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A novel radioguided surgery technique exploiting β^- decays

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The background induced by the high penetration power of the γ radiation is the main limiting factor of the current radio-guided surgery (RGS). To partially mitigate it, a RGS with β^- -emitting radio-tracers has been suggested in literature. Here we propose the use of β^- -emitting radio-tracers and β^- probes and discuss the advantage of this method with respect to the previously explored ones: the electron low penetration power allows for simple and versatile probes and could extend RGS to tumours for which background originating from nearby healthy tissue makes γ probes less effective. We developed a β^- probe prototype and studied its performances on phantoms. By means of a detailed simulation we have also extrapolated the results to estimate the performances in a realistic case of meningioma, pathology which is going to be our first in-vivo test case. A good sensitivity to residuals down to 0.1 ml can be reached within 1 s with an administered activity smaller than those for PET-scans thus making the radiation exposure to medical personnel negligible.

The radio-guided surgery (RGS) is a surgical technique, first developed some 60 years ago, that enables the surgeon to evaluate the completeness of the tumoural lesion resection, while minimizing the amount of healthy tissue removed¹. The impact of the RGS on the surgical management of cancer patients includes providing the surgeon with vital and real-time information regarding the location and the extent of the lesion, as well as assessing surgical resection margins. The technique (see Fig. 1) makes use of a radio-labelled tracer, preferentially taken up by the tumour to mark the cancerous tissue from the healthy organs, and a probe (for a review see²), sensitive to the emission released by the tracer, to identify in real time the targeted tumour loci. The radio-pharmaceutical is administered to the patient just before the surgery.

Current clinical applications of the RGS are: radio-immuno-guided surgery (RIGS) for colon cancer, complete sentinel-node mapping for malignant melanoma and breast cancer, and detection of parathyroid adenoma and bone tumours (such as osteoid osteoma).

Established methods make use of a combination of a γ -emitting tracer with a γ radiation detection probe (see³ and references therein). Since γ radiation can traverse large amounts of tissue, any uptake of the tracer in nearby healthy tissue represents a non-negligible background, often preventing the usage of this technique.

To mitigate this effect it was suggested in literature the use of β^+ decaying tracers⁴⁻⁷. The emitted positrons in fact have a limited penetration and their detection is local. Nonetheless, positrons annihilate with electrons in the body and produce γ s with an energy of 511 keV: the background persists and actually increases in energy. The improvement with respect to the use of pure γ emitters is that a dual system can be devised where the background can be measured separately and subtracted from the observed signal. This approach has been studied in pre-clinical tests⁸⁻¹² but it is not yet in use in the clinical practice. The largest limitations range from the time needed to identify a residual, the dimensions of the probes and the dose absorbed by the medical personnel.

A better solution to the current limits of RGS would be to eliminate the background from γ radiation. This study suggests therefore the use of pure β^- radiation that penetrates only a few millimetres of tissue with

