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Radiological Protection in Therapy with Radiopharmaceuticals

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CONTENTS

EDITORIAL

To be drafted

ABSTRACT

Radiological Protection in Therapy with Radiopharmaceuticals

ICRP Publication 1XX

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Abstract-The use of radiopharmaceuticals for therapy using novel radionuclides, compounds, tracer molecules, and the administration techniques is increasing for the treatment of various tumours. The goal of radiation therapy, including therapy with radiopharmaceuticals, is to optimise the relationship between the probability of control of tumour/target tissue and complications in normal tissue. Essential to this optimisation is ability to quantify radiation dose to both tumour/target tissue and normal tissue. This report provides a framework for calculating radiation doses for various treatment approaches. In radiopharmaceutical therapy, the absorbed dose in an organ or tissue is governed by the radiopharmaceutical uptake, retention in and clearance from the various organs and tissues of the body, together with radionuclide physical half-life. These biokinetic data are based on measurements made using techniques that vary in complexity and the required accuracy will depend on the specific application. For treatment planning, absorbed dose calculations are performed prior to therapy using a trace-labelled diagnostic administration, or post-therapy on the basis of the therapy administration. Uncertainty analyses provide additional information about sources of bias and random variation and their magnitudes; these analyses show the reliability and quality of absorbed dose calculations. Effective dose can provide a measure of lifetime risk of detriment attributable to the stochastic effects of radiation exposure, principally cancer, but effective dose does not apply to short-term deterministic effects associated with radiopharmaceutical therapy. Accident prevention in radiation therapy should be an integral part of the design of facilities, equipment, and administration procedures. Optimisation of staff exposures includes consideration of equipment design, proper shielding and handling of sources, and personal protective equipment and tools, as well as education and training to promote awareness and engagement in radiation protection. The decision to hold or release a patient after radiopharmaceutical therapy should take account of estimates of possible radiation dose to members of the general public and carers from residual activity in the patient. In these situations, specific radiation protection guidance should be provided to patients and caregivers.

Keywords: Radiopharmaceutical therapy; Radionuclide; Dose estimation; Radiological protection

AUTHORS ON BEHALF OF ICRP

PREFACE

Over the years, the International Commission on Radiological Protection (ICRP), referred below as 'the Commission', has issued many reports providing advice on radiological protection and safety in medicine. *Publication 105* is a general overview of this area (ICRP, 2007b). These reports summarise the general principles of radiological protection, and provide advice on the application of these principles to the various uses of ionising radiation in medicine.

The use of radiopharmaceuticals for therapy is increasing for the treatment of various tumours using novel radionuclides, compounds, tracer molecules, and the administration techniques. Radiopharmaceutical therapy is of benefit for the patient; optimising patient benefit implies optimising the factors that are most likely to contribute to positive responses to therapy. The medical community currently does not have easy access to methods and protocols for the collection of useful biokinetic or dosimetric data on such approaches. The report is intended to provide information on reasonable and practical approaches for the management of patient dose in therapy with radiopharmaceuticals as well as for protection of staff and members of the public.

Although ICRP published various recommendations for the use of radiopharmaceuticals, there have been no reports specific to radiopharmaceutical therapy. At the meeting in Bethesda, 2011, the Committee 3 discussed the need for a new report and proposed to establish a working party. The Commission launched a Task Group on Radiological Protection in Therapy with Radiopharmaceuticals in 2016.

The membership of the Task Group 101 was as follows:

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L.T. Dauer	G. Flux	

Corresponding members were:

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(*2009-2013*)

