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Quantitative imaging, dosimetry and metrology; Where do National Metrology Institutes fit in?

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HIGHLIGHTS

- The need for NMIs and DIs to support the field of MRT dosimetry is obvious.
- External Beam Radiotherapy decades ahead of MRT in terms of dosimetry standards.
- Accurate determination of absorbed dose for MRT requires quantitative imaging.
- The complexity of the problem should not be underestimated.
- NMIs must form close links with local clinical sites.

ABSTRACT

In External Beam Radiotherapy, National Metrology Institutes (NMIs) play a critical role in the delivery of accurate absorbed doses to patients undergoing treatment. In contrast for nuclear medicine the role of the NMI is less clear and although significant work has been done in order to establish links for activity measurement, the calculation of administered absorbed doses is not traceable in the same manner as EBRT. Over recent decades the use of novel radiolabelled pharmaceuticals has increased dramatically. The limitation of secondary complications due to radiation damage to non-target tissue has historically been achieved by the use of activity escalation studies during clinical trials and this in turn has led to a chronic under dosing of the majority of patients. This paper looks to address the difficulties in combining clinical everyday practice with the grand challenges laid out by national metrology institutes to improve measurement capability in all walks of life. In the life sciences it can often be difficult to find the correct balance between pure research and practical solutions to measurement problems, and this paper is a discussion regarding these difficulties and how some NMIs have chosen to tackle these issues. The necessity of establishing strong links to underlying standards in the field of quantitative nuclear medicine imaging is highlighted. The difficulties and successes of current methods for providing traceability in nuclear medicine are discussed.

1. Introduction

One of the key roles of a National Metrology Institute (NMI) or a Designated Institute (DI, hereafter included in discussion of NMIs) is to provide a link between fundamental research and industrial applications for all forms of measurement. NMIs have a unique position providing access to both real-world applications and novel experimental processes, with the goal of connecting the two. As a consequence, NMIs have developed considerable expertise to offer traceable measurements alongside world-class data analysis techniques. However, the dissemination of these processes to end-users often requires investment from both parties.

Since the early 1900's, many NMIs have been involved in the calibration of medical isotopes for use in multiple forms of radiotherapy. Initially this was primarily done through the calibration of solid ^{226}Ra seeds (Radium Commission, 1930) used in an early form of External

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Beam Radiotherapy (EBRT), a precursor to modern brachytherapy. Whilst these early therapies would be considered primitive by today's standards, some treatments showed promise and the subsequent refinements and developments eventually led to the use of EBRT in the successful treatment of a variety of cancers. In EBRT it was quickly realised that although calibration of the 'source' (or beam) was critical to the safe delivery of therapies, the method of translating the energy deposited by these beams in patients was of equal importance for delivering improved therapy outcomes. In addition, it was demonstrated that better targeting of energy deposition was required in order to spare healthy tissue from unnecessary damage and therefore lead to improved patient outcomes (Thariat et al., 2013). Recently many NMIs have begun to move away from using traditional research linear accelerators and invest in clinically relevant equipment in order to close the gap between the NMI 'standards' and the clinical application of these standards. EBRT practice is now underpinned across the world by NMIs through the provision of standards, development of QC protocols and guidance and confirmed by a variety of audits, each tailored to the specific therapy of interest. This has necessitated a programme of work to develop knowledge of clinical procedures within the NMI community and the establishment of close links between the NMIs and clinical experts. As a result, there is now enforcement in many countries of regulations ensuring all patient absorbed doses are accurately known and customised to each patient with traceability of measurements enshrined into law, improving outcomes for patients receiving EBRT. For nuclear medicine applications, in which medical isotopes are administered internally, the picture is somewhat different (D'Arienzo et al., 2014; Zimmerman and Judge, 2007). Although developed in parallel with EBRT, the determination of absorbed doses received by patients undergoing diagnostic or therapeutic nuclear medicine procedures has traditionally been mostly limited to either cytotoxic potency or environmental protection issues (established during clinical trials with a limited cohort of patients) rather than diagnostic or therapeutic outcomes.

Diagnostic nuclear medicine is commonly focused on the detection of radiation emission emitted from the decay of an administered radionuclide, attached to a functional targeting vector. Positron Emission computed Tomography (PET) imaging is performed in a quantitative manner and typically reports the relationship between uptake (in Becquerels) and the injected activity to determine a Standardised Uptake Value (SUV) which can then be used for diagnosis, staging and treatment planning (Boellaard, 2009; Thie, 2004). Single Photon Emission Computed Tomography (SPECT), imaging has traditionally been performed and reported in a qualitative or semi quantitative manner and is subsequently used to diagnose disease, treatment planning or staging. There is now an increasing move towards the use of quantitative SPECT imaging (Bardiès and Flux, 2013; Flux et al., 2014), highlighting the urgent need for measurement traceability for all nuclear medicine imaging modalities.