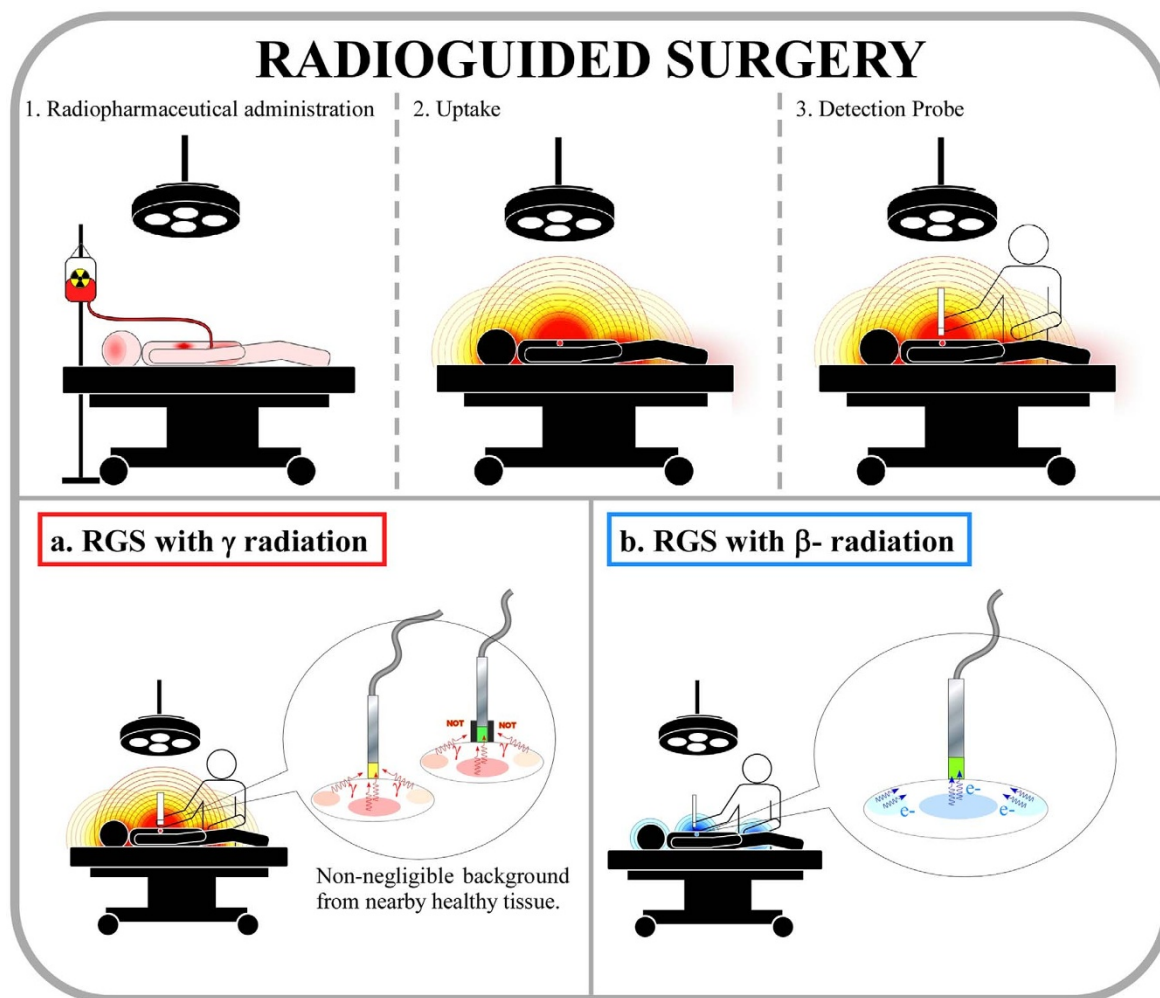


Figure 1 | The radioguided surgery technique (RGS). Steps of the procedure: (1) a radio-labelled tracer is administered to the patient, before the surgery; (2) the emitting tracer is preferentially taken up by the tumour; (3) after the cancerous bulk removal, the surgeon explores the lesion with a radiation detecting probe and looks for targeted tumour residuals in real time. The bottom boxes show the effect of the proposed replacement of the γ -emitting tracers (a) with electron-emitting tracers (b). Due to the high penetration power of the photons, in the first case a non-negligible background can be produced by the healthy organs close to the lesion, sometimes preventing the applicability of the technique. To mitigate this effect a shielding or active veto is applied (see inset of box a) thus making the probes cumbersome. Electrons, instead, provide a clearer delineation of radioactive tissue's margins allowing for a simple and compact probe and requiring a smaller radio-pharmaceutical activity. [Figure drawn by S.M. and E.S.C.].

essentially no γ contamination, being the *bremstrahlung* contribution, with a 0.1% emission probability, negligible. Furthermore, a β^- probe, detecting electrons and operating with lower background, provides a clearer delineation of margins of the radioactive tissue, requires administration of a radio-pharmaceutical with a lower activity and it is smaller and easier to handle in the surgical environment. The lower absorbed dose, together with the short range of electrons, implies an almost negligible radiation exposure to medical personnel and therefore a larger number of RGSs per year for the surgeon.

