhauer K, Schuster T, Kiechle M, Schwaiger M, Navab N, Ziegler SI and Buck AK. First demonstration of 3-D lymphatic mapping in breast cancer using freehand SPECT. *Eur J Nucl Med Mol Imaging* 2010; 37: 1452-1461.
- [28] Wendler T, Hartl A, Lasser T, Traub J, Daghighian F, Ziegler SI and Navab N. Towards intraoperative 3D nuclear imaging: reconstruction of 3D radioactive distributions using tracked gamma probes. *Med Image Comput Comput Assist Interv* 2007; 10: 909-917.
- [29] Fuerst B, Sprung J, Pinto F, Frisch B, Wendler T, Simon H, Mengus L, Van den Berg NS, Van der Poel HG, Van Leeuwen FWB and Navab N. First Robotic SPECT for Minimally Invasive Sentinel Lymph Node Mapping. *IEEE Trans Med Imaging* 2015; [Epub ahead of print].
- [30] Wendler T, Traub J, Ziegler SI and Navab N. Navigated three dimensional beta probe for optimal cancer resection. *Med Image Comput Comput Assist Interv* 2006; 9: 561-569.
- [31] Chin PT, Welling MM, Meskers SC, Olmos RA, Tanke H and van Leeuwen FW. Optical imaging as an expansion of nuclear medicine: Cerenkov-based luminescence vs fluorescence-based luminescence. *Eur J Nucl Med Mol Imaging* 2013; 40: 1283-1291.
- [32] van Leeuwen FW, Hardwick JC and van Erkel AR. Luminescence-based Imaging Approaches in the Field of Interventional Molecular Imaging. *Radiology* 2015; 276: 12-29.
- [33] Garcia-Allende PB, Glatz J, Koch M and Ntzia-christos V. Enriching the interventional vision of cancer with fluorescence and optoacoustic imaging. *J Nucl Med* 2013; 54: 664-667.