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MAIN POINTS

- **Treatment with radiopharmaceuticals requires the development of administration protocols that justify and optimise the treatment. Individual absorbed dose estimates should be performed for treatment planning and post-administration verification of doses received by tumour and normal tissues, as radiation delivered to normal tissues can cause tissue reactions and there is a risk of secondary malignancies.**
- **Special consideration should be given to pregnant women (and children) exposed to ionising radiation. Pregnancy is a strong contraindication to radiopharmaceutical therapy, unless the therapy is life-saving. Breastfeeding should be discontinued in radiopharmaceutical therapy patients.**
- **Radiation sources used in radiopharmaceutical therapy can contribute significant doses to medical personnel and others who may spend time within or adjacent to rooms that contain such sources. Meaningful dose reduction and contamination control can be achieved through the use of appropriate procedures, and facility and room design, including shielding where appropriate, as well as education and training to promote awareness and engagement in radiation protection. Accident prevention and review of near misses in radiopharmaceutical therapy should be an integral part of the design of facilities, equipment, and administration procedures.**
- **Medical practitioners should provide all necessary medical care consistent with patient safety and appropriate medical management. Radiation protection considerations should not prevent or delay life-saving medical procedures or surgery in the event that they may be required/helpful. Staff should be informed when a patient may pose a radioactive hazard, and advice and training should be provided.**
- **The decision to hospitalise or release a patient after therapy should be made based on existing guidance and regulations, as well as on the individual patient situation, considering factors such as the residual activity in the patient, the patient's wishes, family considerations (particularly the presence of children or pregnant family members), and environmental factors. Information on specific radiation protection precautions should be provided to patients and carers.**

GLOSSARY

Absorbed dose, *D*

The quotient of the mean energy (d) imparted to an element of matter by ionosing radiation and the mass (d*m)* of the element.

$$D = \frac{\mathrm{d}\bar{e}}{\mathrm{d}m}$$

Absorbed dose is the basic physical dose quantity and is applicable to all types of ionising radiation and to any material. Absorbed dose is a measurable quantity for which primary standards exist. In the International Systeme of Units (SI), the unit for absorbed dose is joule per kilogramme (J kg^{-1}), and its special name is gray (Gy).

Ambient dose equivalent, $H^*(10)$

The dose equivalent at a point in radiation field that would be produced by the corresponding expanded and aligned field in the ICRU sphere at depth of 10 mm on the radius opposing the direction of the aligned field. The unit of ambient dose equivalent is joule per kilogram (J kg^{-1}) and its special name is sievert (Sv).

Biologically effective dose (BED)

A concept within the linear-quadratic cell survival model, used to calculate the different absorbed doses required to produce the same probability of a specified biological endpoint, when the absorbed doses are delivered with different fractionation schemes or absorbed-dose rate patterns. Theoretically, the BED is the absorbed dose that would be required to produce a specified biological endpoint, if the dose were delivered by infinitesimally small dose fractions, or at a very low dose rate.

Comforters and carers

Individuals, other than staff, who care for and comfort patients. These individuals include parents and others, normally family or close friends who hold children during diagnostic procedures or may close to patients following the administration of rdiopharmaceuticals or during brachytherapy (ICRP, 2007a).

Deterministic effect

Injury in populations of cells, characterised by a threshold dose and an increase in the severity of the reaction as the dose is increased further. Deterministic effect is also termed a ‘tissue reaction’. In some cases, deterministic effects are modifiable by post-irradiation procedures including biological response modifiers (ICRP, 2007a).

Dose equivalent, *H*

The product of *D* and *Q* at a point in tissue, where *D* is the absorbed dose and *Q* is the quality factor for the specific radiation at this point, thus:

$$H = D \cdot Q$$

The unit of dose equivalent is joule per kilogramme (J kg^{-1}), and its special name is sievert (Sv).

Dose limit

The value of the effective dose received by an individual within a specified period from planned exposure situations that shall not be exceeded. Dose limitation is one of three fundamental principles of radiological protection originally defined by ICRP.

Effective dose, E

The tissue-weighted sum of the equivalent doses in all specified tissues and organs of the body, given by the expression:

$$E = \sum_{\mathrm{T}} w_{\mathrm{T}} \sum_{\mathrm{R}} w_{\mathrm{R}} D_{\mathrm{T,R}}$$

where $D_{\mathrm{T,R}}$ is the mean absorbed dose from radiation R in a tissue or organ, T, and w_{T} is the tissue weighting factor and w_{R} is the radiation weighting factor. The unit for the effective dose is the same as for absorbed dose (J kg^{-1}), and its special name is sievert (Sv).

