Intraoperative Beta- Detecting Probe For Radio-Guided Surgery Of Brain Tumors

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***Abstract*—The innovation of the radio-guided surgery exploiting $\beta-$ emitters is the higher tumor-to-non-tumor ratio (TNR) allowing both a smaller radiopharmaceutical absorbed dose to detect cancerous remnants and the possibility of extending the technique also to cases with a large uptake of surrounding healthy organs, as for brain tumors. Our first study cases are meningiomas, since an appropriate $\beta-$ emitting drug is already available (90Y-DOTATOC), but the goal is to apply this technique to gliomas. We verified the uptake of the radiotracer in 8/10 patients affected by meningiomas with TNR $\geq$ 10 and in 9/12 patients with a TNR $\geq$ 4 in case of gliomas. We developed prototypes of an intraoperative probe detecting $\beta-$ radiation. The core of the probe is a millimetric scintillator made of paraterphenyl due to its high light yield and low density. Tests in laboratory showed that with a radiotracer activity on the tumor of 5 kBq/ml and a TNR of 10 a 0.1 ml cancerous residual can be detected in 1s. That corresponds to administer to the patient 1 MBq/kg of radiopharmaceutical, which is a dose comparable to those administered for diagnostic use. Finally we estimated with a detailed simulation the exposure of the surgeon resulted in $\sim$0.1 Sv/h to the whole body and $\sim$1 Sv/h to the hands, well below the corresponding values for established RGS with gamma radiation.**

Manuscript received November 30, 2014.

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I. Purpose

THE radio-guided surgery (RGS) [1] represents a significant surgical adjunct to intraoperatively detect millimetric tumor residues by administering to the patient a radio-marked tracer that is preferentially taken up by the tumor. It is crucial for those tumors where the surgical mass removal is the only possible therapy. It has been demonstrated, in fact, that a radical resection, intended as whole enhancing mass removal, is positive both for a recurrence-free survival and the overall survival of the patients. The innovation of the RGS exploiting pure $\beta-$ emitters [2], [3] is the higher tumor-to-non-tumor ratio (TNR) compared to the established techniques using γ or $\beta+$ radiation [4], [5], [6], [7], [8]. Low background from healthy tissue around the lesion allows both a smaller radiopharmaceutical absorbed dose to detect cancerous remnants and the possibility of extending the technique also to cases with a large uptake of surrounding healthy organs (e.g. abdominal or brain tumors).

II. Methods

As first application of this technique we are investigating brain tumors, where a relapse is particularly dangerous and where other RGS techniques are limited by the large uptake of the brain. The goal is to apply the technique to gliomas, but the first study cases are meningiomas since, based on our experience with the Peptide Receptor Radionuclide Therapy (PRRT) [9], [10], [11], for them an appropriate $\beta-$ emitting drug is already available, namely 90Y-DOTATOC. The same molecule can be marked with 68Ga, thus allowing for an estimate of uptake prior to surgery with a Positron Emission Tomography (PET) exam. Extending the results of meningiomas after considering the different tracer uptakes will allow prediction on gliomas. To this purpose, we performed a study on 68Ga-DOTATOC Positron Emission Tomography (PET) exams on 10 patients affected by meningiomas and 12 patients affected by gliomas. In order to implement the proposed RGS technique, we have developed prototypes of the

intraoperative probe detecting $\beta-$ radiation. Given the short range of electrons and essentially no γ contamination (being the bremsstrahlung contribution, with a 0.1% emission probability, negligible), the sensitive detector is a small scintillator tip made of para-terphenyl. This material was adopted after a detailed study [12] due to its high light yield (3.5 times larger than typical organic scintillators), non-hygroscopic property and low density, minimizing the sensitivity to photons. Different sizes of the sensitive detector were tested. The best candidate resulted in a cylinder of 5 mm of diameter and 3 mm of height, shielded against radiation coming from the sides. The device is encapsulated inside an easy-to-handle aluminum body with the size of a pen, as protection against mechanical stress and has a blinding 10 m-thick aluminum front-end cap. The scintillation light is guided to a photo-multiplier tube (PMT) by optical fibers. A prototype with a silicon photo-multiplier is also under development. The readout electronics is portable and customized to match the surgeon needs. A wireless data transfer to the PC is envisioned [13].

III. Results

From the PET exams, the tracer uptakes from meningioma tumors resulted in 8/10 cases with a TNR equal or greater than 10, whereas for gliomas the uptakes were less evident with TNR $\geq$ 4 in 9/12 cases. With tests in laboratory using the prototype of the $\beta-$ intraoperative probe, we estimated that requiring a TNR of 10 for a cancerous residual of 0.1 ml and acquiring data for 1s, a radio-tracer activity on the tumor of 5 kBq/ml is sufficient. That corresponds to administer about 1 MBq/kg of a radiopharmaceutical to the patient. Such activity approximates that administered for a Computed Tomography (CT) scan. To quantify the exposure of the medical staff during a meningioma resection with $\beta-$ RGS technique, we have implemented a full simulation with FLUKA [14] and found that the surgeon would take 0.1 Sv/h on the whole body, 1 Sv/h on the hands [2]. The corresponding values for established RGS with 99mTc radiolabeled tracer are more than one order greater as estimated with the simulation, which was consistent with [1]. It has to be noted that exploiting pure $\beta-$ emitting tracers before and after the surgery the core of the radiation is screened by the patients body.

