Radio-guided surgery with β^- radiation: test on ex-vivo specimens

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Abstract

A Radio-Guided Surgery (RGS) technique exploiting β^- emitting radiotracers has been suggested, to overcome the impact of the large penetration of γ radiation. The detection of electrons in low radiation background, in fact, provides a clearer delineation of the margins of lesioned tissues. As a start, the clinical cases were selected between the tumors known to express receptors to a β^- emitting radio-tracer: ^{90}Y-labelled DOTATOC. We present the results of tests on ex-vivo specimens of meningioma brain tumour and abdominal neuroendocrine tumours. Voluntary patients were enrolled according to the standard uptake value (SUV>2 g/ml) and the expected tumor-to-non-tumor ratios (TNR$\sim$10) estimated from PET images after administration of ^{68}Ga-DOTATOC. All these tests validated this technique yielding a significant signal on the bulk tumour and a negligible background from the nearby healthy tissue. Even injecting as low as 1.4 MBq/kg of radiotracer, tumour remnants of 0.1 ml would be detectable. The negligible medical staff exposure was confirmed and among the biological wastes only urine had a significant activity.

1 Summary

Introduction A complete removal of tumoral tissue during surgical resection improves the patient outcomes. However, it is often difficult for surgeons to delineate the tumor margin in real-time. To this aim, radio-guided surgery (RGS) techniques were developed to facilitate the removal of tumor remnants by using intraoperative detectors [1] that can image radiotracers accumulated within tumors.

Despite the established methods that make use of γ-emitting tracers and γ detection systems, we proposed a RGS technique based on pure β^- radiotracers [2] and developed the intraoperative β radiation detecting probe [3]. β^- radiation, indeed, is characterized by a short penetration (few millimeters of tissue) with essentially no γ contamination. This approach allows operating with low radiation background and the possibility to apply the technique also to cases with a large uptake of nearby healthy organs. Furthermore, a β^- probe, detecting electrons and operating with low background, provides a clearer delineation of margins of the radioactive tissue, requires administration of low radiopharmaceutical activity ($\approx$1 MBq/kg) to detect millimetric tumour residuals and is compact and easy to handle in the surgical environment. Finally, the radiation exposure of medical personnel is almost negligible [2].

To study the potentialities of this technique we performed several studies where the expected signal from the probe prototypes was estimated on the basis of a simulation and tests on phantoms [4, 5, 3, 6]. We started with the clinical cases where a $beta^-$ radio-tracer is already available for the clinical use: the ^{90}Y-labelled [1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid0-D-Phe1,Tyr3]octreotide (DOTATOC). It is in use for therapy and its specificity is known and well documented for brain tumors (meningioma and glioma) and neuro-endocrine tumors (NET). We estimated that in all the cases, the expected tumour-to-non-tumour ratios (TNR) were high enough to allow a detection of 0.1 ml residuals within few seconds of application of the probe [4, 5].

Methods To implement the proposed RGS technique, we developed several prototypes of the intra-operative probe detecting β^- radiation. The sensitive part is a cylinder of 6 mm in diameter and 3 mm in height made of paraterphenyl scintillator, which having high light yield and low density provides high detection efficiency for low energy electrons ($\sim$1 MeV) and minimizes the sensitivity to bremsstrahlung photons [7]. The device is shielded against radiation coming from the sides and encapsulated inside an easy-to-handle aluminium body. Covering the detector window with a 15 μm-thick aluminium front-end cap ensures the light sealing. The scintillation light is collected by a silicon photo-multiplier and the readout electronics is portable and customised to match the surgeon needs. The probe was completely characterized on sealed sources in laboratory and tested on activated phantoms simulating the surgical cavity with millimetric tumour residuals embedded in healthy tissue [6].

To validate the entire RGS procedure and test the probe in a more realist environment, we performed ex-vivo tests on specimens from patients affected by meningioma [8] and abdominal NETs. The patients were enrolled according to the results of a PET scan after administration of ^{68}Ga-DOTATOC (assuming that the bio-distribution of the tracer does not depend on the labelling radionuclide: ^{90}Y or ^{68}Ga) to assess the receptivity to the radio-tracer and the TNR. If

the uptake was rated sufficient to test the technique (e.g. standard uptake value SUV>2 g/ml and TNR∼10 for meningioma), twenty-four hours before surgical intervention the patient was injected with order of ∼MBq/kg of ^{90}Y-DOTATOC to have an activity on the tumour at the time of the surgical intervention of ∼5 kBq/ml. Such activity approximates those administered for diagnostic imaging exams. After surgery, that is performed as routine clinical indication, the extracted specimens were sectioned in samples and their activity was measured by the probe. Finally, the specimens undergo histology to evaluate their actual tumoural nature.

Results Four voluntary patients affected by meningioma were enrolled and more than 30 specimens from tumor bulk and from margin were measured with the probe. All samples histologically classified as tumour measured rates significantly above the expected rate from the healthy brain [8], even with the smallest injected activity (1.4 MBq/kg).

