FINAL PUBLISHABLE JRP REPORT

JRP-Contract number	HLT11
JRP short name	MetroMRT
JRP full title	Metrology for Molecular radiotherapy
Version numbers of latest contracted Annex Ia and Annex Ib against which the assessment will be made	Annex Ia: V1.3 Annex Ib: V1
Period covered (dates)	From 1 June 2012 To 31 May 2015
JRP-Coordinator	
Name, title, organisation	Dr Vere Smyth, NPL, United Kingdom
Tel:	+44 (0)20 8943 6223
Email:	Vere.smyth@npl.co.uk
JRP website address	http://projects.npl.co.uk/metromrt/
Other JRP-Partners	
Short name, country	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, The Netherlands JRP-Partner 7 AUSL, Italy JRP-Partner 8 Christie, United Kingdom JRP-Partner 9 ICR, United Kingdom JRP-Partner 10 IFO, Italy JRP-Partner 11 ISS, Italy JRP-Partner 12 LUND, Sweden JRP-Partner 13 UCL, United Kingdom JRP-Partner 14 Velindre, United Kingdom

EMRP
European Metrology Research Programme
Programme of EURAMET

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

REG-Researcher
(associated Home Organisation)

Researcher name, title	Emiliano Spezi, United Kingdom	Start date: 1 Oct 2012
(Home organisation Short name, country)	Velindre, United Kingdom	Duration: 30 months

REG-Researcher
(associated Home Organisation)

Researcher name, title	Manuel Bardies, France	Start date: 1 April 2013
(Home organisation Short name, country)	INSERM, France	Duration: 26 months

REG-Researcher
(associated Home Organisation)

Researcher name, title	Glenn Flux	Start date: 1 Feb 2014
(Home organisation Short name, country)	ICR, UK	Duration: 12 months

TABLE OF CONTENTS

1 Executive Summary

Introduction

The MetroMRT project is a watershed in that it is the first time that the disciplines of clinical science and metrology have combined to solve the problem of individual patient dosimetry in molecular radiotherapy, and to bring it into line with all other modalities of radiotherapy.

The Problem

Molecular radiotherapy (MRT – also known as nuclear medicine therapy) uses radioactive pharmaceuticals administered to patients to treat some types of cancer and other non-cancer diseases. Currently the treatment for a particular disease is prescribed on the basis of giving a standard amount of radioactivity to each patient. However, it is now well known that because of the wide range of different biokinetics in patients, the uptake and retention of the therapeutic agent, and hence the radiation dose can vary considerably. As a result the outcome of the treatment is somewhat unpredictable. Prescribing MRT treatments on the basis of measured doses rather than activity would be much more effective and safer. But the reasons why this is not done are many:

- MRT dosimetry is difficult, takes specialised expertise to implement, and takes resources to do regularly;
- MRT dosimetry has been developed in a number of research clinics, but there are no accepted methods for verifying how accurate the results are;
- There is no standardised method for calibrating the dose measurement;
- There is no traceability to primary standards or uncertainty analysis as required for a radiotherapy dosimetry protocol;
- There are no guidelines on best practice or implementation to assist non-research clinics.

The 2 key issues are: development of standard dosimetry protocols so that everyone can be confident they are measuring the same thing, and support to make it easier for non-specialist centres to adopt dosimetry into routine practice.

The Solution

MRT dosimetry needs to be structured as a measurement chain with traceability to the relevant standards (radioactivity and absorbed dose). This will enable the uncertainty in critical stages of the process to be understood, and calibration and verification procedures developed. Furthermore, construction of a formal traceable measurement chain will enable an uncertainty analysis of the end measurement.

The MetroMRT project is designed around addressing each of the key parts of the measurement chain, and providing an overall uncertainty analysis.

Impact

The potential impact from the project is to start the process for a major improvement in the effectiveness and safety of a treatment for cancer and other diseases. The scientific basis will be laid down for development of national and international dosimetry protocols and guidelines that will put MRT at the same level as other modalities of radiotherapy in terms of individual patient care.

In the shorter term, the project has proposed standard procedures and recommendations that can be adopted immediately by MRT clinics to help improve the consistency in doses delivered, and in particular be picked up by clinical trials involving MRT.

2 Project context, rationale and objectives.

2.1 The problem with dosimetry for MRT

Molecular radiotherapy (MRT, or nuclear medicine therapy) is conventionally prescribed to patients on the basis of a standard activity, in some cases adjusted for the weight of the individual patient. The standard activity is determined on the basis of clinical trials to find the activity that causes serious normal tissue damage to less than an acceptable fraction of the trial population (typically 5%). However, it is now well known that because of the wide range of different biokinetics in patients, the uptake and retention of the therapeutic agent, and hence the radiation dose, in normal tissue, from a standard administered activity can vary by up to an order of magnitude [Bodei et al EJNM 2004]. Even more extreme is the variation in radiation doses to the tissues to which the therapy is targeted. This can vary over a range of more than 2 orders of magnitude. For example thyroid cancer metastases treated with a standard activity of ^{131}NaI were shown to vary from 1.2 to 540 grays [Sgouros et al J Nucl Med 2004]. This range represents totally ineffective at one extreme to an overdose at the other. Strictly this is in clear breach of the principles of radiation protection (justification and optimisation). It is only tolerated because the radiation doses are not routinely determined, so the frequency of occurrence is not known.

The unpredictability of absorbed dose to critical tissues in MRT from the administered activity implies a corresponding unpredictability in outcome for the patient. From the clinical trials that established the “safe” activity limits, it can be expected that the average patient will get a beneficial response but the distribution of responses will be broad. If it were possible to predict in individual patients the radiation doses to both the target tissues and critical normal tissues then the administered activity could be optimised to achieve the maximum response, and it would be possible to predict the effectiveness of the treatment.

It is possible, but it is difficult, to measure individual MRT patient doses. A number of clinical research centres have each developed methods of MRT dosimetry based on quantitative imaging (QI) methods and a dose calculation formalism originally developed to estimate the safety of diagnostic nuclear medicine procedures. However each of these methods has taken considerable local expertise to develop, and there are no standard methods that can be readily taken up for routine clinical use.

But this is only part of the problem. MRT is radiotherapy. The other modalities of radiotherapy (external beam and brachytherapy) have been working for decades with the metrology community to establish dosimetry as a formal measurement prescribed in international protocols, with traceability to primary standards of absorbed dose and an analysis of the measurement uncertainty. Compliance with these protocols is accepted as standard good practice (e.g. IAEA, 2014) in order to ensure uniformity of treatments, particularly in multi-national clinical trials. MRT clearly does not meet the dosimetry standards of the other modalities. In most cases dosimetry is not done at all, and where it is there is little knowledge of the accuracy.

The reasons why MRT lags so far behind the other radiotherapy modalities are many. Not least is the complexity of the range of different treatments, radiopharmaceuticals, individual patient presentation of disease, different possible methods, etc. There is also the history and culture of Nuclear Medicine departments for whom radiotherapy is not a primary discipline, and radiopharmaceuticals tend to be considered “cytotoxic drugs” rather than vectors for delivering radiotherapy. This latter point is taken up in Section 4.

2.2 The contribution of metrology

The national metrology institutes have played a major role in the development of the primary standards and protocols that are the basis for dosimetry in external beam radiotherapy (EBRT) and brachytherapy. But up until the start of the MetroMRT project, metrology had made no contribution to MRT dosimetry. The project took as its starting point the formalism used by EBRT. The measurement chain for EBRT is as follows:

1. A clinical dosemeter is calibrated against a primary standard of absorbed dose (units of grays);
2. The dosemeter is used to make a dose rate measurement under reference conditions in the user’s beam (grays per beam monitor unit)

3. Calculation of the 3D dose distribution in the patient (per monitor unit) is done using a treatment planning system (TPS) that has been commissioned and validated using “best practice medical physics”
4. If the protocol is followed the uncertainty in the dose at the centre of the tumour should be less than 5%.

The EBRT measurement chain consists of 2 initial steps that are prescribed by a protocol, (measurement with standard equipment under reference conditions). The next step includes the patient, so reference conditions are replaced by standard best practice. Finally, the chain is sufficiently well determined to allow a statement of the uncertainty of the final measurement.

In the case of MRT (for dosimetry based on QI), it is possible to formulate the chain as follows:

1. Measurement of the activity administered to the patient (units of megabecquerels - MBq);
2. Definition and delineation of the volumes of interest (VOI) of target tissue and/or normal tissue, and quantity (mean over the VOI, voxel dose distribution, etc.);
3. Quantitative imaging (QI) procedure using a tracer activity, the full therapy activity, or a surrogate radiopharmaceutical (RP), to determine the activity in the VOI relative to the administered activity (MBq);
4. Choice of a time sequence of co-registered QI activity measurements in order to determine the biokinetics of the RP in the VOI;
5. Integration procedure under a curve drawn through the sequence of QI measurements to obtain total disintegrations within the defined VOI;
6. Absorbed dose calculation procedure taking account of the size and shape of the VOI (Gy).
7. Statement of uncertainty?

It is more complex. There are 3 separate components traceable to 2 different physical standards (1 and 3 traceable to activity standards, 6 to an absorbed dose standard), and 3 intermediate links (2, 4, and 5) that would be determined by best practice. Nevertheless, the process is not qualitatively different from that for EBRT. It remains to determine standard calibration methods for steps 1, 3, and 6, and to determine the science underlying the sources of uncertainty in the various methods that may be employed in the other steps, in order to be able to specify best practice well enough to enable quantification of the measurement uncertainty.

The MetroMRT project was structured around the links in the above measurement chain.

2.3 Objectives of MetroMRT

At the highest level, the objective of the project is to prepare the way for the development and universal adoption of standardised traceable dosimetry on individual MRT patients, in order to improve considerably the levels of safety and effectiveness of the treatments. This means development and improvement of the standards and calibration methods for measuring radioactivity, QI, and dose calculations, and an investigation of the uncertainties entailed in each step of the measurement chain. The detailed objectives are as follows:

Activity measurement:

- To develop the TDCR Čerenkov technique for primary standard activity measurements of high-activity high-energy beta-emitters (such as 32P, 89Sr, 90Y); the objective is to obtain on the one hand, a primary activity standard for 90Y microspheres based on the TDCR Čerenkov technique, on the other hand, a reliable standard transfer protocol to end-users for 90Y 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
- 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.

Bodei L, Cremonesi M, Grana C, Rocca P, Bartolomei M, Chinol M, Paganelli G. Receptor radionuclide therapy with 90Y-[DOTA]0-Tyr3-octreotide (90Y-DOTATOC) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2004 Jul;31(7):1038-46. Epub 2004 May 19. Review. PMID: 15150675

Sgouros G, Kolbert KS, Sheikh A, Pentlow KS, Mun EF, Barth A, Robbins RJ, Larson SM. Patient-specific dosimetry for 131I thyroid cancer therapy using 124I PET and 3-dimensional-internal dosimetry (3D-ID) software. J Nucl Med. 2004 Aug;45(8):1366-72. PMID: 15299063

IAEA General Safety Requirements Part 3, Vienna: International Atomic Energy Agency, 2014.

3 Research results

3.1 Activity measurement

3.1.1 Development of the TDCR-Čerenkov technique for use as a primary standard for radiopharmaceuticals

Developed in National metrology institutes (NMIs) for radionuclide standardization using liquid scintillation (LS), the Triple to Double Coincidence Ratio (TDCR) method is based on a specifically designed 3-photomultipliers system. (See Figure 1) Knowing the radionuclide decay scheme, the activity is determined using a free-parameter statistical model that allows a mathematical relationship between the detector efficiency (double coincidences between photomultipliers) and the experimental TDCR ratio given by coincidences between photomultipliers to be established. The TDCR value is interpreted as an indicator of the detection efficiency depending on the radionuclide to be standardized.

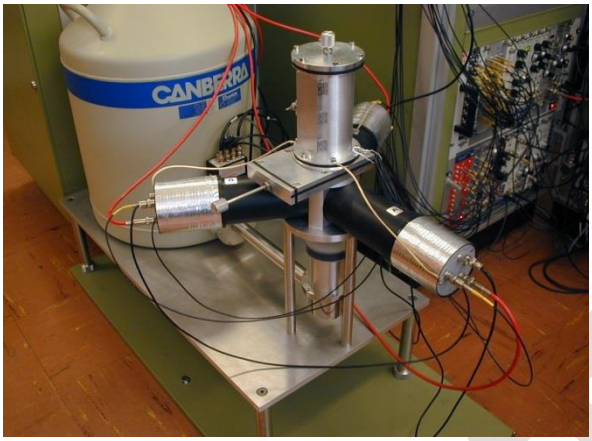

Figure 1. Triple to Double Coincidence Ratio (TDCR) apparatus at CEA.

