An innovative radio-guided surgery technique for complete resection of tumors

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Abstract. Finding new ways to fight cancer is essential to increase the patients life expectancy. This paper reports the latest results of the project CHIRONE finalized to increase the potential of the Radio Guided Surgery through the use of $\beta^-$ emitting radio-tracers and $\beta^-$ probes. This innovation could overcome the present main limiting factor represented by a diffuse background due to the high penetration power of the gamma radiation used. We created a prototype of $\beta^-$ probe and in this paper we report measures of photon efficiency, acquired with commercial photons sources. Then we estimated the signal and background rates in realistic cases of meningioma through a simulation. The device is able to detect residuals of 0.1 ml in 1 s with an administered activity less than 3 MBq/kg.

1. Introduction
Cancer figures among the leading causes of death worldwide [1], so increasing the five-years relative survival rate could be a significant result from a clinical point of view. This rate is calculated as the percentage of patients with a disease that are alive five years after that their disease is diagnosed divided by the percentage of the general population of corresponding sex and age that are alive after five years.

In this contribution we propose an innovative Radio Guided Surgery (RGS) technique that allows to perform complete tumour resection, minimizing the amount of healthy tissue removed. The procedure is based on the administration of a radioactive tracer to the patient before the surgery [2]. A radioactive tracer is a chemical compound in which one or more atoms have been replaced by a radioisotope. The tracer is preferentially taken up by the tumour cells, increasing the radioactivity over the tumour masses with respect to the surrounding healthy tissues. This
implies that each tumour requires its own radio-tracer.

After tumour removal, a real time scanning of the patient is performed by the surgeon, to check for residual radiation through specific probe systems. A widely used marker for the tracer is the $^{99m}$Tc, a gamma emitter, that produces photons with an energy of 140 keV as decay products. Due to the body density, this energy implies a photon mean free path up till 10-15 cm severely limiting the RGS application to few specific sites (i.e. breast, melanoma) not significantly affected by tracer uptake background of nearby healthy organs. On the basis of these considerations, the use of different radio-marker tracers, like beta emitters, was proposed.

The choice of a beta minus emitter, like $^{90}$Y, would allow the emission of electrons with a reduced penetration power ($\sim$ cm, since their maximum energy is 2.2 MeV) in absence of gamma contamination. The physical characteristics of this particles are making $^{90}$Y particularly suitable for an application of the RGS to tumour families that are currently outside its field of application. A wide application of such novel technique will require the research of $\beta^-$ emitter radio tracers, since only few of them are currently well known and tested.

In this paper we report our progress in the development of different $\beta^-$ prototypes and their relative experimental performances. In particular we characterized the photon efficiency and we estimated the potential of the prototypes in clinical applications.

2. Methods

2.1. $\beta^-$ probe prototype

A prototype of $\beta^-$ probe was developed to test the performance of RGS with $\beta^-$ radio-tracers. The prototype is described in detail in ref. [3]. The following targets were established:

- Real time data acquisition (essential during surgery)
- Detector high efficiency (to reduce the administered activity to the patient)
- Compact and handy device (easy of use in complex clinical situations)

An organic crystal, the para-terphenyl [4] doped with 0.1% diphenylbutadiene was chosen as detector. The low density (1.16 g/cm$^3$) of the material implies a scarce sensitivity to Bremsstrahlung emission. The detector has been tested with $^{60}$Co, $^{137}$Cs and $^{133}$Ba photon source, with a copper shield placed in front of the probe. The shield was required to stop the electrons that were produced by the sources, since they were not pure gamma emitters. The efficiency of the probe has been measured as the ratio between the photons' nominal activity and the measured counts, taking into account the presence of the shield.

Two probes, fit for operating on tumour areas of different dimensions, were realized to make possible the application in various clinical situations. The availability of alternative solutions could be helpful for the device compliance to strict medical rules. For localized tumours a para-terphenyl cylinder of 5.1 mm diameter and 3 mm height was used coupled with optical fibres that carried out the light to a photomultiplier tube (probe S4). For wider areas the probe was designed with a cylinder of 10 mm diameter and 3.2 mm height, directly coupled to a silicon photomultiplier (probe SiPM).

Portable electronics based on Arduino Due, with wireless connection to PC or tablet was used for the readout. The Arduino Due is a microcontroller board, based on a 32-bit ARM core microcontroller. The board can operate on an external supply of 6 to 20 volts (for an introduction about Arduino, see ref. [5]).

Ad-hoc phantoms [Figure 1] were conceived for the control experiments using sponge material bathed with a radioactive saline solution (mixture of distilled water and $^{90}$Y) in which the
activity was modulated by the dilution. The phantoms were easy to manage and were assembled to create complex patterns to simulate different clinical situations.