Justification

One of three fundamental principles of radiological protection originally defined by ICRP. The process of determining whether: (i) a planned activity involving radiation is beneficial overall (i.e. whether the benefits to individuals and to society from introducing or continuing the activity outweigh the harm resulting from the activity); or (ii) the decision to control exposure in an emergency or existing exposure situation is likely to be beneficial overall (i.e. whether the benefits to individuals and society outweigh its cost and any harm or damage it causes).

Linear energy transfer (LET)

The average linear energy loss of charged particle radiation in a medium, i.e., the radiation energy lost per unit length of path through a material. That is, the quotient of dE by dl where dE is the mean energy lost by a charged particle owing to collisions with electrons in traversing a distance dl in matter.

$$L = \frac{dE}{dl}$$

The unit of L is J m^{-1}, often given in keV μm^{-1}.

Occupational exposure

All exposure incurred by workers in the course of their work, with the exception of: (1) excluded exposures and exposures from exempt activities involving radiation or exempt sources; (2) any medical exposure; and (3) the normal local natural background radiation.

Optimisation of protection

The principle of optimisation of radiological protection is a source-related process that aims to keep the magnitude of individual doses, the number of people exposed, and the likelihood of potential exposure as low as reasonably achievable below the appropriate dose criteria (constraint or reference level), economic and societal factors being taken into account.

Organ at risk (OAR)

Organs that might be damaged during exposure to radiation. It most frequently refers to healthy organs located in the radiation field during radiotherapy.

Quality factor, $Q(L)$

The factor characterising the biological effectiveness of a radiation, based on the ionisation density along the tracks of ion beams in tissue. Q is defined as a function of the unrestricted linear energy transfer, L_∞ (often denoted as L or LET), of ion beams in water:

$$Q(L) = \begin{cases} 1 & L < 10 \text{ keV}/\mu\text{m} \\ 0.32L - 2.2 & 10 \leqslant L \leqslant 100 \text{ keV}/\mu\text{m} \\ 300/\sqrt{L} & L > 100 \text{ keV}/\mu\text{m} \end{cases}$$

Q has been replaced by the radiation weighting factor, but it is still used in calculating the operational dose equivalent quantities used in monitoring.

Radiation detriment

A concept used to quantify the harmful health effects of radiation exposure in different parts of the body. It is defined by the Commission as a function of several factors, including incidence of radiation-related cancer or heritable effects, lethality of these conditions, quality of life, and years of life lost owing to these conditions.

Radiation induced second cancer

Ionising radiation has paradoxical aspects in both beneficial effects of curing cancer and the risk of inducing cancer. Induction of cancer by medium to high dose of radiation has been demonstrated by the significant increase in the incidence of cancers among workers handling radioactive substances and among atomic bomb survivors, as well as among survivors after radiotherapy.

Radiation weighting factor, w_R

A dimensionless factor by which the organ or tissue absorbed dose is weighted to reflect the higher biological effectiveness of high-LET radiations compared with low-LET radiations.

Relative biological effectiveness (RBE)

The ratio of absorbed dose of a low-LET reference radiation to absorbed dose of the radiation considered that gives an identical biological effect. RBE values vary with absorbed dose, dose rate, and biological endpoint considered.

Risk

Risk relates to the probability that an outcome (e.g. cancer) will occur. Terms relating to risk are grouped together here:

Relative risk is the rate of disease in an exposed population divided by the rate of the disease in an unexposed population.

Excess relative risk is the rate of disease in an exposed population divided by the rate of the disease in an unexposed population minus 1. This is often expressed as the excess relative risk per Sv.

Stochastic effect

The induction of malignant disease or heritable effects, for which the probability of an effect occurring, but not its severity, is regarded for the purpose of radiological protection to be increasing with the dose without a threshold.

Tissue weighting factor, w_T

The factor by which the equivqlent dose to a tissue or organ T is weighted to represent the relative contribution of that tissue or organ to the total health detriment resulting from uniform irradiation of the body (ICRP, 2007b). It is weighted such that:

$$\sum_{T} w_T = 1$$

Voxel phantom

Computational anthropomorphic phantom based on medical tomographic images where the anatomy is described by small three-dimensional volume elements (voxels) specifying the density and the atomic composition of the various organs and tissues of the human body.