Quantification in PET is clearly many years ahead of that in SPECT, however accurate calibration of the device relies heavily on the diligence of the responsible physics team. Groups such as the National Cancer Research Institute (NCRI) in the UK, EANM and EATRIS in Europe and the SNMMI in the US have developed accreditation schemes to help ensure consistency within clinical trials, however the link to primary standards of radioactivity is not always clear. The apparent lack of rigorous uncertainty assessment brings into question the validity of any traceability chain, and the use of un-validated 'black box' software during image reconstruction and processing raises further questions over how traceable such measurements can be. That said, quantification is widely used in PET and the use of this modality in determining patient activity distributions is commonplace.

In SPECT the picture is far less clear; many groups have begun to offer guidance and present papers relating to quantitative imaging (Attarwala et al., 2014; Bailey and Willowson, 2014; IAEA, 2014), however little if any validation of such methods has been performed making it difficult to ascertain how accurate any of the individual methods are. In contrast to PET imaging, no individual group has yet to establish an accreditation program for SPECT to provide harmonisation between imaging devices. Again, a lack of rigorous uncertainty assessment and the use of un-validated black-box software, and even non-standardised phantoms raises questions over how traceable these measurements can claim to be. In spite of this, a current phase II clinical trial (NCT02393690) is using quantitative SPECT imaging in patients with recurrent or metastatic iodine-refractory thyroid cancer to determine the success of the investigation drug (Wadsley et al., 2017). This trial uses the measured uptake of a diagnostic agent to determine if a patient is able to receive therapy following a course of a pharmaceutical designed to increase uptake of iodine. The trial is the first of its kind to require harmonisation between the imaging systems being used in the trial to ensure that the dataset is robust and that all trial patients are judged against the same benchmark. Patients that proceed to treatment will additionally have full absorbed dose calculations performed using both pre- and post- therapy imaging with the intention of correlating treatment outcome to therapeutic absorbed dose. A secondary aim is to compare predicted absorbed doses from the pre-therapy imaging to actual calculated absorbed doses following treatment. The development of the calibration protocol used in this study was conducted in close collaboration between the UK's National Physical Laboratory (NPL) and the clinical research team, demonstrating the feasibility of such a relationship.

For the therapeutic administration of radionuclides in Molecular Radiotherapy (MRT) the red marrow, liver or kidneys are the common organs at risk that may exhibit toxicity and therefore can be a limiting factor in total activity administration to a patient. Quantified PET or SPECT imaging is necessary to both predict and determine the activity distribution for these organs. Presently, the administered activity to obtain a given therapeutic outcome is based on fixed levels or calculated using patient body surface area or weight without consideration of the individual patient biokinetics. As an example, the maximum tolerated activity could be calculated from pre-therapy imaging studies according to a predicted maximum whole-body absorbed dose of 2 Gy as a surrogate of the bone marrow absorbed dose (Dewaraja et al., 2010; George et al., 2016), however this is not a standard clinical protocol for treatment planning in MRT.

MRT can offer distinct advantages over EBRT, with the right combination of labelling vectors effectively targeting cancerous tissue whilst minimizing the radiation dose delivered to healthy tissue. This can be particularly advantageous in the treatment of metastatic disease, where the use of large fields in EBRT can result in soft tissue toxicity and therefore is not always a viable option. There is a clear role for NMIs to provide traceability and confidence in both diagnostic and therapeutic nuclear medicine measurements.

2. So where is the metrology?

The provision of standards for radionuclide calibrators is vital to the accurate assessment of administered activities (Zimmerman and Judge, 2007). In many parts of the world this is done to a relatively high standard, with NMIs and DIs providing traceability directly to the hospitals either by calibration of the devices themselves, or by the provision of calibrated sources or a calibration service to determine sensitivity coefficients (also called dial settings or calibration factors) by the clinical users (Sahagia, 2011). To this end it is fairly well accepted that for 'simple to measure' radionuclides such as ^{99m}Tc, the majority of hospitals can accurately measure an administered activity to within 5% (MacMahon et al., 2007) although some groups still report difficulties in this area (Iwahara et al., 2009). This becomes more varied for 'difficult to measure' radionuclides such as ^{90}Y or ^{125}I however for a conscientious clinical site it could be reasonably expected to obtain an accurate measurement to within 10% (Fenwick et al., 2014). Comparison or proficiency testing exercises have been performed in

quantitative imaging (Zimmerman et al., 2012b) and whilst these are vital in understanding the 'state of the art' and identifying measurement challenges, these exercises do not directly address specific measurement problems. Beyond this point is where EBRT and MRT start to diverge in developing a route of traceability up to the patient administration. In contrast to EBRT, for MRT there is limited accurate knowledge of quantitative measures of uptake, retention, distribution of the radiopharmaceutical or the absorbed doses delivered following administration.