![Image of a phantom and a tablet displaying data]

**Figure 1.** Operator using the probe over a phantom. The result of the data acquisition is displayed on a tablet. The detector is located inside the black cover at the top of the probe. Inset: phantom. The two different sections (yellow and blue) have different activities, to simulate the different uptakes between the tumour and the surrounding healthy tissue of the clinical case in exam. The yellow phantom has a 5 mm diameter and a 2.5 mm height. The blue one has the same height, but a 20 mm diameter.

### 2.2 Monte Carlo simulation

A Monte Carlo simulation, based on FLUKA, was used to investigate the probe performance for a real surgery application. FLUKA is a Monte Carlo package used to simulate interactions between particles and matter [6].

The smallest volume detectable by a PET scan corresponds to 0.1 ml. In our simulation the equivalent tumour mass was represented by a cylinder with a 3 mm radius and a 3.5 mm height. The residual was surrounded by an extended region with a lower uptake [Fig 2]. The uptakes of the radio-tracer for the tumour mass and the surrounding health tissues were calculated from PET images of 10 patients affected by meningioma brain tumour. DOTATOC, a synthetic somatostatin analogues, marked with $^{90}$Y was used as radio-tracer for this simulation. An activity of 3 MBq/Kg, the normally applied dose for PET scan, was used as benchmark. The simulations provided the rates on probe for the signal and the noise for each clinical case. Signal was defined as the rate over the tumour mass, while background as the rate over the healthy tissue.
3. Results

3.1. Photon efficiency
We used probe SiPM to estimate the photons efficiency, since it has the higher geometrical efficiency. We estimate an efficiency from $60.5 \cdot 10^{-6}$ to $6.1 \cdot 10^{-6}$ for photons from 1330 keV to 356 keV, with the efficiency that decreases according to the energy. Considering the probability of bremsstrahlung ($\sim 10^{-3}$) and its energy spectrum [Figure 3] we confirmed that the probe is insensitive to the photons.

![Figure 3. Simulated photons energy spectrum obtained by the simulation of a cylinder with the equivalent density of the human body filled with a diffuse source of $^{90}$Y. The photons are due to bremsstrahlung contribution](image)

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3.2. Estimated rates on probe S4
Table 1 shows the simulations results for each patient of the rates on probe S4 estimated using the Monte Carlo simulation. Rates were converted in the minimum time necessary to diagnose the fraction of tissue under the probe with a false positive probability less than 1% (due to background fluctuation simulating a tumour mass) and a false negative probability less than 5% (probability to miss the residual). Taking into account the fluctuations due the poissonian nature of the process, the minimum time was established as the minimal value of time for which
Table 1. Results of the simulation. For each patient the table shows the probe rates for the signal (S) and for the background (B) for each lesion. The last column shows the minimum time (T) that the surgeon has to wait to be sure to detect the residual. These results are calculated for an administered doses of 3 MBq/kg for meningioma tumour.

| Patient ID | S (Hz) | B (Hz) | T (s) |
|------------|-------|-------|-------|
| 1          | 32.2  | 1.9   | 0.2   |
| 2          | 17.6  | 2.6   | 0.6   |
| 3          | 33.7  | 3.5   | 0.3   |
|            | 50.3  | 3.5   | 0.3   |
|            | 76.8  | 3.5   | 0.1   |
| 4          | 89.4  | 4.5   | 0.1   |
| 5          | 66.7  | 4.4   | 0.2   |
|            | 53.2  | 4.4   | 0.2   |
|            | 57.6  | 4.4   | 0.2   |
| 6          | 107.6 | 1.8   | 0.1   |
|            | 56.1  | 1.8   | 0.2   |
| 7          | 50.2  | 3.9   | 0.2   |
| 8          | 55.7  | 3.6   | 0.2   |
|            | 31.2  | 3.6   | 0.2   |
|            | 29.6  | 3.6   | 0.4   |
| 9          | 13.4  | 2.4   | 0.9   |
|            | 15.1  | 2.4   | 0.7   |
| 10         | 14.6  | 1.2   | 0.6   |
|            | 12.6  | 1.2   | 0.8   |

existed a value of rates threshold for which both the requests were satisfied. This time resulted to be lower than 1 s in all the cases. The administered dose was 3 MBq/kg.

4. Conclusion
In this contribution we presented the results obtained from a Monte Carlo simulation of a β− probe implementing a novel technique for RGS.

The simulation was based on the result of phantom test and showed that we would be able to identify the tumour mass of the volume of 0.1 ml in 1 s at 95% C.L. after the administration of an activity at below 3 MBq/Kg (for patient affected by meningioma), fully supporting the technique potential. An indication that the dose delivered to the patient could be reduced has been obtained and will be explored with dedicated R&D in the future.

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