IPEM topical report: Current molecular radiotherapy service provision and guidance on the implications of setting up a dosimetry service

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Abstract

Despite a growth in molecular radiotherapy (MRT) and an increase in interest in dosimetry, centres still rarely perform MRT dosimetry. The aims of this report were to assess the main reasons why centres are not performing MRT dosimetry and provide advice on the resources required to set-up such a service.

A survey based in the United Kingdom was developed to establish how many centres provide an MRT dosimetry service and the main reasons why it is not commonly performed. 28% of the centres who responded to the survey performed some form of dosimetry, with 88% of those centres performing internal dosimetry. The survey showed that a “lack of clinical evidence”, a “lack of guidelines” and “not current UK practice” were the largest obstacles to setting up an MRT dosimetry service. More practical considerations, such as “lack of software” and “lack of staff training/expertise”, were considered to be of lower significance by the respondents.

Following on from the survey, this report gives an overview of the current guidelines, and the evidence available demonstrating the benefits of performing MRT dosimetry. The resources required to perform such techniques are detailed with reference to guidelines, training resources and currently available software.

It is hoped that the information presented in this report will allow MRT dosimetry to be performed more frequently and in more centres, both in routine clinical practice and in multicentre trials. Such trials are required to harmonise dosimetry techniques between centres, build on the current evidence base, and provide the data necessary to establish the dose response relationship for MRT.

Introduction

Radionuclides have been routinely administered for systemic molecular radiotherapy treatment (MRT) for over a century [1]. The first published use of MRT involved Radium-226 for the treatment of a number of diseases, in particular high blood pressure, pernicious anaemia and leukaemia [2]. Administration of Iodine-131 (^{131}I) for benign and malignant thyroid disease became routine clinical practice over 70 years ago and radioiodine therapy is now one of the most commonly administered MRT in the UK, alongside Radium-223 (^{223}Ra) and peptide receptor radionuclide therapies (PRRT) [1, 3-6].

The main aim of the majority of MRT is to give a lethal radiation dose to cancerous cells. These cells are selectively targeted through the choice of the radiopharmaceutical whilst avoiding damage to normal cells. Currently, common practice in MRT is that therapeutic radionuclide activities are either fixed, or scaled according to patient weight and absorbed dose calculations are not performed [7]. In contrast to this external beam radiotherapy (EBRT) treatments are planned to deliver a prescribed dose to a target volume whilst doses to organs at risk are kept below tolerances to reduce tissue toxicity. Treatment planning for EBRT relies on absorbed dose calculations and an established understanding of dose-response relationships within this field [8]. In MRT the absorbed doses delivered to the individual target tumours vary widely and it has been shown to lead to under treatment in the majority of patients [9]. Therefore, dosimetry-based treatment planning has the potential to improve patient outcomes.

Prospective treatment planning in MRT may be performed using a tracer radionuclide, this can be a small amount of the therapeutic radiopharmaceutical or a diagnostic radionuclide labelled to the same, or a similar, pharmaceutical. The underlying assumption is that the tracer has the same bio-distribution as the therapeutic radiopharmaceutical and does not alter the patient bio-kinetics between tracer and therapeutic administrations. Examples of this include Iodine-123 Meta-iodobenzylguanadine (^{123}I-mIBG) imaging for planning of subsequent ^{131}I-mIBG therapy for neuroendocrine tumours and ^{99m}Tc-MAA imaging for planning Yttrium-90 (^{90}Y) microsphere treatments [10, 11]. Alternatively, for therapies administered in fractions, dosimetry calculations from the first fraction can be used to plan the subsequent fraction [12].

All MRT dosimetry necessitates measurements of the time-integrated activity, the frequency of which is dependent on the radiopharmaceutical and therapy type. The complexity can range from simpler calculations of a whole-body dose to more resource intensive methods such as image-based voxel dosimetry to obtain dose volume histograms.

There is increasing interest in quantifying absorbed doses in MRT in order to establish dose-response relationships with the potential for MRT treatment planning equivalent to EBRT. This is driven in part by a recent EU Directive [2013/59/Euratom] requiring treatment planning for all radiotherapeutic exposures including MRT [13]. This is mirrored within the UK in the Ionising radiation (medical exposures) (amendment) regulations (IRMER) 2018, and the Administration of Radioactive Substances Advisory Committee (ARSAC) who have advised that absorbed doses should be recorded for all MRT in cancer for optimisation of subsequent treatments, and calculated for benign conditions [14, 15]. Therefore, the Institute of Physics and Engineering in Medicine (IPEM) within the UK established a working party for the Implementation of Dosimetry in Molecular Radiotherapy. The aims of this working party were to assess the main reasons why centres were not performing MRT dosimetry and advise centres on the resources required to set-up a dosimetry service.

Survey on current practice

A survey was developed by the IPEM working party to establish how many centres provide an MRT dosimetry service and the main reasons why other centres do not perform MRT dosimetry. The survey was available online and publicised by IPEM and on the medical physics and engineering JISCM@il discussion list [16] based within the UK.

Dosimetry was split into two categories for the survey: whole-body dosimetry and internal dosimetry. Whole-body dosimetry is defined as the non-location specific measurement of the retention of a radiopharmaceutical. This is normally calculated from measurements performed at a distance from the patient and can be used to infer an absorbed dose to the bone marrow. Internal dosimetry is focussed on calculating an absorbed dose to a target or organ at risk, either from measurements with a radiation monitor positioned above an area of interest, or from imaging. Respondents were asked whether they perform each category of dosimetry, and then to rate reasons for not performing whole-body and internal dosimetry for each of six MRTs: radioiodine therapy for thyroid cancer (RAI), ^{131}I-mIBG (mIBG), peptide receptor radionuclide therapy (PRRT), radioimmunotherapy, any MRT for bone metastases, and selective internal radiation therapy (SIRT) for liver tumours. These MRTs were selected as the most commonly performed in the UK following the recent IDUG survey results [5, 17]. Fourteen options were given for reasons not to perform dosimetry and could be rated from 0 (not relevant) to 5 (very relevant). The average rating each reason received per therapy was used to rank the key reasons for not performing whole-body and internal dosimetry. Scores were also averaged across all therapies for an overall perspective. Free text boxes were included for further comments.

Survey results: Levels of dosimetry practice

The survey received 59 responses; two responses were excluded having originated from centres not practising MRT. Of the 57 remaining responses, 44 were from England, 7 from Scotland, 3 from Wales, 1 from Northern Ireland, and 2 from outside of the UK.

The numbers of centres performing MRT dosimetry can be seen in Table 1. Twenty-eight per cent of the surveyed centres perform some form of dosimetry, the majority of whom (88 %) perform internal dosimetry.

Table 1: number of centres performing whole-body and Internal dosimetry

		Wholebody dosimetry	
		Yes	**No**
Internal dosimetry	**Yes**	10	4
	No	2	41

Survey results: Obstacles to MRT dosimetry

Table 2 shows the key reasons for not performing whole-body and internal dosimetry, and Figure 1 demonstrates all of the results as Coxcomb plots.

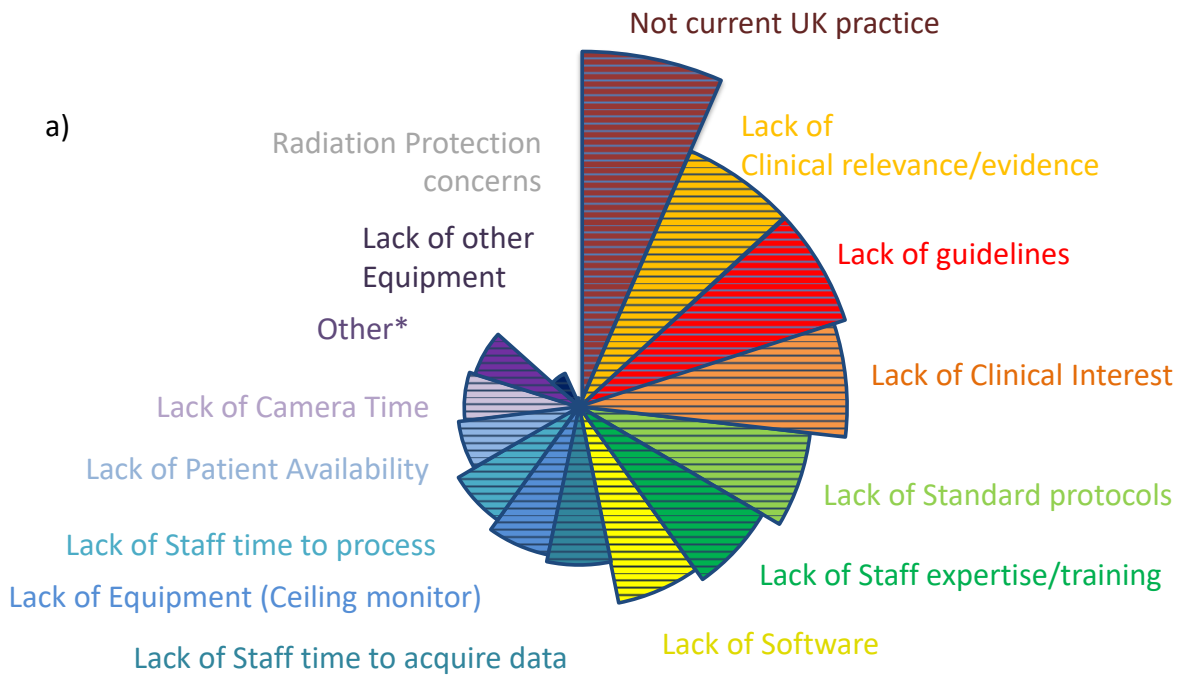
Table 2: The three highest ranked reasons for each therapy for not performing whole-body and internal dosimetry.

Type of dosimetry/scores		Radioiodine	mIBG	PRRT	Radioimmuno-therapy	Bone Metastases	SIRT
Whole-body dosimetry	1st	Not current UK practice					
	2nd	Lack of clinical relevance/evidence of benefit	Lack of Clinical Interest	Lack of guidelines	Lack of software	Lack of guidelines	Lack of clinical relevance/evidence of benefit
	3rd	Lack of Clinical Interest	Lack of guidelines	Patient availability (for measurements)	Lack of staff expertise/training Lack of guidelines	Lack of clinical relevance/evidence of benefit	Lack of Clinical Interest
Internal dosimetry	1st	Not current UK practice	Not current UK practice	Patient availability (for measurements)	Lack of guidelines	Not current UK practice	Not current UK practice
	2nd	Lack of guidelines	Lack of Clinical Interest	Lack of Clinical Interest	Lack of staff time to acquire No standard protocol	Lack of guidelines	Lack of Clinical Interest
	3rd	Lack of clinical relevance/evidence of benefit	Lack of guidelines	Not current UK practice Lack of staff expertise/training	Lack of Clinical Interest	Lack of clinical relevance/evidence of benefit	Lack of clinical relevance/evidence of benefit

In the case of whole-body dosimetry, centres consistently rated “Not current UK practice” as the main obstacle (overall average score 4.1/5) across all five of the MRT’s. Other obstacles rated highly were “Lack of clinical relevance/evidence of benefit” (3.9/5), “Lack of guidelines” (3.6/5) and “Lack of clinical interest” (3.5/5). Similarly for internal dosimetry “Not current UK practice” was rated highest (3.9/5) followed by “Lack of guidelines” (3.5/5) and “Lack of clinical interest” (3.5/5).