Accurate determination of absorbed dose for MRT requires quantitative imaging of radiopharmaceutical distributions, adding considerable additional complexity in comparison to EBRT. The challenges for MRT dosimetry therefore lie in accurately determining uptake following injection of the radiopharmaceutical. This can easily be done in a qualitative manner for many radionuclides through the use of SPECT or PET imaging, with said imaging often forming part of the therapy procedure. The translation of this qualitative information into an accurate radioactivity distribution within the patient however is fraught with difficulties and the link to primary standards of radioactivity is questionable at best. Whilst many NMIs can standardise a host of medical radionuclides with high degrees of accuracy, the transfer of these standards into clinically relevant situations is not as closely defined as it is in EBRT. NMIs have an extensive breadth of experience providing calibration and traceability for dosimetry measurements in EBRT and could therefore have a huge impact by providing the same in MRT. The benefit of this approach is demonstrated by the recent development of a primary standard for absorbed dose from unsealed radionuclide solutions (Billas et al., 2016), which creates the first link in the traceability chain for MRT dosimetry.

Arguments against the consideration of dosimetry in MRT are primarily focused on the dominant application of nuclear medicine being diagnostic imaging and the limited evidence for the therapeutic effect of MRT (Giammarile et al., 2017). These arguments are flawed (Flux et al., 2017); the advent of PET imaging led to the widespread adopted use of the SUV (Thie, 2004) which uses quantitative imaging for the diagnosis and staging of cancer and although not perfect, has proven to be useful in improving diagnosis and staging (Buvat, 2007; Kohutek et al., 2015; Mattes et al., 2015). Furthermore, the use of radionuclides such as ^{131}I for the treatment of thyroid disease or ^{223}Ra for the treatment of metastatic prostate cancer demonstrates that MRT is not restricted to palliative care and must be considered therapeutic in most cases (McCready, 2017; Parker et al., 2013). Studies have also shown that absorbed dose correlates well with therapeutic outcome (Flux et al., 2010; Klubo-Gwiezdzinska et al., 2011). Whilst groups such as the American Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the European Association of Nuclear Medicine (EANM) have established some guidelines for nuclear medicine procedures to establish 'standards' in the field, these do not necessarily align with the ideology of a true metrological solution. It is therefore critical that links between NMIs and these organisations are established in order to provide cohesive advice, guidance and methodologies.

3. So why haven't these issues been addressed?

The failure to address the above issues comes from several sources and the complexity of the problem should not be underestimated. To date although there is involvement from NMIs in the provision of standards of radioactivity, traceability for the use of medical isotopes in the diagnosis or treatment of disease has been sadly neglected. As a result of the lack of consensus it is difficult to construct clear legislation. Therefore, there is little or no obligation for pharmaceutical companies, clinical centres and professional societies to develop routine practice resulting in a limited engagement between these groups and NMIs.

Traditionally radioiodine treatments with fixed administered activities have been proven very successful in the treatment of benign and malignant thyroid disorders since their first administration in 1941 (McCready, 2017), without consideration of the biological variation between patients. MRT is currently stuck in a vicious circle where the lack of extensive evidence of absorbed dose response relationships is often due to the low number of patients receiving MRT and a lack of randomised controlled clinical trials, whilst these relationships cannot be established without the necessary clinical studies to provide the evidence (McGowan and Guy, 2015). To perform a calibration of a PET or SPECT system, a host of geometrical and mathematical functions must be considered (Attarwala et al., 2014; Bailey and Willowson, 2014; Erlandsson et al., 2011; Fleming, 1989; Frey and Tsui, 1996) alongside the typical calibration procedures for detectors of this type (English and Brown, 1986; NEMA, 2007). PET and SPECT both typically employ scintillation crystals optically coupled to photomultiplier tubes in order to detect the photons emitted by the radionuclides in use. These detectors are the same as those used in radioactivity counting experiments worldwide, but the processing of the acquired counts and subsequent algorithms used to form an image adds significant challenges to any calibration procedure. This complexity is further increased by a lack of standardisation across the industry in how datasets are handled and presented, as well as a reluctance from the manufacturers in sharing proprietary information. The financial cost associated with purchasing and maintaining such devices is significant. To date only the National Institute for Standards and Technology (NIST) in the US owns a dedicated PET system for such research, with a complimentary SPECT and PET system being installed at the NPL in 2017. The net result of these combined issues leads to a level of confusion in the sector with several groups working seemingly independently and with limited resources to solve what is a very complex measurement problem. One area of commonality is the need for standardisation in the field with reports from almost every institution involved calling for unity (BIR, 2011; NCRI, 2016).