1. INTRODUCTION

(1) In radiation therapy, including therapy with radiopharmaceuticals, the dose to the patient is intentional and its potentially cell-killing properties are the very purpose of the treatment. In such cases, optimisation becomes an effort in minimising doses (and/or their deleterious effects) to surrounding tissues without compromising the pre-determined and intentionally lethal dose and effect on the target region. Basically, the aim is to eradicate the neoplastic target tissue or to palliate the patient's symptoms. If the dose to the target tissue is too low, the therapy will be ineffective and the exposure is not justified. The emphasis should be on the justification of the medical procedures and on the optimisation of treatment and of protection. Current ICRP recommendations related to therapy with radiopharmaceuticals are found in ICRP *Publications 73* (ICRP, 1996a), *94* (ICRP, 2004), *103* (ICRP, 2007a), *105* (ICRP, 2007b) and *128* (ICRP, 2015a).

(2) The medical community currently does not have easy access to methods and protocols for the collection of useful biokinetic or dosimetric data for such procedures. Many centres, even academic facilities, do not have such methods available despite performing research in this area. This severely constrains development. As quantitative imaging and dosimetry is seldom performed, many treatments are not appropriately optimised. Quantitative imaging and dosimetry should be the basis for treatment planning for radiopharmaceutical therapy[1] just as it is for external beam radiotherapy.

(3) A collection and review of the existing information and literature in the context of therapeutic uses will help to optimise therapeutic use of radiopharmaceuticals, particularly for newer approaches. It is essential to alert the community to the variation in patient kinetics at therapeutic levels of activity. This information can facilitate the introduction of new radiopharmaceuticals, particularly with regard to the levels of the administered activity prescribed.

(4) In general, there are many papers dealing with absorbed doses delivered to critical organs and to tumours. Many of these include varying degrees of detail on the biokinetics of uptake and retention, and uptake phases are often assumed to be instantaneous rather than measured. The focus on therapy procedures has been on the absorbed doses delivered, so that the biokinetics have not always been detailed. This information is presumably available. It would be very valuable if biokinetic information for the increasing number of studies that are being performed could be compiled and made publicly available. It would also be beneficial to assess the integrity of data gathered from descriptions of the methods used to acquire the data.

(5) The report is intended to explore, provide, and explain a framework for estimating dosimetry for novel treatment approaches and identify those situations with unique aspects that should be considered. Such a framework includes items such as: individual dosimetry to plan the therapy, test activities and pre-treatment tracers, measurement of whole body/tumour/organ kinetics, analysis of urine or blood samples, quantitative measurements of the test activity; absorbed dose calculation based on 3D-patient images or patient-like

[1] Therapy with radiopharamaceutical is also referred to by many terms, including '(targeted) radionuclide therapy', 'unsealed source therapy', 'systemic radiation therapy' and 'molecular raddiotherapy'. In this publication the generic term 'radiopharmaceutical therapy' is used to be consistent with other ICRP and ICRU publication.

phantoms using Monte-Carlo or analytical techniques, an evaluation of how to scale-up to therapeutic activity levels, and written guidelines for the therapy.

(6) Dosimetry is necessary to provide justification for treatment with radiation with respect to both the deterministic and stochastic effects. Radiopharmaceutical therapy practice and optimisation require involvement of representatives of different competencies, including medical physicists, nuclear medicine technologists, nuclear medicine physicians, endocrinologists and oncologists.

(7) The target audience includes; nuclear medicine physicians and oncologists, medical physicists, clinicians, practitioners and prescribers/referrers, radiopharmacists and nuclear medicine technologists, radiation protection officers, regulatory authorities, medical and scientific societies, industry, patients, patient advocacy groups and public protection officers.