Using the same detection set-up, the TDCR method can be extended to Čerenkov emission. In this case, light emission is characterized by a threshold effect that limits the production of photons by a charged particle (Čerenkov photons result from an electromagnetic perturbation in a transparent medium such as aqueous solutions) and permits discriminating low-energy pure-beta radioactive impurities in the measurements, usually performed in LS counting techniques by taking into account the different half-life of each impurity of the solution. Nevertheless, Čerenkov measurements are not frequently used for radionuclide standardization because higher detection efficiencies are obtained with liquid scintillation. However, the application of the TDCR method using Čerenkov emission is an interesting alternative to liquid scintillation in the case of high-energy beta-emitters used as radiopharmaceuticals for molecular radiotherapy, as ^{90}Y resin or glass microspheres. Indeed, since measurements are directly carried out in aqueous solutions, source preparation of radionuclides is easier and the mixing with a liquid scintillator is avoided. The TDCR-Čerenkov technique can also minimize the influence of possible gamma emitting impurities in the activity measurements. For activity calculation, the statistical modelling used for LS measurements has to be modified in order to take into account the physical characteristics of Čerenkov effect (anisotropy of light emission, threshold effect, continuous spectral bandwidth).

During the MetroMRT project, the development of the modelling for TDCR-Čerenkov measurements was performed according to two approaches. Briefly, an analytical statistical model was constructed using a free parameter for the anisotropy of light emission (NPL, CEA, ENEA). By using the Monte Carlo code Geant4, the other approach (CEA, ENEA) is based on a comprehensive description of the geometry and optical properties of the detector. In that stochastic modelling, triple and double coincidences between photomultipliers are calculated from the simulation of Čerenkov photons created in the optical cavity to the production of photoelectrons in photomultipliers.

Both approaches were tested and validated in NMIs by measuring various radiopharmaceuticals (NPL, CEA, ENEA): ^{11}C (β^+emitter, Emax ~ 960 keV), ^{32}P (β^- emitter, Emax ~ 1711 keV), ^{56}Mn (β^--γ emitter, Emax ~ 2850 keV) ^{89}Sr (β^-emitter, Emax ~ 1495 keV), ^{90}Y (β^-emitter, Emax ~ 2280 keV). Depending on the energy emitted by the radionuclides, the detection efficiencies calculated from the experimental TDCR values were ranged between 20% (^{11}C) to approximately 70% (^{90}Y). As expected these results are lower than those obtained with LS measurements due the threshold effect in Čerenkov measurements. For instance, in the case of ^{90}Y measurements, the detection efficiency obtained with a LS counter is greater than 99%. Activity measurements with the TDCR-Čerenkov technique were in good agreement within uncertainties with the expected values. Because of the lower detection efficiency, the uncertainties (less than 1%) related to Čerenkov measurements were slightly greater than those obtained with LS counting. Nevertheless, the good agreement between Čerenkov and LS counting is a good indicator that the activity measurements are not significantly influenced by the presence of impurities. Indeed, potential impurities are not always easy to identify even in time-consuming methods such as those based on the follow-up of radionuclide decays (ENEA).

To summarize, good results were obtained in NMIs (CEA, ENEA, NPL) during the MetroMRT project on the standardization of various radiopharmaceuticals using the TDCR-Čerenkov technique. The availability of new primary standards, based on this technique, for short-lived and pure-beta radionuclides allows the calibration of secondary standard activity measurements systems, such as Ionization chambers, particularly used and useful in Nuclear Medicine Departments. The developments achieved for the TDCR-Čerenkov technique were also important for the standardization of ^{90}Y-microspheres used for the treatment of liver cancer.

3.1.2 Development of standards and transfer methods for ^{90}Y microsphere samples

The development of techniques for the measurement of ^{90}Y microspheres is a key outcome of this project due to the increased clinical use of these products for the treatment of liver cancer with selective internal radiotherapy (SIRT). The accurate measurement of administered activity is critical when calculating the dose received by target organs and healthy tissue in SIRT. The properties of the supplied microsphere solution compound the already well-known measurement problems associated with pure beta emitting radionuclides using clinical devices such as radionuclide calibrators. These systems are typically based on ionisation chambers and are designed to measure mid- high-energy (between ~100 keV and ~2 MeV) photon emitting radionuclides however with ^{90}Y the response of these chambers becomes governed by the generation of bremsstrahlung radiation in the sample itself, the container geometry and the component parts of the measurement device. This leads to significant measurement challenges that must be overcome if accurate knowledge of the activity is to be determined. To address this specific measurement problem several key concepts were investigated: the physical parameters of the microspheres needed when creating Monte Carlo models of the measurement devices, primary standardisation of the activity of the microspheres, and a validated protocol for transferring activity standards to clinical sites.

Physical Parameters of ^{90}Y Microspheres

Microspheres are supplied in a resin format (known as SIRSpheres® and supplied by Sirtex Medical Limited) or a glass format (known as TheraSphere® by BTG International). This work focussed on the measurement of resin microspheres as they own the dominant market share across Europe. (See Figure 2.) ^{90}Y SIRSpheres® are composed of a commercial cation exchange resin (namely Aminex 50W-X4) which is similar to the types typically used in the nuclear industry for the separation for radiometals. However, this resin is chosen for this specific medical application due to the particle size being convenient for lodging in the capillaries of the liver (20-50 µm). ^{90}Y may be strongly adsorbed onto the resin provided the pH is maintained close to neutral and the product may then be selectively implanted to target regions within the liver itself, delivering a highly targeted dose with minimal damage to surrounding healthy tissue.

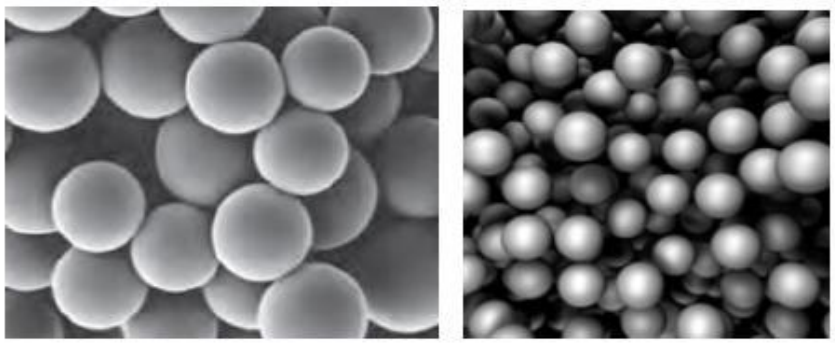

Figure 2 – electronic micrography of the microspheres

The SIRSphere® format is such that typical primary measurement techniques cannot be used, mainly due to sample inhomogeneity and insolubility. The SIRSpheres® are supplied as a slurry of resin and water which also leads to measurement issues relating to a changing geometry when using typical secondary instruments such as radionuclide calibrators.

Primary measurement of ^{90}Y microspheres

Many methods were investigated at the different National Metrology Institutes (NMIs), involved in the project, to dissolve the ^{90}Y microspheres in order to standardize the obtained solution by primary methods. In particular, some preliminary studies were performed on cold microspheres provided by SIRTeX to dissolve them by using different chemical solvents (HF/HCl mix, NaOH satured solution, $CHCl_3$, CH_3COCH_3, CH_3CN) giving all a maximum of solubilization of 50%. A different approach on the solubilization problem was also carried out by investigating the alkaline fusion; although the method is very aggressive, a solubilization of about 90% was reached in different tests performed always on cold micropsheres. A mineralization of the raw material by using microwave acid digestion apparatus was also investigated giving an interest results in the production of a limpid liquid solution by using cold SIRTeX micropsheres. A further method to dissolve the SIRSpheres® using a combination of hydrogen peroxide and nitric acid (known as the Fenton reaction) was implemented and validated with subsequent primary standardisation of the dissolved solution. Primary measurements were performed using the Triple to Double Coincidence Ratio (TDCR) method by means of liquid scintillation and Čerenkov counting as well as the CIEMAT/NIST method, and a good agreement between all techniques was obtained thanks to the chemical preparation of the dissolved microspheres. Because these techniques are based on two different physical processes of light emission, this agreement yields a high degree of confidence in the primary measurements. Because of the Čerenkov threshold, the agreement is also a good indicator that the measurements are not significantly biased by potential pure β-emitting impurities in the samples. This has provided, for the first time, a truly traceable measurement of the ^{90}Y activity contained in the commercial product as used in the clinic.

Validated Monte Carlo simulation of ^{90}Y in radionuclide calibrators

In order to provide an indication of measurement uncertainty, simulations of commonly used radionuclide calibrators and ionisation chambers were developed and used to investigate relative differences observed due to small changes in vial wall thickness and microsphere distribution. It was found that small changes within the manufacturing tolerances (quoted as ±0.2 mm) can lead to variations of between 10 % and 20 % in the radionuclide calibrator output, depending on the nuclear data and model used. Experimental results confirmed these discrepancies identifying differences of up to 14 % for vial variation by mass. Further tests were done to simulate the microsphere distribution and to test the use of attenuating filters to reduce the overall variation in response resulting in recommendations to use a copper filter in some instances. The development of the Monte Carlo models suggested the need to deepen the correct use of bremsstrahlung cross sections within codes for the specific application of pure β-emitting radionuclides and the proper assessment of the parameters which characterize the sensitive part of the radionuclide calibrators to the ionizing radiations . The results of these tests have also identified a significant measurement problem when using the current glass vial type. The variations observed would be significantly reduced if a more reproducible geometry were to be implemented by the supplier.

Transfer protocol for ^{90}Y microsphere measurements

Arguably the ultimate goal of this work package is to improve measurement capability at the clinical level and therefore the means to transfer primary measurements performed at NMIs to the clinical partners is vital. Three methods for this transfer were developed in this project involving dissolution, acid leaching and determination of calibration factors for secondary standard systems and commonly used radionuclide calibrators. Figures 3 and 4 and equation 1 show proposed transfer routes using these methods and Table 1 shows determined calibration factors and dial settings for a commercially available radionuclide calibrator. The transfer routes will allow clinical sites to send samples to a calibration laboratory, which in turn can provide a traceable activity value to the site. Due to variability of vial used by the supplier, large variations in the measurement of subsequent samples will still be observed, and in this regard it is vital that the supplier addresses this problem on order to reduce the uncertainty in administered activity to patients.

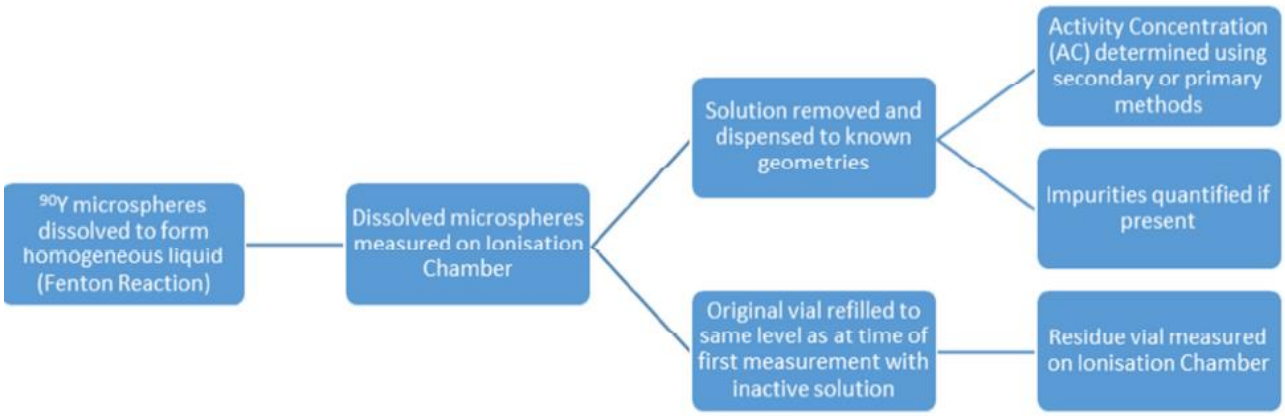

Figure 3: Transfer protocol using dissolution method

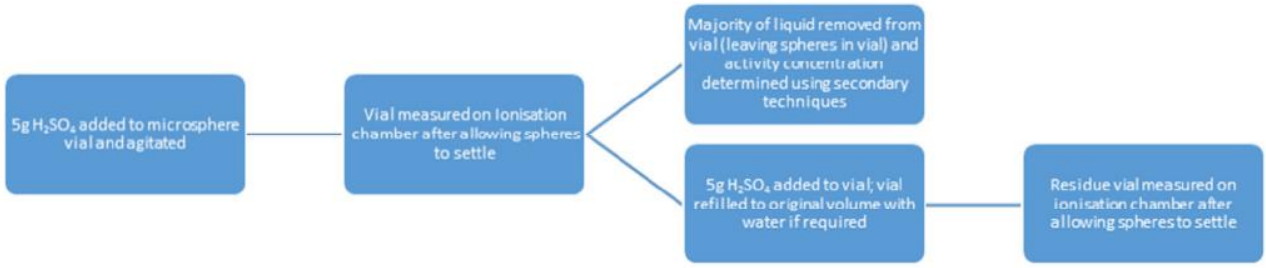

Figure 4: Transfer protocol using acid leaching method

Capintec CRC-25R	90Y-Chloride		90Y-Microspheres	
	Dial Setting	Uncertainty (%)	Dial Setting	Uncertainty (%)
v-vial with acrylic holder*	39 x 10	3	43 x 10	3
v-vial in syringe hole	53 x 10	3	57 x 10	3
Sirtex vial	31 x 10	3	32 x 10	3

Table 1: Dial settings determined for a commercially available Capintec CRC-25R© radionuclide calibrator. (*measured using NPL-designed holder)

$$A_{vial} = \frac{AC \cdot M}{\left(1 - \frac{I_{res}}{I_{vial}}\right)} \qquad \text{(Equation 1)}$$

3.1.3 Determination of beta spectra

Precise knowledge of the shape of energy spectra (coupled with well-established uncertainties) is sought by users from nuclear medicine (dose calculations) or ionizing radiation metrology (activity standardization). The Laboratoire National Henri Becquerel (CEA/LNHB) is developing the computer code BetaShape, to meet the demands of these users. This code calculates analytically the beta spectra for allowed and forbidden unique transitions and takes into account the screening effect due to the electron cloud, the finite nuclear size effect with regard to the electron Compton wavelength, and the radiative corrections. This program must be tested and validated by experiments. Hence, an operational device using a semiconductor Si detector (easy to implement, linear response function, good energy resolution) has been developed in order to measure spectral shapes and to quantify uncertainties.

