Publishable Summary for 15HLT06 MRTDosimetry
Metrology for clinical implementation of dosimetry in molecular radiotherapy

Overview

The overall aim of this project was to provide the metrology for the clinical implementation of absorbed dose calculations in Molecular Radiotherapy (MRT). The project built on the results and outputs from the preceding EMRP project HLT11 MetroMRT, which took the first steps towards providing data, methods, protocols and guidance for MRT dosimetry in collaboration with many European MRT clinics as well as radiopharmaceutical companies and camera manufacturers. The focus of this follow-on project was “clinical implementation” and it is strongly directed by the involvement of leading MRT clinics across Europe as well as building on metrology expertise.

Need

Over the past few years there has been an increase in Europe in the development and use of radiopharmaceuticals for treating cancer as well as an increase in the number of MRT clinical trials. However, in spite of the growing acceptance that an accurate knowledge of the radiation absorbed dose to critical tissues would provide a more effective targeted use of MRT, most patient treatments still follow the historical practice of administering a nominal activity of the radiopharmaceutical.

It is well known that the administered activity is not a good predictor of tissue dose and hence the outcome of patient treatment, due to individual variation in uptake and retention. However, one of the main reasons for a reluctance to perform individual patient dose measurements is that the process is complicated and there are no standard methods for calibrating or implementing MRT dosimetry in clinics. Therefore, prior to this project the MRT community had an urgent need for dosimetry calibration standards, validation methods, and clear guidance on how to implement MRT dosimetry in every European clinic offering MRT. As without this, it would not be possible to comply with EC Directive 2013/59/EURATOM, Article 56, which states that individual dose planning for radiotherapy patients (including MRT) must be enforced in legislation by EU member states.

The preceding EMRP project HLT11 MetroMRT clearly identified the key needs for obtaining dose measurements for MRT patients. These are: (1) measurement of the administered activity, (2) quantitative imaging (QI) of the activity localised in the patient using Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), (3) integration of activity measurements over the time of treatment, (4) calculation of the dose from activity measurements and (5) estimation of the overall uncertainty of the measurement. Each of these needs is addressed in the MRTDosimetry project’s objectives. The first objective addresses a specific need for more accurate QI measurement of the administered activity, for emerging beta-emitters therapies with ^{90}Y and ^{166}Ho, which are used with microspheres for liver cancer treatment. The remaining objectives are focused on meeting the generalised needs of MRT dosimetry.

Prior to this project the main sources of uncertainty in MRT dosimetry were in taking the step from dose measurements on simple reference geometries to QI measurements of the complex and varying geometries of the activity localised in real patients, as well as activity measurements over the time of treatment. All of these issues were addressed within this project for SPECT and PET based imaging, through the development of 3D printed quasi-realistic anthropomorphic phantoms and by creating a database of reference images of geometries covering typical clinical situations.

Dosimetry for MRT, as routinely performed, has no traceability to primary standards of absorbed dose. Therefore, prior to this project there was an urgent need to achieve traceability and to validate the dose calculation methods. Further to this, and central to any recommendations for dosimetry methods, is knowledge of the overall uncertainty associated with any particular method. Hence, the uncertainties in relation to the full MRT dose measurement chain (i.e. from a primary standard to a dosimetry calculation platform) also needed to be determined.

Objectives

The overall aim of this project was to provide the metrology for the clinical implementation of absorbed dose calculations in MRT. In order to do this, the specific objectives of this project were:

