Intraoperative probe detecting β^- decays in brain tumour radio-guided surgery

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Abstract

Radio-guided surgery (RGS) is a technique to intraoperatively detect tumour remnants, favouring a radical resection. Exploiting β^- emitting tracers provides a higher signal to background ratio compared to the established technique with γ radiation, allowing the extension of the RGS applicability range. We developed and tested a detector based on para-terphenyl scintillator with high sensitivity to low energy electrons and almost transparent to γs to be used as intraoperative probe for RGS with β^- emitting tracer. Portable read out electronics was customised to match the surgeon needs. This probe was used for preclinical test on specific phantoms and test on "ex-vivo" specimens from patients affected by meningioma showing very promising results for the application of this new technique on brain tumors. In this article, the prototype of the intraoperative probe and the tests are discussed; then, the results on meningioma are used to make predictions on the performance of the probe detecting residuals of a more challenging and more interesting brain tumor: the glioma.

Keywords: Radioguided surgery, Intraoperative probe, Beta decays, Para-terphenyl

1. Introduction

The main advantage of the radioguided surgery (RGS) [1] exploiting pure β^- emitters [2] is the intrinsic high signal to noise ratio, also in presence of uptake from healthy tissue surrounding the lesion. This allows the identification of small tumor remnants by injecting a radiopharmaceutical activity as low as what is normally administered for diagnostic purposes; the possibility of extending the RGS to cases that would mostly profit from the low background around the lesion; the reduction of the exposure of the medical personnel to almost negligible levels.

Our goal is to make the RGS method available also for those tumors where the background from the healthy organs prevents the application of the traditional technique with γ or β^+ emitters, like abdominal or brain tumors and pediatric neoplastic diseases. Concerning the brain tumors, we studied the applicability of the RGS with β^- radiation on abdominal neuroendocrine tumors [6] and high grade glioma (HGG) [3], where complete resection of neoplastic cells is crucial for the patient outcome. However, we decided to validate the technique on meningioma brain tumors because of the well known high receptivity of meningioma to an appropriate β^- emitting tracer, ^{90}Y-DOTATOC a synthetic somatostatine analogue, which is administered to patient affected by meningioma for therapy (peptide receptor radionuclide therapy [4]).

The key element for the effectiveness of the novel approach is the intraoperative probe, which detecting electrons and operating with a low radiation background, better delineates the margins of the lesion. We realised and tested a prototype of the probe based on para-terphenyl scintillator and optimised for ^{90}Y radio-nuclides. The probe prototype is described in Sect. 2,

This probe was used for clinical tests on "ex-vivo" specimens of meningioma extracted from a patient administered with ^{90}Y-DOTATOC. The results, summarised in Sect. 3, showed that the RGS with β^- decays could be effective for meningioma.

Once validated on meningioma, we aim to apply the RGS on glioma where the outcome of the patient is strictly correlated to the completeness of the resection. Therefore, we tried to evaluated the performance of the RGS on glioma and compared with the results for the meningioma. In this article we discussed the prediction of the performance on glioma, obtained performing preclinical tests with dedicated phantoms and full Monte Carlo simulations with the FLUKA programm [5].

2. The intraoperative probe

The prototype of the intraoperative β^- probe used in the measurements and described in this paper is in Fig. 1. Small size and compactness are required for a handy surgical tool and high

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sensitivity to low energy electrons for ensuring a maximal reduction of the injected activity, with obvious advantages for the patient and the medical staff.

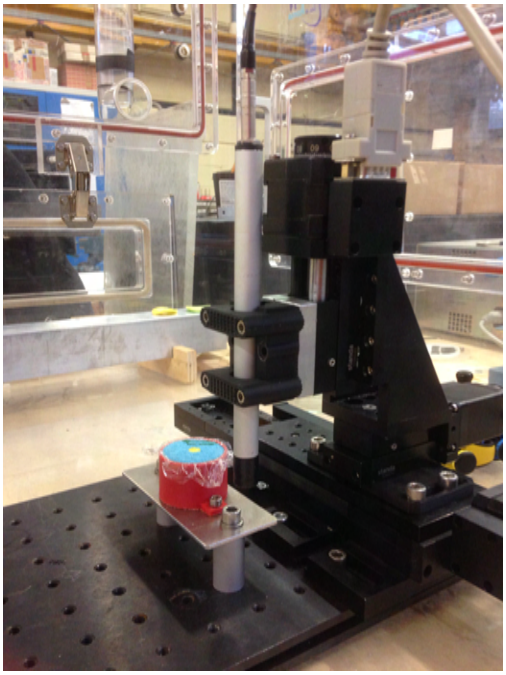

Figure 1: The intraoperative probe prototype.

