Final Publishable JRP Summary for HLT11 MetroMRT Metrology for Molecular Radiotherapy

Overview

MetroMRT was the first European project to develop standard methods for the measurement of the absorbed dose received by patients undergoing molecular radiotherapy. The project successfully analysed the measurement process into a series of steps that could be calibrated against primary standards, and developed methods for verifying the accuracy of each step. A method was developed enabling an estimation of the uncertainty in the measurement of individual patient doses. The project results will form a valuable basis for implementation of standard dosimetry methods in MRT clinics.

Need for the project

Molecular radiotherapy (MRT), also known as nuclear medicine therapy, has been used for many decades for treating both benign and malignant diseases such as thyroid disease and neuroendocrine tumours. MRT involves the administration of a measured quantity of radioactive material (radiopharmaceutical) into the body to deliver a therapeutic dose of radiation to the target tissue, as opposed to external radiotherapy that delivers the dose using a beam of radiation generated in a medical linear accelerator. 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.

There is a growing awareness of the importance of accurate dosimetry for the effective use of MRT, and a number of clinical research centres have been making good progress in developing methods of assessing absorbed dose to tissues from radiopharmaceuticals, based on quantitative imaging (QI) technology. But each of the methods developed has 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 are 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 have been clinical trials held that show poor correlation between absorbed dose and response, but this may have been due to poor dosimetry. There is clearly a need for standardised dosimetry methods for MRT, just as there are in all other modalities of radiotherapy.

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

EMRP European Metrology Research Programme
Programme of EURAMET

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

Scientific and technical objectives

The MetroMRT project took the well-established dosimetry approach used for external beam radiotherapy as a model, and formulated 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 activity of the administered radiopharmaceutical;
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 in order to account for the retention of the radionuclide in the tissue volume;
4. Calculation of the absorbed dose from the activity-time integral.

The objectives of the project were as follows:

Activity measurement:

- To develop a modification of the standard laboratory triple-to-double-coincidence-ratio method (TDCR) in order to measure the activity of high-activity high-energy beta-emitters typically used in MRT (such as ^{32}P, ^{89}Sr, ^{90}Y) more accurately
- To improve the accuracy of the knowledge of the shape of beta spectra required for activity measurements using the modified TDCR technique as well as for absorbed dose calculations

Quantitative imaging

- To investigate methods for calibration and validation of QI, 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 QI, using measurements and Monte Carlo computer 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;

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 dose 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 Monte Carlo-based 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.

Results

Initially the project- consortium had to go through a steep learning curve. National Metrology Institutes 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. However by the end of the project, following an exchange of complementary knowledge and skills, the need to work towards a universally accepted dosimetry protocol was well understood.

Activity measurement

A new radioactivity counting method was developed, using the established triple-to-double coincidence ratio (TDCR) technique, but based on detection of the Čerenkov light produced by high-energy charged particles in water. The new method will lead to the production of instruments, which will be able to measure the activity of high-energy beta-emitters (such as Y-90) both in the laboratory and in the clinic prior to administration with greater accuracy than was previously achievable. The validity of the new method was demonstrated with a comparison of measurements of the activities of ^{32}P, ^{56}Mn and ^{90}Y using TDCR-Čerenkov with conventional methods. A transfer protocol was developed to enable clinical use of the new measurements. Equipment was also developed to enable the measured verification of the Y-90 beta spectrum. The beta spectrum is critical both to accurate activity measurements and dose calculations.

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 were clarified following discussions with clinical project partners and collaborators. A commercially available phantom (an elliptical Jaszczak phantom) was chosen as suitable reference object for QI calibration, and a standard procedure proposed. The procedure was trialled using a ^{177}Lu source at partner and collaborator clinics in Netherlands, Germany, Czech Republic and the UK. The results indicate that the proposed protocol is suitable as the basis for the calibration of QI for MRT dosimetry.

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 was 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 were undertaken using radiochromic film, alanine pellets, thermo-luminescence detectors (TLD) and radiochromic gels. The results generally confirm and give confidence to dose calculations based on Monte Carlo computer simulation methods. At NPL an absolute primary standard of absorbed dose was developed using extrapolation ionisation chamber technology. A pilot series of measurements on a ^{90}Y chloride solution showed good agreement with expected doses calculated from nuclear decay data, within an experimental uncertainty of 2.8 % (k = 2). Overall, these measurements showed that the calculation methods used in MRT dosimetry, which are based on Monte Carlo simulations from nuclear decay data, give results that agree with primary standard measurements of absorbed dose within an uncertainty acceptable for clinical applications.

Uncertainty analysis

A key to the success of the project was the definition of 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 was determined for two commonly used clinical treatment protocols (^{131}I-MIBG radionuclide therapy for neuroblastoma and ^{90}Y-DOTATATE therapy for neuroendocrine tumours) and, in particular, statistical methods were employed to analyse the effects of

different time sequences and activity-time integration methods on the accuracy and uncertainty of determination of cumulated activity, a major contributor to absorbed dose.

Actual and potential impact

Dissemination

The first of a planned series of themed public workshops on calibration activities and accuracy verification in quantitative imaging 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 was held at NPL in April 2015 with 84 attendees. It provided 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. Two key points arising from the workshop were the general lack of software qualifying as a "medical device" for use in routine MRT dosimetry, and the important role of clinical trials in developing and promoting an acceptance of robust standard dosimetry methods.

There was continuing interest in the project by the wider nuclear medicine community. By the end of the project 33 clinical departments and other institutions from 12 different countries had signed the exchange of letters as collaborators. A particularly exciting development was 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.

Papers have been regularly presented at European conferences where they have attracted considerable interest, particularly the annual congress of the European Association of Nuclear Medicine (EANM), where dosimetry is now a regular topic stream.

Actual and potential impact

The results from MetroMRT are of direct interest both to the scientific and MRT communities. In the former case, the activity and beta spectra measurement methods, the primary standard measurement of absorbed dose to radioactive liquid, and the methodology for uncertainty analysis of the MRT dosimetry chain are all new. In the latter case, recommendations have been provided on activity measurement in the clinic of ^{90}Y microspheres, QI calibration, choice of time points of QI measurements, and uncertainty analysis of practical MRT dose measurements. Each of these provides valuable support for future development of a standard dosimetry protocol for MRT. Individuals from 6 of the project partners are members of a working group developing an MRT dosimetry handbook and protocols within the IAEA Human Health Series, incorporating results from the MetroMRT project for dosimetry in each of the main applications of MRT.

The overall impact that the project will have on the MRT community (including clinical practice, research and manufacturers) will be that, by treating the dosimetry procedure 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. 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. 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 providing better control of 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.

List of publications

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