Publishable Summary for 19SIP01 PINICAL-MRT
Protocols for clinical impact in molecular radiotherapy

Overview

An estimated 4.3 million new cases of cancer are being diagnosed annually and treatments based on molecular radiotherapy (MRT) are being increasingly used to treat them, creating a $7.27 billion market in radiopharmaceuticals. Ensuring patients receive the prescribed therapeutic doses whilst mapping drug delivery to tumour sites is routinely performed using Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET). For clinicians to comply with EC Directive 2013/59/EURATOM, Article 56, which requires confirmation that the administered patient dose matches the prescription, whilst delivering optimised healthcare outcomes, requires the adoption of improved practices in the commissioning, calibration and quality control of these mapping instruments. This project has provided the nuclear medicine community with calibration protocols, and commissioning and quality control guidance, for quantitative SPECT imaging and absorbed dose calculations that were developed in EMPIR JRP 15HLT06 MRTDosimetry. Supported by the European Association of Nuclear Medicine (EANM), the largest organisation facilitating nuclear medicine communication worldwide, the project's goal was to increase the adoption of best practice in clinics using MRT, fostering greater harmonisation in delivery. This work has enabled improved assessments of radiopharmaceuticals during clinical trials thus speeding the introduction of more effective cancer therapies.

Need

One in two people will develop cancer during their life and there were an estimated 4.3 million new cases diagnosed in 2018, which lead to 1.9 million deaths. This makes cancer the second most common cause of death in Europe. Molecular radiotherapy using radiopharmaceuticals is becoming a first line cancer treatment, and it represents a global radiopharmaceuticals market that is expected to reach $7.27 billion by 2021. However, despite 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.

Delivering optimised, patient specific therapies through the clinical application of MRT dosimetry, supported by training (objective 3) and published good practice guidelines for calibrating, commissioning and QC (quality control) of quantitative imaging (objective 1) based on the outcomes from EMPIR JRP 15HLT06 MRTDosimetry will improve healthcare delivery and reduce clinical costs.

Clinical trials play a major role in the development of standardised dosimetry (including MRT). Absorbed dose is a critical parameter in both assessing treatment effectiveness and harmful side-effects, therefore a reduction in the uncertainty of the absorbed dose calculation (currently estimated to be of the order of 8 % - 40 %) will give a corresponding greater statistical power to clinical trials. In turn, this should support the incorporation of standardised dosimetry into clinical trials and hence this will lead to the greater adoption of MRT as a routine treatment.

EC Directive 2013/59/EURATOM, Article 56 introduces requirements for individual dose planning for radiotherapy patients (including MRT) which is being introduced in legislation by EU member states. Quantitative imaging using SPECT or PET enables the precise location of administered activity in the tissue to be assessed. The EMRP JRP HLT11 MetroMRT and EMPIR JRP 15HLT06 MRTDosimetry put in place the foundations for a traceable MRT calibration infrastructure. EMPIR JRP 15HLT06 MRTDosimetry developed a traceable SPECT/CT calibration protocol and demonstrated the capability for harmonising imaging across multiple centres, systems and countries. It performed the first cross comparison "ground truth" exercise between clinical centres and the project's commercial partners using "known dose" to establish uncertainties and accuracy for a given clinical dosimetry system. This project's novel range of quasi-realistic 3D printed anthropomorphic phantoms, the dataset of SPECT/CT images and the associated Monte Carlo dosimetry calculations can provide a unique tool for the validation of the dosimetry chain.

The long-term results of EMPIR JRP 15HLT06 MRTDosimetry have been extended and promoted in this project as training materials and good practice guidance providing a significant contribution to delivering more

effective, better targeted cancer treatments, improved patient outcomes, a more harmonised approach to determining the dosimetry underpinning clinical trials, and significant cost savings to national and European cancer treatment centres. This project has prepared calibration, commissioning and QC best practice guidance for quantified SPECT imaging for MRT dosimetry for use in clinical centres. It also prepared a practical protocol (objective 2) for the commissioning and validation of a clinical MRT dosimetry calculation platform (with accompanying freely available validation datasets). This will allow the nuclear medicine community to set standards for dosimetry imaging with clinical equipment that commercial companies can incorporate into these systems. It has extended the e-learning training material produced in EMPIR JRP 15HLT06 MRTDosimetry to support the use of the project developed guidance and protocols in clinical centres delivering cancer treatments (objective 3).