2. RADIOPHARMACEUTICAL THERAPY METHODS: JUSTIFICATION AND OPTIMISATION

- **Treatment with radiopharmaceuticals involves the development of administration protocols that justify and optimise the treatment. Individual absorbed dose estimates should be performed for treatment planning and post-administration verification of doses received by tumour and normal tissues. Records of individual dose estimates should be kept.**
- **Excess radiation delivered to normal tissues can cause tissue reactions and there are risks of secondary malignancies. Dosimetry should be performed for each treatment, particularly to children and young people.**
- **In ^{131}I treatment of hyperthyroidism, a fully personalised approach based on patient-specific measurements can ensure that the administered activity is the minimum required for an effective treatment, thereby minimising the potential for long term risks, offering the potential to render patients euthyroid, and also minimising the radiation doses delivered to patients, staff, family and comforters and carers.**
- **For ^{131}I treatment of differentiated thyroid cancer, limited survival for high risk patients indicates the need for stratification in treatment. To optimise treatments, dosimetry should be performed for each treatment following therapy and further studies are needed to investigate the role of pre-therapy dosimetry planning.**
- **Radiopharmaceuticals that target bone tissues, such as the beta particle emitters ^{89}Sr chloride and ^{153}Sm-EDTMP, have important roles in the management of painful bone metastases, but optimal treatment protocols are not yet established. An investigation of the optimal absorbed dose to deliver for the alpha emitter, ^{223}Ra, would help to determine optimal treatment regimens.**
- **In ^{131}I-mIBG treatment of neuroblastoma in children and young adults, the probability of inducing acute myelotoxicity, the potential for secondary neoplasms and the need to justify administrations of high activity to children and young people underline the need for personalised dosimetry planning and verification.**

2.1. Introduction

(8) Radiopharmaceutical therapy is a complex procedure, encompassing a wide range of radionuclides, different targeting mechanisms and various methods of administration. Each radiotherapeutic procedure presents a unique set of challenges for dosimetry calculations, related either to quantitative imaging, the absorbed dose calculations themselves or considerations of the deterministic or stochastic biological effects. The combined need for a highly multidisciplinary approach and the relatively small number of patients treated, has resulted in a lack of development within the field compared with that for external beam radiotherapy (NCRP, 2006).

(9) Treatment objectives vary. In many cases the intention is to provide a palliative effect, as in the case of beta emitters for bone metastases from castration resistant prostate cancer (CRPC). In limited cases, as for the ablation of thyroid remnants following thyroidectomy, complete responses are common. In the majority of treatments, a range of responses are seen.

(10) Radionuclide therapy using ^{131}I-iodide for the treatment of thyrotoxicosis and thyroid cancer, and ^{32}P-orthophosphate for polycythaemia and for palliation of bone pain, has been practised for over 70 years. The technique is increasingly being used for the treatment of various tumours using several novel radionuclides, compounds, tracer molecules, and application techniques. Examples of recently developed methods used in clinical practice are ^{177}Lu-labelled peptides for therapy of neuroendocrine tumours and ^{223}Ra-dichloride for treatment of painful bone metastases.

(11) It is important that the clinical introduction of a new radiotherapeutic method involves the development of administration protocols that justify and optimise the treatment and are not simply based on existing procedures for different radiopharmaceuticals administered for different indications.

(12) At present, there are known to be a large number of radiotherapeutics in development. Each new agent must be considered separately and the potential benefits and risks involved must be considered in relation to individual patient status and the aim of treatment.

(13) Records of the specifics of therapy with unsealed radionuclides should be maintained at the hospital. Data from dose planning and about administered activity should be included in the patients' records.

(14) Dose coefficients presented in ICRP *Publications 128* (ICRP, 2015a), *106* (ICRP, 2008) as well as *80* (ICRP, 1998) and *53* (ICRP, 1987) are intended for diagnostic nuclear medicine and not for therapeutic applications. The use of radiopharmaceuticals for therapy requires more detailed and patient-specific dosimetry and dose planning, including both tumour and normal tissue.

2.2. Treatment of Hyperthyroidism and Other Benign Thyroid Conditions

(15) ^{131}I-iodide, first used in the 1940s (Seidlin et al., 1946), is a routine treatment for diffuse or nodular toxic goitre, hyperthyroidism, or large non-toxic goitre (Leiter et al., 1946). The treatment is usually performed by oral administration of a capsule containing ^{131}I-iodide, but ^{131}I solution is also used for individualized administration of the activity. Radioactive iodine accumulates in the thyroid gland, and beta particles emitted by ^{131}I destroy the cells of the thyroid gland. Although this is firmly established as a first line treatment, there is little consensus concerning treatment regimens, and ongoing controversy over the aims of treatment.