1. To determine branching ratios and emission probabilities for ^{90}Y and ^{166}Ho in order to enable improved quantitative imaging (QI) accuracy and dose estimation for these radionuclides, and to exploit new technologies in order to develop a suitable transfer instrument optimised for accuracy of measurements of the activity of MRT agents in clinics and radiopharmaceutical companies.
2. To develop 3D printing methods in order to generate a range of quasi-realistic anthropomorphic phantoms containing compartments fillable with known activities of radioactive liquid or standardised sealed radioactive test sources, having a range of geometrical complexity for validation of multimodal QI or absorbed dose measurement, and estimation of the uncertainties of measurement. In addition, to expand the protocol developed in JRP HLT11 for traceable calibration of SPECT QI for ^{177}Lu activity to include PET-CT QI of ^{90}Y and SPECT QI of ^{131}I, validated by measurements using the quasi-realistic anthropomorphic 3D printed phantoms.
3. To generate multimodal images either from SPECT or PET-CT phantom measurements or Monte Carlo (MC) simulations to provide material for an open-access database of reference images to be used as reference data for commissioning and Quality Control (QC) of QI using SPECT or PET-CT. In addition, to develop an architecture for and host the open-access database.
4. To improve the accuracy and metrological traceability in the calculation of dose from time-sequences of QI measurements by optimisation of the time points (i.e. obtaining cumulated activity from a time-activity-curve (TAC)), choice of measurement modality (imaging or non-imaging), refinement of absorbed dose standards, and validation of alternative absorbed dose calculation methods in phantoms using physical measurement techniques such as Magnetic Resonance (MR) sensitive gel-based and film-based dosimetry and Monte Carlo simulations.
5. To determine uncertainties in relation to the full MRT dose measurement chain from a primary standard to a range of commercial and non-commercial dosimetry calculation platforms. This includes image quantification (such as uncertainties in the selection of volumes of interest (VOI) and image reconstruction); integration of TACs, propagation of uncertainties in NTCP models, and determination of the overall evaluated uncertainty in the absorbed dose quantification process.
6. To facilitate the take up by healthcare professionals (clinical centres) and industry (scanner manufacturers and software developers) of the technology and measurement infrastructure developed by the project.

Progress beyond the state of the art

The preceding project HLT11 MetroMRT was the first time that the disciplines of clinical science and metrology were combined to address individual patient dosimetry in MRT. This project has built upon this and made significant advances on two fronts: firstly, scientific development aimed at reducing the uncertainty of each of the key links in the measurement chain to obtain a robust measurement protocol with traceability to primary standards. Secondly, the provision of standardised methods, test objects, open-access databases, and implementation/commissioning guidelines to support MRT clinics in setting up and validating dosimetry. In particular the project has gone beyond the state of the art in:

- Primary standardisation measurements for ^{166}Ho have been performed and the probability of ^{90}Y positron emission has been measured (Objective 1). Gamma-spectrometry and radioactive decay measurements were also carried out to improve the decay data with the aim of significantly reducing the uncertainty attached to the decay period. New hardware has been commissioned for production of a new high activity transfer instrument based on Cherenkov counting.
- To address objective 2, 3D printing has been used to develop a range of quasi-realistic anthropomorphic phantoms that can be filled with accurately known activities of radionuclides. These can then be used to mimic measurements of real patients, to validate QI measurements and to estimate the uncertainties associated with different QI methods. These novel quasi-realistic anthropomorphic phantoms and

surrogate solid radioactive sources were also distributed to project partners as part of an international comparison exercise to validate the calibration protocol developed within the project.

- Objective 3 has led to the development of a design for an open-access database of measured or MC-simulated test images of phantoms that are readable by contemporary clinical camera systems and that are accessible to most commercial software packages to allow clinics to test their MRT dosimetry methods. These images each have a "correct" activity and dose-rate calculated by MC simulation. Furthermore, simulations of two different commercial SPECT/CT systems and software enabling the simulations to be interfaced with commercial nuclear medicine workstation software were also developed.
- As part of objective 4 the project has further developed measurement methods introduced in the preceding project HLT11 MetroMRT, such as a primary standard of absorbed dose to water from a radionuclide solution; used to verify the accuracy of the MC results that are the basis of MRT absorbed dose calculations. Methods for the integration of activity measurements over the time of treatment have also been developed. As well as a comparison of measurement modalities (imaging or non-imaging) and refinement of absorbed dose standards. In addition, a common experimental framework for MR sensitive gel-based and film-based measurements that can be used to validate dose calculations has been established.
- Finally, the techniques developed in this project have been combined to continue the development of uncertainty analysis methods in relation to the full MRT dose measurement chain and allow uncertainty estimation methods for different dosimetry techniques and different patient geometries (Objective 5).