More practical considerations were also rated highly for both whole-body and internal dosimetry including “Lack of software” (3.4/5) and “Lack of staff training/expertise” (3.2/5). For radioimmunotherapy and PRRT reasons were more varied across centres with more practical barriers rated highest. The lack of “patient availability (for measurements)” ranked top for PRRT (2.4/5) and the “Lack of software” for immunotherapy (2.2/5).

Comments in the free text boxes highlighted that many centres have large geographical catchment areas, which makes repeat imaging difficult on an out-patient basis. There were also several centres where the therapy was performed on a separate site from where the imaging equipment was situated. One centre stated that they had the expertise to perform dosimetry but no imaging was performed as standard after ^{131}I and ^{223}Ra administrations. Some centres performed single time point imaging only and felt this was inadequate information to perform dosimetry. Limited funding for staffing, imaging and equipment (such as ceiling monitors) was mentioned in multiple instances.



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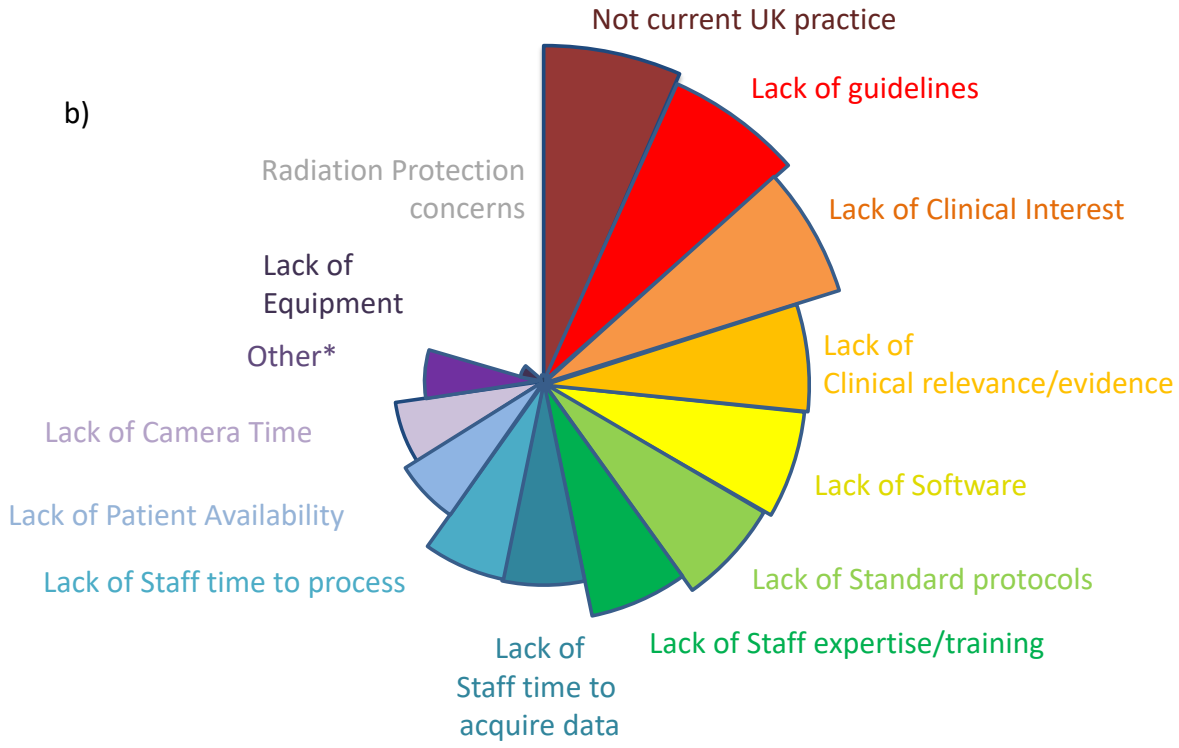

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22 Figure 1: Coxcomb plots of the obstacles given by centres for not being able to provide a dosimetry service for
23 (a) whole-body and (b) and internal dosimetry (averaged over all therapies). The lengths of the arcs are
24 proportional to the number of centres indicating each reason is relevant to their site.

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Clinical interest, relevance and evidence of benefit

Dosimetry of new radiopharmaceuticals is a legal requirement to gain approval for routine clinical use [18]. This approval process is where the majority of dosimetry measurements are performed. Once the toxicity of a procedure has been characterised, these measurements are often used to define a fixed administration activity or weight-based activity prescription. This has been a successful approach to radioiodine treatment of thyroid cancer for decades [19]. Therefore, dosimetry measurements are not routinely continued after this point and the clinical benefit of MRT dosimetry is rarely assessed with a view to the potential of treatment optimisation. However, previous literature has shown that absorbed radiation doses and their distributions vary widely between patients [20]. Published dose-response thresholds for some MRT procedures suggest that the use of fixed activities may under- or over-treat patients [21-25]. Therefore, more routine dosimetry is required to establish Absorbed Dose-Effect/Response relationships (ADER) to avoid this in the future [9, 26, 27].

Encouragingly, the evidence for the clinical benefit of dosimetry in MRT is mounting [27]. This is in contrast with the survey results which found that a large proportion of centres believed there was no perceived benefit, which is unsurprising as there have been no randomised trials of dosimetry based MRT and providing clinical evidence is challenging [28]. However, multicentre trials which increase the sample sizes, and therefore improve the statistical significance of studies using dosimetry in MRT planning, are emerging and will build the evidence base for dosimetry [29]. The following details some of the evidence available for ^{131}I therapies for thyroid disease, ^{131}I-mIBG therapy, PRRT and SIRT.

The majority of the available evidence is for the more established ^{131}I therapies. It has been shown that there is a significant gain in survival for differentiated thyroid cancer patients with loco-regional advanced disease in studies using the Benua-Leeper approach. This aims to administer the maximum tolerated activity that does not exceed a 2 Gy dose to the blood, which acts as a surrogate of bone marrow [30-35]. Additionally significant correlations have been shown between whole-body absorbed dose and myelotoxicity. Internal dosimetry measurements have been performed to determine dose response thresholds for ^{131}I thyroid ablation. These are method dependant with Maxon et al [36] establishing a mean absorbed dose threshold of 300 Gy versus the more recently identified 50 Gy maximum voxel absorbed dose threshold [23]. Additionally an 85 Gy threshold was established for successful treatment of metastatic disease using a rectilinear scanner [22]. However, more recent Iodine-124 (^{124}I) PET measurements indicated a lower threshold at 40 Gy [24]. Clearly these methods require standardisation through robust guidelines, protocols, and multicentre trials to provide response thresholds which can be used clinically across all centres. SEL-I-METRY is the first multicentre UK study performing ^{123}I and ^{131}I SPECT-CT based dosimetry for radioiodine therapy of advanced

thyroid cancer enhanced using the MAP kinase inhibitor Selumetinib [37, 38]. In addition, the Horizon 2020 MEDIRAD (NFRP-2016-2017-9) project is a multi-national study investigating the dose response relationship in radioiodine therapy ablation of thyroid remnants

In the treatment of neuroendocrine tumours several centres plan ^{131}I-mIBG therapies for neuroblastoma using administered activities that limit the whole-body dose to 2 Gy [39, 40]. A multicentre PRRT trial is also underway in Sweden to assess tumour responses for ^{177}Lu DOTATATE treatment administered such that the biological effective dose to the kidneys is restricted [25, 41]. Initial results have shown a significant correlation between the absorbed dose and the tumour response [25].

Liver toxicity and fatal radiation induced liver disease have been observed following SIRT of hepatic tumours, and the importance of dosimetry has been recognised to avoid these toxicities [42]. Dosimetry based on the pre-therapy ^{99m}Tc-MAA imaging has been used successfully for prospective treatment planning [11, 43-45]. The absorbed dose delivered to tumours has been found to correlate with tumour response and survival after SIRT; and threshold absorbed doses for tumour response have been reported [43, 46-57]. However, a definitive response threshold is difficult to establish. Centres use different dosimetry calculation methods and types of microsphere, and the methods to evaluate tumour response vary widely [42, 58, 59]. Some studies have shown a relationship between toxicity and the absorbed dose received by the normal liver in SIRT [44, 55, 60-63]. More work is needed to establish threshold doses for normal liver toxicity which depend on the underlying disease and disease stage, the liver function, concurrent therapies and the type of microspheres [51, 64, 65].

It is clear that there is evidence available demonstrating the relationship between absorbed dose and treatment response. However, more multicentre studies are required to encourage a change in practise to include dosimetry. These rely on the reproducibility of dosimetry results between centres and must be set up to obtain quantitative data and perform dosimetry calculations in a standardised way across a network of centres. These types of studies will be pivotal in rolling-out the harmonised dosimetry methods and expertise between centres that are vital to establish the required clinical evidence and guidelines for dosimetry in MRT.

Guidelines

Comprehensive guidelines are required to establish good standards of practice in dosimetry and to support the measurement of absorbed radiation doses by standardised methods. The currently available guidelines are listed in Table 3 and summarised below in order of complexity.

Whole-body, bone marrow and blood dosimetry

Whole-body dosimetry measurements can be performed for all MRTs but are most commonly performed for ^{131}I thyroid therapies, ^{131}I mIBG and PRRTs. The absorbed dose to the whole-body can be assumed to be a surrogate for the absorbed dose to the bone marrow [66]. A simple method to perform whole-body dosimetry, using calibrated radiation monitors, is described in the Internal Dosimetry Users Group (IDUG) report on whole-body dosimetry guidance [67] and the *IPEM report 104* [66]. Whole-body measurements can be combined with other measurements, such as blood samples, and the *European Association of Nuclear Medicine* (*EANM) Dosimetry Committee guidelines for bone marrow and whole-body dosimetry* [34] provide a useful flowchart to determine the best technique depending on the uptake pattern. The *EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy* [30] also describes a procedure for the calculation of the absorbed dose to the blood (as a surrogate for bone marrow) to plan ^{131}I therapy such that this dose does not exceed 2 Gy. The *EANM Dosimetry Committee series on standard operational procedures for internal dosimetry for ^{131}I mIBG treatment of neuroendocrine tumours* [68] similarly describes whole-body measurements specifically for ^{131}I mIBG treatments.