IV. Discussion

The applicability of the traditional RGS to other tumors is limited by the highly penetrating behavior of the γ radiation that can traverse large amounts of tissue: an eventual uptake of the tracer in nearby healthy tissue would represent a non-negligible background. A significant background requires a larger dose to increase the TNR and sometimes prevents the applicability of the technique. Such considerations apply also in the comparison with the RGS exploiting $\beta+$ emitters since in this case the γ background is in any case present. From the detector side, this problem forces the probes to be shielded or vetoed against photons coming from sources other than the tumor, thus limiting the configurations and in particular not allowing for very compact detectors. A $\beta-$ probe, instead, detecting electrons and operating with low radiation background, provides a clearer delineation of margins of radioactive tissue and it is a simple and compact tool, an essential feature for application in surgery as the access to the lesion is limited. Furthermore, measurements performed in absence of background require by definition read-out times shorter than measurements with background subtraction, as in the case of RGS exploiting $\beta+$ emitters, to acquire the same significance on the detected signal. 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, even with the development of specific radio-tracers.

V. Conclusions

A very promising technique for radio-guided surgery is being developed. The low background and the low dose delivered by the $\beta-$ radiotracer can allow for a large diffusion of such technique and extending the technique also to cases with a large uptake of surrounding healthy organs (e.g. abdominal or brain tumors) where the established approach with gamma radiation suffers the non-negligible background. Lower background rates also result in smaller radiopharmaceutical dose required to detect a tumor remnant and lower exposure for the medical team.

References

[1] Mariani, G., Giuliano, A. E., Strauss, H. W. (eds), Radioguided Surgery: A Comprehensive Team Approach. Springer, New York, (2006).

[2] Solfaroli Camillocci, E. et al. A novel radioguided surgery technique exploiting $\beta-$ decays. Sci. Rep. 4, 4401; DOI:10.1038/srep04401 (2014).

[3] Patent PCT/IT2014/000025 entitled Intraoperative detection of tumor residues using beta- radiation and corresponding beta- probes has been deposited by Universit degli studi di Roma La Sapienza, Istituto Nazionale di Fisica Nucleare and Museo storico della fisica e centro studi e ricerche E. Fermi.

[4] Tsuchimochi, M., Hayamaand, K. Intraoperative gamma cameras for radioguided surgery: Technical characteristics, performance parameters, and clinical application. Phys. Med. 29, 12638 (2013).

[5] Hickernell, T. S. et al. Dual detector Probe for surgical Tumor Staging. J. Nucl. Med. 29, 1101 (1988).

[6] Daghighian, F. et al. Intraoperative beta probe: A device for detecting tissue labeled with positron or electron emitting isotopes during surgery. Med. Phys. 21, 153 (1994).

[7] Raylman, R. R., Wahl, R. L. A fiber-optically coupled positron-sensitive surgical probe. J. Nucl. Med. 35, 909 (1994).

[8] Bonzom, S. An Intraoperative Beta Probe Dedicated to Glioma Surgery: Design and Feasibility Study. IEEE Trans. Nucl. Sci. 54, 1 (2007).

[9] Cremonesi, M. Ferrari, M. Bodei, L. Tosi, G., Paganelli, G. Dosimetry in peptide radionuclide receptor therapy: a review. J. Nucl. Med. 47, 14671475 (2006).

[10] Bartolomei, M. et al. Peptide receptor radionuclide therapy with 90Y-DOTATOC in recurrent meningioma. Eur. J. Nucl. Med. Mol. Imaging 36, 14071416 (2009).

[11] Cremonesi, M. et al. Dosimetry for treatment with radiolabelled somatostatin analogues. A review. Q. J. Nucl. Med. Mol. Imaging 54, 3751 (2010).

[12] Angelone, M. et al. Properties of para-terphenyl as detector for alpha, beta and gamma radiation. IEEE Trans. Nucl. Sci. 61-3, 1483 (2014).
[13] Talk N51-3 The ArduSiPM a Compact Trasportable Software/Hardware Data Acquisition System for SiPM Detector. V. Bocci, G. Chiodi, F. Iacoangeli, M. Nuccetelli, L. Recchia @INFN, Italy
[14] Battistoni, G. et al. The FLUKA code: Description and benchmarking. AIP Conf. Proc. 896, 3149 (2006).