Results

Objective 1: To determine branching ratios and emission probabilities for ^{90}Y and ^{166}Ho in order to enable improved QI accuracy and dose estimation for these radionuclides, and to exploit new technologies in order to develop a suitable transfer instrument optimised for accuracy of measurements of the activity of MRT agents in clinics and radiopharmaceutical companies.

As part of this project the world's first primary standard activity measurements for ^{166}Ho, coupled with significant improvements to the nuclear data and half-life have been performed. This work will, for the first time, enable traceability and improved precision for measurements of ^{166}Ho made by clinical centres and radiopharmaceutical companies. For ^{90}Y new precise measurements of the e+/e- branching ratio have been made that will improve confidence in clinical quantitative PET measurements for this isotope; measurements that are particularly challenging.

In addition, the project has successfully demonstrated at several clinical sites the use of transfer instruments for the measurement of activity for high-energy betta-emitters in a clinical setting. This work has led to reduced uncertainties for the calibration of ionisation chambers and imaging at all centres involved. Thus, highlighting the benefits of reducing the traceability chain for beta-emitting radionuclide. The exciting prospect of a new design for a transfer instrument which can be operated without specialised radionuclide metrology training has also been developed in this project. The promising results on this prototype device have provide an excellent platform for its continued development to produce a field instrument for routine clinical use.

Objective 2: To develop 3D printing methods in order to generate a range of quasi-realistic anthropomorphic phantoms containing compartments fillable with known activities of radioactive liquid or standardised sealed radioactive test sources, having a range of geometrical complexity for validation of multimodal QI or absorbed dose measurement, and estimation of the uncertainties of measurement. In addition, to expand the protocol developed in JRP HLT11 for traceable calibration of SPECT QI for ^{177}Lu activity to include PET CT QI of ^{90}Y and SPECT QI of ^{131}I, validated by measurements using the quasi-realistic anthropomorphic 3D printed phantoms.

A unique new range of quasi-realistic anthropomorphic phantoms suitable for 3D printing has been developed. These phantoms are partly based on the International Commission on Radiological Protection (ICRP) 110 dosimetry standard model (for Adult Reference Computational Phantoms) which is a well established standard for dosimetry phantoms. The use of 3D printing for production also means that they can be made available to clinical sites at a fraction of the cost of conventional commercial phantoms. To compliment the 3D printed quasi-realistic anthropomorphic phantoms a range of long-lived traceable solid sources such as ^{133}Ba and ^{68}Ge, have been produced which can be used for QC of SPECT and PET systems.

Coupling these phantoms and sources with a newly expanded calibration protocol (based on the protocol developed in JRP HLT11) has allowed quantitative SPECT/CT imaging to be traceably calibrated. This is a major step forward and has demonstrated the capability for the harmonisation of imaging across multiple centres, systems and countries – a major step towards personalised therapies. The project successfully completed a multi-site inter-comparison exercise (covering 8 clinical sites in 5 countries) and has demonstrated the feasibility of clinical application of the newly expanded calibration protocol and the 3D printed quasi-realistic anthropomorphic phantoms plus sources.

Objective 3: To generate multimodal images either from SPECT or PET CT phantom measurements or MC simulations to provide material for an open-access database of reference images to be used as reference data for commissioning and QC of QI using SPECT or PET CT. In addition, to develop an architecture for and host the open-access database.

A series of SPECT/CT images of the 3D printed quasi-realistic anthropomorphic phantoms (from Objective 2), filled with ^{177}Lu to demonstrate time points of a representative MRT therapy, were produced. Complimentary MC SPECT simulations were also performed to generating realistic images from complex activity distributions in complex geometries. The imaging data produced from this has provided this project with a unique dataset that has uses in both QI and dosimetry. In addition, the design of the phantom has provided a realistic set of activity distributions to validate a number of parts of the QI chain.