Internal dosimetry

Internal dosimetry measures the mean absorbed doses to volumes and can be performed where an organ at risk or a specific tumour target has been identified such as for SIRT, ^{131}I thyroid therapies, ^{131}I mIBG, PRRTs and MRTs for bone metastases. Calibrated images of the radioactivity distribution are often required making these methods more complex than simple whole body dosimetry. One of the most accessible forms of MRT internal dosimetry calculations is for SIRT when only one imaging time point is required. The time-integrated activity is simple to calculate because the microspheres are assumed to stay within the tumour, therefore the effective half-life of the radiopharmaceutical is equal to the physical half-life. The *EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds* [69] discusses the various methods for determining absorbed doses that are available. It is worth highlighting that of the methods given in this guideline only the compartmental MIRD macrodosimetry considers the tumour uptake.

Absorbed dose calculations for radioiodine treatment are covered in multiple guidelines. The *EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry II: Dosimetry prior to radioiodine therapy of benign thyroid diseases* [70] describes prescribing the administered activity based on pre-therapeutic ^{131}I dosimetry. The *EANM Therapy Committee guidelines for radioiodine therapy of differentiated thyroid cancer* [71] also details the concepts of pre-therapeutic dosimetry in Appendix 1. The *MIRD Pamphlet No. 24: Guidelines for Quantitative I-131 SPECT in Dosimetry Applications* [72] provides guidance on performing quantitative ^{131}I SPECT scanning and the subsequent absorbed dose calculations. This includes a discussion of dead-time correction, partial volume correction and the calibration of SPECT systems to allow for quantification. This pamphlet also includes two examples of patient data for organ and tumour dosimetry. The *EANM Dosimetry Committee series on standard operational procedures for internal dosimetry for ^{131}I mIBG treatment of neuroendocrine tumours* [68] also describes internal dosimetry calculations and associated measurements specifically for ^{131}I mIBG treatments. In addition to these guidelines, planar and SPECT quantification are covered in *IPEM report 104* [66] and approaches for dosimetry for both benign thyroid disease and differentiated thyroid cancer are discussed.

The *MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative Lu-177 SPECT Applied for Dosimetry of Radiopharmaceutical Therapy* [73] discusses image quantification for ^{177}Lu, including optimal collimator choice, dead-time and reconstruction techniques. Camera calibration is also covered and examples of clinical absorbed dose calculations are given.

Internal dosimetry of alpha particle emitters, most commonly used for treating bone metastases, can be challenging due to poor image quality, but can be performed as demonstrated by Chittenden et al [74]. The *MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy* [75] describes dosimetry techniques specifically for alpha particle emitters.

Voxel dosimetry

Voxel dosimetry can be performed on any of the MRTs where internal dosimetry is required. It measures the absorbed dose distribution within an organ or target lesion without assuming uniformity within that region, this requires Monte Carlo methods, the use of voxel S-values or predefined absorbed dose kernels (described in the MIRD schema section). The *MIRD pamphlet No. 17: The dosimetry of non-uniform activity distributions - Radionuclide S values at the voxel level* [76] discusses different methods of voxel dose calculation and their advantages and disadvantages with several examples. More specifically, the *MIRD Pamphlet No. 24: Guidelines for Quantitative I-131 SPECT in Dosimetry Applications* [72] discusses voxel dosimetry for ^{131}I, the *MIRD Pamphlet No. 26: Joint*

EANM/MIRD Guidelines for Quantitative Lu-177 SPECT Applied for Dosimetry of Radiopharmaceutical Therapy [73] covers voxel dosimetry for ^{177}Lu, and *MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy* [75] describes dosimetry calculations for alpha emitters.

Other useful guidance

Additional guidance can be found in the *EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting* [77]. This provides recommendations for documenting and reporting in enough detail to allow evaluation and reproduction of the dosimetry methods.

Other MIRD pamphlets provide useful information, such as *MIRD pamphlet No. 16: Techniques for Quantitative Radiopharmaceutical Biodistribution Data Acquisition and Analysis for Use in Human Radiation Dose Estimates* [78] and *MIRD Pamphlet No 23: Quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy* [79]. These describe dosimetry techniques, the MIRD schema, data collection and analysis, frequency of sampling and quantitative measurement techniques. In addition, the *EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations* [80] introduces a framework to model the uncertainty in absorbed dose calculations.

174 **Table 3: List of currently available guidelines**

Target		Hardware	Measurement Schedule	Guidelines
Whole-Body (bone marrow)		Dose monitor (Hand held or ceiling mounted) or gamma camera	Pre-void whole-body count followed by 2 hourly monitoring when possible.	*IPEM report 104: Dosimetry for radionuclide therapy*, Bardies et al, 2011 [66]. *EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry,* Hindorf et al, 2010 [34]. https://eanm.org/publications/guidelines/EJNMMI_Bone_Marrow_Dosimetry_06_2010.pdf *Whole Body Dosimetry Guidance,* IDUG, 2015 [67]. http://www.IDUG.org.uk/wp-content/uploads/2017/05/IDUGI-131-Whole-Body-Dosimetry-Final.pdf *EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy,* Lassman et al, 2008 [30]. https://www.eanm.org/publications/guidelines/gl_dosi_standards1.pdf *EANM Dosimetry Committee series on standard operational procedures for internal dosimetry for ^{131}I mIBG treatment of neuroendocrine tumours, Gear et al 2020 [68].* https://ejnmmiphys.springeropen.com/articles/10.1186/s40658-020-0282-7
Bone Marrow and blood		Dose monitor or gamma camera and blood sampling	Blood samples: I-131 for thyroid cancer: 2, 6, 24, 48 and 96 hours post-administration. Or 10 minutes post-administration for IV admin. Whole-body as above	*IPEM report 104: Dosimetry for radionuclide therapy*, Bardies et al, 2011 [66]. *EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry,* Hindorf et al, 2010 [34]. https://eanm.org/publications/guidelines/EJNMMI_Bone_Marrow_Dosimetry_06_2010.pdf *EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy,* Lassman et al, 2008 [30]. https://www.eanm.org/publications/guidelines/gl_dosi_standards1.pdf
Internal dosimetry for other	For intra-arterial/cyst delivery (e.g.	Gamma camera, SPECT-CT or PET-CT system (modality depends on	One scan and assume only physical decay.	SIRT: *EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds,* Giammarile et al, 2011 [69].

organs at risk (e.g. kidneys) and tumours	microspheres)	radiopharmaceutical emissions)		https://www.eanm.org/publications/guidelines/EANM_liver_treatment_guidelines_2012.pdf
	For Systemic delivery (e.g. radioiodine, PRRT, mIBG etc.)		Ideal scanning frequency depends on effective half-life of radiopharmaceutical.	^{131}I: *EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases,* Hansheid et al, 2013 [70]. https://www.eanm.org/publications/guidelines/2013_published_DC_SOP_Benign_Thyroid_Diseases.pdf *MIRD Pamphlet No. 24: Guidelines for Quantitative I-131 SPECT in Dosimetry Applications,* Dewaraja et al, 2013 [72]. https://www.ncbi.nlm.nih.gov/pubmed/24130233 *EANM Therapy Committee: Guidelines for radioiodine therapy of differentiated thyroid cancer,* Luster et al, 2008 [71]. https://eanm.org/publications/guidelines/gl_radio_ther_259_883.pdf *IPEM report 104: Dosimetry for radionuclide therapy*, Bardies et al, 2011 [66]. *EANM Dosimetry Committee series on standard operational procedures for internal dosimetry for ^{131}I mIBG treatment of neuroendocrine tumours, Gear et al 2020 [68].* https://ejnmmiphys.springeropen.com/articles/10.1186/s40658-020-0282-7 ^{177}Lu DOTATATE: *MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative Lu-177 SPECT Applied for Dosimetry of Radiopharmaceutical Therapy,* Ljungberg et al, 2016 [73]. https://www.ncbi.nlm.nih.gov/pubmed/26471692 Alpha-emitters: *MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy,* Sgouros et al, 2010 [75]. https://www.ncbi.nlm.nih.gov/pubmed/20080889

Voxel dosimetry to assess dose distribution (e.g. to produce Dose volume hisotgrams to assess dose uniformity)		Ideal scanning frequency depends on effective half-life of radiopharmaceutical.	*MIRD pamphlet No. 17: The dosimetry of nonuniform activity distributions - Radionuclide S values at the voxel level,* Bolch et al, 1999 [76]. https://www.ncbi.nlm.nih.gov/pubmed/9935083
Other useful guidelines			EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting, Lassmann et al, 2010, [77]. https://www.eanm.org/publications/guidelines/EANM_guidance_document_good_dosimetry_reporting.pdf MIRD Pamphlet No. 16: Techniques for Quantitative Radiopharmaceutical Biodistribution Data Acquisition and Analysis for Use in Human Radiation Dose Estimates, Siegel et al, 1999 [78] https://www.ncbi.nlm.nih.gov/pubmed/10025848 MIRD Pamphlet No 23: Quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy, Dewaraja et al, 2012 [79] https://www.ncbi.nlm.nih.gov/pubmed/22743252 EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations, Gear et al, 2018 [80] https://pubmed.ncbi.nlm.nih.gov/30218316/

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MIRD schema

All of the guidelines in Table 3 advise on absorbed dose calculations following the MIRD schema; this section gives a brief summary of the schema and appropriate resources. The MIRD schema determines the mean absorbed dose to an object as the energy absorbed per unit mass assuming a uniform distribution of a radionuclide. The calculation of mean absorbed dose ($\overline{D}$) is expressed as [81]:

$$\overline{D}(r_T, T_D) = \sum_{r_s} \tilde{A}\,(r_s, T_D) S(r_T \leftarrow r_s)$$

where

$\tilde{A}(r_s, T_D)$ is the time-integrated activity over time T_D in the object r_s. Measurements of the time-integrated activity are described in the next section.

r_T is the target object

r_S is the source object

T_D is the defined time over which the dose is calculated

$S(r_T \leftarrow r_s)$ is the absorbed dose in r_T per nuclear transformation in r_S – this is the S-value.