As far as the exposure of the medical personnel is concerned, a Victoreen 450P gamma camera measured 0.80 (0.19) μSv/hr 10 (100) cm from the abdomen of the patient 5 hours after injection (and 18 before the surgical interventions). The same device did not detect any significant radiation in the surgical room or in the wastes after the intervention, apart from the urine pack. The readings of all personal dosimeters (Hp(10)) were consistent with zero, meaning that the operators effective doses and the equivalent dose to hands were less than dosimeters threshold dose (40 μSv).

Clinical tests on abdominal NETs have just started. A first patient affected by ileum neuroendocrine carcinoma underwent the surgery and the extracted ileum tract has been explored with the probe. The tumour bulk and an infected lymph node have been definitely distinguished from the background. Others tests on patients have been enrolled and the surgeries are foreseen before this summer. More results of clinical tests on NET will be presented.

Discussion The results of the clinical tests are showing the validity of the underlying assumptions and strengthening the feasibility studies already published [4, 5].

Although few patients are not statistically sufficient to drive conclusions on the medical efficacy of a technique, we can say that the method of assessment of signals in the probe starting from PET scans with ^{68}Ga-DOTATOC is reliable at the 10-20% level.

The comparison with results from the histology confirmed that all the samples identified by the probe as malignant were actually of tumour tissue. The measurements on the small samples showed that a volume of 0.1 ml of residual would yield a signal that could be clearly discriminated from the background within 1 s and with an administration of radiotracer activity at the level of those administered for diagnostic purpose.

Finally, the presumed extremely low level of exposure of the medical personnel was confirmed. However, the exposure of the patient is higher than in case of the conventional diagnostic examinations due to the long half-life of ^{90}Y. Nonetheless, it needs to be considered that the patient will undergo only one treatment with RGS during his life, while potentially several diagnostic scans.

Once the technique will be validated with meningioma and NETs, it will be

possible to extend it to other clinically relevant cases, eventually together with the development of specific radio-tracers. For such a reason we evaluated the $\beta-$ probe prototype capability to different radio-nuclide chosen among those used in nuclear medicine (see Ref. [9]).

Conclusion A potentially very promising technique for radio-guided surgery is being developed. The low background and the low dose delivered by the radio-tracer can allow for a large diffusion of such a technique and extending it also to cases with a large uptake of surrounding healthy organs (e.g. abdominal or brain tumours), where the established approach with γ radiation suffers due to the non-negligible background. Lower background rates also result in smaller radiopharmaceutical activity required to detect a tumour remnant and lower exposure for the medical team.

To strengthen these assumptions and validate the entire RGS procedure, we performed ex-vivo tests on specimens from patients affected by meningioma brain tumour and similar tests on abdominal neuroendocrine tumour are foreseen before the summer. We will present the results of these clinical tests and discuss the potentialities of extending the RGS technique to other clinical cases.

References

[1] E.J. Hoffman et al. "Intraoperative probes and imaging probes". In: *Eur. J. Nucl. Med.* (1999), pp. 913–935.

[2] E. Solfaroli Camillocci et al. "A novel radioguided surgery technique exploiting β^- decays." In: *Sci Rep.* 4.4401 (2014).

[3] A. Russomando et al. "An Intraoperative beta- Detecting Probe For Radio-Guided Surgery in Tumour Resection." In: *IEEE-TNS* 63.5 (2016), pp. 2533–2539.

[4] F. Collamati et al. "Toward Radioguided Surgery with beta- Decays: Uptake of a Somatostatin Analogue, DOTATOC, in Meningioma and High-Grade Glioma." In: *J Nucl Med.* 56 (2015), pp. 1–6.

[5] F. Collamati et al. "Time evolution of DOTATOC uptake in Neuroendocrine Tumors in view of a possible application of Radio-guided Surgery with beta- Decays". In: *J Nucl Med.* 56.1501-6 (2015).

[6] E. Solfaroli Camillocci et al. "Intraoperative probe detecting β^- decays in brain tumour radio-guided surgery". In: *Nuclear Instruments and Methods in Physics Research A* 845 (Feb. 2017), pp. 689–692. DOI: 10.1016/j.nima.2016.04.107.

[7] M. Angelone et al. "Properties of para-terphenyl as detector for alpha, beta and gamma radiation." In: *IEEE Transactions on Nuclear Science* 61.3 (2014), pp. 1483–87.

[8] E. Solfaroli Camillocci et al. "First Ex-Vivo Validation of a Radioguided Surgery Technique with beta- Radiation". In: *Physica Medica* 32.9 (2016), pp. 1139 –1144.

[9] C. Mancini Terracciano et al. "Feasibility of the $\beta-$ Radio-Guided Surgery with a Variety of Radio-Nuclides of Interest to Nuclear Medicine". In: *arXiv, submitted to Physica Medica* (Mar. 2017). arXiv: 1610.09246.