The idea of detecting β^- emission was first proposed at the very beginning of the development of RGS¹³. However, it was soon abandoned due to the particular phenomenology of this emission. The short electron free-path demanded for low invasiveness detectors to be used intra-operatively in contact with the tissues and sensitive enough to absorbed dose normally accepted in nuclear medicine. Both requirements were not satisfied by instruments and materials available at the time, while are easily reachable with modern technologies.

In particular, we report on the developments in the field of the radio-tracers and in the development and test of a specific intra-operative probe device that make the RGS with β^- decays feasible.

Results

The clinical case. There are several possible applications of this technique, many of which probably have not yet been thought of. First, complete removal of tumour is critical for brain tumours, where a relapse is particularly dangerous and where other RGS techniques are limited by the high uptake of the brain. Next, particular attention should be paid to the complete resection of the main tumour and of infected lymph-nodes in the case of pediatric tumours where life expectancy is long. Such tumours are typically abdominal and therefore probe signals are blinded by background from kidneys, liver and bladder. Finally, there are abdominal tumours in adults, like non-palpable metastases in liver and insulinoma, that would profit from RGS.

Testing this novel technique with most of the above-mentioned clinical cases requires first to identify and test an appropriate β^- -emitting tracer. We then focused on a brain tumor for which such a tracer already exists. Based on our experience with the Peptide Receptor Radionuclide Therapy (PRRT)¹⁴⁻¹⁶, the meningioma has been chosen: this brain tumor is particularly receptive to synthetic somatostatin analogues, such as DOTATOC, that can be labelled with the β^- emitting ⁹⁰Y. Furthermore, the same tracer can be marked with ⁶⁸Ga, thus allowing for an estimate of uptake prior to

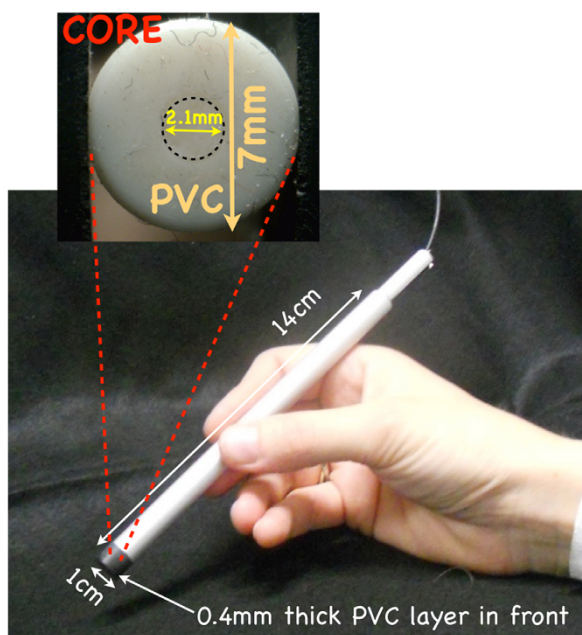


Figure 2 | First prototype of the intraoperative β^- probe. The core is a cylindrical scintillator (diameter 2.1 mm, height 1.7 mm) of polycrystalline p-terphenyl. A ring of PVC wraps the scintillator and shields it against radiation coming from the sides. The device is encapsulated inside an easy-to-handle aluminum body as protection against mechanical stress and it is protected against light by a thin PVC layer.

surgery with a Positron Emission Tomography (PET) exam. Finally, it was recently shown that with an appropriate SPECT device also the bremsstrahlung emission of the ^{90}Y can be used to verify the receptivity¹⁷.