Just as the success of EMPIR JRP 15HLT06 MRTDosimetry was primarily due to strong engagement with the clinical MRT community as demonstrated by the 250 attendees at project workshops; ***the defining impact from the project, in improving outcomes for patients, will only be delivered through clinical uptake of project outputs***. The support from the EANM in promoting the outputs from this project to European MRT dosimetry clinics will provide the strongest possible pathway to deliver this impact.

Objectives

The overall aim of this project was to deliver practical impact from the outputs of JRP 15HLT06 MRTDosimetry by incorporating them into protocols and guidelines which were promoted and made available by the project's primary supporter, EANM to MRT dosimetry clinics. The protocols were supported by training materials and by the provision of freely available datasets and 3D printed phantoms.

The objectives of this project were:

1. To prepare good practice guidance and guidelines based on the protocols developed in EMPIR JRP 15HLT06 MRTDosimetry for the calibration, commissioning and QC of SPECT dosimetry for use in clinical centres. In addition, to enable the protocol to be used, validated 3D printed phantoms will be loaned to clinical sites that do not have the capability to make their own. The project's primary supporter, EANM, will promote and make the guidance documents available to European MRT dosimetry clinics and will also assess the suitability of the guidance documents for use in a new EARL accreditation service for SPECT/CT systems analogous to those for Fludeoxyglucose-PET/CT.
2. To publish a practical protocol for the commissioning and validation of a clinical MRT dosimetry calculation platform (with accompanying freely available validation datasets). The protocol will be based on the commissioning procedure developed in the EMPIR JRP 15HLT06 MRTDosimetry and it will incorporate input from external funded partners that are experts in MRT dosimetry calculations.
3. To further develop the elearning training material produced in EMPIR JRP 15HLT06 MRTDosimetry to support the use of the protocol. These materials will be incorporated into the ESMPE lectures that are dedicated to nuclear medicine dosimetry and into other national training schemes. The Christie leads the MRT component of the UK National Health Service Higher Specialist Training Programme (HSST) through which these training materials will be disseminated

Results

Objective 1. To prepare good practice guidance and guidelines based on the protocols developed in EMPIR JRP 15HLT06 MRTDosimetry.

A paper presenting the results of a multicentre and multi-national evaluation of the accuracy of quantitative ^{177}Lu SPECT/CT imaging has been published (https://doi.org/10.1186/s40658-021-00397-0). This work demonstrates that reliable quantitative SPECT/CT is feasible following the dedicated calibration protocol developed within the MRTDosimetry project. The 3D printable phantom designs used in this work (consisting of a kidney and spleen model) have been made publicly available on the project's open-access data repository [1] allowing them to be used by clinical centres. Further details of the phantom have been published in [2].

Within the project it was identified that all SPECT activity calibration methodologies depend on the preparation of a phantom, or source, with known activity. These phantoms, when combined with an appropriate calibration protocol, provide the primary route for traceability for quantitative SPECT imaging. A Good Practice Guide (GPG) on preparing these phantoms in a clinical setting, based on routine techniques used in national measurement institutes, has been prepared. The current draft of the document has been made available on

the project data repository [1] ahead of final publication. An accompanying guidance document which provides a practical methodology for establishing measurement traceability for SPECT Quantitative Imaging for Molecular Radiotherapy Dosimetry has also been produced and is now being prepared for publication. This work provides an example of the application of the methodologies, presented in (https://doi.org/10.1186/s40658-021-00397-0) and the GPG on "Preparation of radioactive phantoms with an activity traceable to national standards", to the traceable calibration of SPECT/CT for quantitative imaging with ^{177}Lu. This objective has been fully achieved.