Within the MetroMRT project, an experimental setup was successfully developed using a 500 µm thick PIPS semiconductor detector. Beta spectra from ^{14}C, ^{151}Sm and ^{99}Tc decays were measured and Geant4 Monte Carlo (MC) simulations were implemented at CEA and a deconvolution process was established for unfolding the detector response. The ENEA contributed to the project by implementing in the Penelope MC code the experimental set-up of the CEA beta spectrometer. The Laedermann's routine sch2for was included in the Penelope code as event generator of the MC program and in order to simulate the decay schema of different radionuclides.

The main difficulties in beta spectrometry arise because the spectra may be distorted by the detection system. Specific requirements are necessary to limit the sources of deformation and to maximize the signal-to-noise ratio. Silicon detectors are operable at room temperature, however thermally-generated leakage currents contribute heavily to the noise level. Operation at liquid nitrogen temperature offers marked improvements in energy resolution and to the signal-to-noise ratio, especially for low energies. Operation at low temperature, in turn, dictates a further design criterion: the detector must be kept under vacuum to prevent atmospheric moisture from condensing and freezing on the detector's surface. However, the vacuum pump induces microphonics that have to be attenuated. Otherwise, physical phenomena like self-absorption in the source, detector dead zones, angle of incidence, scattering and backscattering or bremsstrahlung have also a great influence on the measured spectral shape. A high vacuum provides another advantage, namely a low scattering environment. However, we must also carefully choose the materials and define the geometry of the detection chamber and source holder. Finally, for each radionuclide, a chemical study must be undertaken to determine the best method for preparing thin and homogeneous sources.

We want to avoid, as far as possible, the detection of backscattered electrons coming from the source holder. Backscattering is more pronounced for electrons of low energy and absorbers with high atomic number. Geant4 simulations were conducted by CEA from the Geant4 benchmark TestEm5 adapted to our application. Two materials were tested for the source holder: aluminium and PEEK (polyether ether ketone) which is an organic polymer thermoplastic. PEEK is the best plastic to use for vacuum applications because it does not outgas. A 500 keV mono-energetic beam was simulated, impinging on a full block of material and then, conserving the same geometry, with a 1 cm recess milled into the block.

A preliminary measurement of a ^{36}Cl source was carried out. The radioactive material was deposited on an ion-exchange resin. As expected, the electrons of high energy that go through the 500 µm thickness of the detector induce a folding of the spectrum, i.e. only a fraction of the energy of the electrons is deposited in the active volume of the detector resulting in an over-counting at low energy and an under-counting at high energy. The realistic geometry of the experimental setup was implemented in our simulations. The data were adjusted using an approximate linear energy calibration. The Geant4 simulation reproduced well the main distortion of the measured spectrum of ^{36}Cl. The data simulated with the Penelope MC code, implemented by ENEA, for two radionuclides, ^{14}C and ^{60}Co, were shared with CEA.

The measurement of ^{89}Sr and ^{90}Y beta spectra requires a thicker detector to ensure stopping even the most energetic electrons. The setup has thus been adapted implementing a 5 mm thick Si(Li) detector. The energy calibration was performed measuring screened and unscreened ^{133}Ba and ^{207}Bi sources. Electrons from ^{133}Ba decay were stopped using a 1 mm thick PEEK screen, while a 1 mm thick Copper screen was preferred for those from ^{207}Bi decay. Two kinds of fit were tested: a linear calibration and a second order polynomial fit. Below 1.7 MeV where peaks exist for these two sources, the energy calibration was found to be very linear. A possible method to determine the best calibration could be the extraction of endpoint energy of ^{90}Y spectrum, but this task would require a deconvolution process based on Monte Carlo simulations.

Beta spectra from ^{89}Sr and ^{90}Y decays were measured. However, electronics problems were encountered during the acquisition, resulting in noise and gain instabilities. Therefore, spectrum measurements are not trustworthy because of these instabilities. These measurements clearly needed to be verified with validated Monte Carlo simulations. As both ^{89}Sr and ^{90}Y decays exhibit significant emission probability of betas above 1 MeV, bremsstrahlung is significant. Its contribution was roughly estimated by subtracting the simulated spectra with new simulated spectra determined from identical Geant4 simulations but for which the bremsstrahlung process was turned off. The bremsstrahlung contribution for ^{89}Sr and ^{90}Y beta spectra is very small over the entire energy range of the spectrum except at the lowest energies, namely at most 4% for ^{89}Sr and 6% for ^{90}Y at 8 keV. If confidence exists in the simulation of the bremsstrahlung process, its contribution can be removed during the deconvolution process.

The experimental detection system dedicated to the Si(Li) detector has to be improved in order to stabilize and to minimize the electronic noise. This work is in progress. Beta spectra from ^{89}Sr and ^{90}Y will then be measured again. Geant4 Monte Carlo simulations of the complete setup will be performed with monoenergetic electron beams for unfolding the detector response. However, the excellent agreement between improved beta calculations and published form factors has proved that ^{90}Y and ^{89}Sr beta spectra are well known. For end-users from nuclear medicine, these calculations can therefore be used confidently for absorbed dose estimations. The comparison of the results obtained in the simulation of beta emitting radionuclides with other MC codes, such as the Penelope MC code implemented by ENEA, could open interesting perspectives in the topic of beta spectrometry both at the fundamental level and for its applications, in order to assess the energy spectra measurements of pure-beta and short-lived radionuclides, such as ^{90}Y, useful in MRT.

3.2 Quantitative imaging

3.2.1 SPECT/PET activity quantification and imaging techniques

The aim of this task was to determine and validate the optimum imaging techniques for the radionuclides corresponding to the radiopharmaceuticals most likely to benefit from the wide scale clinical introduction of quantitative imaging. The research has led to the development of practical advice on the use of different modalities, strategies for determining uptake and retention within an anatomical volume (optimal measurement time sequence), and the uncertainties inherent in each modality.

Survey of current and emerging MRT practice

In June 2012, an online survey was sent to all clinics that were part of the consortium asking them to rank and propose suitable radionuclides that should be investigated as part of the work package on quantitative imaging. From eight responses, the survey identified ^{177}Lu as a potentially suitable radionuclide for developing a calibration and verification protocol for Quantitative Imaging (QI) and indicated that most sites use SPECT/CT. Several partners also indicated in the survey that they have (or are currently developing) Monte Carlo (MC) models of their own gamma-camera systems, which was regarded as a significant benefit to the project. In addition to ^{177}Lu, the survey revealed that ^{131}I and ^{90}Y were also of interest in QI due to previous work done (with ^{131}I) and challenges encountered (with ^{90}Y). After this initial on-line survey it was decided to travel to several of the participating clinics to get a deeper understanding of clinical practice with these suggested radionuclides and to evaluate the practicality of choosing one or more radionuclides for the purpose of the project.

The outcome of the visits was that the main focus should lie with ^{177}Lu due to it being both the highest ranked in the survey and because it is a relatively new radiopharmaceutical of high research interest at this time. This radiopharmaceutical also presented an interesting set of challenges with regards to QI, which must be addressed to thoroughly evaluate a newly developed standard and standard procedure.

Methods and recommendations for uptake and retention modelling

The main goal of MRT is to deliver a high dose to the tumour and metastatic lesions and as low as possibly achievable dose to other organs, with special attention to the dose given to organs at risk. Balancing these two requirements gives the “therapeutic window”. In Peptide Receptor Radionuclide Therapy (PRRNT) using ^{177}Lu as the therapeutic agent, the ratio between the absorbed dose to the target and non-target tissues is not very high.

The current method of deciding on the administered activity for PRRNT is more or less based on the administration of a fixed activity (e.g. four consecutive therapeutic cycles of 7.4 GBq) to most of the patients or with adjustments for patient total body weight. The IAEA Report (2013) suggests that current treatment regimens in use are using ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC and for non-compromised patients, the administered activity is between 5.55 and 7.4 GBq with 3 to 5 cycles of treatments with a time interval between cycles of 10–12 weeks. This approach is deliberately conservative, so as not to harm the main organs at risk, in the absence of any knowledge of the actucal dose they will receive. However, there is a likelihood of under-treatment of a significant number of patients. Patient-individualised dosimetry is an essential tool to comply with the principles of radiation protection and to optimise treatment outcome, maximizing dose to the tumour and decrease radiation exposure to the normal organs and tissues, with special attention to the organs at risk, preventing toxicity. To identify the organs of interest, different methods can be applied: imaging techniques and non-imaging techniques (discrete probe monitoring, tissue sample and excreta counting).

To characterize the distribution, retention and excretion of the radiopharmaceutical over time, the following criteria are essential: catch the early peak uptake and rapid washout phase, cover at least 3-5 effective-half-lives of the radiopharmaceutical, collect at least at least two time points per clearance phase, account for 100 % of the activity at all times and account for all the major paths of excretion. For long-lived radionuclides such as ^{177}Lu it is crucial to quantify the radiopharmaceutical excretion. Otherwise it must be assumed that the radiopharmaceutical is retained in the body and consequently eliminated only by radioactive decay. The assumption that the radiopharmaceutical is retained in the body and removed only by physical radioactive decay can cause an overestimation of the absorbed for most of the organs and an underestimation for the kidneys and excretory organs.

The total number of time points needed to fully describe the activity in a source region as a function of time after administration depends on the pharmacokinetics of the particular radiopharmaceutical administered to each individual patient. Similar considerations also apply to the time intervals between measurements which should be adjusted according to the expected biological half-life. A general convention is to include at least three measurements for each biological uptake and elimination phase for the source region. This is also emphasised in international reports on how to best describe the pharmacokinetics of the radiopharmaceutical (Siegel et al., 1999; ICRU Report 67, 2002; Lassman et al., 2010) where it is recommended to have at least three measurements to define the time-activity curve for each kinetic phase, which should cover from the highest uptake until retention is negligible. To characterise the long-term retention of the radiopharmaceutical, ICRU (ICRU report 67) proposed data acquisition at times equal to multiples of the effective half-life (1/3, 2/3, 1.5, 3 and 5 times the effective half-life). For the long retention phase of the radiopharmaceutical, the effective half-life is usually longer, depending on the physical half-life and biological half-life; therefore data must be acquired at a later time to best represent the retention in the organs of interest. All the regions showing significant uptake should be considered regions of interest and when feasible the uptake and retention should be measured directly (by means of imaging and/or excreta sampling). In some cases when direct measurement is not possible, mathematical models play an important role describing the kinetic of a radiopharmaceutical (Siegel et al., 1999). Additionally poorly chosen timing of measurements could hide an elimination phase and thereby give the wrong cumulated activity and consequently absorbed dose. It is also necessary to choose the measurement time points to ensure that the contribution to the cumulated activity obtained from extrapolation from the first measurement back to the time of administration and from the last measurement to infinity is minimal.

This review shows that there are a number of different ways to determine the time activity curve in ^{177}Lu therapies. It is very difficult to say that any one of the described methods are better than another just from the literature, however, in this Joint Research Project a model for the uncertainty estimation of the time activity integral has been developed whereby it is possible to feed in data taken at different time points.

The recommendations from this task is to take advice from current practice (above) and feed in clinical data into the uncertainty model developed in WP4 in order to determine realistic uncertainties for different options that can then be reviewed and used as a guidance.