S-values have been derived for radionuclides using Monte Carlo modelling of phantoms for adults and children [82-84]. These are based on standard patient geometry and organ masses, therefore organ S-values should be corrected for patient specific organ masses where possible [85]. MIRD pamphlets No. 11 and 17 are a good source of S-values [76, 86]. However, updated dose factors have been published by Cristy and Eckerman [83] and Stabin and Watson [84] which give the absorbed fractions from sources to targets for different energies. These absorbed fractions can be used in conjunction with decay information to calculate absorbed doses, a description of the calculation involved can be found in MIRD pamphlet No. 21 [81]. S-values and specific absorbed fractions (the ratio of the absorbed fraction and the target mass) can be obtained online from the Opendose website (https://www.opendose.org/) [87, 88]. S-values are also available from OLINDA (Hermes Medical Solutions) [89].

Alternatively, voxel dosimetry can be performed which uses patient specific geometry and removes the need for standard phantoms. S-values for use in voxel dosimetry were produced for some radionuclides in MIRD pamphlet No. 17 [76]. The equation above may be used for voxel dose calculations based on an assumption of complete absorption within each voxel. Another method is voxel dose kernel convolution [76], which uses a dose point kernel convolved with a time-integrated activity map to produce an absorbed dose map. Full Monte

Carlo modelling of the radiation transport can also be undertaken based on an anatomical scan and a source [76]. This method is accurate but computationally intensive.

Equipment and Resources

The time-integrated activity used in the MIRD calculations is measured as the area under the time-activity curve; for whole-body dosimetry this can be measured using a radiation monitor, for more complex internal tumour and organ dosimetry quantitative imaging is required. The resources required to measure the time-activity curve for use in dosimetry calculations are:

1. A radionuclide calibrator with a calibration traceable to a primary standard.
2. Activity or dose rate measurement hardware, e.g. dose rate monitor, whole-body counter, well counter, gamma camera, SPECT-CT system or a PET-CT system, each with a system of routine quality control in place.
3. A practical measurement schedule which will depend on the radiopharmaceutical, required information and patient availability.
4. A robust conversion between measurement and time-integrated activity:
    a. Whole-body counting self-calibrated against the first measurement for the known administered activity.
    b. Well counters must either be calibrated to report activity in samples, or calibration factors obtained in order to convert acquired counts to activity.
    c. Calibration factors are required for imaging to convert acquired counts to activity.

Radionuclide Calibrators

Within an MRT dosimetry calculation protocol, radionuclide calibrators are positioned at the start of the traceability chain in the hospital. Accurate activity measurements will be used to calibrate other equipment as well as the measurement of the activity administered to the patient. Thus, the maintenance and traceability of the radionuclide calibrator is a priority and therefore each calibrator should have a robust quality assurance programme and be traceable to a primary standard for each radionuclide in use [90-92].

Non-Image Based Quantification for Dosimetry

Whole-body retention measurements may be performed with hand-held radiation monitors, ceiling-mounted radiation monitors or gamma cameras [10, 30, 34, 67]. It is important to maintain a quality assurance programme for any radiation monitors as stated in the NPL Measurement Good Practice Guide 14 [93]. Linearity and dead-time should be assessed for each radioisotope over the range of clinical activities administered.

It is assumed the redistribution of the activity within the patient has little effect on the measurements. Thus, as long as the geometry is accurately reproduced this measurement is highly accurate [76, 78]. The use of ceiling-mounted monitors has the advantage of a fixed geometry. However, they need to be shielded from radioactivity emissions from nearby patients, which adds weight to the detector requiring additional support. A hand-held radiation monitor, at a fixed distance from the patient, is a suitable alternative and should be available in the majority of Nuclear Medicine departments. Established guidance on performing these measurements is available, and detailed in Table 3 [30, 34, 66-68]. The first measurement after administration should be performed before the patient voids to prevent any loss of activity in bodily excretions. This baseline measurement establishes the count rate per administered activity (cps/MBq) for that individual patient.

It is also possible to estimate the absorbed dose to other organs using non-image based techniques. A collimated sodium iodide detector can be used to count the photons in the region of the thyroid on successive days [94]. Biological samples may be used to establish the pharmacokinetics of the radiopharmaceutical to determine the absorbed dose to organs in the excretion pathway. For instance, urine can be collected to determine the dose to the urinary bladder walls [74].

Image Based Quantification for Dosimetry

The clinically available quantitative imaging methods are summarised in Table 4 and detailed in the next section.

Planar Imaging

Planar imaging using a gamma camera is less time consuming than 3D imaging, and readily available within the majority of Nuclear Medicine departments. Whole-body images can be obtained in under twenty minutes with the scan speed dependent on the activity in the patient to maximise the statistical quality of the scan, whilst avoiding patient discomfort and movement artefacts. Multiple planar imaging can then be used to derive time-activity curves for source regions as described in MIRD pamphlet no. 16 [78].

To correct for attenuation the geometric mean counts derived from anterior and posterior planar images can be combined to give a count independent of depth [95]. This method is described in IPEM report 104 [66], the MIRD pamphlet No. 16 [78] and the review paper by Ljungberg et al [95]. Other methods of attenuation correction for planar images are available using a transmission source, such as ^{57}Co, or the use of an X-ray scout on a SPECT-CT system. In this instance the scout can be converted for attenuation correction and be used to aid organ delineation [95]. Using these methods planar imaging can be quantitatively accurate for large organ quantification, in the situation where there is no overlap of other organ's activity and background counts [96]. Background counts can be corrected for smaller organs or tumours with inhomogeneous activity distributions that are overlapped by other active organs. However, SPECT imaging will provide more accurate quantification.

266 Table 4: Summary of quantitative Imaging Modalities

Modality		Advantages	Disadvantages
Gamma Camera		Widely available [97, 98] Longer radionuclide physical half-lives better reflect the biological half-lives (than many PET tracers) [97] (e.g., 6.02 hours for ^{99m}Tc and 13.2 hours for ^{123}I compared to 109.8 minutes for ^{18}F)	Poor spatial resolution compared to PET images. For example: 4.6mm for ^{18}F PET and 5.0-10.6 mm for ^{90}Y PET, compared to 13-15 mm for ^{99m}Tc SPECT and 20 mm for ^{90}Y SPECT) [97, 99-101]. Gamma cameras are optimised to image ^{99m}Tc (not therapeutic radionuclides such as ^{131}I and ^{177}Lu), therefore additional collimators are often required.
	Planar	2D whole-body images can be acquired in a short time (~ 20 minutes)	The quantitative accuracy of 2D images is limited in the presence of overlying physiological activity with less accurate attenuation correction [68, 78, 95]. Planar methods can lead to large errors of over 100% in the dosimetry results and incorporation of 3D SPECT imaging can reduce these errors to below 4% [102, 103].
	SPECT	3D images [97].	Multiple projections/bed-positions take relatively long time to acquire (up to 80 minutes) [95]
	SPECT-CT	CT can be used to improve attenuation and scatter correction for improved quantification of 3D images, for instance a ratio of 1.00 mean activity to reference activity was found for SPECT-CT compared to 0.94 for SPECT alone [97, 104] CT can aid VOI definition [95].	Extra CT absorbed dose [105]

PET-CT	Improved quantitative accuracy compared to SPECT-CT (2-44% for ^{18}F PET-CT compared to 4-65% ^{99m}Tc SPECT-CT) [97] Better spatial resolution than SPECT (see resolution values above) and better photon detection efficiency by two to three orders of magnitude [106]. CT used to provide accurate attenuation, scatter, random and cascade coincidence event correction.	Few positron emitting therapeutic radionuclides in common use Not widely available for non-routine diagnostic imaging [97] Requires accurate scatter, random and cascade coincidence (non-pure positron emitters) event correction. [97]

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SPECT imaging

In order to produce accurate quantification in SPECT imaging, the localisation of the SPECT scan, the duration of the scan, and the acquisition parameters must be optimised whilst taking into account patient comfort and competing clinical service needs. MIRD Pamphlet no. 23 [79] and IPEM report 104 [66] provide general recommendations for SPECT quantitative imaging; for guidelines for specific radioisotopes see those listed in Table 3. MIRD Pamphlet no. 23 discusses all aspects of SPECT imaging including collimator selection for different isotopes, matrix size to optimise spatial resolution versus noise, orbit choice, and number of projection angles. It also discusses correction and reconstruction options [79]. In most modern SPECT systems, a CT scanner is now incorporated [79] and attenuation correction with CT is considered the standard for accurate quantification [72, 73, 97, 104]. The CT also provides an anatomical image that aids volume outlining for dosimetry purposes. The additional CT will result in an increased radiation dose to the patient, however a low dose CT is sufficient for attenuation correction [79]. Scatter correction may be performed by setting energy windows adjacent to the photo-peak for use in scatter estimation methods such as triple-energy-window correction (TEWC). This is a relatively simple method available in all SPECT systems. However, it may lead to poorer quantitative accuracy than correction methods that incorporate Monte Carlo or analytical Klein-Nishina formula based estimates [107, 108].

Iterative reconstruction algorithms are recommended for quantitative SPECT studies [79]. Increased image noise with increasing iterations is a well-known feature of iterative reconstruction. Therefore, the number of iterations needs to be optimised to reach full recovery of the image counts before unacceptable degradation of the statistical quality of the image [79].

The spatial resolution of SPECT is limited by both resolution and partial volume effects. The review by Erlandsson et al [109] provides a full description of available partial volume correction (PVC) methods. The simplest form of PVC is the application of recovery coefficients to regions [110-112]. Phantom measurements of spheres of varied size are measured to provide PVC factors that are applied during the dosimetry calculation [68, 72]. Voxel based corrections are more complicated and require knowledge of the point spread function (PSF) of the imaging system. They often use anatomical regions defined on a CT or MR scan and assume uniform uptake within regions [113-117]. Therefore, these methods are limited where highly heterogeneous activity distributions are to be measured. Many of the modern reconstruction software incorporate collimator detector response (CDR) compensation and/or resolution recovery through deconvolution of a PSF. These methods can improve the spatial resolution of the images and may suppress the noise. However, they are known to introduce ‘Gibbs-like’ ringing artefacts at object boundaries [109]. Therefore these methods help

confine the counts within object boundaries; however they distort the distribution within the object which is counterproductive for voxelised dosimetry.

Collimator choice

Careful consideration needs to be given to collimator choice for both planar and SPECT imaging, especially for radioisotopes with high energy gamma emissions and multiple emissions. For instance, medium-energy collimators are required to avoid septal penetration of the higher energy γ-photons that would downgrade the quantitative accuracy of ^{123}I or ^{177}Lu images acquired with low-energy collimators [73].