The project has designed an open-access database to host these images. Future public access to this database will be provided through an appropriate standards body and will be linked from the project website. The open-source availability of the images means that they can be used in the majority of clinical camera systems in Europe. These images, together with the traceable SPECT QI calibration protocol developed for Objective 2, will allow ready calibration and validation of clinical dosimetry systems routinely used by hospital physicists.

Objective 4: To improve the accuracy and metrological traceability in the calculation of dose from time-sequences of QI measurements by optimisation of the time points (i.e. obtaining cumulated activity from a TAC), choice of measurement modality (imaging or non-imaging), refinement of absorbed dose standards, and validation of alternative absorbed dose calculation methods in phantoms using physical measurement techniques such as MR sensitive gel based and film-based dosimetry and MC simulations.

The project used image and non-image based methods to obtain absorbed doses for organs and bone marrow, which were then compared. Specifically, the potential differences between 3D imaging, planar whole-body scans and whole-body scans with measured or calculated attenuation correction and external probes with respect to the integration of the TAC were assessed. This comparison exercise highlighted two serious problems within the clinical practice of dosimetry. Firstly, there is no common standard for defining and transfer of Voxel of Interest (VOI) information for clinical dosimetry (as there is in external beam therapy). In fact, currently the external beam format is not accepted by commercial nuclear medicine systems without a great deal of work, if at all. Secondly, the comparison highlighted the paucity of software available to clinical groups that is able to perform advanced uncertainty analysis on the fits produced. Both these problems indicate a clear need for solutions to be developed with regards to commercial software so that clinical groups can take advantage and use this information.

A method for the determination of optimal scan times (optimised for the reduction of uncertainties) was developed. This was achieved for MRT, based on an activity standard uncertainty for a reference TAC, but the expected improvements were limited to patient data that closely matched the reference TAC.

The project also extended the use of a primary standard of absorbed dose of absorbed dose to water from a radionuclide solution, to other isotopes with improved uncertainties. Good results were achieved for ^{90}Y and ^{177}Lu albeit with reduced success for ^{131}I. The combined standard uncertainty for each of these measurements was is in the range of 0.95-1 %, a significant reduction from the 1.56 % uncertainty for the initial measurement in the preceding project HLT11 MetroMRT.

The project's work on the development of MR dose sensitive gels also showed promise with a clearly established reproducible dose response for isotope doped gels and results showing the potential of these gels to be used in realistic 3D printed phantoms. However widespread use of the MR gels will require the addressing of problems with temperature control and oxygen sensitivity which currently limit the MR dose sensitive gels use to specialist laboratories.

Objective 5: To determine uncertainties in relation to the full MRT dose measurement chain from a primary standard to a range of commercial and non-commercial dosimetry calculation platforms.

A key achievement of this project was the implementation of a "ground truth" exercise to establish uncertainties and accuracy for a given clinical dosimetry system. This is the first cross comparison using "known dose" between clinical centres and with commercial partners and has highlighted key areas that need to be addressed in order to improve MRT dosimetry. Another major result was the preparation of a procedure for the full commissioning of a dosimetry platform, from camera calibration to the final dose estimate, where the uncertainty budget is considered at every step. The full commissioning procedure is designed to allow users to determine the accuracy and uncertainties within their dosimetry technique and compare the output of the clinical system with the ground truth.

Impact

The project output has been disseminated through journal publications and presentations at a range of national and international meetings. Highlights of this engagement included; an invited presentation at the European Association of Nuclear Medicine (EANM) congress 2017 – the world's leading nuclear medicine meeting with over 6000 delegates, and a recent EANM Guideline on "Practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations". In addition, the project has hosted four very well attended European workshops covering, "Quantitative Imaging for molecular radiotherapy – metrology for clinical practice", "The principles and clinical implementation of dose calculation in molecular radiotherapy" and "Molecular Radiotherapy Dosimetry: Clinical Implementation of Personalised Dosimetry in Molecular Radiotherapy". A final workshop presenting the output of the project was attended by 80+ representatives from clinical centres, academia, industry and international standards bodies. Further details and presentations from these workshops can be found on the project website http://mrtdosimetry-empir.eu/?page_id=210.