The radiation sensitive element is a 5 mm in diameter and 3 mm in height scintillator tip made of commercial mono-crystalline para-terphenyl doped to 0.1% in mass with diphenylbutadiene. This material resulted the best candidate [7] due to its high light yield, non-hygroscopic property and low density, that minimises the sensitivity to photons. The scintillator is directly coupled to a SiPM (sensL B-series 10035) biassed with 24.5 V, spectral range 300-800 nm and peak wavelength 420 nm.

The scintillator tip is enclosed by a black ABS (Acrilonitrile Butadiene Stirene) ring with external diameter of 12 mm for mechanical strength and frontal vision. A 15 µm-thick aluminum front-end sheet covers the detector window to ensure light sealing. This assembly is encapsulated in an easy-to-handle aluminum cylindrical body (diameter 12 mm and length 14 cm), the total weight being 60 g. The prototype is compatible with a standard sterile covering of sub-millimetric film for using in surgical environment.

A portable read out electronics based on Arduino Due [8] was customised to match the surgeon needs and provides: data elaboration cycle of 1 s, acoustic and visual feedbacks and optional wireless data transfer.

Laboratory tests with point like and extended $^{90}Sr/^{90}Y$ sources, following the procedure described in [9, 10], allowed to conclude that the probe is sensitive to electrons above ~400 keV with an efficiency within the acceptance greater than ≈70% and almost transparent to *Bremsstrahlung* photons (sensitivity $<10^{-4}$). Moreover, tests with specific phantoms showed that the probe is able to detect 0.1 ml tumoral residuals within 1 s with a ^{90}Y activity of 5 kBq/ml (this activity is equivalent to the those measured on tumor tissue during a PET scan).

3. Performance estimated on specimens from meningioma

The probe prototype was used for the validation of the RGS technique with β^- radiation in a test on "ex-vivo" specimens from a patient affected by meningioma (details of the test are in [11]).

The patient was enrolled according to the results of a PET scan after administration of 4 MBq/kg of ^{68}Ga-DOTATOC to assess the receptivity to the radiotracer. The diagnostic exam revealed a bulk tumor of ~4.1 ml with an average standardized uptake value (SUV) for the radio-tracer of ~2.3 g/ml and a tumor-to-non-tumor ratio (TNR) of 16. Assuming that substituting the radionuclide does not alter the bio-distribution of the tracer, the uptake was rated sufficient to test the technique, in particular in an "ex-vivo" (i.e. background-free) environment.

Therefore, twenty-four hours before surgical intervention the patient was injected with 4.5 MBq/kg of ^{90}Y-DOTATOC to have an activity on the tumor at the time of the surgical intervention of about 10 kBq/ml. After surgery, that was performed as routine clinical indication, the extracted tumor and the attached Dura Mater were sectioned in samples and measured by the probe. Finally, the specimens underwent histology to evaluate their actual tumoural nature.

The feasibility study was confirmed: after administration of activity comparable with those for diagnostic treatment all the tumoral samples were clearly identified and there was margin for further reduction of the administered activity. The rate measured with the probe (105 cps on the bulk) matched the expected rates (115 cps) predicted by a detailed Monte Carlo simulation, based on the PET scan (see procedure in [3]). Tumoral volume as small as 0.2 ml were detected (30cps) and could be clearly discriminated from the background (1cps predicted by simulation) within 1 s of acquisition.

4. Test on phantom simulating glioma brain tumors

RGS for high grade glioma is more challenging than for meningioma due to the limited receptivity to DOTATOC: lower SUVs (≈1/10) and TNRs (≈1/2) are expected [3]. To evaluate how these values impact on the effectiveness of the RGS technique, a specific phantom reproducing a 0.07 ml glioma remnant embedded in 8 ml of healthy brain tissue was designed and realised with commercially available sponge. The large volume was obtained with three overlapping disks and a ring. The spot reproducing the infected residual was inserted in the ring but uncoupled by a sub-millimetric plastic film. A sketch of the phantom assembly is in Fig. 2 (it was realised following the procedure described in [10]).