Dead-time correction

Dead-time should be characterised up to a maximum activity of at least that to be imaged for therapeutic radioisotopes, such as ^{131}I, that result in high count rates [79]. Methods for dead-time corrections are described in MIRD pamphlet No. 23 [79], in MIRD pamphlet No. 24 [79] for ^{131}I, and in the EANM/MIRD Guidelines [73] for ^{177}Lu. Count rates may be measured over a period of time and true count rates at higher activities obtained by extrapolating from the lowest count rates acquired [79, 118]. Other dead-time correction methods are available such as dual time point and reference source imaging [119, 120]. Manufacturers are also now producing software to account for dead-time losses within the reconstruction [121].

Calibration factors

A calibration factor (cps/MBq) is required to convert the corrected count rate to activity for both planar [78, 122] and reconstructed SPECT data [79]. MIRD pamphlet 16 [78] provides a detailed description of methods to obtain calibration factors for planar imaging. Methods to determine calibration factors for SPECT are described in MIRD pamphlet No. 23 [79], and specifically for ^{131}I in MIRD pamphlet No. 24 [79] and ^{177}Lu in the EANM/MIRD Guidelines [73]. These calibration factors should be obtained from images of a phantom geometry that can approximate the scatter and attenuation found in a patient geometry such as a uniformly filled phantom, or hot spheres in a uniform background, as recommended in MIRD pamphlet No. 23 [79]. Measurements should be repeated to account for any variation in the camera performance over time [79].

The new generation of reconstruction software are increasingly quantitative in nature producing SPECT reconstructed images in units of kBq/ml [123]. Although initially developed for diagnostic imaging this is now becoming increasingly available for therapeutic radionuclides [124, 125].

Any quantification requires additional validation, to ensure that quantification methods are correctly applied and to assess the accuracy that may be achieved [38, 97, 123, 126].

Hybrid SPECT and planar imaging

Planar images can be combined with more quantitative SPECT images, as recommended by MIRD pamphlets No. 23 and 26 when multiple SPECT scans are not practical [73, 79]. Combining the two methods allows the normalisation of the time-integrated activity curves produced from planar images to a quantitative single SPECT image. However, this method can introduce errors as it is based on the assumption that the spatial distribution of the activity is fixed over time [73, 79]. This hybrid method was recently implemented in a ^{177}Lu-(DOTA0, Tyr3) dosimetry multicentre clinical trial [73], and a study by Garkavij et al [127] describes the differences in the absorbed doses derived from planar scans, SPECT scans and a hybrid planar/SPECT methodology.

PET-CT imaging

Positron Emission Tomography (PET) imaging has long been accepted as an inherently quantitative 3D imaging modality through the routine use of standard uptake values (SUV) and has been used for dosimetry purposes [128]. However, the use of PET is limited to positron emitters, which are mainly diagnostic radionuclides. One exception is ^{90}Y, which, despite the low branching ratio, has demonstrated successful post-therapy clinical imaging [129, 130]. The QUEST study [131] demonstrates the quantitative accuracy of ^{90}Y PET for multiple PET scanners and reconstructions.

Dosimetry Measurement Schedule

It is important that measurements/imaging are performed often enough and over a long enough period of time to minimise errors and introduce more confidence to the fit of the time-activity curve. Research into previous literature on each radiopharmaceutical can be used to determine the expected uptake and retention curves and can be used to plan the acquisition of patient data. MIRD pamphlet 16 fully describes the considerations needed to set-up a dosimetry protocol [78]. Ideally, a minimum of three data points for each phase should be collected to allow full characterisation of the time-activity curve and estimation of the errors in the time-integrated activity [77, 78].

However, with competing demands on resources and a desire to reduce the burden on patients there is growing interest in determining the minimum imaging schedule that will allow for sufficiently accurate dosimetry. Several groups have investigated the use of a single imaging time point to determine the absorbed dose to the kidney in PRRT therapy, and it has been shown that this can be adequately determined with a single scan at the correct time point [132-135]. However, this method is only valid if the half-life falls within a predictable range. Single time point dosimetry is not realistic where the half-life of the organs or disease is not known. A more practical approach has been suggested where the half-life of the organ has been determined from one complete dosimetry dataset on the first cycle and only a single SPECT-CT scan on the second treatment cycle [134, 135].

Uncertainty Analysis

It is recommended to report the accuracy of any absorbed doses by providing a measurement of the uncertainty in the absorbed dose calculation [80, 136]. The *EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations* [80] provides a framework with which to calculate these and lists areas of potential uncertainty. A careful analysis of factors affecting the uncertainty will enable identification of areas with high uncertainty with the possibility of reducing these through optimisation. Simple whole-body dosimetry will have a lower uncertainty than internal dosimetry as it can be easier to obtain a large number of data points, whereas internal dosimetry is limited to the number of scans obtained, often with a large delay between administration and the first imaging time point [68]. It has been shown for an absorbed dose calculation after an administration of ^{131}I-mIBG that uncertainties were less than 15% with careful image optimisation [68]. In another example, of ^{90}Y-DOTATATE therapy, the largest uncertainty was 38% from a small hepatic lesion, while uncertainties in the organs at risk varied from 5% to 24% [80]. The accuracy required depends on the clinical question for which the dosimetry is to be used and the uncertainty should be commensurate with the range of measured doses.

Dosimetry Software

Software is required to perform activity quantification, determine time-integrated activity and implement the MIRD schema after measurements of the patient have been acquired. In the case of whole-body dosimetry this is relatively simple and can be done using in-house tools such as spreadsheets. As far as the authors are aware, there are no appropriate commercially available alternatives. Whilst in-house tools can also be used to perform organ dosimetry there are several commercially available software packages for this application. Table 5 lists the currently available dosimetry software to date.

Table 5: List of commercially available dosimetry software

Dosimetry Type	**Software**	**Manufacturer**
SIRT only	Simplicit^{90}Y™	Mirada
Organ	Organ Dosimetry with Olinda/EXM®	Hermes Medical Solutions
	Dosimetrix®	GE
Voxel	Voxel Dosimetry™	Hermes Medical Solutions
	Stratos™	Philips

	Planet® dose	Dosisoft
	QDOSE®	ABX-CRO advanced pharmaceutical

Historically in-house developed software tools may have not been considered a medical device and may have been developed and validated following appropriate guidance. However, the regulatory framework around such tools will change when the EU Medical Devices Regulation 2017/745 fully applies in May 2021 [137, 138]. These tools are likely to be considered medical devices as they inform patient management. Therefore, they will need to be developed in a manner consistent with these regulations. Although the regulations provide an exemption for health institutions from the full set of requirements (in Article 5(5)), the requirements for developing in-house software even within the exemption are likely still to be far more rigorous than the majority of current practice.

Staff Training

The need for staff training and expertise in MRT dosimetry was identified in our survey. This training should be both theoretical and practical [139, 140]. A comprehensive list of knowledge, skills and competence for an internal radionuclide dosimetry service is provided by the EANM Physics Committee, the EANM Dosimetry Committee and the European Federations of Organisation for Medical Physics (EFOMP) [139], and by the Internal Atomic Energy Agency (IAEA) [140].

Adequate MRT dosimetry training should be included in any Nuclear Medicine Physics training scheme. However, there is often little or no provision locally and thus trainees and existing members of the workforce should consider external sources. There are courses available to teach the fundamentals of dosimetry such as those provided by the European School of Multimodality Imaging & Therapy (ESMIT) (http://www.eanm.org/esmit) [141] and EFOMP (https://www.efomp.org/) [142]. Within the UK the internal Dosimetry Users Group (IDUG) [143] and the Royal Marsden Hospital/Institute of Cancer Research (https://www.icr.ac.uk/studying-and-training/opportunities-for-clinicians/radiotherapy-and-imaging-training-courses/nuclear-medicine-and-pet-imaging-course) [144] also run practical dosimetry workshops. Course attendance needs to be built upon through further in-house training by experienced staff or follow up support from training courses to strengthen knowledge retention and application.

Other important resources include textbooks such as the *IPEM Report 104: Dosimetry for Radionuclide Therapy* [66]. The IAEA provide several resources including: the IAEA Nuclear Medicine Physics A Handbook for Teachers and Students (https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1617web-1294055.pdf) [145] and accompanying slides (https://humanhealth.iaea.org/HHW/MedicalPhysics/e-learning/Nuclear_Medicine_Handbook_slides/) [146] and the *IAEA Human Health Report no. 9: Quantitative Nuclear Medicine Imaging: Concepts, Requirements And Methods* [147].

Discussion and conclusions

The results of the survey presented in this work indicated that 28% of the responding centres perform dosimetry. This was broadly in line with recent published data from the EANM Internal Dosimetry Task Force which stated that 26% of centres performed dosimetry "always or in the majority of treatments" [148].

The results, presented in this work, reported that a "lack of clinical evidence", a "lack of guidelines" and "not current UK practice" were the largest obstacles to setting up an MRT dosimetry service. However, this finding was in contrast to those found by the EANM Internal Dosimetry Task Force. The EANM reported the main limitations to be: shortage of knowledge, shortage of medical physicists and limited access to scanner, other equipment needed, and lack of dedicated software [148]. It is assumed these differences are due to this survey having 97% of responders from the UK while the EANM survey had 208 responders from over 26 European countries (13% from the UK) and reflects the differences in practice throughout Europe. It is clear from these results that more work is needed to implement MRT dosimetry in all centres, but UK medical physics departments are relatively well resourced to provide a dosimetry service.

Multicentre trials will be key to enabling harmonisation of dosimetry methods between centres to produce accurate reproducible results that will build on the clinical evidence of the benefits of dosimetry in MRT. Although it has been shown that relationships have been established between absorbed dose and response, the evidence from these multicentre trials will increase this evidence base and hopefully generate more confidence in dosimetry guided MRT [11, 19, 21-25, 27, 30-35, 39, 40, 43-57, 149]. This report has shown that numerous guidelines are available for all different forms of dosimetry calculations. It is hoped that centres can follow those guidelines and set-up their own service; more evidence can then be collected and best practice in molecular radiotherapy can begin to incorporate dosimetry-based planning.

Although this report does not go into specific costings, it is clear that there will be a time and cost impact on the set-up and running of a dosimetry service. An overview of the modern methods and hardware currently available to the majority of these centres have been given in this report. One of the purposes of this report was to emphasise that simple dosimetry can be performed with equipment that most centres already own and maintain. However, for some departments there may be an initial outlay for equipment. This initial outlay will also include the cost to perform the extra calibrations and measurements needed before starting the service. Training may also have cost implications depending on the type of training necessary and the training already received. Resources for training, including those that are freely available, have been listed in this report. There will be employment implications dependent on the complexity of the dosimetry performed as extra staff time will be required to perform the dosimetry calculations and scan or take samples from patients. There will also be implications for service provision of camera time and in-patient hospital stays. It can be difficult to justify an in-patient hospital stay to allow patients to have multiple scans. It is hoped that in the future once MRT dosimetry has become established and commonplace then patients can return to hospital for scans where possible. This may not be unreasonable considering patients undertake repeated trips to hospital when undergoing EBRT.

