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

Overview

The overall aim of this project is to provide the metrology for the clinical implementation of absorbed dose calculations in Molecular Radiotherapy (MRT). The project builds on the results and outputs from the preceding EMRP JRP 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 is "clinical implementation" and it is strongly directed by the involvement of leading MRT clinics across Europe as well as building on metrology expertise.

Need

In the last 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 that are expected to start in the near future. 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, the MRT community has an urgent need for dosimetry calibration standards, validation methods, and clear guidance on how to implement MRT dosimetry in every European clinic offering MRT. Without this, it will 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 by 6 February 2018.

The previous EMRP JRP 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) Computed Tomography (CT), (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 current project's objectives, with the first being in response to the need for more accurate QI measurement of the administered activity, such as the beta-emitters ^{90}Y and ^{166}Ho, which are used with microspheres for liver cancer treatment.

The current main source of uncertainty in MRT dosimetry is 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 these issues will be addressed by this project using SPECT and PET methods, 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 currently performed, has no traceability to primary standards of absorbed dose. Therefore there is 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 need to be determined.

Objectives

The overall aim of this project is 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 are:

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 MC 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 previous JRP HLT11 MetroMRT defined the key needs in MRT dosimetry. Using this information, this project will address these needs on two fronts: firstly, scientific development aimed at reducing the uncertainty of each of the key links in the measurement chain in order 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 in order to support MRT clinics in setting up and validating dosimetry. In particular:

Objective 1 will provide new data to enable more accurate PET imaging of ^{90}Y (widely used for liver and neuroendocrine tumours) and will design a new transfer instrument to provide greater accuracy in the calibration of activity measurements in clinical departments. Work is currently underway to make the first direct measurement of the probability of ^{90}Y positron emission by the direct detection of positrons emitted from ^{90}Y. This novel technique is a powerful alternative to indirect detection of photons from the annihilation of the emission positrons. Monte Carlo (MC) simulations of the new activity transfer instrument have been completed and the designs are now being finalised for production.

Objective 2 will use 3D printing to develop a range of quasi-realistic anthropomorphic phantoms that can be filled in various ways with accurately known activities of radionuclides, used to mimic measurements of real patients, in order to validate QI measurements and to estimate the uncertainties associated with different QI methods. In particular the QI calibration protocol developed in JRP HLT11 will be expanded and tested.

Objective 3 will develop 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 in order to allow clinics to test their MRT dosimetry methods. These images will each have a “correct” activity and dose-rate calculated by MC models and also verified by measurements. In addition, protocols will be developed for the commissioning and QC of QI and MRT dosimetry systems.

Objective 4 will further develop measurement methods introduced in JRP HLT11 MetroMRT, such as a primary standard of absorbed dose to water from a radionuclide solution; in order to verify the accuracy of the MC methods that are the basis of MRT absorbed dose calculation. Methods for the integration of activity measurements over the time of treatment will be developed as well as, the choice of measurement modality (imaging or non-imaging), refinement of absorbed dose standards, and validation of alternative absorbed dose calculation methods, such as MR sensitive gel-based and film-based dosimetry.

Objective 5 will continue the development of uncertainty analysis methods in relation to the full MRT dose measurement chain, and will generate uncertainty estimation methods for different dosimetry techniques and different patient geometries.

Results

The first nine months of the project have focused on the design of several new technologies which allow the validation of quantitative imaging and subsequent dose calculations based on this imaging. These technologies address the accuracy of clinical activity measurements (a new activity transfer instrument) and provide more realistic and complex test objects (anthropomorphic phantoms and radioactive test sources).

Objective 1: To determine branching ratios and emission probabilities for 90Y and 166Ho 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

A highlight of this work has been establishing the specifications and a prototype design for a new transfer instrument for high-energy beta-emitters i.e. ^{90}Y and ^{166}Ho that will be optimised for accuracy of measurements of the activity of MRT agents in clinics and radiopharmaceutical companies. The designs for this transfer instrument, which will increase the accuracy of measurements of activity in clinics and radiopharmaceutical companies, have now been extensively tested using Monte Carlo simulations, allowing construction of the device to now proceed.