The TNR=4 (realistic for the glioma clinical case [3]) was obtained saturating the sponge with properly diluted ^{90}Y-DOTATOC saline solution. Lastly, the disks and the ring were steeped in water to obtain a density equivalent to the human tissue.

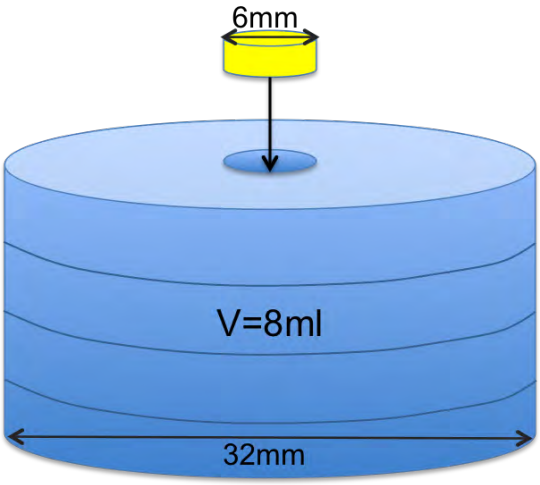

Figure 2: Sketch of the assembly of the phantom simulating a 0.07 ml tumour remnant (yellow spot) embedded in healthy tissue (blue large volume). The large volume was obtained with 3 overlapped disks and a ring (thickness 2.5 mm each).

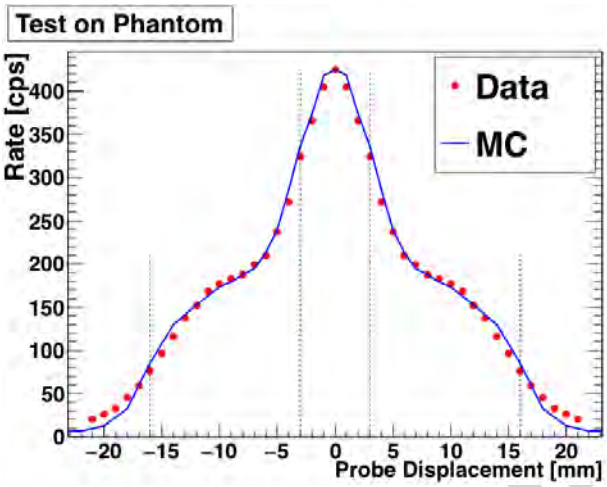

Figure 3: Scan of the probe over the glioma phantom with TNR=4: data (point) and MC simulation (line). The diameters of the spot (6 mm) and the ring (32 mm) are indicated by the dashed lines.

A scan over the described assembly was performed by running the probe in 1 mm steps with a motorized system. The tip to surface distance was ~100 µm and the measurement time per position was 100 s. At the scan moment the nominal activity of the spot was 45 kBq/ml.

The rates measured by the probe are shown in Fig. 3. The spot was correctly discriminated by the background since the rates induced on the probe had a signal-to-noise ratio S/N~2.5 (hot spot peak over the background plateau). The result of the MC simulation with FLUKA is superimposed and is in good agreement with data.

Using this simulation and a SUV value of 0.2 g/ml as observed in PET scans of 10 HGG patients [3] we rescaled the experimental shape to predict the signal rate expected from a tumour remnants within the surgical cavity. In particular, administering the same activity injected for the "ex-vivo" test (4.5 MBq/kg) the specific activity of the tumour bulk and the brain tissue were 1 kBq/ml and 0.25 kBq/ml respectively.