The β^- detecting probe. As far as the probe design is concerned, the choice of the materials and the readout electronics is driven by the need to maximize the sensitivity to electrons while minimizing the sensitivity to photons. Para-terphenyl, or p-terphenyl, was adopted as electron detector after a detailed study¹⁸ due to its high light yield and low density, with consequent low sensitivity to photons.

A first prototype of the β^- probe was developed (see Fig. 2) and tested with phantoms using ^{90}Y diluted in a physiological saline solution (see Methods for the experimental set-up and Supplementary Information for more details on the test results). We explored the range of activity concentration from 22 to 5 kBq/ml to be compared with the 20 kBq/ml value estimated by analyzing PET DICOM images obtained administering 3 MBq/kg of ^{68}Ga -DOTATOC to patients affected by meningioma. We therefore studied the probe performance close and below the activity range achieved for diagnostic investigation.

We explored the first prototype response with four phantoms simulating cancerous residuals with different topologies (see Supplementary Fig. S1). The 0.1 ml volume phantom, referred to as “RESIDUAL”, has dimensions compatible with residuals well identified with the nuclear magnetic resonance. To check the effect of the phantom depth on the probe response and resolution in distinguishing the residual edge, the other three cylindrical phantoms have the same activity concentration, footprint (13 mm²) but different heights: 1, 2, and 3 mm referred to as “H1”, “H2”, “H3” respectively.

A 1.5 mm step blind automated scan over the phantom engraved surface was performed when the activity concentration reached 16 kBq/ml. Even by limiting the acquisition time to 1 s per step the test demonstrated that all the residuals would be identifiable in absence of background from nearby organs. The signal from the tumor residuals was studied at maximum and minimum activity concentrations, 22 and 5 kBq/ml, and the observed rates are reported in Tab. 1. The electronic noise was found to be negligible. Background rates, dominated by the signal coming from the uptake of nearby healthy tissue, were estimated using a full simulation of the system with FLUKA program¹⁹, based on the above mentioned DICOM images showing that the nearby healthy tissue uptake is approximately 10 times smaller than the tumour.

From the signal and background rates, taking into account the Poisson fluctuations of the measured counts, we computed the false-positive (FP) and the false-negative (FN) rates for a given time interval measurement with the probe. We estimated (see Tab. 1) the time needed to achieve FP \approx 1% and FN < 5% and found it to be 1 s for 22 kBq/ml activity concentration and up to 10 s in the case of a concentration as low as 5 kBq/ml. Further improvements of the probe are needed to reduce such time at a level compatible with surgical environment and administer down to 5 kBq/ml.

The effect of an off-axis measurement has been verified by moving the probe away from the phantom centre. The test showed that the rate is reduced by a factor 2 when moving the probe 0.5 mm far from the phantom edge (see Supplementary Fig. S4). This allows us to conclude that the probe distinguishes the residual edge. This test also demonstrated the lateral shielding effectiveness of this prototype making the probe insensitive to electrons coming from the sides hence increasing the tumor-spotting capability. This test also shows that the probe is insensitive of long-range radiation that could be caused by the activity of the ^{90}Y in nearby samples.

Radiation exposure to patient and medical personnel. One of the key points of this technique is the low irradiation of the patient and above all of the medical staff. As previously mentioned, we estimated that a 22 kBq/ml activity concentration, corresponding to administering approximately 3 MBq/kg, would be more than sufficient for the technique to be effective.