Siegel J, Thomas S, Stubbs J, Stabin M, hays M, Koral K, Robertson J, Howell R, Wessels B, Fisher D, Weber D and Brill A 1999 MIRD Pamphlet No. 16: Techniques for Quantitative Radiopharmaceutical Biodistribution Data Acquisition and Analysis for use in Human Radiation Dose Estimates J Nucl Med 40:37S-61S

ICRU Report 67, 2002, Absorbed-Dose Specification in Nuclear Medicine

Lassman M, Chiesa C, Flux G and Bardiès M (2010) EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting Eur J Nucl Med Mol Imaging DOI 10.1007/s00259-010-1549-3

3.2.2 Calibration phantom

A survey of suitable phantoms for calibration and verification of Quantitative Imaging was undertaken by both literature review and personal communications with clinical partners. Things that were considered important in the selection of suitable phantoms were: commercial availability, cost, availability in clinics, and practicality of use. The main methods identified for calibration of a SPECT system in terms of counts per MBq were:

a) A Jaszczak phantom imaged with a large (>2cm) active sphere. The SPECT/CT acquisition is acquired using typical clinical energy and scatter window settings and reconstructed using standard OSEM protocols with scatter and attenuation correction. This then provides the sensitivity and calibration of the system and can be verified by measurements using an anthropomorphic phantom.

b) Planar measurement of a petri dish containing known amounts of activity to determine a calibration 'in air'. This method relies on the commercial reconstruction software performing accurate attenuation correction and can again be verified using anthropomorphic phantom measurements.

The survey results were discussed by all partners and the conclusion was to use an adaptation of the Jaszczak phantom (shown in Figure 5) which would enable both calibration and verification measurements to be performed using modified versions of the same phantom.

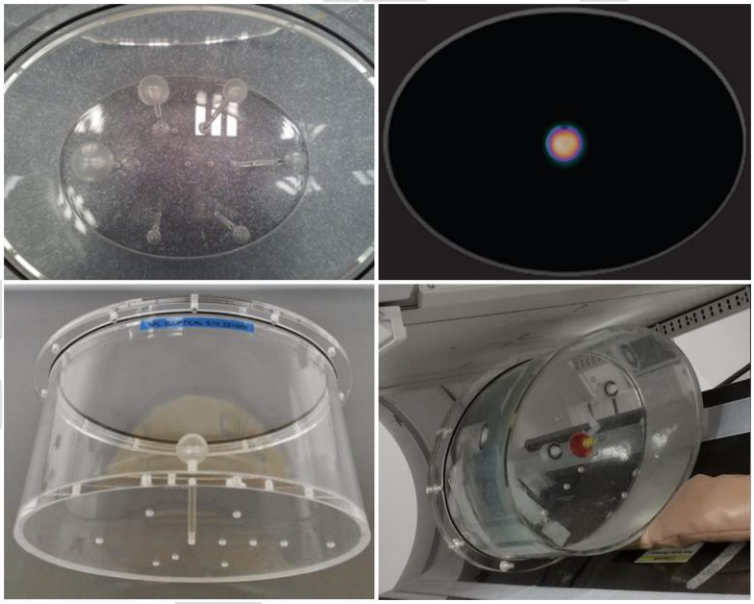

Figure 5: The Data Spectrum Corporation Elliptical Jaszczak Phantom. The phantom was used without the image quality features present and fillable spheres inserted in defined positions

In order to determine the practicality of using this phantom, three independent SPECT/CT systems were tested using a 33mm diameter sphere filled with a known amount of radioactivity and placed at different locations within the phantom. The cameras tested showed that when correction algorithms are enabled, the reproducibility of the camera (the ability to recover the real activity concentration in each different geometry) produced a maximum standard deviation of 15% and minimum of 3.3 %. The total estimated uncertainty was also determined by propagating the uncertainties from the measurements and adding the uncertainty of the ^{177}Lu activity due to standardisation and weighing. The results showed that diagnostic quality CT and resolution recovery techniques are beneficial when making quantitative measurements. The results also indicated that partial volume effects can be corrected for when imaging simple spheres but the application of these corrections to realistic patient geometries still needs further investigation.

Using the three measurements it was proposed that a calibration factor could be derived from the mean value obtained from the measurements and on the basis of this a calibration protocol was developed and tested within the project. The calibration protocol specifies a phantom preparation method, required acquisitions (along with specific acquisition parameters), reconstruction parameters and calculations required to determine the final recovery coefficients in counts per second per mega-Becquerel.

To fully identify the ability of clinical sites to perform quantitative imaging measurement, a comparison exercise took place over a period of 4 months between November 2014 and February 2015. The phantom used is shown in Figure 6 and was based on the elliptical Jaszczak phantom used for the calibration measurements with a lung and spine insert and body contour rings added. The spine insert was filled with bone equivalent solution of dipotassium hydrogen orthophosphate and the lungs were filled with lung equivalent materials to try to mimic a patient geometry as realistically as possible.

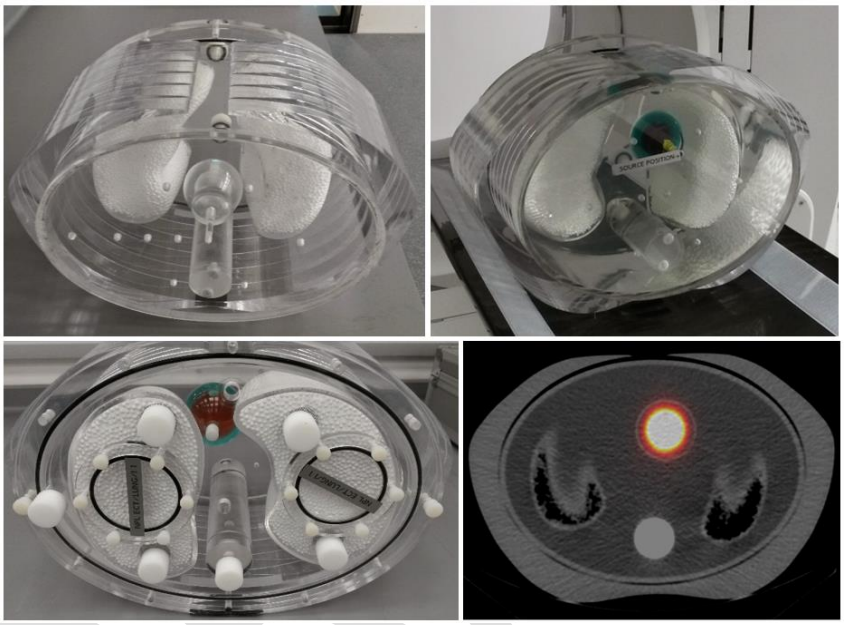

Figure 6: Elliptical jaszczak phantom adapted for use as part of the comparison exercise

The results indicate (Figure 7) that in order to perform comparative measurements at multiple sites then standard calibration, acquisition and reconstruction protocols should be followed throughout the campaign and allowing individual sites to use independent methods may invalidate any comparison of results within (for example) a clinical trial. Participants described a variety of methods used to determine the recovery coefficient (or calibration factor), mostly centred on the measurement of a simple sphere in a Jaszczak phantom, however no single method identified itself as a significantly improved method over the others.

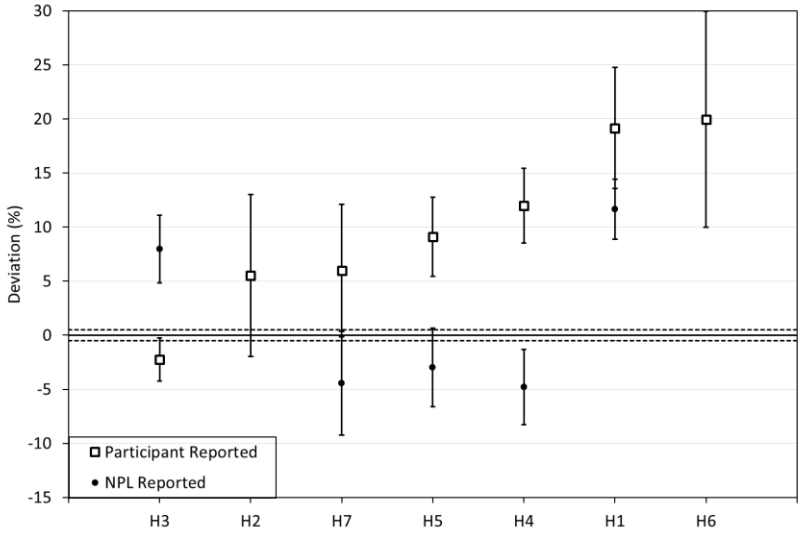

Figure 7: Results from the comparison exercise using participants own independent methods and a standard NPL calibration and reconstruction protocol.

The results also show that a great deal of work is still required to reduce the uncertainties in quantitative SPECT to enable individual patient doses to both tumours and (more importantly) surrounding healthy tissue to be calculated within limits generally considered acceptable in external beam (within 5 %). Reasonable uncertainties were reported by many of the participants and various methods were used to determine these uncertainties, however further research into the sources of uncertainty should be performed in order to fully determine a realistic uncertainty budget. This comparison only investigated a reasonably simple geometry and problems such as partial volume effect, dead time or background concentration have not been fully incorporated, however the results still indicate the need for more guidance and standards in this area.

3.2.3 Correction factors and algorithms

Scatter, attenuation, partial volume effects, and dead-time play a major role in quantitative imaging as they contribute to image degradation. The aim of Task 2.3 was to evaluate the impact of such correction factors and algorithms necessary to perform quantitative estimations of the source activity from a radionuclide image. This task focussed on three radionuclides (^{177}Lu-SPECT, ^{131}I-SPECT and ^{90}Y-PET) and was performed in close collaboration with unfunded partners' facilities. At each of the unfunded partner institutions quantitative evaluation of the activity was performed both in reference conditions and non-reference conditions assessing the effect of a number of correction factors. Reference conditions were realized through the reference phantom described in the previous section, filled with uniform activity distribution and absence of background activity. Non-reference conditions were realized by an anthropomorphic torso phantom (ENEA) and by an anthropomorphic Jasczcak phantom (NPL). The activity of each radionuclide was measured through secondary instruments available at NMI's sites.

Number of iterations. The effect of number of iterations was studied by ENEA in a number of reference geometries (point source, uniform cylindrical phantoms). The effect of number of iterations and substeps was also studied using a NEMA phantom containing six spherical inserts filled with a known amount of ^{177}Lu. NEMA spheres in-air were reconstructed at 10 iterations and changing the number of substeps. Convergence for all spheres was reached after about 80-100 updates.

Effect of scatter and attenuation. The effect of scatter and attenuation was studied for ^{177}Lu and ^{131}I in a number of geometries. Quantitative imaging in reference conditions with ^{131}I provided corrected values within 20% after correcting for scatter and attenuation, with correction for attenuation playing a major role (Standard Jaszczak 16ml sphere imaged in air, NPL). When the same experiment is repeated with ^{177}Lu, gamma cameras returned corrected values to within 8% (NPL). Using the standard Jaszczak 16ml sphere,

scatter correction decreases counts for measurements in air and water (~10-15%) while attenuation correction leads to ~3x increase in counts (NPL).

For quantitative imaging in reference conditions with ^{177}Lu performed over the 208 keV peak, corrected values in the range 5-7% were obtained after compensation for scatter and attenuation, with correction for attenuation playing a major role (ENEA). Further studies done on ^{177}Lu indicate that scatter and attenuation are highly dependent on the reference geometry considered. No matter what reference geometry is used, scatter and attenuation play a major role for acquisitions at the lower (113 keV) photopeak (ENEA). For acquisition at 113 keV, scatter radiation contributes to approximately 50% of the total counts both for the Jaszczak sphere in water and the cylindrical phantom (ENEA). For the same phantoms, scatter contribution is in the range 10-20% for acquisitions at 208 keV. As expected, attenuation correction without scatter compensation leads to important overestimations of the activity concentration in all geometries. This is particularly true for acquisitions at 113 keV (ENEA). Further measurements with a ^{177}Lu point source in air confirmed that the scatter fraction can be as high as 70% for acquisitions in the lower window and around 60% for acquisitions in the upper window (CMI).

Despite scatter and attenuation playing a major role in quantification, it is generally believed that if gamma camera calibration is performed with a source geometry mimicking the scatter and attenuation properties in patient imaging (such as a tank of uniform activity or hot spheres in uniform background activity) the effects of imperfect compensation will be partly reduced.

Partial volume effects. Partial volume effects play a major role, resulting in systematic activity underestimation in small volumes. This finding was confirmed by all NMIs. Partial volume effects were assessed for ^{177}Lu and ^{90}Y in terms of recovery coefficients (RCs) for spheres of varying sizes (NEMA phantom). Studies on ^{177}Lu provided a RC of about 0.5 on the largest NEMA sphere. For the same sphere, the RC is about 0.9 if the selected VOI is as large as the physical size of the sphere + 1 cm margin (ENEA). For ^{90}Y-PET quantitative imaging, partial volume effects provided RCs in the range 0.2-0.8, approximately (ENEA). Recovery coefficients determined for a Jaszczak phantom with cylindrical insets showed that if the selected VOI is as large as the physical size of the sphere + 0.5 cm margin the smallest sphere severely underestimate the activity in the insert (CMI). Satisfactory results can be obtained when the selected VOI is as large as the physical size of the sphere + 1 cm margin (about -5% underestimation if compared to the largest sphere (CMI). Similar results were obtained for ^{177}Lu using a set of 6 spheres (16ml – 0.5ml) to assess PVE (NPL). As a general rule, the smaller the sphere volume, the more the activity underestimation, both in air and in water (NPL).

