EMRP Call 2011 - Health, SI Broader Scope & New Technologies

Selected Research Topic number: **SRT-h13**
Version: 1.0

Title: Metrology for molecular radiotherapy

Abstract

Molecular Radiotherapy (MRT) is gaining acceptance as a cancer treatment modality since new therapeutic radiopharmaceuticals have been developed. Currently radioactivity is administered on the basis of nominal measured activity or patient mass, without knowing the dose received by critical tissue within individual patients. This is despite evidence that treatment effect is dependent on the dose delivered to tumours and critical organs. The metrology is difficult, and there is no consensus approach to the problem. This SRT outlines the basic metrological problems associated with obtaining a measurement of absorbed dose from a radionuclide within a patient traceable to a primary standard, and the possibility of developing a practical dosimetry protocol.

Conformity with the Work Programme

This Call for JRPs conforms to the EMRP Outline 2008, section on “Grand Challenges” related to Health, New Technologies & Fundamental Metrology on pages 7 and 41.

Keywords

Molecular; Radiotherapy; Radionuclide; Radiopharmaceutical; Quantitative; Imaging; Activity; Dose; Cancer; Dosimetry

Background to the Metrological Challenges

For the majority of currently available cancer treatment options the approach is to destroy cell populations that are growing uncontrollably. This potentially leads to a non-selective treatment that can damage rapidly dividing cells that are non-cancerous. Recently there is increasing interest in developing “targeted therapies” such as Molecular Radiotherapy (MRT) that kills cancer cells by delivering a lethal dose of radiation, usually attached to a ‘carrier’ that selectively attaches to tumour cells or localises in the host tissue. As with external beam radiotherapy, MRT offers the advantage of delivering high radiation doses to a specific target; however in common with chemotherapy it can deliver the treatment systemically, attacking multiple sites throughout the body, and additionally it has relatively few side-effects.

MRT, in its earliest form has been used since the first half of the 20th century, when radioactive iodine was first used to treat hyperthyroidism. At that time there was no accurate way of measuring how much of the radioiodine was taken up and retained in the thyroid, so the treatment was based on administering a standard dose and repeating the treatment if needed. The potential of MRT has not been fully exploited, because rigorous treatment planning has been unavailable leading to non-optimal MRT implementations. There are two reasons for this:

1. The first reason is that it is not widely known how uptake and retention varies from patient to patient and therefore how much the individual dose to the target can vary between patients given the same administered “dose”.
2. The second reason is that the metrology required to measure the absorbed dose to tissue from a radionuclide is difficult.

When compared with conventional external beam radiotherapy, in which the dosimetry is strictly controlled according to agreed protocols, there is full traceability to primary standards, and there are even legal requirements for accuracy, it is clear that MRT is urgently in need of metrological support. MRT is also being recognised as competitive or superior to current early stage treatments, in particular given the low observed toxicity. The primary need is for a practical measurement procedure that can be adopted widely in clinical

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EMRP
European Metrology Research Programme
Programme of EURAMET

The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union

departments, and is supported both by metrology laboratories in the provision of calibration and verification services and by the consensus of the nuclear medicine community. This need has been widely reported in publications from hospitals working in the field [Flux et al 2007, Stabin 2008]. There has been considerable support from them for a metrology initiative to help ensure consistent protocols for effective treatment and patient safety. There is currently no primary standard for absorbed dose from radionuclides, so there is no traceability of dose measurements to a primary standard.

Scientific and Technological Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the JRP-Protocol.

The reliable, accurate measurement of the absorbed dose delivered to an individual patient by a molecular radiotherapy procedure requires a sequence of metrological steps. Each of these steps poses specific metrological challenges, which shall be addressed comprehensively in order to provide a complete package for the development of practical dosimetry protocols.

The specific objectives are:

1. Establishment of a phantom for calibration of quantitative imaging using a PET-CT or SPECT camera on the basis of new or existing standard phantoms, that enables a traceable measurement chain from an activity standard to a PET or SPECT measurement of activity
2. Validation with the help of Monte Carlo simulations
3. Development and dissemination of a suitable protocol for making and interpreting quantitative activity measurements in the standard phantom
4. Development of a Cerenkov counter, based on the TDCR (triple to double coincidence ratio) principle, to improve accuracy in therapeutic administrations of pure beta emitting radiopharmaceuticals
5. Establishment of dosimetry technology/ies to be used in the construction of a primary standard of absorbed dose to an appropriate medium from selected radionuclides, including the development and performance testing of prototype instruments, Monte Carlo simulations and uncertainty calculations.

The radionuclides under consideration have to be carefully prioritised according to recommendations from the relevant stakeholders.

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners and industry is strongly recommended.

The total eligible cost of any proposal received for this SRT is expected to be around the 2.7 M€ guideline for proposals in this call.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community. This may be through the inclusion of unfunded JRP partners or collaborators, or by including links to industrial/policy advisory committees, standards committees or other bodies. Evidence of support from the “end user” community (eg letters of support) is encouraged.

You should detail other impacts of your proposed JRP as detailed in the document “Guide 4: Writing a Joint Research Project”

You should detail how your JRP results are going to:

- feed into the development of urgent documentary standards through appropriate standards bodies
- transfer knowledge to the Medical sector.

You should also detail how your approach to realising the objectives will further the aim of the EMRP to develop a coherent approach at the European level in the field of metrology. Specifically the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of Member States and countries associated with the Seventh Framework Programme whose metrology programmes are at an early stage of development to be increased
- outside researchers & research organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.

Additional information

The references were provided by the PRT submitters; proposers should therefore establish the relevance of any references.

[1] Fisher, R. I., M. S. Kaminski, et al., Tositumomab and Iodine-131 Tositumomab Produces Durable Complete Remissions in a Subset of Heavily Pretreated Patients With Low-Grade and Transformed Non-HodgkinÂ's Lymphomas, *Journal of Clinical Oncology* (2005) 23(30): 7565-7573

[2] Flux, G. D., Bardies, M., Chiesa, C., Monsieurs, M., Savolainen, S., Strand, S-E., Lassmann, M. Clinical radionuclide therapy dosimetry: the quest for the "Holy Gray", *Eur J Nucl Med Mol Imaging* (2007) 34:1699–1700)

[3] Nilsson, S., C. Parker, et al., Clinical Experience and Radiation Safety of the First-in-Class Alpha-Pharmaceutical, Alpharadin (radium-223) in Patients with Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases, *International Journal of Radiation Oncology*Biology*Physics* (2010) 78(3, Supplement 1): S375-S376

[4] Bolch, W. E., Eckerman, K. F., Sgouros, G., Thomas S. R; MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry—Standardization of Nomenclature; J Nucl Med 2009; 50:477–484.