From Ref. 16 we obtained that the total body dose absorbed by a 70 kg patient after administration of 210 MBq of ^{90}Y -DOTATOC is approximately 21 mSv, while the effective dose is about 70 mSv. This

Table 1 | Results of the test on the first probe prototype. The probe was tested on phantoms sized as possible tumour residuals of interest, filled with ^{90}Y in saline solution to simulate the situation after bulk meningioma removal. The rates measured with two different ^{90}Y activity concentrations (22 and 5 kBq/ml) are reported (Rate). The minimal acquisition time (T) needed to detect tumour residuals with a false-negative probability <5% and a false-positive probability \sim 1% was estimated extrapolating the laboratory test results to a real case by means of a detailed simulation

Phantom	Diameter (mm)	Height (mm)	Volume (ml)	Rate (cps) 22 kBq/ml	T (s) 22 kBq/ml	Rate (cps) 5 kBq/ml	T (s) 5 kBq/ml
Residual	6	3.5	0.10	31.6	1	6.6	2
H1	4	1	0.01	12.4	2	2.6	>10
H2	4	2	0.02	17.7	1	3.7	4
H3	4	3	0.04	20.1	1	4.2	4



corresponds to approximately two Computed Tomography (CT) exams and therefore there is room for improvement in reducing the required activity.

To evaluate the dose absorbed by the surgeons we simulated a set-up similar to the common situation of an operating room. Both activities of neoplastic cells and normal tissue were taken into account, according to the ratios obtained from the aforementioned studies on PET images. The equivalent dose absorbed by the surgeon's hands computed for RGS with a ^{90}Y emitting tracer is expected to be smaller than $1 \mu\text{Sv}/\text{hour}$. The corresponding value for established RGS with ^{99m}Tc radio-label tracer is $24 \mu\text{Sv}/\text{hour}$ as estimated with the simulation, which was consistent with Ref. 1. Similarly, the total-body dose to the surgeon is $0.13 \mu\text{Sv}/\text{hour}$ with the β^- RGS here proposed, to be compared with approximately $6 \mu\text{Sv}/\text{hour}$ of the ^{99m}Tc RGS.

Discussion

The radio-guided surgery represents a very useful surgical adjunct in those cases where a complete resection, intended as full enhancing mass removal, is crucial both for recurrence-free survival and the overall survival of the patients, particularly for those tumours where the surgical mass removal is the only possible therapy.

We are proposing a radical change in the paradigm of this technique: the use of β^- radiation instead of γ or β^+ radiation. The reduced penetration power of electrons should allow the extension of this technique to clinical cases that would be otherwise prevented by the presence of nearby healthy organs taking up the tracer.

This novel approach allows to develop a simple and compact probe which, detecting electrons and operating with low radiation background, provides a clearer delineation of margins of radioactive tissue and requires a smaller radio-pharmaceutical activity to detect tumour remnants compared to traditional RGS approaches. Moreover, due to the lower absorbed dose and the short range of electrons, the radiation exposure to the patient and medical personnel becomes almost negligible. Such considerations apply also in the comparison with the β^+ RGS, since in the latter the γ background is in any case present, albeit subtracted with the dual-probe approach. Furthermore, measurements performed in absence of background, as in the case of the proposed β^- RGS, require by definition shorter read-out times than measurements with background subtraction. Finally, the need to duplicate the probe for the background estimation makes β^+ probes intrinsically less compact.

We have presented pre-clinical tests of a prototype probe supporting the above statements. From these measurements we extrapolated with a detailed simulation the expected performance with meningioma, representing our test clinical case. Nonetheless, the actual uptake on the margins of the lesion, the impact of tissue between the probe and the residual and the effect of the nearby blood is something to be estimated in clinical tests. Once the feasibility of such technique will be demonstrated with meningioma, it will be possible to extend it to other clinically relevant cases, eventually together with the development of specific radio-tracers.

Methods

The probe prototype. The core of the probe (see Fig. 2) is a cylindrical scintillator (diameter 2.1 mm, height 1.7 mm) of poli-crystalline para-terphenyl doped by 0.1% in mass of diphenylbutadiene. Para-terphenyl was adopted, after a detailed study¹⁸, due to its high light yield (3.5 times larger than typical organic scintillators), non-hygroscopic property and low density. The scintillator is shielding against radiation coming from the sides by wrapping it with a 7 mm external diameter ring of PVC. The device is encapsulated inside an easy-to-handle aluminum body, as protection against mechanical stress, and has a blinding 0.4 mm-thick black PVC front end cap. The scintillation light is transported to a photo-multiplier tube (PMT, Hamamatsu H10721-210), through an optical fibre, and read out by a portable custom electronics with wireless connection to a PC or tablet. This prototype is compatible with a standard sterile covering of sub-millimetric film for surgical environment. Also the very low bias required by the PMT, 5 V, makes the device easily portable.