Radiation protection issues cannot be ignored, the more time staff spend with patients the larger the radiation protection implications. Appropriate training following the time, distance and shielding principles can be used to keep doses to a minimum. The staff dose will depend on the activity administered, the energies of radionuclide emissions and the effective half-life. Risk assessments should be performed prior to setting up any new service to assess any additional dose to staff, caregivers and the public. Extensive literature on dose rates for therapy patients are available for most radiopharmaceuticals such as ^{177}Lu and ^{131}I [150-152]. This data additionally exists for pre-therapy planning and diagnostic scans [153].

In conclusion, as medicine moves towards a more personalised approach, with interest in dosimetry increasing and the evidence for the clinical benefit of MRT dosimetry mounting, centres are becoming better equipped to provide a routine clinical dosimetry service. This report provides advice on the resources necessary to set-up a dosimetry service, and demonstrates that none of the challenges addressed in this report should prevent personalised MRT.

References

1. Hertz, S. and A. Roberts, *Radioactive iodine in the study of thyroid physiology; the use of radioactive iodine therapy in hyperthyroidism.* J Am Med Assoc, 1946. **131**: p. 81-6.
2. Proescher, F., *Influence of intravenous injection of soluble radium salts in high blood pressure.* Radium, 1913. **1**(1).
3. Chapman, E.M. and R.D. Evans, *The treatment of hyperthyroidism with radioactive iodine.* J Am Med Assoc, 1946. **131**: p. 86-91.
4. Seidlin, S.M., L.D. Marinelli, and E. Oshry, *Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid.* J Am Med Assoc, 1946. **132**(14): p. 838-47.
5. Rojas, B., et al., *Eight years of growth and change in UK molecular radiotherapy with implications for the future: Internal Dosimetry Users Group survey results from 2007 to 2015.* Nuclear Medicine Communications, 2017. **38**(3): p. 201-204.
6. Rojas, B., et al., *Eighty per cent more patients in 10 years of UK molecular radiotherapy Internal Dosimetry Users Group survey results from 2007 to 2017.* Nucl Med Commun, 2019. **40**(7): p. 657-661.
7. Rojas, B., et al., *Five years of molecular radiotherapy growth in the UK: survey results from 2007 to 2012.* Nucl Med Commun, 2015. **36**(8): p. 761-5.
8. Joiner, M.C. and A.J. van der Kogel, *Basic Clinical Radiobiology*. 4th edition ed. 2009: CRC Press.
9. McGowan, D.R. and M.J. Guy, *Time to demand dosimetry for molecular radiotherapy?* The British Journal of Radiology, 2015. **88**(1047): p. 20140720.
10. Monsieurs, M., et al., *Patient dosimetry for ^{131}I-MIBG therapy for neuroendocrine tumours based on ^{123}I-MIBG scans.* Eur J Nucl Med Mol Imaging, 2002. **29**(12): p. 1581-7.
11. Garin, E., et al., *Personalized Dosimetry with Intensification Using ^{90}Y-Loaded Glass Microsphere Radioembolization Induces Prolonged Overall Survival in Hepatocellular Carcinoma Patients with Portal Vein Thrombosis.* Journal of Nuclear Medicine, 2015. **56**(3): p. 339-346.
12. Gaze, M., et al., *Feasibility of Dosimetry-Based High-Dose ^{131}I-Meta-Iodobenzylguanidine with Topotecan as a Radiosensitizer in Children with Metastatic Neuroblastoma.* Cancer Biother Radiopharm, 2005. **20**(2): p. 195-199.
13. *Council Directive 2013/59/EURATOM.* Official Journal of the European Union, 2014.
14. ARSAC, *Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources*. 2020, Administration of Radioactive Substances Advisory Committee.
15. *The Ionising Radiation (Medical Exposure) (Amendment) Regulations 2018*. 2018, Department of Health and Social care.
16. *JISCM@il*. Available from: https://www.jiscmail.ac.uk/cgi-bin/webadmin?A0=MEDICAL-PHYSICS-ENGINEERING)
17. Rojas, B., et al., *Eighty per cent more patients in 10 years of UK molecular radiotherapy: Internal Dosimetry Users Group survey results from 2007 to 2017.* Nuclear Medicine Communications, 2019. **40**(7): p. 657-661.
18. Eberlein, U., et al., *Biokinetics and dosimetry of commonly used radiopharmaceuticals in diagnostic nuclear medicine - a review.* Eur J Nucl Med Mol Imaging, 2011. **38**(12): p. 2269-81.
19. Perros, P., et al., *Guidelines for the management of thyroid cancer.* Clin Endocrinol (Oxf), 2014. **81 Suppl 1**: p. 1-122.
20. Sgouros, G., et al., *Three-dimensional radiobiological dosimetry (3D-RD) with 124I PET for 131I therapy of thyroid cancer.* Eur J Nucl Med Mol Imaging, 2011. **38 Suppl 1**: p. S41-7.
21. Maxon, H.R., et al., *Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer.* N Engl J Med, 1983. **309**(16): p. 937-41.

22. Maxon, H.R., 3rd, et al., *Radioiodine-131 therapy for well-differentiated thyroid cancer--a quantitative radiation dosimetric approach: outcome and validation in 85 patients.* J Nucl Med, 1992. **33**(6): p. 1132-6.
23. Flux, G.D., et al., *A dose-effect correlation for radioiodine ablation in differentiated thyroid cancer.* European Journal of Nuclear Medicine and Molecular Imaging, 2010. **37**(2): p. 270-275.
24. Wierts, R., et al., *Dose-Response Relationship in Differentiated Thyroid Cancer Patients Undergoing Radioiodine Treatment Assessed by Means of 124I PET/CT.* J Nucl Med, 2016. **57**(7): p. 1027-32.
25. Ilan, E., et al., *Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using 177Lu-DOTATATE.* J Nucl Med, 2015. **56**(2): p. 177-82.
26. Eberlein, U., M. Cremonesi, and M. Lassmann, *Individualized Dosimetry for Theranostics: Necessary, Nice to Have, or Counterproductive?* J Nucl Med, 2017. **58**(Suppl 2): p. 97S-103S.
27. Strigari, L., et al., *The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy.* European Journal of Nuclear Medicine and Molecular Imaging, 2014. **41**(10): p. 1976-1988.
28. Lassmann, M. and U. Eberlein, *The Relevance of Dosimetry in Precision Medicine.* Journal of Nuclear Medicine, 2018. **59**(10): p. 1494-1499.
29. *CTRad*. Available from: https://ctrad.ncri.org.uk/.
30. Lassmann, M., et al., *EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy.* Eur J Nucl Med Mol Imaging, 2008. **35**(7): p. 1405-12.
31. Klubo-Gwiezdzinska, J., et al., *Efficacy of Dosimetric Versus Empiric Prescribed Activity of I-131 for Therapy of Differentiated Thyroid Cancer.* Journal of Clinical Endocrinology & Metabolism, 2011. **96**(10): p. 3217-3225.
32. Benau, R.S., et al., *The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer.* American journal of Roentgenology, Radium Therapy, and Nuclear Medicine, 1962. **87**: p. 171-182.
33. Leeper, R.D., *The effect of 131 I therapy on survival of patients with metastatic papillary or follicular thyroid carcinoma.* J Clin Endocrinol Metab, 1973. **36**(6): p. 1143-52.
34. Hindorf, C., et al., *EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry.* Eur J Nucl Med Mol Imaging, 2010. **37**(6): p. 1238-50.
35. Lee, J.J., et al., *Maximal safe dose of I-131 after failure of standard fixed dose therapy in patients with differentiated thyroid carcinoma.* Ann Nucl Med, 2008. **22**(9): p. 727-34.
36. Maxon, H.R., et al., *Relation between Effective Radiation-Dose and Outcome of Radioiodine Therapy for Thyroid-Cancer.* New England Journal of Medicine, 1983. **309**(16): p. 937-941.
37. Wadsley, J., et al., *SELIMETRY-a multicentre I-131 dosimetry trial: a clinical perspective.* Br J Radiol, 2017. **90**(1073): p. 20160637.
38. Gregory, R.A., et al., *Standardised quantitative radioiodine SPECT/CT Imaging for multicentre dosimetry trials in molecular radiotherapy.* Phys Med Biol, 2019. **64**(24): p. 245013.
39. Flux, G.D., et al., *Clinical applications of dosimetry for mIBG therapy.* Quarterly Journal of Nuclear Medicine and Molecular Imaging, 2011. **55**(2): p. 116-125.
40. Gaze, M.N., et al., *Optimization of molecular radiotherapy with [I-131]-meta Iodobenzylguanidine for high-risk neuroblastoma.* Quarterly Journal of Nuclear Medicine and Molecular Imaging, 2013. **57**(1): p. 66-78.
41. Sundlov, A., et al., *Individualised (177)Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry.* Eur J Nucl Med Mol Imaging, 2017. **44**(9): p. 1480-1489.
42. Cremonesi, M., et al., *Radioembolization of hepatic lesions from a radiobiology and dosimetric perspective.* Front Oncol, 2014. **4**: p. 210.
43. Garin, E., et al., *Dosimetry Based on Tc-99m-Macroaggregated Albumin SPECT/CT Accurately Predicts Tumor Response and Survival in Hepatocellular Carcinoma Patients Treated with Y-*