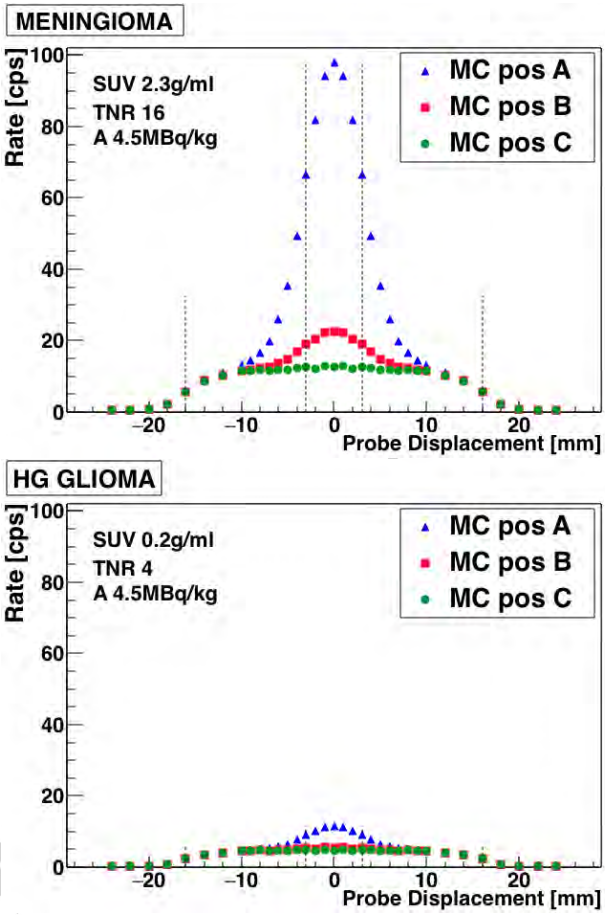

Figure 4: Rate profiles expected for the probe on a tumour remnant of 0.07 ml embedded in healthy tissue: Meningioma (top) and High Grade Glioma (bottom). The residual was simulated at different depths in the healthy brain tissue: on the surgical cavity surface (A) and below 2.5 mm (B) and 5 mm (C) of healthy tissue.

Fig. 4 (bottom) shows the rates expected on a 0.07 ml glioma remnant as would be measured by the probe. The probe signal to noise ratio is S/N~2.5.

The same analysis on a meningioma case is shown in Fig. 4 (top). In this case the administered activity was the same but the higher TNR (TNR=16) and SUV typical of this disease [3] made the S/N more favourable (S/N= 8.5) and the measured rate higher.

Finally, to estimate if the RGS is effective, we defined the minimum acquisition time (t_{min}) as the minimal time that a surgeon needs to spend on a 0.07 ml sample to evaluate whether it is healthy at 95% of Confidence Level. It is obtained from the probe rates for the activated spot and the background requiring that, according to the Poisson probability distribution, the probability of false-positives is less than 1% and the probability of false-negatives is less than 5%.

The t_{min} resulted <1 s for the meningioma and 3 s for the glioma (see Tab. 1). In both cases the RGS is effective since according to the common experience of surgeons few seconds

	Meningioma		HG Glioma	
Spot Depth	S/N	t_{min}	S/N	t_{min}
0 mm	8.4	<1 s	2.5	3 s
2.5 mm	1.9	4 s	1.2	>10 s
5 mm	1.1	>10 s	1.0	>10 s

Table 1: Signal to noise ratio expected for the probe and minimum acquisition time needed to detect a 0.07 ml meningioma and glioma tumour residual at 95% CL. Different depths of the residual in the healthy brain tissue were studied.

are needed to take a decision.

The rates discussed above refers to tissues on the surface of the surgical bed. Actually, tumour remnants could be partially or totally covered by fluids or healthy tissue. We used the simulation of the phantom assembly to study the potentiality of the probe for tumour remnant identification in the first millimetres of tissue, after the primary lesion removal.

Fig. 4 shows as the shape measured on meningioma (top) or glioma (bottom) changes when the activated spot is hidden by one (pos B) or two (pos C) disks corresponding to 2.5 mm and 5 mm of healthy tissue respectively.

The S/N expected for the probe and the minimum acquisition time t_{min} were calculated for each configuration and are summarised in Tab. 1.

5. Conclusion

A key element of the RGS technique with β^- decays is the probe that detects the low energy electrons. We developed a prototype based on para-terphenyl scintillator due to its high light yield and scarce sensitivity to Bremsstrahlung photons. The probe was used to test the effectiveness of the RGS for glioma brain tumour according to the realistic SUV and TNR and the results were compared with those obtained for the meningioma. Despite the lower receptivity to the radio-tracer, administering to the patient 4.5 MBq/kg of ^{90}Y-DOTATOC the probe was able to detect a 0.07 ml of glioma residual within 3 s, making the RGS effective also for glioma where the completeness of the resection is crucial for the outcome of the patient.

When the TNR is more favourable, the probe was able to detect also residual not completely exposed with an identification capability up to a depth of 2-3 mm of tissue.

The current detector is not fully optimised. A more sensitive prototype is under development with improvements of the light collection and the new generated SiPM with lower dark current that could lower the energy threshold of the probe and increase the sensitivity in depth.

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