Experimental set-up of the ^{90}Y test. The phantoms are cylindrical vessels, engraved at a fixed radius on a PMMA (PlexiglassTM) disk mounted on a rotating table, as shown in supplementary Fig. S1. Their dimensions are listed in Tab. 1 and are known with a precision of $10 \mu\text{m}$.

During the test, the probe was fixed in vertical position over the disk and the phantoms were moved under the probe by rotating the disk with a step motor, controlled via PC. The relative position of the sensitive head of the probe and the phantom was known with a precision of $10 \mu\text{m}$. Two probe-disk distances were studied: 50 and 150 μm . At the optimal working point (PMT gain $\sim 10^6$ and signal readout threshold of 21 mV), the background rate due to the photo-multiplier tube dark current and casual events was measured to be 0.2 counts per second (cps). It was checked to be stable when operating at room-temperature and with ambient light conditions.

Estimate of false positive and false negative rates. The rate of false positive and false negative (FP and FN) is computed from the signal (v_s) and background (v_b , mostly due to tracer uptake in healthy tissue) rates estimated, for each phantom, as described in the Results section. For a given value of the probe acquisition time (t_{daq}), the number of signal counts from the tumour and the background is distributed according to a poisson distribution with mean $\mu_s = v_s t_{daq}$ and $\mu_b = v_b t_{daq}$ respectively. Given the minimum number of signal counts needed to flag a positive identification th , FP is computed as the fraction of times the background would yield a positive signal:

$$FP = 1 - \sum_{N=0}^{th-1} \mathcal{P}_{\mu_b}(N) \quad (1)$$

where $\mathcal{P}_{\mu}(N)$ indicates the Poisson probability to have N if the mean is μ . Similarly FN is the fraction of times a tumour residual would not yield a signal

$$FN = \sum_{N=0}^{th-1} \mathcal{P}_{\mu_s}(N). \quad (2)$$

To determine the minimum acquisition time reported in Tab. 1, FN and FP are computed in a grid of t_{daq} and th (see Supplementary Fig. S5) and the smallest value of t_{daq} for which $FN < 5\%$ and $FP \approx 1\%$ is determined.

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Author contributions

R.F., A.Sc. and S.F. ideated the project and supervise it by identifying the materials and their supply; S.M., E.S.C., A.R., F.C., F.B., M.M. and A.Sa. worked on the design and construction of the probe prototype, automated test station implementation, data analysis and interpretation, probe optimization; R.F., E.S.C., S.M. and F.C. prepared the manuscript; F.C., V.P., L.P., I.M., C.V. and E.D.L. implemented the Monte Carlo simulation aimed to compare different materials and to understand the probe behavior; G.B., P.F. and M.S. provided the medical background and defined the clinical case; G.P., C.M.G. and M.C. provided the nuclear medicine knowledge and supplied DICOM data to study use cases; V.B. and L.R. developed and optimized custom electronics for the probe readout; all authors discussed the results and implications and commented on the manuscript at all stages.

Additional information

Supplementary information accompanies this paper at <http://www.nature.com/scientificreports>

Competing financial interests F.B., F.C., E.D.L., S.F., M.M., I.M., V.P., L.P., A.Sa., A.Sc., C.V. and R.F. are listed as inventors on an Italian patent application (RM2013A000053) entitled “Utilizzo di radiazione β^- per la identificazione intraoperatoria di residui tumorali e la corrispondente sonda di rivelazione” dealing with the implementation of an intra-operative β^- 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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