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Feasibility of beta-particle radioguided surgery for a variety of "nuclear medicine" radionuclides

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ABSTRACT

Purpose: Beta-particle radioguided tumor resection may potentially overcome the limitations of conventional gamma-ray guided surgery by eliminating, or at least minimizing, the confounding effect of counts contributed by activity in adjacent normal tissues. The current study evaluates the clinical feasibility of this approach for a variety of radionuclides. Nowadays, the only β^- radioisotope suited to radioguided surgery is ^{90}Y. Here, we study the β^- probe prototype capability to different radionuclides chosen among those used in nuclear medicine.
Methods: The counting efficiency of our probe prototype was evaluated for sources of electrons and photons of different energies. Such measurements were used to benchmark the Monte Carlo (MC) simulation of the probe behavior, especially the parameters related to the simulation of the optical photon propagation in the scintillation crystal. Then, the MC simulation was used to derive the signal and the background we would measure from a small tumor embedded in the patient body if one of the selected radionuclides is used.
Results: Based on the criterion of detectability of a 0.1 ml tumor for a counting interval of 1 s and an administered activity of 3 MBq/kg, the current probe yields a detectable signal over a wide range of Standard Uptake Values (SUVs) and tumor-to-non-tumor activity-concentration ratios (TNRs) for ^{31}Si, ^{32}P, ^{97}Zr, and ^{188}Re. Although efficient counting of ^{83}Br, ^{133}I, and ^{153}Sm proved somewhat more problematic, the foregoing criterion can be satisfied for these isotopes as well for sufficiently high SUVs and TNRs.

1. Introduction

Radioguided surgery (RGS) is a technique that may enable the surgeon to evaluate in real time the completeness of the tumor lesion resection. At the same time, RGS may minimize the amount of healthy tissue removed. It represents a significant adjunct to intra-operative detection of millimetre-sized tumor residues, providing the surgeon with vital and real-time information regarding the location and the extent of the lesion. It is crucial for those tumors where surgical resection is the only possible therapy, since it reduces the probability of tumor recurrence by assessing surgical resection margins.

RGS makes use of a radiolabeled tracer and a probe. The

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radiopharmaceutical is administered to the patient before surgery and its uptake has to be higher in the tumor than in healthy organs, allowing their counting-based discrimination.

Traditional RGS makes use of γ emitters as the radiolabel [1–6]. However this technique is severely limited, and often prohibitively so, by the background counts from activity in distal as well as proximal healthy tissue. Such background is often significant, since γ radiation can penetrate fairly large thicknesses of tissue. Moreover, the large mean free path of γ radiation exposes the medical personnel to measurable radiation doses.

The use of β^- radiation to overcome the limitations of traditional RGS was recently proposed [7,8]. Electrons have a very short range in tissue and therefore β^- RGS should yield a more favorable ratio of the signal from the tumor to that from the rest of the body. An ex-vivo test has shown the feasibility of this technique for a meningioma case [9]. Meningioma has been chosen because it is known to express receptors to DOTATOC [10], a somatostatin analogue that could be labeled with ^{90}Y, a pure β^- emitter with a 2.3-MeV electron energy endpoint.

However, limiting β-particle RGS to this radionuclide would mean restricting this technique to very few tumors, mainly glioma [11] and neuro-endocrine tumors [12], that demonstrate high uptake of ^{90}Y-DOTATOC (the only commercially available ^{90}Y-labeled radiopharmaceutical). To further broaden the applicability of the technique, the use of different radioisotopes, with higher gamma contamination and lower β-particle endpoint energies, is under investigation.

Among the β^--emitting radioisotopes that have the widest application in nuclear therapy [13], we considered those that have an electron energy end-point of at least 500 keV, dominant γ lines below 400 keV and total γ intensities below 100%: ^{32}P, ^{131}I, ^{133}I, ^{153}Sm, ^{177}Lu, and ^{188}Re. In addition, we considered isotopes that are chemically in the same family as nuclides already used to label radiotracers, since these are most likely to be used to label new radiotherapeutic agents. We thus also included in our studies ^{31}Si, ^{67}Cu, ^{83}Br, and ^{97}Zr. The characteristics of the decays of the considered isotopes are detailed in Table 1.