The PVE problems require further work in order to enable quantitative imaging of small legions with a reasonable uncertainty and a correction approach based on recovery coefficients (RCs) may not be adequate in the clinical practice. The major limitation of partial volume corrections through the RC compensation method is that anatomical structures can hardly ever be approximated by simple (often spherical) geometrical objects. Furthermore, RCs can be only applied to the mean value in spherical objects and no pixel-by-pixel compensation is allowed.

Dead time. Dead time effects were studied for ^{17}7Lu, both for an IRIX and an AXIS gamma camera system (both acting as non-paralyzable systems). Percentage losses were in the range 0.4%-1.2% for count rates in the range 1-3·103 cps (0.2-06 GBq, ENEA). Dead time effects are likely to have an impact in the clinical practice, where higher administered activities can be used (ENEA).

Activity quantification in non-reference geometry. ENEA performed measurements in non-reference conditions at IFO hospital using an anthropomorphic torso phantom filled with ^{177}Lu. The anthropomorphic phantom was provided with a home-made PMMA cylindrical insert simulating a hepatic lesion. Three different tumor to background activity concentration ratios were used. Both the insert and the background activity concentrations were recovered with increasing accuracy for decreasing tumor to background ratio. The same phantom was used for ^{90}Y PET acquisitions at AULS hospital. The anthropomorphic phantom was acquired at days 1, 4, 5, 6, 12 down to activity concentrations of 0.31 MBq/mL and 0.051 MBq/mL for tumor and liver regions, respectively. As a general rule, the lower the activity the poorer the accuracy in activity quantification into the insert.

NPL assessed the deviation of activity measured using reference phantoms from that assessed with quantitative imaging measurements of complex phantoms under reference and non-reference conditions in a number of UK hospitals. Radionuclides of interest were ^{177}Lu and ^{131}I. Acquisitions were performed placing a

16 mL sphere in air and in water (in a number of off-axis positions) and using the spheres available for the anthropomorphic phantom. Measurements were performed in Portsmouth, Southampton, Guilford, Manchester and London hospitals, respectively.

Uncertainties in quantitative imaging related to MRT. Phantom measurements in reference conditions performed by NMIs at unfunded partners' facilities suggest that the gamma camera calibration factor can be determined with an uncertainty below (or in the order of) 3%, From quantitative imaging performed in non-reference conditions, one can expect uncertainties in absolute activity quantification at a clinical level in the range 5-10% in an anthropomorphic geometry when measuring large (> 16ml) lesions, after proper compensation for scatter and attenuation. However, due to PVE, larger uncertainties are to be expected for smaller volumes. Activity measurements may play a major role on the final quantification uncertainty and if activity is determined by an NMI uncertainties can be reduced dramatically.

It is desirable that in the near future the final uncertainty in absolute quantification in complex phantoms be below 5% to ensure the uncertainty in clinical absorbed dose estimations comply with the requirement of 5% to a reference point. Preliminary results obtained from task 2.3 of the MetroMRT project suggest that quantitative imaging in radionuclide therapy is still in need of a robust metrological support in order to bring MRT dosimetry practice up to an acceptable standard.

3.3 Absorbed dose calculation and measurement

The final link in the chain to obtain a measurement of the radiation absorbed dose from an administered radiopharmaceutical is to calculate the mean dose, or 3D dose distribution, from the integrated activity-time within a defined volume. Thus ultimately the result relies on the accuracy of a calculation. This in turn relies on the accuracy of the input data, the assumptions and simplifications made in the calculation model, and how well the conditions of the problem have been specified. In order to achieve a measurement of dose that is traceable to a primary standard of absorbed dose, it is necessary to evaluate the uncertainty of measurements, and to establish a valid primary standard. The project developed several methods for measurement of the relative dose distribution within and adjacent to radionuclide solutions, and developed a primary standard for measurement of absolute dose within a radionuclide solution. Thus it was possible to validate the calculation of radiation transport (by comparison with the measured dose distributions) and the calculation of absolute dose.

3.3.1 Development of absorbed dose measurement techniques and procedures for MRT dosimetry based on dosimeter calibrations against the existing absorbed dose primary standards for external beams

After a review of measurement methods published in the literature, the following techniques were developed by project partners. The results of the measurements and comparison with calculated values are presented in Section 3.4.4.

VSL: radiochromic film dosimetry of ^{131}I

The type of film used was GAFCHROMIC® EBT2. The film was clamped between the two halves of a Perspex cylinder containing a cylindrical cavity (5cm diameter by 5cm long) containing radioactive solution. In order to account for irregularities in the film, a 1 Gy pre-exposure with ^{60}Co gammas was given, and then the subsequent exposure was scaled according to the response to 1 Gy. The film had to remain immersed in the radioactive liquid for up to 17 hours in order to receive an estimated 1 Gy in the centre of the solution, and this caused a change in response due to water damage. This effect was evaluated as a 2.5% change and a correction was made for this. The film optical density was calibrated using a ^{60}Co gamma beam in a Perspex phantom, and the ratio of response to ^{60}Co in Perspex to ^{131}I in water was calculated using Monte Carlo simulation. The combined standard uncertainty was evaluated as 3.4% (k = 1).

CMI: Fricke-infused gel dosimetry of ^{177}Lu

Two types of gel were used (Fricke-infused xylenol orange ion indicator gel, (FX gel) and a gel based on Turnbull Blue dye (TB gel)). To measure absolute dose, each gel was to be mixed with radionuclide solution. However it was found both gels reacted chemically with the carriers for yttrium and iodine, and that only lutetium could be used for dose measurements. Ultimately it was found that the TB gel also reacted to the acidic carrier for lutetium as well, so only the FX gel could be used with inter-mixed radionuclide solution. The gel response was evaluated using UV-VIS spectrophotometry, or photographing with a CCD camera with a suitable light source and a colour filter. The gels were used in two configurations: with ^{177}Lu inter-mixed to measure absolute dose calibrated by ^{60}Co gamma radiation, and surrounding a thin-walled tube containing ^{77}Lu solution in order to measure the dose gradient within the gel. Both the relative response to ^{177}Lu compared to ^{60}Co gammas and the depth dose distributions were calculated using Monte Carlo simulation. The evaluated combined standard uncertainty for the absolute measurement was 10.7% and for the relative measurement 7.6%.

NPL: radiochromic film and alanine dosimetry of ^{90}Y

The film type used was GAFCHROMIC® EBT3, using a similar set-up to VSL, with the film clamped between the halves of a Perspex cylinder, as shown in Figure 8. The effects of water degradation were assessed, and it was decided to enclose the film in a protective Mylar layer to avoid the need for a correction. This also prevented radioactive contamination. The relative optical density was calibrated both by exposing for different times to the ^{90}Y solution in the phantom, and exposure to ^{60}Co. There was no significant difference seen in the 2 methods. The film measurement procedure was adopted from a paper published by Bouchard et al (2009) in order to account for inhomogeneity in the film. Sample results are shown in Figure 9. The combined standard uncertainty for the film measurements was dependent on the dose, ranging from 1% at 5Gy to 4% at 0.5Gy.

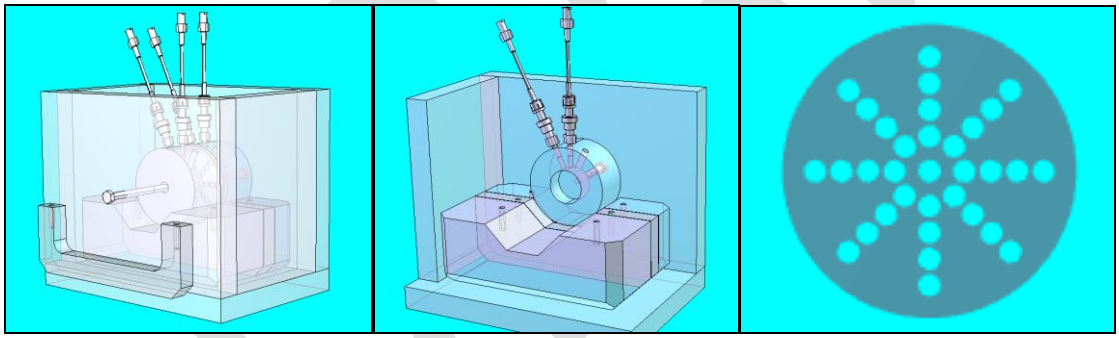

Figure 8: Radio-chromic film/alanine phantom (a, b) and alanine pellet holder (c).

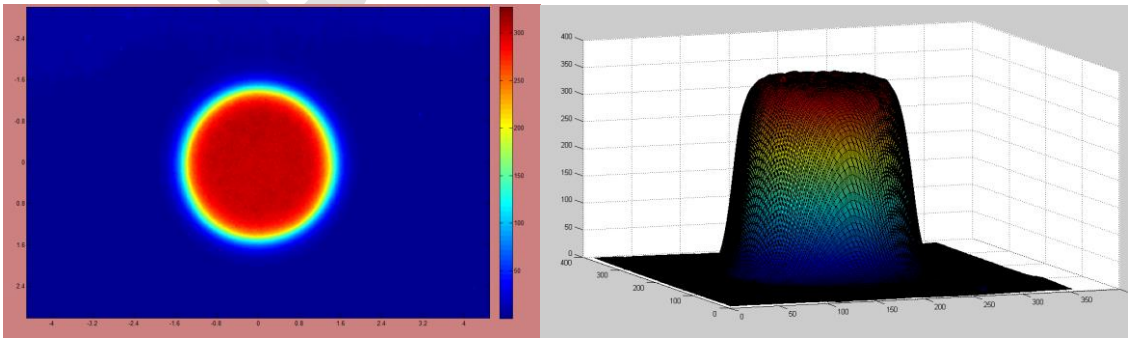

Figure 9: 2D and 3D dose distribution.

The alanine pellets were of standard NPL supply consisting of high purity L-α-alanine (90% w/v) with high melting point paraffin wax (10% w/w). The variety selected for this work was the thin version with an approximate 0.5 mm thickness and 5.0 mm diameter. They were calibrated in ^{60}Co and exposed in the jig shown in Figure 8. The combined standard uncertainty for alanine was also dose-dependent, ranging from 1.8% at 100Gy to 4.3% at 10Gy.

H. Bouchard, F. Lacroix, G. Beaudoin, J. F. Carrier, I. Kawrakow "On the characterization and uncertainty analysis of radiochromic film dosimetry" Med. Phys. 36, 1931 (2009); http://dx.doi.org/10.1118/1.3121488

ENEA: thermo-luminescence dosimetry (TLD)of ^{90}Y

GR-200A TLD chips were used (Solid Dosimetric Detector and Methods Laboratory, GR series, China). They have an extremely low detectable threshold, and are approximately tissue equivalent. An array of 3 was encapsulated in a polystyrene envelope and suspended in a container of ^{90}Y chloride solution, as shown in Figure 10. They were calibrated in a water phantom in a ^{60}Co gamma beam, and the relative response of the TLDs to ^{90}Y beta radiation in solution relative to ^{60}Co radiation and the conversion from dose-to-TLD to dose-to-water was calculated by Monte Carlo simulation. The combined standard uncertainty was 3.1 – 3.7%.

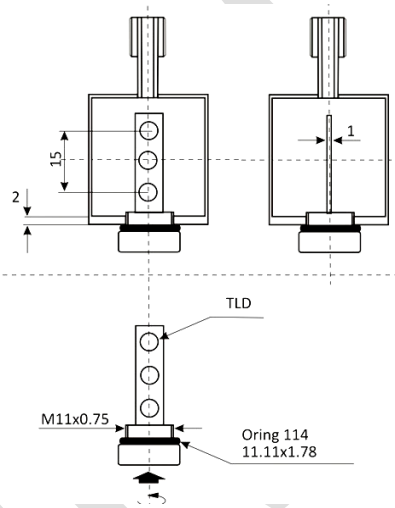

Figure 10. Cylindrical water phantom containing the holder for 3 TLD chips.

3.3.2 Feasibility study for the development of a primary absorbed dose standard for radionuclides

Current practice for obtaining absorbed dose from measured cumulative activity is to use a calculation method, with no verification measurements and with no knowledge of the uncertainty involved. At the beginning of the project (June 2012) there were no primary standards anywhere in the world realising absorbed dose from unsealed radionuclides. Therefore the aim of task 3.2 was to introduce the absorbed dose to water for a given radionuclide as a reference quantity, based on primary absorbed dose to water standards as recommended by the international IAEA protocol 398.

ENEA studied the feasibility of a graphite calorimeter for the measurement of the absorbed dose to water from 90Y liquid sources used in molecular radiotherapy. However both Monte Carlo and heat transfer calculations showed that the realization of such a graphite calorimeter presents some major drawbacks that required further studies. These limitations were not likely to be overcome within the time constraints of the MetroMRT project, and would have therefore hindered both the practical realization and the following operation of the primary standard. Therefore the realization of such a primary standard seemed not to be feasible in the framework of the MetroMRT project.