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 177Lu activity to include PET CT QI of 90Y and SPECT QI of 131I, validated by measurements using the quasi-realistic anthropomorphic 3D printed phantoms.

Novel designs have been made for: (1) a series of long-lived radioactive test sources based on ^{133}Ba which can be used as an analogue for shorted lived medical isotopes to compare the performance of QI across clinical centres, and (2) quasi-realistic anthropomorphic phantoms which provide realistic analogues for the human body.

Impact

The key to the success of this project will be in ensuring that the methods and tools developed are taken up by the European MRT community. The previous JRP HLT11 MetroMRT attracted a network of 33 European collaborating clinics, camera manufacturers, and radiopharmaceutical companies and the stakeholders for this project will be built upon this network to support maximum participation and uptake. The project will also be working with the European Federation of Organisations in Medical Physics (EFOMP), and the International Atomic Energy Agency (IAEA). 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 (objective 3).

Members of the consortium are also members of several ISO committees such as (ISO/TC 85 and ISO/TC 69) and are members of the Dosimetry Committee of the EANM (which produces European guidelines for applications of MRT dosimetry) and every opportunity will be taken to exploit the project's results with these committees. Further to this, the project will make a submission to the Committee on Medical Internal Radiation Dose (MIRD) on the methodology of uncertainty analysis for imaging and non-imaging methods for obtaining cumulated activity from a TAC (objective 5). The MIRD has been accepted for many decades as 'the' international standard for radiopharmaceutical dose calculation.

There will be many tangible outputs from this project which will be of direct use to the MRT community, including not only MRT clinics, but software, imaging equipment, and radiopharmaceutical manufacturers. The continuation of the development of a primary standard of absorbed dose to water from a radionuclide solution (started in JRP HLT11) will be an essential part of establishing traceability of MRT dosimetry to primary standards. This is the only standard of this type worldwide, and it will be of considerable interest to the ionising radiation metrology community (objective 4). The details of this standard have recently been published in Metrologia, the leading international journal for this research area (doi:10.1088/0026-1394/53/6/1259). A recent publication by project members also addresses the validation of clinical scale absorbed dose calculations in nuclear medicine dosimetry (objective 3, doi:10.1088/1361-6560/62/5/1885).

In addition to this, the designs for the 3D printed quasi-realistic anthropomorphic phantoms (objective 2) will also be made available to end-users (via the scientific literature), as will the open-access database of test images, 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. In addition, it is planned that the new transfer instrument (objective 1) will become commercially available and that this will lead to an improvement in the accuracy of the calibration of activity measurements in clinical departments.

Further to this, the new data to enable more accurate PET imaging of ^{90}Y and new activity standards and measurements of the decay scheme for ^{166}Ho (objective 1) will be published in peer-reviewed scientific journals. Nuclear data published in this way will be evaluated by the Decay Data Evaluation Project (DDEP) for inclusion in their internationally-recognised database of nuclear data.

The ultimate aim of the project is to encourage and assist European MRT clinics, and those worldwide, to adopt dosimetry as a routine part of patient treatment. The project will also support compliance with the EC Directive 2013/59/EURATOM, and bring MRT into line with other radiotherapy modalities. The end result should be more effective, better targeted treatment, for the benefit of patients and the healthcare system.

List of publications

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

Villoing, D., Marcatili, S., Garcia, M.-P., & Bardiès, M. (2017). "Internal dosimetry with the Monte Carlo code GATE: validation using the ICRP/ICRU female reference computational model". *Physics in Medicine and Biology*, *62*(5), 1885–1904. http://doi.org/10.1088/1361-6560/62/5/1885

Project start date and duration:	June 2016, 36 months	
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Internal Funded Partners: 1 NPL, Germany 2 BEV-PTP, Austria 3 CEA, France 4 CMI, Czech Republic 5 ENEA, Italy 6 SCK•CEN, Belgium	External Funded Partners: 7 ASMN, 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, UK 16 OPBG, Italy 17 OUHT, UK 18 RSCH, UK