This is where the role of the NMI should really come into its own as with their unique perspective on measurement challenges they are ideally placed to offer advice and guidance on the best way to bring the different groups together in the name of standardisation. This process has already begun with the work undertaken by the NIST in the USA (Bergeron et al., 2015; Zimmerman et al., 2012a, 2012b, 2014), the NPL-led consortia (MRTDosimetry, 2017) across Europe and the IAEA group working worldwide.

4. What is being done?

Some NMIs have begun to address the problems associated with quantitative imaging and dosimetry through pan European projects and national research programmes. The UK's NPL has successfully led a European Metrology Research Programme (EMRP) project (MetroMRT, 2012) involving a large pan European collaboration including 6 NMIs and 31 collaborating institutions, and is presently leading a follow up project focused on metrology for the clinical implementation of dosimetry in molecular radiotherapy (MRTDosimetry, 2017). Both of these projects seek to address the issue of metrology in MRT and specifically look at the calibration and validation of quantitative imaging measurements using SPECT. These projects have come about thanks to close interaction with the user community and specific demands identified during liaisons with hospitals physicists, national and international societies and workshops such as the Nuclear Medicine Metrology Meeting and Radionuclide Calibrator Users Forum (NPL, 2017) organised by NPL.

The NIST has worked closely with the Quantitative Imaging Biomarker Alliance (QIBA) (Huang et al., 2015; Sullivan et al., 2015), the Food and Drug Administration (FDA) and the National Cancer Institute through the Quantitative Imaging Network (QIN) (Clarke et al., 2014) and the Cancer Imaging Program phase I and II Imaging trials (Shankar, 2012) initiatives in the US in an effort to introduce better traceability in PET imaging studies, primarily to support multi-centre clinical trials and development of imaging biomarkers (Zimmerman

et al., 2009). Scientists from the ENEA in Italy have been involved in performing small research projects in nuclear medicine imaging in collaboration with clinical sites (D'Arienzo et al., 2014). As previously mentioned, the NPL has been involved in the design of measurement protocols for clinical trials involving quantitative imaging (Wadsley et al., 2017).

Consensus guidelines for the acquisition and analysis of imaging biomarkers are typically developed by working groups formed by organisation such as the SNMMI, the EANM or the IAEA. Recognizing the need for improved translation of imaging biomarkers, representatives from Cancer Research UK (CRUK) and the European (Organisation for Research and Treatment of Cancer) EORTC, together with other experts in multiple medical fields, have formulated an imaging biomarker roadmap for cancer studies (O'Connor et al., 2017). A recent review of the use of internal dosimetry in the clinical practice of molecular radiotherapy has also shown that the evidence strongly implies a correlation between the absorbed doses delivered and the response and toxicity, which indicates that dosimetry-based personalized treatments would improve outcome and increase survival (Strigari et al., 2014). All of these are prime examples of measurement problems that could benefit from NMI involvement provided an optimal balance of clinical practice and fundamental research can be established. To reach this optimal balance the transfer of knowledge in both directions is required and both NMIs and clinical sites should strive to form collaborations in order to address these issues, as has been both necessary and successful in EBRT.

5. Conclusion

The need for NMIs and DIs to support the field of MRT dosimetry is obvious, with a set of clear measurement challenges requiring attention. There is currently an expanding void forming between medical imaging and traditional radioactivity measurement. In order to address the measurement challenges, it is vital that NMIs come together in the same way as it done in other areas of radioactivity measurement in order to offer the appropriate support to the user community. NMIs must form close links with clinical sites to ensure that the measurement needs of the user community are met and addressed by the NMI. Engagement with relevant societies and participation in appropriate working groups, workshops and conferences is essential to integrate the fundamental science performed at an NMI into the formation of guidance and regulation. NMIs can support this formation through the development of validation techniques and traceability chains. NMIs and associated clinical sites may also find new relevance and greater impact for existing skills and provided they can secure a suitable resource can help to improve traceability, comparability, and ultimately drive down uncertainties in the field. Areas where NMIs could have the upper hand in terms of research capability would be to ensure the completion of traceability chains in areas such as absorbed dose from radionuclides, and uncertainty assessment of image acquisition and reconstruction. The authors would urge anyone reading this paper to consider the need for research in this field and perhaps to begin to re-focus some efforts in this direction where possible.

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