Impact on industrial and other user communities

The key to the long-term success of this project will be in ensuring that the methods and tools developed are taken up by the European MRT community. In addition to the 12 clinical consortium members the project had 22 collaborators representing commercial, clinical and academic organisations.

There are many tangible outputs from this project which can be of direct use to the MRT community, including not only MRT clinics, but manufacturers of software, imaging equipment, and radiopharmaceuticals. The establishment of a primary standard for ^{166}Ho (Objective 1) will allow Quirem Medical (a manufacturer of ^{166}Ho microspheres) to standardise activity measurements for their product across multiple sites in different countries. Over the course of the project Quirem Medical have increased their engagement with the metrology community, becoming a collaborator in the project and presenting at the final project workshop.

A major route for maximising clinical uptake of the output from this project is engagement with SPECT/CT camera manufacturers. Representatives from all three major commercial SPECT camera vendors (GE Healthcare, Siemens Healthineers and Mediso Medical Imaging Systems) attended the public workshops held by the project. Mediso Medical Imaging Systems is also a project collaborator.

The calibration protocol from objective 2 and commissioning guidance from objective 5 has recently been incorporated into prototype clinical nuclear medicine dosimetry software of a commercial vendor Mirada Medical Ltd who collaborated on the project. The software has been publicly demonstrated at the British Nuclear Medicine Society (BNMS) meeting in 2019.

The designs for the 3D printed quasi-realistic anthropomorphic phantoms produced by the project (Objective 2) will be made available to end-users (via scientific publications), as will the open-access database of test images (Objective 3), which is intended to be readable by contemporary clinical camera systems and accessible to most commercial software packages, so that it can be used for commissioning dosimetry systems. The project's protocols for the clinical use of these phantoms and the database of test images for the commissioning of quantitative SPECT imaging and dosimetry calculation platforms were also presented to the MRT dosimetry community at the project's final workshop in Teddington, UK in May 2019 and are currently being developed into eLearning teaching modules.

Impact on the metrology and scientific communities

The project's continuation of the development of a primary standard of absorbed dose to water from a radionuclide solution (Objective 4) is an essential part of establishing traceability of MRT dosimetry to primary standards. This is the only primary standard of this type worldwide and is of considerable interest to the ionising radiation metrology community.

The project has also produced new nuclear data to enable more accurate PET imaging of ^{90}Y and new activity standards and measurements of the decay scheme and half-life for ^{166}Ho (Objective 1). This data has been submitted to peer-reviewed scientific journals, thus making it available to the radionuclide metrology, nuclear structure and the nuclear medicine communities. Nuclear data published in this way will consequently be evaluated by the Decay Data Evaluation Project (DDEP) for inclusion in their internationally-recognised database of evaluated nuclear data.

Impact on relevant standards

The project has engaged with a variety of standards bodies throughout the project including the:

BIPM (Bureau International des Poids et Mesures): where primary standards activity measurements of ^{166}Ho made during this project have been submitted to BIPM under the EURAMET.RI(II)-K2.Ho-166 comparison. This comparison exercise will demonstrate equivalence between primary standard measurements at 4 NMIs for this important emerging medical radionuclide.

EANM (European Association of Nuclear Medicine): A key achievement of the project is the adoption and publication of its practical guidance on uncertainty analysis for MRT dosimetry by the EANM as an EANM guideline (objective 5). Furthermore, reports developed in this project on "Recommendations for the Best Imaging and Non-Imaging Methods for Obtaining Cumulated Activity from a Time-Activity-Curve (TAC), and the Associated Uncertainties" (objective 4) and a "Procedure for Commissioning a Clinical Dosimetry Platform" (objective 5) have recently been submitted to the EANM Dosimetry committee. In response the EANM has scheduled a special Pre-Congress Symposium at the EANM Annual Congress 2019 dedicated to "European Projects for Clinical Implementation of Dosimetry in Molecular Radiotherapy" to present the protocols developed during this project.