2.2.1. Aim of treatment

(16) The aim of treatment is to destroy the thyroid glands' cells and suppress the hyperactive thyroid function to render the patient euthyroid or in a hypothyroid state.

2.2.2. Treatment protocols

(17) Treatment protocols fall into 3 categories according to the purpose of treatment:

- An administration of a fixed activity with an aim to render patients hypothyroid within a short period of time, whereupon patients continue on life-long thyroid replacement hormones (Royal College of Physicians, 2007).

- A personalised approach to inducing hypothyroidism, in order to achieve a swift response albeit with the minimal administered activity necessary (Kobe et al., 2008; Stokkel et al., 2010; Schiavo et al., 2011).
- A personalised approach to treatment with the aim of rendering patients euthyroid where possible, to delay the need for supplementary medication (Flower et al., 1994; Howarth et al., 2001).

2.2.3. Radiation dose to friends and family

(18) Radioiodine is primarily excreted via urine, but also through faeces and perspiration (Hänscheid et al., 2013; ICRP, 2015a, 2015b). The mean effective half-life for excretion of ^{131}I from the thyroid is about 5 days, although this has been shown to vary widely. Assessments should be performed for individual treatments, taking into account patient-specific circumstances and detailed written instructions, and written guidance should be provided to the patient and their family.

2.2.4. Radiation dose to staff and carers

(19) The levels of activity administered for treatments of benign thyroid conditions are often substantially less than those administered for ablation or therapy procedures, although they are commonly greater than those administered for diagnostic studies. Effective dose estimates for staff members are therefore necessary for administration procedures, and there may also be a need to follow the thyroid doses for those working with ^{131}I. Precautions must be taken considering time, distance and shielding, and to avoid contamination. Comforter and carer consent is required if in close contact with the patient.

2.2.5. Patient organ dosimetry

(20) The role of internal dosimetry in the management of benign thyroid disease with radioiodine remains a matter of debate. In some cases fixed activities are administered while in others, dosimetry is routinely performed and may be used to guide treatment. A number of methods have been employed (Stokkel et al., 2010). Advances in quantitative imaging and dosimetry enable more precise dosimetry calculations that may take into account volume and sequential retention measurements acquired from ^{131}I or ^{123}I SPECT, MRI, and ^{124}I PET. The accuracy and reproducibility of internal dosimetry have been subject to increased investigation and should be further developed (Metso et al., 2007; Merrill et al., 2011) when reporting absorbed doses. Dosimetry guidelines have been published by the European Association of Nuclear Medicine (EANM) (Hänscheid et al., 2013).

2.2.6. Risks to patients

(21) As with all therapeutic procedures, pregnancy and breastfeeding are a contraindication to treatment and patients should avoid conception for 4-6 months, dependent on national guidelines. Patients to be treated with radioactive iodine should not undergo tests with iodinated contrast media within two months prior to the therapy due to the risk of iodine blockage with low uptake of radioactive iodine (Luster et al., 2008).

2.2.7. Recommendations

(22) At present there are no standardised protocols for treatment, which reflects the lack of evidence base for best practice. There is evidence that a fixed activity administration, without dosimetry calculations, while convenient for many centres, results in the administration of higher activities than is necessary, in contravention of the ALARA principle (Jönsson and Mattsson, 2004; Sisson et al., 2007).

(23) In principle, a fully personalised approach, based on patient-specific measurements can ensure the administration of a minimal effective activity, thereby minimising the potential for long term risks and the radiation doses delivered to staff, family and comforters and carers. Of particular importance to this treatment, a personalised approach also offers the potential to render patients euthyroid where this may be desired and reports have indicated that such an approach is possible, at least in a subset of patients. There have been a limited number of trials to date to investigate the potential of a personalised approach to treatment (Leslie et al., 2003) and further trials are needed to determine the relationship between the absorbed doses delivered to the thyroid and to normal organs and outcome. Such trials should be stratified according to the volume of the thyroid, initial uptake and retention as there is some evidence that these may be confounding factors (Howarth et al., 2001; Reinhardt et al., 2002).