VSL investigated the feasibility of using an existing extrapolation chamber (for standardization of encapsulated beta emitters) as a primary standard for dosimetry on beta-emitting radionuclide solutions. Preliminary studies were performed considering ^{90}Y, ^{131}I and ^{177}Lu. A primary standard based on an existing extrapolation chamber seemed to be technically feasible. However, VSL deemed the mechanical realization of such primary standard not to be feasible within the time constraints of the MetroMRT project.

NPL proposed to use a commercial Physikalisch-Technische Werkstätten (PTW) type 23392 extrapolation ionisation chamber to measure the dose rate (to water) at the surface of a radionuclide solution. A suitable container for holding radionuclide solution and performing measurements with the NPL extrapolation chamber was designed. Following the feasibility study, NPL proposed to proceed and develop the primary standard.

3.3.3 Development of a prototype primary standard of absorbed dose at NPL

The use of an ionisation chamber with a thin entrance window and variable plate separation has a long history as a primary standard of radiation absorbed dose [Böhm and Schneider, 1986]. The absorbed dose can be obtained from first principles using Bragg-Gray theory [Spencer and Attix, 1955]. By taking measurements with a sequence of reducing chamber depths (plate separations) it is possible to extrapolate to a limiting depth which is small compared to most charged particle track-lengths. This then satisfies the conditions for the application of the Bragg-Gray cavity theory. (The charged particle fluence within the medium surrounding the cavity should be unchanged by the presence of the cavity.) For radiation from radionuclides that arebeta-emitters, this needs to accommodate the low-energy short-range betas present in any beta spectrum. Typically until now an extrapolation chamber has been used for low-energy X-rays, or external beta radiation from sealed sources. This work is the first application to unsealed radionuclides.

The set-up used a PTW type 23392 extrapolation chamber (EC) together with a purpose-designed holder that both contained a well that could be filled with radioactive solution, and located the EC such that the front window was suspended just above the liquid surface. Illustrations of the holder and the set-up are given in Figures 11 and 12.

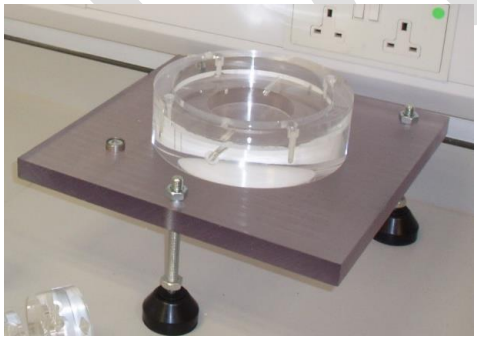

Figure 11 Holder for the EC

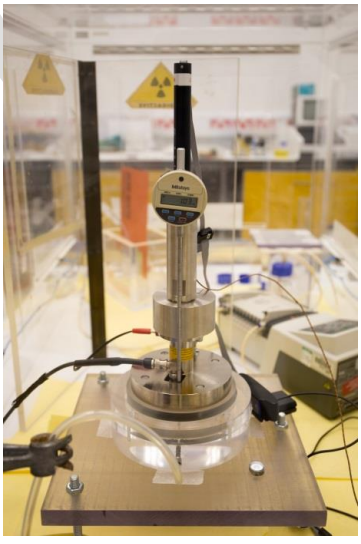

Figure 12 EC located in the holder

In order for the EC to act as a primary standard it was necessary to calculate correction factors to account for attenuation by the front window (and the mylar protective film and air gap between the solution and chamber to avoid contamination), and scatter from the non-water material of the body of the EC, and also the conversion from dose-to-air to dose-to-water. This was done using the usercode CAVRZnrc that forms part of the EGSnrc code system (release V4-r2-3-2) [Kawrakow et al. 2011]. It was found while checking the

performance of the EGSnrc code that the Monte Carlo simulation of the EC represented well the behaviour of the ionisation chamber at all plate separations. So there was no need to rely on the assumptions and extrapolation process implicit in using the Bragg-Gray theory. The energy deposited in the cavity as a function of the activity concentration in the solution could be calculated directly for each plate separation. Each measurement was made as the mean of a set of readings from 10 different plate separations, in order to minimise the uncertainty from each individual calculation.

The reference quantity being measured was taken as the absorbed dose to water within the interior of a large water phantom where there is full equilibrium with all radiation emissions from the radionuclide. The EC measures directly the dose rate to water at the surface of the liquid (which with full back-scatter from the body of the EC is about half the internal value). The ratio between the surface dose rate and interior dose rate was calculated using EGSnrc.

The question arises whether this measurement has any independence, since the physical measurement will be used to make a comparison with the absorbed dose rate in solution obtained by Monte Carlo calculation. But a careful analysis shows that all of the calculations used to derive correction factors and conversion factors were ratios of MC calculations, and did not depend in an absolute way on the absorbed dose. The measurement was being used to verify the absolute MC-calculated absorbed dose (as used for MRT). Any error in the absolute values would cause only a second order deviation in the ratios. So the measurement is valid.

The uncertainty of measurement was derived by considering in turn the values and uncertainties of the correction factors and quantities which do not depend on the chamber depth and do not vary during the EC measurements at each depth (combined standard uncertainty 1.28%), the values and uncertainties of the quantities which do depend on the chamber depth and vary during the EC measurements at each depth (combined standard uncertainty 0.38%) and the uncertainty in Monte Carlo factor (combined standard uncertainty 0.40%). The total combined standard uncertainty was 1.4%.

The set-up was intended to be used for solutions of ^{90}Y, ^{131}I, and ^{177}Lu. But in the end, because of time, cost, and safety considerations, only one series of pilot measurements was performed using ^{90}Y. Seventeen sets of measurements were completed in a period of 6 days with a 5.1 MBq activity solution of ^{90}Y chloride. For each set, measurements at each of the 10 EC plate separations were performed.

The mean energies of the ^{90}Y source emission spectra published by MIRD (Eckerman, 1989), and RADAR (2002) were used to directly determine the analytic (expected) absorbed dose to water value at the interior of a water phantom. The difference between the two analytic dose values and the measured dose is as shown in Table 2. The Table compares the data obtained when including all EC depths and when excluding the smallest 0.25 mm EC depth, which increases the combined standard uncertainty by 0.1% because of the increased uncertainty of the low current measurement.

Table 2. Difference between the analytic and the measured absorbed dose values.

All depths			
	Measured	**MIRD**	**RADAR**
Dose (Gy)	*2.421E-12*	*2.377E-12*	*2.379E-12*
Difference, analytic/measured (%)	-	*-1.8*	*-1.8*
Excluding 0.25 mm depth			
	Measured	**MIRD**	**RADAR**
Dose (Gy)	*2.418E-12*	*2.377E-12*	*2.379E-12*
Difference, analytic/measured (%)	-	*-1.7*	*-1.6*

In conclusion, this work demonstrated that it is possible to make a primary standard measurement of absorbed dose to water within a radioactive solution (at least in the case of a solution of ^{90}Y chloride) with a standard uncertainty of 1.4%. The measurement agreed with values from the usual dose calculation methods well with the expanded uncertainty of 2.8% (k = 2). This is a very useful measurement in that within the level of uncertainty needed for MRT dose calculations, (typically 5% is more than adequate), calculations

based on the published nuclear data are validated against a primary standard. This (in the case of ^{90}Y) effectively achieves traceability of the calculations to a primary standard of absorbed dose. Only a single trial measurement has been completed. This should be repeated in order to confirm the results, and it should be extended to the other radionuclides used for MRT.

Böhm J. and U. Schneider, Review of Extrapolation Chamber Measurements of Beta Rays and Low Energy X Rays, Radiat Prot Dosimetry 14 (2): 193-198. (1986)

Spencer L. V. and F. H. Attix. A Theory of Cavity Ionization. Radiation Research: November 1955, Vol. 3, No. 3, pp. 239-254. 1955

Kawrakow I, Mainegra-Hing E, Rogers D W O, Tessier F and Walters B R B. The EGSnrc code system: Monte Carlo simulation of Electron and Photon Transport. NRCC Report PIRS-701. 2011.

Eckerman K F and Endo A. MIRD: Radionuclide Data and Decay Schemes. 2nd Edition. 1989.

RADAR. RADAR – The Decay Data: http://www.doseinfo-radar.com/RADARDecay.html. 2002.

3.3.4 Assessment and validation of methods for calculating absorbed dose from cumulative activity

The choice of method of calculation of absorbed dose from cumulated activity in a patient depends on the input data and the radionuclide.

The input data can be one of the following:

1. Non-imaging, such as point radiation measurements at a distance from the patient, blood or urine assays, etc. In this case the measurements are calibrating in terms of the dose being estimated (e.g. “whole body” dose as an indicator of red bone marrow dose) using an appropriate phantom or other method. In this method of dosimetry the greatest contribution to the uncertainty is the relationship between the parameter measured and dose to the relevant tissue, rather than the dose calculation method. Therefore this method is not considered further here.

2. Total activity within a volume of interest (VOI) defined on SPECT images. Here the integrated activity-time within the VOI is multiplied by an appropriate “S-factor” in accordance with the standard MIRD formalism [Bolch et al 2009]. The choice of S-factor is determined by the shape and size of the VOI. The S-factor, as provided for example by OLINDA [http://www.doseinfo-radar.com/RADARSoft.html], is based on Monte Carlo calculations.

3. Voxel-based SPECT images. In this case a 3-dimensional distribution of the dose to each voxel is calculated from the integrated activity-time in each voxel, taking account of the contributions from neighbouring voxels. The 2 methods usually used are convolution of the activity-time distribution with a voxel dose kernel, or a full Monte Carlo simulation and dose calculation. The dose kernels are pre-calculated by Monte Carlo as the dose distribution within a uniform medium from activity in a voxel-sized volume.

The complexity of the method of dose calculation used for MRT depends also on the particular radionuclide. Considering the 3 most commonly used radionuclides:

^{90}Y has high-energy betas (max. 2.2MeV) but negligible photon emission. Therefore radiation transport needs to be modelled up to a range of about 1cm, but no further than this. The limit of resolution of a (bremsstrahlung) SPECT image using a conventional collimator is of the order of 1cm. A method for calculating a dose distribution taking account of image blurring has not yet been determined. A PET image (obtained from the positron emitted by ^{90}Y) has better resolution, but not sufficient to avoid the problem.

^{131}I has lower-energy betas (max. 0.6MeV) but abundant 364keV gammas. Up to 20% of the dose can come from the gamma contribution. The betas have a maximum range in soft tissue of about 2mm, so for the sake of SPECT images this can be considered “local” deposition. However, the possible dose from concentrations of ^{131}I in neighbouring organs and the loss of dose within the target volume must be accounted for.

^{177}Lu has low-energy betas (max. 0.5 MeV) with maximum range 1.8mm. Only 10% of the disintegrations produce gammas, so the contribution to the dose from gammas is much smaller than for ^{131}I, and potentially negligible when taking account of the uncertainties caused by the image data.

There are some clear conclusions from this. First, all of the calculated doses are ultimately dependent on Monte Carlo calculations using accepted nuclear data, both in terms of absolute values, and relative values distributed through a volume. If the accuracy of Monte Carlo calculations can be verified by physical measurements, then the foundation of MRT dosimetry is established. The question of the accuracy of a particular application (the methods listed above) remains, but this can be investigated either by phantom measurements that incorporate imaging measurements, or by use of the validated Monte Carlo codes.

The results from the measurement methods described above were all compared with Monte Carlo calculations. The results were as follows:

VSL: The phantom geometry used for the film irradiation was passed to Velindre (MetroMRT partner and REG) for simulation using the Raydose software developed as part of the REG-Researcher contract. The simulation used the GEANT4 Monte Carlo code. Due to an error that could not be explained within the time of the project there was a disagreement between the calculated and measured results for the absolute dose well beyond the experimental uncertainty. The most likely source of the error is the calibration procedure using ^{60}Co.

CMI: The measurements of absolute dose using ^{177}Lu mixed into the FX gel calibrated with ^{60}Co were compared with calculations using the MCNPX code. The measured doses were all low by between 2.8% and 10.6%. This is within the estimated standard uncertainty, but it is likely that further development of the technique could improve the agreement. This was not possible within the time of the project. The relative measurement of the depth dose surrounding a thin tube containing ^{177}Lu solution showed good agreement with MCNPX beyond about 5mm from the radiation source, but gave unrealistic results where the dose was predominantly from beta radiation. This is most likely to be due to difficulties with the optical read-out system in proximity to the central tube.

NPL: The absolute dose measured using alanine, calibrated with ^{60}Co differed from the corresponding dose calculated using EGSnrc by 9.5%. This is outside the measurement uncertainty, and as with the other discrepancies, is most likely to be due to the problem of applying a calibration in ^{60}Co to exposure from submersion in radioactive liquid. This is in spite of simulating the relative response using EGSnrc. The film measurements were used only as a relative measurement to compare with the calculated depth dose curve near and within the wall of the Perspex container. There is a difference greater than the experimental uncertainty at the point of greatest slope (at the surface of the container wall). This was identified as being caused by averaging over profiles across different diameters through the cylinder, when there was a slight misalignment of the centre. Averaging the sigmoid profiles had the effect of broadening the curve.