Objective 2. *To publish a practical protocol for the commissioning and validation of a clinical MRT dosimetry calculation platform (with accompanying freely available validation datasets).*

Validation of a Molecular Radiotherapy (MRT) dosimetry system requires imaging data for which an accompanying ''ground truth'' pharmacokinetic model and absorbed dose calculation are known. During the MRTDosimetry project a validation imaging dataset for a Molecular Radiotherapy dosimetry multicentre intercomparison exercise was produced [2]. The adoption of a standard reference dataset for assessing performance and providing Quality Assurance (QA) for MRT dosimetry platforms is an important step towards harmonisation and reproducibility for clinical MRT dose calculations. The complete imaging dataset from MRTDosimetry has been made available along with the STL files required to print a copy of the phantom [1]. A guidance protocol for the commissioning and validation of clinical MRT dosimetry systems has been produced which provides a comprehensive roadmap to establishing routine commissioning and validation of clinical MRT dosimetry systems. This is an essential step to increasing the uptake and efficacy of MRT and improving outcomes for patients. This objective has been fully achieved.

Objective 3. *To further develop the e-learning training material produced in EMPIR JRP 15HLT06 MRTDosimetry to support the use of the protocol*.

The consortium has to date delivered 15 lectures as part of training courses endorsed by EFOMP, SGNM, SSRMP, BAG, DGMAP and NHS HSST, providing training to over 1500 medical physicists, physicians, technologists and researchers. Work from the project has also been presented at 8 international and national workshops to a combined audience of >1000 participants. This objective has been fully achieved.

Impact

During the project the consortium has contributed to the development of training which has been disseminated to over 1500 participants at multiple training events courses endorsed by EFOMP, SGNM, SSRMP, BAG, DGMAP, IDUG and NHS HSST. This training has addressed a wide of career paths in medical physics including medical physicists, physicians, technologists, researchers, future consultant level healthcare scientists and Medical Physics Experts (MPE).

The project's open-access data repository, containing a range of open access data from the MRTDosimetry is available, hosted on the Open Science Framework (https://doi.org/10.17605/OSF.IO/69NGE). This repository provides a range of resources related to the calibration of quantitative SPECT imaging and commissioning of MRT dosimetry platforms. These included design for 3D printable phantoms and a validation imaging dataset with accompanying ''ground truth'' pharmacokinetic model and absorbed dose calculation [2]. Additional 3D printed designs for fillable cylindrical sources with varying diameters, suitable for measuring partial volume effects are also included. The repository also includes open access papers and good practice guidance from the consortium, released ahead of publication. This resource has seen a significant increase in unique visits throughout the project.

The consortium has presented results from the project at 8 international and national conferences during the project and provided input to 6 per-reviewed publications associated with the MRTDosimetry project. Members of the consortium have provided input and expertise to upcoming EARL accreditation for the harmonisation of ^{177}Lu quantitative SPECT/CT to improve multi-centre research studies and clinical trials. They have also contributed to new EANM practice guidance for quantitative SPECT-CT intended to assist practitioners in improving the diagnosis and treatment of a variety of diseases using nuclear medicine imaging (https://doi.org/10.1007/s00259-022-06028-9).

The outcomes from this project are in line with EANM's mission to facilitate communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. Currently, the EANM represents

more than 9,000 specialists from 41 different countries within Europe and it serves the interests of a community that goes far beyond these numbers and geographical boundaries. This project has provided the EANM and nuclear medicine standardisation bodies with easily available practical guidelines to support the robust application of MRT dosimetry in clinics. Combing the disciplines of clinical science and metrology couple traceability and a metrological treatment of the clinical measurement chain with medical expertise for the delivery of MRT across a range of European healthcare systems. This project has formed an important metrology contribution to delivering more effective, better targeted treatments, improved outcomes for the patients receiving them, and savings to the national and European health systems that are providing this care.

List of publications

[1] A. P. Robinson *et al.*, "MRTDosimetry data repository". *Open Science Framework*; 2021, doi: 10.17605/OSF.IO/69NG, Updated Mar 21, 2021, Accessed 21 March 2022.

[2] A. P. Robinson *et al.*, "Development of a validation imaging dataset for Molecular Radiotherapy dosimetry multicenter intercomparison exercises based on anthropomorphic phantoms," *Physica Medica*, vol. 109, p. 102583, May 2023, doi: 10.1016/j.ejmp.2023.102583.

This list is also available here: https://www.euramet.org/repository/research-publications-repository-link/

Project start date and duration:	1 September 2020, 30 months	
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Primary Supporter: Michael Lassmann, European Association of Nuclear Medicine		
Internal Funded Partners: 1. NPL, UK	External Funded Partners: 2. Christie, UK 3. INSERM, France 4. UKW, Germany	Unfunded Partners: -