Publishable JRP Summary Report for JRP HLT11 MetroMRT Metrology for Molecular Radiotherapy

Background

The medical treatment modality of molecular radiotherapy (MRT), or nuclear medicine therapy, has been used for many decades for treating both benign and malignant diseases. However, from the start, treatment was based on the administration of a measured activity of radioactive material in a form taken up in the tissue to be treated. It is now clear that, for a given administered activity of radiopharmaceutical, the quantity taken up and retained in tissue varies widely among individuals. The therapeutic effect (or harmful effect in the case of normal tissues) depends on the absorbed radiation dose, and research has shown that the range in absorbed dose, for the same administered activity in different patients, can be up to 2 orders of magnitude. This has meant that the outcomes following MRT treatments based on a standard administered activity have been somewhat unpredictable, leading to a reluctance to use the modality. Furthermore development of new therapeutic radiopharmaceuticals, such as those using alpha-particles or Auger electron emitters targeting the cell nucleus, is hampered because the effectiveness on individuals is not well determined by the administered activity

There is a growing awareness of the importance of accurate dosimetry for the effective (and ethically responsible) use of MRT, and a number of clinical research centres have been making good progress developing methods of assessing absorbed dose to tissues from radiopharmaceuticals, based on quantitative imaging (QI) technology. But each of the methods developed have been one-off and there has been almost no adoption of routine dosimetry into clinical MRT practice. The reasons are many: the methodology is difficult, there is no standardisation of procedures, there is no objective means of verifying the accuracy of dose estimates, and as yet no way of predicting how much difference individual patient dosimetry would make to treatment outcomes. There are clinical trials that show poor correlation between absorbed dose and response, but this may have been due to poor dosimetry. So there is no clear argument for clinics to commit considerable resources to developing MRT dosimetry, when standard accepted practice has not required it up until now. This attitude would be totally unacceptable in the practice of external beam radiotherapy, where treatment planning in order to deliver a prescribed dose within tightly constrained limits is mandatory.

Need for the project

MRT has the potential to become a valuable component in the armamentarium against cancer. However, as explained in the previous section, widespread use is hampered by a reluctance to adopt individual dosimetry, because it is perceived to be difficult and resource intensive, and there is a lack of persuasive evidence that it is justified by improvement in treatment outcomes. There is clearly a need for an MRT “dosimetry culture” to be nurtured, which is readily accessible to any clinic and supported by national metrology infrastructure in a way analogous to dosimetry practice for external beam radiotherapy.

The MetroMRT JRP is addressing this need by developing and providing the background metrology to support routine individual MRT patient dosimetry, and by working with the MRT community to develop

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standard procedures that incorporate the essential elements of calibration and verification. The MetroMRT consortium comprises 6 National Metrology Institutes and 8 clinical research centres. The combination of scientific expertise and experience in both metrology and MRT will serve the project well.

Scientific and technical objectives

The MetroMRT project takes the well-established dosimetry formalism used for external beam radiotherapy as a model, and is formulating MRT dosimetry in an analogous way as a measurement chain which is traceable to primary physical standards and allows analysis of the propagation of measurement uncertainties. The basic links in the chain are:

1. Measurement of the administered activity;
2. Measurement of activity within a defined tissue volume using a quantitative imaging (QI) method (SPECT or PET);
3. Integration of a time-sequence of QI activity measurements to give the activity-time integral within the defined volume;
4. Calculation of the absorbed dose from the activity-time integral.

The objectives of the project address each of these links:

Activity measurement:

- To develop the TDCR Čerenkov technique for primary standard activity measurements of high-activity high-energy beta-emitters (such as ^{32}P, ^{89}Sr, ^{90}Y); the objective is to obtain on the one hand, a primary activity standard for ^{90}Y microspheres based on the TDCR Čerenkov technique, on the other hand, a reliable standard transfer protocol to end-users for ^{90}Y microspheres
- To improve the accuracy of the knowledge of the shape of beta spectra required for activity measurements using the TDCR Čerenkov technique as well as for absorbed dose calculations

Quantitative imaging

- To investigate methods for calibration and validation of quantitative radionuclide imaging, and to develop suitable phantoms and practical standard protocols to be used for traceable calibration transfer and dosimetry audits
- To investigate the performance of a range of image reconstruction and correction algorithms employed for quantitative imaging, using measurements and Monte Carlo simulation, in order to determine their relative accuracy/reliability and to provide objective evidence for preferred methods
- To develop advice and guidelines for standard procedures for quantitative activity measurements and verification/calibration using SPECT-CT and PET-CT

Activity-time integration

- To analyse the dependence of the accuracy of the activity-time integral on choice of activity measurement sequence and integration method, and develop practice guidelines

Absorbed dose calculation and measurement

- To investigate possible methodologies for the direct measurement of absorbed energy in a range of suitable media and geometries, from a selected number of radionuclides, for the purposes of achieving measurement traceability to a primary standard of absorbed dose and for validating the dose calculation methods used in patient dosimetry

Uncertainty analysis

- To analyse and model the dosimetry chain in order to estimate the uncertainty component in each link, and to assess the implications for the health and medical research communities of reducing these uncertainties.

Expected results and potential impact

Initially the JRP-Consortium had to go through a steep learning curve. Standards laboratories had no prior experience with quantitative imaging (QI) and dose measurement in radioactive liquids, and MRT clinics had very little experience with standard measurement procedures and reference measurement conditions. Most of the clinical JRP-Partners had each individually contributed to developing greater accuracy in MRT dosimetry, but were not easily persuaded to adopt standard procedures which may not be as accurate as their own.