The results from the measurement using the extrapolation chamber primary standard developed by NPL have already been mentioned in the previous Section. The agreement in this case is within experimental uncertainty.

ENEA: The measured dose-rate was compared to calculated values using Raydose (Velindre) and MCNP-4C. After averaging a sequence of TLD measurements, the weighted standard uncertainty was estimated as 6.3%. The differences between the measured result and the two calculated results were 1% and 3% respectively.

There are several conclusions to be drawn from this work:

First, the primary standard measurement is consistent with the accepted nuclear data being correct. This work needs to be extended, but the result effectively achieves traceability for doses calculated for ^{90}Y. The primary standard approach has proven to be more productive than attempting to measure absolute dose based on calibrations using an external beam of ^{60}Co gamma radiation and converting the calibration to response to radionuclide emissions.

Second, making physical measurements of the dose from radionuclide solutions is difficult. While there were areas of disagreement, it is unlikely that these are due to inaccuracy of the Monte Carlo calculations.

Third, taking account of the comments at the beginning of this Section, 2D and 3D dose measurements would be better employed investigating dose distributions calculated from SPECT image data, to help resolve problems arising from partial volume effects, and other sources of inaccuracy. It will be difficult to achieve sufficient accuracy to challenge the current state-of-the-art Monte Carlo codes.

Bolch W. E., K. F. Eckerman, G. Sgouros, S. R. Thomas. MIRD Pamphlet No. 21: A Generalized Schema for Radiopharmaceutical Dosimetry—Standardization of Nomenclature. JNM, V50 No. 3, p477, 2009

3.3.5 Feasibility of a dosimeter measuring biological outcomes of radionuclide exposure

In molecular radiotherapy, the dose distribution in the target volume is currently estimated from the activity distribution by employing Monte Carlo simulation in combination with microdosimetric measurements. This estimate is, however, based on the track structures of ionizing radiation in gaseous tissue-analog materials, neglecting the condensed phase effects and various processes occurring after primary physical interactions. For a realistic estimate of biologically effective dose, it is desirable to provide a tool which more closely reflects the dose response of the biological system in real physical conditions.

The present task aimed at the development of a prototype of a nanometric DNA dosemeter. It is based on the change of the electrical conductivity of the DNA macromolecule, which is generally regarded as the radiosensitive target on the cellular level, upon damages induced by ionizing radiation. For this purpose, DNA macromolecules of different lengths, ranging from a few thousands of base pairs to several ten thousand base pairs were captured between two gold electrodes after the thiolization of their ends. (See Figure 13.) The production of DNA oligonuclides about 200 nm in length and their thiolization were carried out by Ilko Bald from University of Potsdam (MetroMRT collaborator) and the attachment of the DNA molecules to gold electrodes was performed by the group of Jussi Toppari from University of Jyväskylä (MetroMRT collaborator). Additionally, longer λ-DNA molecules, a few µm in length, were purchased from University of San Diego in USA.

After the setup of the electrical detection system using Lock-in amplifier and preparing experiments, the DNA macromolecules were irradiated by 5.5 MeV-α-particles from ^{241}Am-source and their impedance was measured at different frequencies as function of the irradiation time. After several days of irradiation, a clear increase of the ohmic resistance and a transition from ohmic to capacitive electrical behaviour of the DNA, especially of the longer λ-DNA molecule, were observed while non-irradiated samples under the same atmospheric condition showed no significant changes in their electrical behaviour. (Figure 13)

The results of the measurement, the first of this kind, suggest that a DNA molecule can be used as a biological sensor for radiation induced damages. At the final stage of the project, a waterproof DNA sensor system has been built so that it can be used in solutions containing radionuclides. Since the size of the DNA sensor is smaller than a few µm, a miniature radiation detector reading a signal more closely related to the biological effective dose may be in principle fabricated.

Due to the project, expertise in different facilities across the EU could be brought together. The know-how of Ilko Bald from University of Potsdam / Germany in fabricating DNA oligonuclides, that of the group of Jussi Toppari from University of Jyväskylä / Finland in the immobilization and electrical characterization of DNA macromolecules, and that of the group of Hans Rabus of the PTB / Germany in radiation physics enabled the viable outcome of the project. Furthermore, a gold electrode with a gap of about 10 nm has been already fabricated in the PTB / Germany with the aim of the improvement of signal-to-noise ratio.

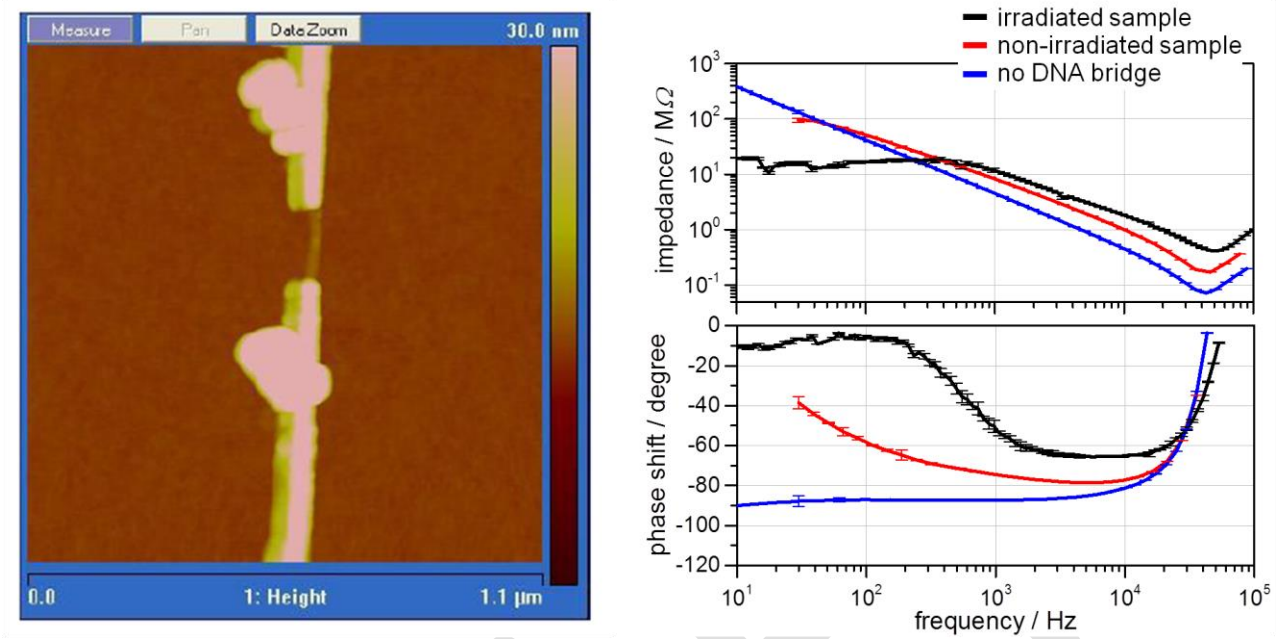

Figure 13 The picture on the left-hand side shows the DNA captured between two gold electrodes with a gap of about 200 nm. The black and red coloured curves in the diagrams on the right-hand side depict the change of the impedance (top) and phase shift (bottom) for irradiated, non-irradiated λ-DNA sample, respectively. The blue curves represent those for blank gold electrodes without λ-DNA bridge.

3.4 Modelling and uncertainty analysis

3.4.1 Optimization of quantitative imaging activity measurement time points

The determination of optimal time points at which to acquire measured activity values as part of the quantitative imaging process in molecular radiotherapy was considered. The measure of optimality used is the standard uncertainty associated with cumulated activity. A completely new approach for determining optimal time points was developed. There was nothing in place previously that was clinically relevant, the new approach taking account of operational hospital constraints such as night time working. Results of applying the approach for determining optimal time points to therapy with ^{90}Y Zevelin for non-Hodgkin lymphoma and with ^{131}I for differentiated thyroid cancer were obtained. Project partners ENEA and the Theagenion Cancer Hospital provided anonymized patient records and interpreted the results in the context of their organizations. An invited presentation given on the approach at the 2015 MIRD/SNMII Radiopharmaceutical Dosimetry Symposium in Baltimore was exceptionally well received with suggestions for future collaboration.

3.4.2 Major sources of error and their quantification in terms of uncertainties related to molecular radiotherapy

The major sources of error in molecular radiotherapy (MRT) were considered. These errors were quantified in terms of standard uncertainties, an aspect that had previously received little attention in MRT work. Doing so enabled recognized international guidance on uncertainty propagation to be applied to yield the standard uncertainty associated with absorbed dose. For this purpose, models of the links in the dosimetry chain (Figure 14) from initial administration of a radiopharmaceutical to the calculation of absorbed dose relating to a volume of interest (VOI) were used. Collaboration with Lund, ICR, UCL, ENEA and CMI ensured an excellent balance between theoretical rigour and practical need. A paper based on the work is being submitted to a peer-reviewed journal in the field.

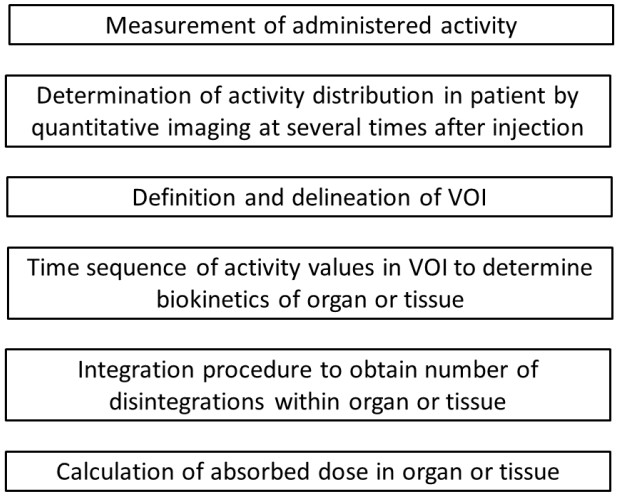

Figure 14: Links in the dosimetry chain

3.4.3 Mathematical models of the measurement chain for molecular radiotherapy treatment protocols and the associated uncertainty evaluation methodology

The early links in the dosimetry chain corresponding to the image-reconstruction process, that is, the determination of a 3D quantitative image from a set of planar quantitative images, were considered. A methodology was developed for propagating uncertainties associated with those planer images through the reconstruction process to provide uncertainties associated with activities in the voxels in the 3D image. It was established that to carry out this propagation process without losing essential information is infeasible because of the massive computational complexity of the task, a point that was agreed with project partners at a six-monthly JRP meeting.

3.4.4 Formal methodology for an uncertainty analysis protocol of the complete process of measurement of absorbed dose for MRT treatments

A top-down approach was taken in collaboration with ICR to modelling the processes constituting the dosimetry chain that are involved in internal dose calculations. The approach offers a viable alternative to propagating uncertainties in the manner in section 3.4.3. The starting point was the basic model for absorbed dose in a VOI as the product of cumulated activity and a dose factor. In turn, the cumulated activity is given by the area under a time-activity curve (TAC) derived from a time sequence of activity values. Each activity value is obtained as the product of a calibration factor and a count rate. Means of determining the calibration factor and the dose factor, both depending on mass in the VOI, were proposed. Consideration was given to propagating estimates of the quantities concerned and their associated uncertainties through the dosimetry chain to obtain an estimate of mean absorbed dose in the VOI and its accompanying uncertainty. A paper based on the work has been submitted to a peer-reviewed journal. The EANM dosimetry committee is considering that the paper be regarded as an official EANM guideline. The committee remarked on the impressive progress of the MetroMRT consortium that would give weight to such a publication.

3.4.5 Mathematical modelling of absorbed dose calculation and associated uncertainty evaluation through the construction of a time-activity curve

This aspect of the work is concerned with the later links in the dosimetry chain, thus complementing that in section 3.4.3. It was shown that, given activity values averaged over the VOI at each time point and an associated covariance matrix, containing activity uncertainties and covariances between those activities (as obtained in section 3.4.4), a TAC could be provided that respected that information. The cumulated activity as the area under the TAC and its associated uncertainty could thence be derived. It was further shown how

the choice of model for the TAC (mono-exponential, bi-exponential, etc.), which influences the results, could be taken into consideration as a further source of uncertainty. Collaboration with UKW and the Dade Moeller Health Group, Washington proved invaluable, the principal medical dosimetrist at the latter organization requesting a review of a draft of the 20-year old MIRD primer concerned with modelling time-activity data that is undergoing major revision.

3.4.6 Application of modelling and uncertainty analysis to a whole-body treatment protocol

The mathematical modelling and the uncertainty evaluation methodology in section 3.4.3 were applied collaboratively with ICR and UCL to the protocol used by the Royal Marsden NHS Foundation Trust for whole-body (WB) dosimetry. That protocol applies to individualized treatment planning of 131I MIBG radionuclide therapy for neuroblastoma. The models were adapted to reflect the steps in the protocol. The measurement result constitutes an estimate of WB absorbed dose with a standard uncertainty that is traceable as far as possible to national standards. WB dosimetry covers some of the essential links in the chain for more general MRT treatment protocols for a specified VOI, and thus an early understanding of these links benefited work on the complete chain.