90-Loaded Glass Microspheres: Preliminary Results. Journal of Nuclear Medicine, 2012. **53**(2): p. 255-263.
44. Garin, E., et al., *Boosted selective internal radiation therapy with ^{90}Y-loaded glass microspheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept.* Eur J Nucl Med Mol Imaging, 2013. **40**(7): p. 1057-68.
45. Manceau, V., et al., *A MAA-based dosimetric study in patients with intrahepatic cholangiocarcinoma treated with a combination of chemotherapy and ^{90}Y-loaded glass microsphere selective internal radiation therapy.* Eur J Nucl Med Mol Imaging, 2018. **45**: p. 1731-1741.
46. Ho, S., et al., *Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer.* European Journal of Nuclear Medicine, 1997. **24**(3): p. 293-298.
47. Demirelli, S., et al., *Evaluation of factors affecting tumor response and survival in patients with primary and metastatic liver cancer treated with microspheres.* Nuclear Medicine Communications, 2015. **36**(4): p. 340-349.
48. Chiesa, C., et al., *Need, feasibility and convenience of dosimetric treatment planning in liver selective internal radiation therapy with Y-90 microspheres: the experience of the National Cancer Institute of Milan.* Quarterly Journal of Nuclear Medicine and Molecular Imaging, 2011. **55**(2): p. 168-197.
49. Mazzaferro, V., et al., *Yttrium-90 Radioembolization for Intermediate-Advanced Hepatocellular Carcinoma: A Phase 2 Study.* Hepatology, 2013. **57**(5): p. 1826-1837.
50. Chan, K.T., et al., *Prospective trial using internal pair-production positron emission tomography to establish the Yttrium-90 radioembolization dose required for response of hepatocellular carcinoma.* International Journal of Radiation Oncology • Biology • Physics, 2018. **101**(2): p. 358-365.
51. Lau, W.Y., et al., *Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study.* Br J Cancer, 1994. **70**(5): p. 994-9.
52. Ho, C.L., et al., *Radioembolization with ^{90}Y glass microspheres for hepatocellular carcinoma: significance of pretreatment ^{11}C-acetate and ^{18}F-FDG PET/CT and posttreatment ^{90}Y PET/CT in individualized dose prescription.* Eur J Nucl Med Mol Imaging, 2018.
53. Lam, M.G., et al., *Prognostic Utility of ^{90}Y Radioembolization Dosimetry Based on Fusion ^{99m}Tc-Macroaggregated Albumin-^{99m}Tc-Sulfur Colloid SPECT.* Journal of Nuclear Medicine, 2013.
54. Gulec, S.A., et al., *Safety and efficacy of Y-90 microsphere treatment in patients with primary and metastatic liver cancer: The tumor selectivity of the treatment as a function of tumor to liver flow ratio.* Journal of Translational Medicine, 2007. **5**(15).
55. Chiesa, C., et al., *Radioembolization of hepatocarcinoma with ^{90}Y glass microspheres: development of an individualized treatment planning strategy based on dosimetry and radiobiology.* Eur J Nucl Med Mol Imaging, 2015.
56. Willowson, K.P., et al., *Clinical and imaging-based prognostic factors in radioembolisation of liver metastases from colorectal cancer: a retrospective exploratory analysis.* EJNMMI Res, 2017. **7**(1): p. 46.
57. van den Hoven, A., et al., *Insights into the dose-response relationship of radioembolization with resin yttrium-90 microspheres: a prospective cohort study in patients with colorectal cancer liver metastases.* J Nucl Med, 2016. **57**(7): p. 1014-1019.
58. Adcock, C.S., et al., *Assessment of Treatment Response Following Yttrium-90 Transarterial Radioembolization of Liver Malignancies.* Cureus, 2018. **10**(6): p. e2895.
59. Bastiaannet, R., et al., *The physics of radioembolization.* EJNMMI Phys, 2018. **5**(1): p. 22.
60. Chiesa, C., et al., *A dosimetric treatment planning strategy in radioembolization of hepatocarcinoma with ^{90}Y glass microspheres.* Q J Nucl Med Mol Imaging, 2012. **56**(6): p. 503-8.

61. Srinivas, S.M., et al., *Determination of Radiation Absorbed Dose to Primary Liver Tumors and Normal Liver Tissue Using Post-Radioembolization ^{90}Y PET.* Front Oncol, 2014. **4**: p. 255.
62. Sangro, B., et al., *Radioembolization using ^{90}Y-resin microspheres for patients with advanced hepatocellular carcinoma.* Int J Radiat Oncol Biol Phys, 2006. **66**(3): p. 792-800.
63. Zuckerman, D.A., et al., *Outcomes and toxicity following Yttrium-90 radioembolization for hepatic metastases from neuroendocrine tumors-a single-institution experience.* Journal of Gastrointestinal Oncology, 2019. **10**(1): p. 118-127.
64. Cheng, J.C., et al., *Biologic susceptibility of hepatocellular carcinoma patients treated with radiotherapy to radiation-induced liver disease.* Int J Radiat Oncol Biol Phys, 2004. **60**(5): p. 1502-9.
65. Dawson, L.A. and R.K. Ten Haken, *Partial volume tolerance of the liver to radiation.* Semin Radiat Oncol, 2005. **15**(4): p. 279-83.
66. Bardies, M., et al., *Dosimetry for radionuclide therapy*, in *IPEM reports series 104*. 2011.
67. group, I.D.U., *Whole Body Dosimetry Guidance*.
68. Gear, J., et al., *EANM Dosimetry Committee series on standard operational procedures for internal dosimetry for (131)I mIBG treatment of neuroendocrine tumours.* EJNMMI Phys, 2020. **7**(1): p. 15.
69. Giammarile, F., et al., *EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds.* European Journal of Nuclear Medicine and Molecular Imaging, 2011. **38**(7): p. 1393-1406.
70. Hanscheid, H., et al., *EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases.* Eur J Nucl Med Mol Imaging, 2013. **40**(7): p. 1126-34.
71. Luster, M., et al., *Guidelines for radioiodine therapy of differentiated thyroid cancer.* Eur J Nucl Med Mol Imaging, 2008. **35**(10): p. 1941-59.
72. Dewaraja, Y.K., et al., *MIRD Pamphlet No. 24: Guidelines for Quantitative I-131 SPECT in Dosimetry Applications.* Journal of Nuclear Medicine, 2013. **54**(12): p. 2182-2188.
73. Ljungberg, M., et al., *MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative Lu-177 SPECT Applied for Dosimetry of Radiopharmaceutical Therapy.* Journal of Nuclear Medicine, 2016. **57**(1): p. 151-162.
74. Chittenden, S.J., et al., *A Phase 1, Open-Label Study of the Biodistribution, Pharmacokinetics, and Dosimetry of Ra-223-Dichloride in Patients with Hormone-Refractory Prostate Cancer and Skeletal Metastases.* Journal of Nuclear Medicine, 2015. **56**(9): p. 1304-1309.
75. Sgouros, G., et al., *MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy.* J Nucl Med, 2010. **51**(2): p. 311-28.
76. Bolch, W.E., et al., *MIRD pamphlet No. 17: The dosimetry of nonuniform activity distributions - Radionuclide S values at the voxel level.* Journal of Nuclear Medicine, 1999. **40**(1): p. 11s-36s.
77. Lassmann, M., et al., *EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting.* Eur J Nucl Med Mol Imaging, 2011. **38**(1): p. 192-200.
78. Siegel, J.A., et al., *MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates.* Journal of Nuclear Medicine, 1999. **40**(2): p. 37s-61s.
79. Dewaraja, Y.K., et al., *MIRD Pamphlet No. 23: Quantitative SPECT for Patient-Specific 3-Dimensional Dosimetry in Internal Radionuclide Therapy.* Journal of Nuclear Medicine, 2012. **53**(8): p. 1310-1325.
80. Gear, J.I., et al., *EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations.* Eur J Nucl Med Mol Imaging, 2018. **45**(13): p. 2456-2474.
81. Bolch, W.E., et al., *MIRD pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry--standardization of nomenclature.* J Nucl Med, 2009. **50**(3): p. 477-84.

82. Snyder, W.S., et al., *Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogeneous phantom.* J Nucl Med, 1969: p. Suppl 3:7-52.
83. Cristy, M. and K.F. Eckerman, *Specific Absorbed Fractions of Energy At Various Ages from Internal Photon Sources. I Methods, II One year old, III Five Year old, IV Ten year old, V Fifteen year old male and adult female, VI New born and VII Adult male.* ORNL Reports: ORNL/TM-8381/V1 - ORNL/TM-8381/V7, 1987.
84. Stabin, M., et al., *Mathematical Models and Specific Absorbed Fractions of Photon Energy in the Nonpregnant Adult Female and at the End of Each Trimester of Pregnancy.* 1995.
85. Williams, L.E., et al., *The two types of correction of absorbed dose estimates for internal emitters.* Cancer, 2002. **94**(4 Suppl): p. 1231-4.
86. Snyder, W.S., et al., *"S" absorbed dose per unit cumulated activity for selected radionuclides and organs.* MIRD Pamphlet No. 11, 1975.
87. Chauvin, M., et al., *OpenDose: Generating reference data for Nuclear Medicine dosimetry.* European Journal of Nuclear Medicine and Molecular Imaging, 2017. **44**: p. S807-S807.
88. Chauvin, M., et al., *OpenDose: open access resources for nuclear medicine dosimetry.* J Nucl Med, 2020.
89. Solutions, H.M. *OLINDA*. [cited 2020 25th February]; Available from: https://www.hermesmedical.com/dosimetry/.
90. Zanzonico, P., *Routine quality control of clinical nuclear medicine instrumentation: A brief review.* Journal of Nuclear Medicine, 2008. **49**(7): p. 1114-1131.
91. Gadd, R., et al., *Protocol for Establishing and Maintaining the Calibration of Medical Radionuclide Calibrators and their Quality Control* 2006, National Physical Laboratory
92. Busemann Sokole, E., et al., *Acceptance testing for nuclear medicine instrumentation.* Eur J Nucl Med Mol Imaging, 2010. **37**(3): p. 672-81.
93. Lee, C.J. and P.H. Burgess, *The examination, testing and calibration of portable radiation protection instruments. Measurement Good Practice Guide. 14*. 2014: National Physical Laboratory.
94. Hyer, S.L., et al., *Dosimetry-based treatment for Graves' disease.* Nucl Med Commun, 2018. **39**(6): p. 486-492.
95. Ljungberg, M. and K.S. Gleisner, *Hybrid Imaging for Patient-Specific Dosimetry in Radionuclide Therapy.* Diagnostics (Basel), 2015. **5**(3): p. 296-317.
96. Thomas, S.R., H.R. Maxon, and J.G. Kereiakes, *In vivo quantitation of lesion radioactivity using external counting methods.* Med Phys, 1976. **03**(04): p. 253-5.
97. Bailey, D.L. and K.P. Willowson, *An evidence-based review of quantitative SPECT imaging and potential clinical applications.* Journal of Nuclear Medicine, 2013. **54**(1): p. 83-9.
98. Dewaraja, Y.K., et al., *Improved quantitative ^{90}Y bremsstrahlung SPECT/CT reconstruction with Monte Carlo scatter modeling.* Med Phys, 2017. **44**(12): p. 6364-6376.
99. Pasciak, A.S., A.C. Bourgeois, and Y.C. Bradley, *A Comparison of Techniques for ^{90}Y PET/CT Image-Based Dosimetry Following Radioembolization with Resin Microspheres.* Front Oncol, 2014. **4**: p. 121.
100. Jacob, J., et al., *Comparison of gamma camera spatial resolution measurements with use of a point source, a line source and a Jaszczak phantom.* Journal of nuclear medicine, 2006. **47**(Suppl 1): p. 554P.
101. Mikell, J.K., et al., *Comparing voxel-based absorbed dosimetry methods in tumors, liver, lung, and at the liver-lung interface for ^{90}Y microsphere selective internal radiation therapy.* EJNMMI Physics, 2015. **2**(1).
102. He, B., et al., *Comparison of residence time estimation methods for radioimmunotherapy dosimetry and treatment planning--Monte Carlo simulation studies.* IEEE Trans Med Imaging, 2008. **27**(4): p. 521-30.