Activity measurement

A new radioactivity counting method has been developed, using the established triple-to-double coincidence ratio (TDCR) technique, but based on detection of the Cerenkov light produced by high-energy charged particles in water. The method will lead to the production of both laboratory and portable instruments, which will be able to measure the activity of high-energy beta-emitters (such as Y-90) with greater accuracy than was previously achievable. This has been completed. A comparison of measurements of the activities of P-32, Mn-56 and Y-90 using TDCR-Cerenkov with conventional methods has been used to validate the new method.

Quantitative imaging

It was recognised early on that one of the most difficult parts of the project was developing a procedure or procedures for the calibration of quantitative imaging (QI). The various approaches have been clarified following discussions with clinical JRP-Partners and collaborators. A commercially available phantom (an elliptical Jaszczak phantom) has been chosen as a suitable candidate for QI calibration, and a standard procedure has been proposed. The procedure has been trialled using a Lu-177 source calibrated at NPL, and measurements have been taken at partner and collaborator clinics in Netherlands, Germany, Czech Republic and the UK.

Activity-time integration

The radiation absorbed dose to a critical volume within a patient is calculated from the total number of radioactive disintegrations within the volume, as estimated from a sequence of quantitative images. A method for determining the optimum sequence of time points at which to take the images has been developed in order to evaluate the most accurate activity-time integral given a set of clinical constraints.

Absorbed dose calculation and measurement

Measurements of absorbed dose from radionuclides in solution using radiochromic film, alanine pellets, TLD, and radiochromic gels are underway. Measurements have been completed at VSL on I-131 and at ENEA with high-sensitivity TLDs on Y-90 but the results have not yet been analysed. At NPL an extrapolation ionisation chamber is being developed as an absolute primary standard of absorbed dose in order to validate the doses calculated from QI measurements. The equipment has been designed and built, and a Monte Carlo computer model of the system has been set up to simulate the response of the instrument and calculate the correction factors in order for it to be used as a primary standard. The logistics of safely handling the high activities of the required radionuclides have been finalised and commissioning measurements will proceed shortly.

Uncertainty analysis

A key to the success of the project has been defining a traceable measurement chain of MRT absorbed dose measurement with sufficient rigour so that it satisfies the principles of metrology while maintaining relevance to clinical practice. The measurement chain has been determined for two clinical treatment protocols and, in particular, statistical methods have been employed to analyse the effects of different time sequences and activity-time integration methods on the accuracy and uncertainty of determination of cumulative activity.

Dissemination

The first of a planned series of themed public workshops was held in Rome in July 2013, on QI. The workshop was well received by around 80 participants, and reviewed both the difficulties faced and the way forward to a reliable calibration methodology. A second workshop was held in Paris in May 2014 on the topics of Input data for activity measurements, quantitative imaging and dosimetry. The workshop involved both project participants and leading outside experts, and attracted 50 attendees. The final workshop will be held at NPL in April 2015 and will provide a summary of the results and recommendations from the project as well as investigating the legal and practical aspects of implementing MRT dosimetry in clinical practice.

There has been a continuing interest in the project by the wider nuclear medicine community. To date 28 clinical departments and other institutions from 12 different countries have signed the exchange of letters as collaborators, with still more making enquiries. A particularly exciting development has been interest from commercial software developers, because collaboration with this group will be an essential component of promoting and distributing routine MRT dosimetry capability to the MRT community as a whole. Two of the major companies have signed the exchange of letters and a third is also interested.

Potential impact

The overall impact that the JRP will have on the MRT community (including clinical practice, research and manufacturers) will be that, by treating dosimetry as a formal traceable measurement with an associated uncertainty, the culture of treating patients with a nominal activity of a radiopharmaceutical will change to individualised patient treatments based on absorbed dose measurements. MRT will be much more accurately targeted, and as a direct result become more effective. With support from the metrology sector and with increasing confidence in the effectiveness of MRT the modality will become much more widely used as part of the frontline armamentarium against cancer. Accurate dose measurement will be a valuable tool in continuing research and development of new radiopharmaceuticals and technologies. In particular:

- It will be possible to target patients to a treatment that will be both effective and safe by using measurements to predict the tumour dose and normal tissue dose for individual patients.
- Patient safety will be improved by being able to more accurately control the treatment, ensuring that the patient will not be administered more radionuclide than is necessary for the desired therapeutic effect (otherwise this is in breach of radiation protection legislation).
- Patient safety will be improved by not being given a large dose of radiation if treatment can be shown to be ineffective in their case (again, such treatment is in breach of radiation protection legislation).
- Increased confidence in the application of MRT will lead to increased usage of radical curative treatments than at present, instead of for late stage palliative treatments.

JRP start date and duration:	1 June 2012, 36 months
JRP-Coordinator: Dr Vere SMYTH, NPL Tel: +44 20 8943 6223 E-mail: vere.smyth@npl.co.uk JRP website address: http://projects.npl.co.uk/metromrt/	
JRP-Partners: JRP-Partner 1 NPL, UK JRP-Partner 2 CEA, France JRP-Partner 3 CMI, Czech Republic JRP-Partner 4 ENEA, Italy JRP-Partner 5 PTB, Germany JRP-Partner 6 VSL, Netherlands JRP-Partner 7 AUSL, Italy	 JRP-Partner 8 Christie, UK JRP-Partner 9 ICR, UK JRP-Partner 10 IFO, Italy JRP-Partner 11 ISS, Italy JRP-Partner 12 LUND, Sweden JRP-Partner 13 UCL, UK JRP-Partner 14 Velindre, UK
REG-Researcher (associated Home Organisation):	Emiliano Spezi Velindre, UK
REG-Researcher (associated Home Organisation):	Manuel Bardies INSERM, France
REG-Researcher (associated Home Organisation):	Glenn Flux ICR, UK

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