IAEA (International Atomic Energy Agency): A Working Group has been set up by the Dosimetry and Medical Radiation Physics section of the Division of Human Health at the IAEA, to produce a publication on MRT dosimetry in the Human Health Series and this Working Group includes 4 of the project partners. The IAEA is considered to be the main international authority on medical radiation dosimetry protocols and has also agreed in principle to host the open-access database of test images produced by the project and to publish the SPECT calibration and dosimetry commissioning protocols developed in this project (in objectives 3 and 5). The IAEA have invited the project to present its final results on the development of a primary standard for absorbed dose to water from a radionuclide at the International Symposium on Standards, Applications and Quality Assurance in Medical Radiation Dosimetry (IDOS) to be held in Vienna in June 2019. The procedure for commissioning a clinical dosimetry platform (objective 5) has also been submitted to the IAEA.

MIRD (Committee on Medical Internal Radiation Dose): The project's results have been cited in and influenced the upcoming update to the MIRD primer of absorbed dose calculations. The schema set out in previous versions of this MIRD publication has been adopted as a de facto standard for clinical absorbed dose calculations. In addition, the project's recommendations for the best imaging and non-imaging methods for obtaining cumulated activity from a TAC (objective 4), and the associated uncertainties have also been submitted to the MIRD.

Members of the consortium are also members of several ISO committees such as (ISO/TC 85 and ISO/TC 69) and have liaised with the European Federation of Organisations in Medical Physics (EFOMP) to provide information on the project's results to them. Finally, the upcoming ICRP (International Commission on Radiological Protection) publication "ICRP 140: Radiological protection in therapy with radiopharmaceuticals" has also cited and been influenced by this project's results.

Longer-term economic, social and environmental impacts

The overall goal of this project was to encourage and assist European MRT clinics, as well as those worldwide, to adopt dosimetry as a routine part of patient treatment. To this end the project has help support compliance with the EC Directive 2013/59/EURATOM primarily through the production of guidance which can be used in the implantation of the directive within member states and through the educational workshops delivered by the project. This work will provide a significant step in bringing MRT into line with other radiotherapy modalities. Adoption of the techniques and protocols developed during the project should also allow clinical sites to use MRT with greater confidence and help predict patient treatment outcomes.

Clinical trials play a major role in the development of standardised dosimetry (including MRT). Absorbed dose is a critical parameter in both treatment effectiveness and harmful side-effects, therefore a reduction in the uncertainty of absorbed dose determination will give a greater statistical power to clinical trials. In turn, this should support the incorporation of standardised dosimetry into clinical trials and hence lead to the adoption of MRT in routine clinical treatment. The final results from this project are also being disseminated to national radiotherapy clinical trials quality assurance organisations, such as IAEA, EANM and MIRD, an important step towards widespread adoption.

The long-term results of the MRTDosimetry project will be a significant contribution to delivering more effective, better targeted treatments, improved outcome for the patients receiving them, and savings to national and European health systems providing this care.

List of publications

[1]. Billas, I., Shipley, D., Galer, S., Bass, G., Sander, T., Fenwick, A., & Smyth, V. (2016). “Development of a primary standard for absorbed dose from unsealed radionuclide solutions”. *Metrologia*, *53*(6), 1259–1271. http://doi.org/10.1088/0026-1394/53/6/1259;

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Project start date and duration:		June 2016, 36 months
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Internal Funded Partners: 1 NPL, United Kingdom 2 BEV-PTP, Austria 3 CEA, France 4 CMI, Czech Republic 5 ENEA, Italy 6 SCK•CEN, Belgium	External Funded Partners: 7 ASUL RE, Italy 8 Christie, UK 9 INSERM, France 10 LUND, Sweden 11 THG, Greece 12 UKW, Germany	Unfunded Partners: 13 AOSP, Italy 14 BRFAA, Greece 15 CARD, United Kingdom 16 OPBG, Italy 17 OUHT, United Kingdom 18 RSCH, United Kingdom
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