103. Pereira, J.M., et al., *Image quantification for radiation dose calculations--limitations and uncertainties.* Health Phys, 2010. **99**(5): p. 688-701.
104. Zimmerman, B.E., et al., *Multi-centre evaluation of accuracy and reproducibility of planar and SPECT image quantification: An IAEA phantom study.* Zeitschrift Fur Medizinische Physik, 2017. **27**(2): p. 98-112.
105. Ferrari, M., et al., *SPECT/CT radiation dosimetry.* Clinical and Translational Imaging, 2014. **2**(6): p. 557-569.
106. Rahmim, A. and H. Zaidi, *PET versus SPECT: strengths, limitations and challenges.* Nucl Med Commun, 2008. **29**(3): p. 193-207.
107. Robinson, A.P., et al., *The influence of triple energy window scatter correction on activity quantification for (1 7 7)Lu molecular radiotherapy.* Phys Med Biol, 2016. **61**(14): p. 5107-27.
108. van Gils, C.A.J., et al., *Impact of reconstruction parameters on quantitative I-131 SPECT.* Physics in Medicine and Biology, 2016. **61**(14): p. 5166-5182.
109. Erlandsson, K., et al., *A review of partial volume correction techniques for emission tomography and their applications in neurology, cardiology and oncology.* Physics in Medicine and Biology, 2012. **57**(21): p. R119-R159.
110. Hoffman, E.J., S.-C. Huang, and M.E. Phelps, *Quantitation in Positron Emission Computed Tomography: 1. Effect of Object Size.* Journal of Computer Assisted Tomography, 1979. **3**(3): p. 299-308.
111. Henze, E., et al., *Measurements of Regional Tissue and Blood-Pool Radiotracer Concentrations from Serial Tomographic-Images of the Heart.* Journal of Nuclear Medicine, 1983. **24**(11): p. 987-996.
112. Rousset, O.G., Y.L. Ma, and A.C. Evans, *Correction for partial volume effects in PET: Principle and validation.* Journal of Nuclear Medicine, 1998. **39**(5): p. 904-911.
113. Videen, T.O., et al., *Regional Correction of Positron Emission Tomography Data for the Effects of Cerebral Atrophy.* Journal of Cerebral Blood Flow and Metabolism, 1988. **8**(5): p. 662-670.
114. Müller-Gärtner, H.W., et al., *Measurement of radiotracer concentration in brain gray matter using positron emission tomography: MRI-based correction for partial volume effects.* J Cereb Blood Flow Metab, 1992. **12**(4): p. 571-83.
115. Quarantelli, M., et al., *Integrated software for the analysis of brain PET/SPECT studies with partial-volume-effect correction.* Journal of Nuclear Medicine, 2004. **45**(2): p. 192-201.
116. Erlandsson, K., et al., *An improved method for voxel-based partial volume correction in PET and SPECT.* NeuroImage, 2006. **31**: p. T84.
117. Yang, J., et al., *Investigation of partial volume correction methods for brain FDG PET studies.* Ieee Transactions on Nuclear Science, 1996. **43**(6): p. 3322-3327.
118. *NEMA NU 1-2018: Performance measurements of Gamma Cameras*. 2019: Virginia.
119. Silosky, M., et al., *Characterization of the count rate performance of modern gamma cameras.* Medical Physics, 2013. **40**(3).
120. Madsen, M.T. and R.J. Nickles, *A precise method for correcting count-rate losses in scintillation cameras.* Med Phys, 1986. **13**(3): p. 344-9.
121. Vija, A.H. and J. Zeintl, *OP-028: Quantitative Assessment Of Accuracy And Precision For High Count Rate Spect Imaging Of 99mtc And 177lu* Eur J Nucl Med Mol Imaging, 2018. **45**: p. S16-S17.
122. Miller, C., L. Filipow, and S. Jackson, *A Review of Activity Quantification by Planar Imaging Methods* J Nucl Med Technol, 1995. **25**(1): p. 3-9.
123. Dickson, J., J. Ross, and S. Voo, *Quantitative SPECT: the time is now.* Ejnmmi Physics, 2019. **6**.
124. Tran-Gia, J. and M. Lassmann, *Characterization of Noise and Resolution for Quantitative Lu-177 SPECT/CT with xSPECT Quant.* Journal of Nuclear Medicine, 2019. **60**(1): p. 50-59.
125. Peters, S.M.B., et al., *Variability in lutetium-177 SPECT quantification between different state-of-the-art SPECT/CT systems.* Ejnmmi Physics, 2020. **7**(1).

126. Wevrett, J., et al., *Inter-comparison of quantitative imaging of lutetium-177 (Lu-177) in European hospitals.* Ejnmmi Physics, 2018. **5**.
127. Garkavij, M., et al., *177Lu-[DOTA0,Tyr3] octreotate therapy in patients with disseminated neuroendocrine tumors: Analysis of dosimetry with impact on future therapeutic strategy.* Cancer, 2010. **116**(4 Suppl): p. 1084-92.
128. Flower, M.A., et al., *Dose-Response Study on Thyrotoxic Patients Undergoing Positron Emission Tomography and Radioiodine Therapy.* European Journal of Nuclear Medicine, 1994. **21**(6): p. 531-536.
129. Lhommel, R., et al., *Yttrium-90 TOF PET scan demonstrates high-resolution biodistribution after liver SIRT.* European Journal of Nuclear Medicine and Molecular Imaging, 2009. **36**(10): p. 1696-1696.
130. Lhommel, R., et al., *Feasibility of ^{90}Y TOF PET-based dosimetry in liver metastasis therapy using SIR-Spheres.* Eur J Nucl Med Mol Imaging, 2010. **37**(9): p. 1654-62.
131. Willowson, K.P., et al., *A multicentre comparison of quantitative ^{90}Y PET/CT for dosimetric purposes after radioembolization with resin microspheres : The QUEST Phantom Study.* Eur J Nucl Med Mol Imaging, 2015. **42**(8): p. 1202-22.
132. Hanscheid, H., et al., *Dose Mapping After Endoradiotherapy with (177)Lu-DOTATATE/DOTATOC by a Single Measurement After 4 Days.* J Nucl Med, 2018. **59**(1): p. 75-81.
133. Sundlov, A., et al., *Feasibility of simplifying renal dosimetry in (177)Lu peptide receptor radionuclide therapy.* EJNMMI Phys, 2018. **5**(1): p. 12.
134. Garske, U., et al., *Minor changes in effective half-life during fractionated 177Lu-octreotate therapy.* Acta Oncol, 2012. **51**(1): p. 86-96.
135. Willowson, K.P., et al., *Feasibility and accuracy of single time point imaging for renal dosimetry following (177)Lu-DOTATATE ('Lutate') therapy.* EJNMMI Phys, 2018. **5**(1): p. 33.
136. Flux, G.D., et al., *Estimation and implications of random errors in whole-body dosimetry for targeted radionuclide therapy.* Physics in Medicine and Biology, 2002. **47**(17): p. 3211-3223.
137. UNION, T.E.P.A.T.C.O.T.E., *Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.* Official Journal of the European Union, 2017.
138. UNION, T.E.P.A.T.C.O.T.E., *Regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices, as regards the dates of application of certain of its provisions.* Official Journal of the European Union, 2020.
139. Del Guerra, A., et al., *Curriculum for education and training of medical physicists in nuclear medicine: recommendations from the EANM Physics Committee, the EANM Dosimetry Committee and EFOMP.* Phys Med, 2013. **29**(2): p. 139-62.
140. *Clinical Training of Medical Physicists Specializing in Nuclear Medicine*. 2011, Vienna: INTERNATIONAL ATOMIC ENERGY AGENCY.
141. *The European School of Multimodality Imaging & Therapy (ESMIT)*. Available from: http://www.eanm.org/esmit/.
142. *EFOMP*. Available from: https://www.efomp.org/.
143. *IDUG*. Available from: http://www.idug.org.uk/.
144. *ICR: Nuclear medicine and PET imaging course*. Available from: https://www.icr.ac.uk/studying-and-training/opportunities-for-clinicians/radiotherapy-and-imaging-training-courses/nuclear-medicine-and-pet-imaging-course.
145. Bailey, D.L., et al. *Nuclear Medicine Physics A Handbook for Teachers and Students* 2014; Available from: https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1617web-1294055.pdf.

146. *Nuclear Medicine Handbook slides*. 2014; Available from: https://humanhealth.iaea.org/HHW/MedicalPhysics/e-learning/Nuclear_Medicine_Handbook_slides/.
147. *Quantitative Nuclear Medicine Imaging: Concepts, Requirements and Methods*, in *IAEA Human Health Reports* 2014, International Atomic Energy Agency: Vienna.
148. Stokke, C., et al., *Dosimetry-based treatment planning for molecular radiotherapy: a summary of the 2017 report from the Internal Dosimetry Task Force.* EJNMMI Phys, 2017. **4**(1): p. 27.
149. Falzone, N., et al., *Clinical trials in molecular radiotherapy—Tribulations and Triumphs Report of the NCRI CTRad meeting held at the Lift Islington, 8 June 2018.* The British Journal of Radiology, 2019. **92**(1100): p. 20190117.
150. Emmett, L., et al., *Lutetium (177) PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy.* J Med Radiat Sci, 2017. **64**(1): p. 52-60.
151. Barrington, S.F., et al., *Radiation dose rates from patients receiving iodine-131 therapy for carcinoma of the thyroid.* Eur J Nucl Med, 1996. **23**(2): p. 123-30.
152. Zhang, H., et al., *The study of external dose rate and retained body activity of patients receiving 131I therapy for differentiated thyroid carcinoma.* International journal of environmental research and public health, 2014. **11**(10): p. 10991-11003.
153. Zhang-Yin, J., et al., *Equivalent Dose Rate 1 Meter from Neuroendocrine Tumor Patients Exiting the Nuclear Medicine Department After Undergoing Imaging.* J Nucl Med, 2017. **58**(8): p. 1230-1235.