3.4.7 Implications for the overall uncertainty associated with the measurement of absorbed dose resulting from using different measurement techniques

The overall absorbed dose model, and the models that lead to it, were used to determine the inherent uncertainties associated with the various methods of MRT dosimetry that are being developed by unfunded JRP partners. The results were used to make statements about the relative importance of the links in the metrology chain. Since there are as yet no standardized methods, several links in the chain have different possible approaches. It was demonstrated that the adoption of an alternative technique in a particular step has the potential to reduce the overall uncertainty associated with absorbed dose.

3.4.8 Ramifications for patient outcomes and clinical research resulting from reducing the overall uncertainty associated with the measurement of absorbed dose

Simple empirical models for tumour control probability (TCP) and normal tissue complication probability (NCTP) in the form of a logistic function and a scaled and shifted Gaussian distribution function were considered. These models can be used in a forward sense to evaluate TCP or NTCP given a value of absorbed dose or inversely to evaluate absorbed dose given TCP or NTCP. This work, seemingly for the first time, enables uncertainties to be propagated thorough the forward and inverse models. Reduced uncertainties in dosimetry can positively affect the outcome and conclusions of a clinical trial, or mean that a smaller number of patients are needed to give it a stipulated statistical power. An uncertainty threshold was suggested to make such a reduction worthwhile taking into consideration the biological variability across patients.

4 Actual and potential impact

4.1 Stakeholder Engagement

The main element of stakeholder engagement has been through the (8) unfunded JRP-partners and (33) project collaborators. This group in fact represents a significant proportion of the main players in the development of MRT dosimetry in Europe, and included nuclear medicine clinics, camera and software manufacturers, and a radiopharmaceutical manufacturer. A wider mailing list of interested individuals has been maintained to advertise the project workshops.

The project membership has maintained very close links with the European Association of Nuclear Medicine (EANM). Including papers accepted at the 2015 EANM annual Congress, there has been a total of 13 presentations and posters on project work. Of the 9 members of the EANM Dosimetry Committee, 6 are

MetroMRT members or collaborators. This Committee is the group which formulates standards of practice for dosimetry in nuclear medicine for the European community, and will be the main conduit for recommendations from the project.

The project has engaged with stakeholders through the holding of 3 themed public workshops. The first of a planned series of themed public workshops was held in Rome in July 2013, on quantitative imaging, (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 for QI. A second workshop was held in Paris in May 2014 on the topics of input data for activity measurements, QI, and dosimetry methods. 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 in MRT.

There has been a continuing interest in the project by the wider nuclear medicine community. A particularly exciting development has been interest from commercial software developers, because collaboration with this group will be an essential component of exploiting the results and recommendations of the project, and promoting and distributing routine MRT dosimetry capability to the MRT community as a whole.

4.2 Dissemination:

4.2.1 Standards

The extensive engagement with the EANM Dosimetry Committee has already been reported above. As well as this, project members have been involved as individuals with the following standards committees:

- The ISO Joint Committee for Guides (Maurice Cox, NPL)
- ISO/TS 28038, Determination and use of polynomial calibration functions (Maurice Cox, NPL)
- ISO Technical Committee 85/Subcommittee 2/WG, providing input to the proposed document ISO/DIS 16644-1 "Measurement of activity in nuclear medicine using gamma camera planar image for thyroid treatments with 131I": (Michael Lassmann, collaborator UKW)
- International Committee for Radionuclide Metrology, Life Sciences Working Group (Andrew Fenwick, NPL).
- USA Committee on Medical Internal Radiation Dosimetry (MIRD), (George Sgouros, MetroMRT Scientific Advisor)
- Scientific Committee of the IAEA/WHO Network of Secondary Standards Dosimetry Laboratories. (George Sgouros, MetroMRT Scientific Advisor)

The respective committees have been kept informed by the members on the work in MetroMRT.

A promising development with the IAEA Division of Human Health possibly leading to development of an international dosimetry protocol is mentioned in 4.3 below.

4.2.2 Scientific output

There are several new scientific results arising from the project, all detailed in Section 3 above. These include activity measurement using the TDCR Čerenkov method, development of a primary standard of absorbed dose within a radioactive liquid, and development of a methodology for uncertainty analysis of MRT dosimetry. This work is being disseminated to the scientific community through the usual channels of conference presentations and peer-reviewed publications. Some of this work was completed only at the end of the project and papers for submission to journals are still in preparation.

4.3 Wider longer-term potential impacts

The greatest long-term impact from MetroMRT will be the change in how the MRT community views its own methods that has been seeded by the project. The change will see the move from the standard of care for MRT being no dosimetry at all, to patient management based on individual dosimetry.

There is still resistance to MRT dosimetry in some quarters. Radiopharmaceutical manufacturers generally try to convince users that dosimetry makes no significant difference, because it would give an added cost to a product competing against possible chemotherapy alternatives. Many clinicians who have been using the traditional MRT, such as I-131 thyroid treatment, for decades are not persuaded they should change their ways. Indeed, dosimetry promises to have a greater impact on more recent MRT treatments (e.g. peptide receptor radionuclide therapy, PRRNT) than thyroid treatments, which are based on more than 50 years of clinical experience. Dosimetry is difficult, and with no standard methods available the implementation requires a level of commitment that regular non-research clinics cannot afford. So there is a considerable inertia to be overcome before individual MRT dosimetry becomes the standard of care in every clinic.

It is interesting at this point in time to compare the stage MRT is at as a branch of radiotherapy with external beam radiotherapy in 1970-1980. At that time, radiotherapy was moving from cobalt-60 treatments to the new linear accelerators, and learning how to take advantage of the greater ability to make the dose conform to the target. But this also placed greater demands on dosimetry. Individual research centres each developed their own improved dosimetry methods, but it was soon realised that radiotherapy moved forward through multi-centre trials, and it was essential that all the participants were using the "same gray". So initially national standard protocols were introduced, then wider groups (e.g. the Nordic Protocol), then the IAEA took up the work and produced an international protocol, first as Technical Reports Series 277 in 1987, then TRS-398 in 2000. Now, most countries have adopted either TRS-398, or an equivalent protocol, for external beam radiotherapy. The current IAEA Basic Safety Standards (GSR Part 3, 2014) require the use of "internationally accepted or nationally accepted protocols" for dosimetry, and this has become standard practice. Compare this with MRT in 2015. An old traditional technique is being joined by new techniques (e.g. PRRNT), which call for new dosimetry methods. Individual research clinics are addressing the problem, but there is no consensus. History suggests that the next move will be to wider standardisation of methods, leading ultimately to in international protocol. MetroMRT will have played a role in this.

The first step will be production of guidelines and recommendations by the Dosimetry Committee of the EANM. As already mentioned, the majority of the committee membership had direct involvement in MetroMRT. Preparation of a document on guidelines for uncertainty analysis of MRT dosimetry based on work done in the project is already underway (see Section 3.4.4). Further documents picking up other MetroMRT recommendations are planned.

Correspondence has also been initiated with the IAEA Division of Human Health concerning the possible development of an international MRT dosimetry protocol or handbook on MRT dosimetry. (See http://projects.npl.co.uk/metromrt/news-events/20150420-21_workshop/04-poli.pdf for a description of the IAEA publications.) There is considerable enthusiasm on the part of the Agency, and a meeting has been arranged for later in 2015 to explore the options. The principle aim is the provide guidance to enable any clinic to incorporate dosimetry into their routine practice, whatever the level of sophistication of their equipment. The science developed by the MetroMRT project will underpin the recommendations.

And what will this mean for the MRT community and the patients receiving the treatments? Better targeted treatments planned for the individual patient producing better and more reliable outcomes. MRT will move from being largely a last-resort palliative treatment to a frontline cancer therapy. Clinical trials will provide more precise results with the reduced uncertainty in one of the key parameters, leading to faster development of new therapeutic agents, and faster improvement of treatment protocols. This is potentially a time for great change.

5 Website address and contact details

The MetroMRT public website is at http://projects.npl.co.uk/metromrt/

A partners' restricted area contains all of the detailed internal reports of the project. Access may be given to this on request.

For general questions about the project please contact Vere Smyth: vere.smyth@npl.co.uk

For questions on activity measurements please contact Christophe Bobin: Christophe.bobin@cea.fr

For questions about quantitative imaging please contact Lena Johansson: lena.johansson@npl.co.uk

For questions about dose measurements please contact Marco D'Arienzo: marco.darienzo@enea.it

For questions on uncertainty analysis please contact Maurice Cox: Maurice.cox@npl.co.uk

6 List of publications

[1] C. Bisch, X. Mougeot, M.-M. Bé, A.-M. Nourreddine. Development of a system for measuring the shape of beta spectra using a semiconductor Si detector, Nuclear Data Sheets, doi: 10.1016/j.nds.2014.07.016 http://www.sciencedirect.com/science/article/pii/S0090375214004682

[2] Marco DArienzo, Marco Capogni, Vere Smyth, Maurice Cox, Lena Johansson, Jaroslav Solc, Christophe Bobin, Hans Rabus, Leila Joulaeizadeh Metrological Issues in Molecular radiotherapy, European Physical Journal. doi: 10.1051/epjconf/20147700022 http://www.epj-conferences.org/articles/epjconf/pdf/2014/14/epjconf_icm2014_00022.pdf

[3] V. Lourenço, Ch. Bobin, V. Chisté, D. Lacour, F. Rigoulay, M. Tapner, C. Thiam, L. Ferreux. Primary standardization of SIR-Spheres based on the dissolution of the 90Y-labelled resin microspheres, Applied Radiation and Isotopes, doi: 10.1016/j.apradiso.2014.12.024 http://www.sciencedirect.com/science/article/pii/S0969804314004515

[4] Andrew Fenwick, Phantom Development for Molecular Radiotherapy, PhD Thesis, 1 Sep 2012 - University of Surrey, UK

[5] S Marcatili, D Villoing, T Mauxion, B J McParland, M Bardiès, Model-based versus specific dosimetry in diagnostic context: Comparison of three dosimetric approaches. Medical Physics 42, 1288 (2015); doi: 10.1118/1.4907957 http://www.ncbi.nlm.nih.gov/pubmed/25735284

[6] M P Garcia, D Villoing, E McKay, L Ferrer, H Der Sarkissian, M Poirot, M Bardiès, Generation of Whole-Body Scintigraphic Images with New GATE Output Capacities IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), CRCT Toulouse, IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), Oct 2013, Seoul, South Korea. IEEE, 2013 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), pp.1-3. doi: 10.1109/NSSMIC.2013.6829150 http://ieeexplore.ieee.org/xpl/login.jsp?tp=&arnumber=6829150&url=http%3A%2F%2Fieeexplore.ieee.org%2Fxpls%2Fabs_all.jsp%3Farnumber%3D6829150

[7] Bagni, O.; Spezi, E.; Patterson, N.; et al. A workflow for treatment evaluation of 90Y microspheres SIRT therapy of hepatic lesions based on FDG-PET and Y90-PET, European Journal of Nuclear Medicine and Molecular Imaging, doi:10.1007/s00259-014-2901-9 (Vol 41, Suppl. 2, Pages S255-S255, Meeting Abstract: OP432, Published: OCT 2014)

[8] N. Patterson, E. Spezi, E. Grassi et al., Patient specific 3D dose calculation for 177Lu treatment of neuroendocrine tumours using the Raydose MC code, Radiotherapy and Oncology, Vol. 115, Suppl. 1, Pages: S459-S460, Meeting Abstract: PO-0894, APR 2015, ISSN 0167-8140. Conference: Annual Congress of the European-Association-of-Radiotherapy-Oncology ESTRO Location: Barcelona SPAIN Date: APR 24-28 2015

Papers submitted for publication:

M. Capogni, P. Carconi, P. De Felice, A. Fazio, F-18 primary standard at ENEA-INMRI by three absolute techniques and calibration of a well-type IG11 ionization chamber, Submitted to Applied Radiation and Isotopes

D Villoing, S Marcatili, M P Garcia, M Bardiès, Internal dosimetry with the Monte Carlo code GATE: Validation on the ICRP/ICRU female reference computational model, Submitted to Physics in Medicine and Biology

M P Garcia, D Villoing, E McKay, L Ferrer, M Cremonesi, F Botta, M Ferrari, M Bardiès, TestDose: a nuclear medicine software based on Monte-Carlo modelling for generating gamma camera acquisitions and dosimetry, submitted to Medical Physics

Pavel Dryák, Jana Sochorová, Jaroslav Šolc, Pavel Auerbach,l Activity Standardization, Photon Emission Probabilities and Half-life Measurements of 177Lu, submitted to Applied Radiation and Isotopes

Jaroslav Šolc, Martin Kačur, Vladimír Sochor and Ludmila Burianová. Feasibility study of radionuclide dosimetry with radiochromic gel dosimeters, submitted to Physics in Medicine and Biology