Another alternative is to consider ^{18}F, which has $T_{1/2}$ = 1.8 h and a β^+ emission with end-point at 633.5 keV and 97% intensity, and is used to radiolabel fluorodeoxyglucose (FDG). It is widely used as marker for positron emission tomography (PET) and, therefore, if the developed probe were sensitive to ^{18}F with low background, there would be a significant extension of the applicability of the technique. It is to be noted that in this case the probe would detect the positrons before they stop or annihilate, while annihilation photons would contribute to background. The possibility of intra-operative counting of positrons has been reported [14–17] with the development of dual detectors for the simultaneous measurement of positrons and γs. The emitted positrons in fact have a limited penetration and their detection is local. Nonetheless, positrons annihilate with electrons in the body and produce γs with an energy of 511 keV. 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 preclinical tests [18–22] but it is not yet in use in clinical practice. The major limitations range from the time needed to efficiently detect a tumor residual, the dimensions of the probes and the dose absorbed by the medical personnel [23–25].

This paper describes laboratory tests performed to measure the probe efficiency for beta particles and gamma rays by using several sources with different beta-particle energy spectra and gamma-ray lines. These efficiency measurements were translated in potential sensitivity of RGS for the different radionuclides listed in Table 1. The electron and photon efficiencies were input to a full simulation of patients and the corresponding response of the probe was studied.

Finally, to compare the radioisotopes we also estimated the expected dose rate delivered to the medical personnel during surgery. This requirement, in addition to the need to minimize the dose to the patient, limits the activity that can be administered.

Table 1
Characteristics of the β^- radioisotopes of interest for the proposed RGS technique: half-life ($T_{1/2}$), γ and β^- intensities (I_γ and I_β respectively), photon line energies (E_γ), and β^- end-point energies (EP_β). Only components with $I > 5\%$ are listed. (*) the second line of ^{97}Zr is due to the subsequent decay with $T_{1/2}$ = 72 min of the ^{97}Nb produced in the primary decay.

Isotope	$T_{1/2}(h)$	E_γ (keV)	I_γ (%)	EP_β (keV)	I_β (%)
^{31}Si	2.62			1491	100
^{32}P	343			1710	100
^{67}Cu	62	93	16	377	57
		184	48	468	22
				561	20
^{83}Br	2.4			935	99
^{90}Y	64			2280	100
^{97}Zr	17	743	93	1915	88
(Secondary*)		657	86	1277	86
^{131}I	192	365	82	334	7
		637	7	606	90
^{133}I	20.8	530	87	1227	83.4
^{153}Sm	46	103	29	635	31
				704	49
				808	18
^{177}Lu	160	112	6	177	12
		208	10	500	79
^{188}Re	17	155	15	1962	25
				2118	72

2. Material and methods

2.1. The probe prototype

The probe prototype considered in this paper is shown in Fig. 1. The lower black part of the picture is a ring of 12 mm external diameter in Acrilonitrile Butadiene Stirene (ABS) that shields the sensitive element in it from the radiation coming from the side. The sensitive part of the probe is a cylinder 3 mm height and 5 mm diameter of mono-crystalline para-terphenyl doped to 0.1% in mass with diphenylbutadiene. This plastic scintillator was adopted because of its high light yield (~3 times higher than typical organic scintillators), non-hygroscopic property, and low density [26] that minimises the sensitivity to photons. The light tightness around the scintillator is ensured by a 15 μm thick aluminum sheet. The scintillation light is read out by a Silicon photomultiplier (SiPM) (sensL B-series 10035) biased with 24.5 V. Its spectral range is 300–800 nm and the peak wavelength is 420 nm. An aluminum cylindrical body (diameter 12 mm and length 14 cm) houses this assembly. Portable electronics based on ArduSiPM, with ethernet connection to a personal computer, were used for the read out [27].

2.2. Experimental setups

We measured the probe sensitivity to the radiation emitted by several long-lived radioisotopes with different energies, contained in sealed sources and in liquid ^{18}F samples. These measurements were used to optimize the parameters for the MC simulations (see Section 2.3) to describe the probe behavior and, in particular, the optical properties of para-terphenyl. The MC is in turn used to estimate the RGS performance.

These measurements have been performed with two different setups: the setup used for the sealed laboratory sources and the one made to measure the probe efficiency to liquid ^{18}F. These two setups will be described separately in the next subsections.

2.2.1. Sealed sources setup

The sealed sources were chosen in order to test the efficiency to photons and electrons at several energies. Their relevant characteristics are listed in Table 2. The γ sources have also electron emissions from internal conversion. Since the number of electrons exiting the source depends strongly on its details, we added a 2.8-mm thick copper