2.3. Treatment of Differentiated Thyroid Cancer

(24) ^{131}I-iodide, first used in the 1940s (Seidlin et al., 1946), has become a treatment of choice for the ablation and therapy of papillary and follicular thyroid cancer. Patients are typically given a low iodine diet prior to administration (Haugen et al., 2016). Some guidelines now also indicate the use of recombinant human thyroid stimulating hormone (rhTSH; Thyrogen, Genzyme Corp.) as an adjunctive treatment to stimulate uptake for radioiodine ablation of thyroid tissue remnants in patients who have undergone near-total or total thyroidectomy for well-differentiated thyroid cancer and who have evidence of distant metastatic thyroid cancer. Subsequent administrations are given for further therapy of recurrent or persistent disease, particularly in the case of metastatic spread. Administrations are continued, typically at 6-8 month intervals, until patients become iodine negative or fail to show response.

(25) Management guidelines have been published for adult patients with thyroid nodules and differentiated thyroid cancer (Haugen et al., 2016) and for the diagnosis and management of thyroid disease during pregnancy and the postpartum period (Alexander et al., 2017). However, practical guidelines for therapy of thyroid disease with ^{131}I still vary and are increasingly based on patient preferences (Silberstein et al., 2012).

2.3.1. Aim of treatment

(26) For ablation, the aim of treatment is to eradicate residual thyroid tissue. With further therapy, the aim of treatment is to eradicate malignant tissues. Several professional medical societies have provided management guidelines for patients with thyroid nodules and differentiated thyroid cancer (Luster et al., 2008; Haugen et al., 2016). For some staging criteria, there are uncertainties over the potential usefulness of radioiodine (Perros et al., 2014). In some cases, for those concerning children and young people, persistent yet stable disease is expected.

2.3.2. Treatment protocols

(27) In spite of the widespread use of this treatment over many decades, the level of evidence for optimal radioiodine treatments is extremely low (Luster et al., 2008). No multicentre trials have yet been conducted to establish the optimal activity to administer for either ablation or for subsequent therapeutic procedures. Consequently guidelines do not give recommendations regarding levels of administration, and such recommendations that are provided are necessarily based on expert advice.

(28) In recent years the UK HiLo trial and the French ESTIMABL trial demonstrated that 1.1 GBq is as effective as 3.7 GBq for ablation in low or intermediate risk patients, although the interpretation of these results is debated. There is ongoing discussion as to whether radioiodine should be administered at all in low risk patients (Mallick et al., 20012b; Schlumberger et al., 2012; Haugen et al., 2016).

(29) In the absence of trial-based evidence, activity schedules have been proposed to minimise the likelihood of secondary malignancies although a 'safe' level of activity is yet to be determined. There is no evidence to suggest whether interval or high single treatments are optimal for response and toxicity measurements.

(30) To date there have been no randomised controlled clinical trials for the treatment of children with differentiated thyroid cancer, and only one set of guidelines have been produced (Francis et al., 2015). Administrations for radioiodine ablation in children vary widely. Activity may be adjusted by body weight (usually 1.85–7.4 MBq kg^{-1}), by body surface area or by age (Jarzab et al., 2005; Luster et al., 2008). A hybrid approach of combining 24-hour-uptake measurements with body weight is favoured by the German procedure guidelines (Franzius et al., 2007).

(31) Treatment protocols for therapy administrations also vary. Fixed activities of 1.1 GBq – 11.0 GBq have been administered to children, as well as a range of activities based on body weight (Jarzab et al., 2005; Franzius et al., 2007; Luster et al., 2008; Verburg et al., 2011).

2.3.3. Radiation dose to friends and family

(32) Radioiodine is primarily excreted via the urine, but also through faeces and perspiration (Hänscheid et al., 2013; ICRP, 2015a, 2015b). The mean effective half-life for excretion after total thyroidectomy is much less than that with hyperthyroidism (Hänscheid et al., 2006; Remy et al., 2008). Assessments should be performed for individual treatments, taking into account patient-specific circumstances and detailed written instructions, and written guidance should be provided to the patient and their family. Comforter and carer consent is required if in close contact with the patient.

(33) Patients undergoing treatment may require hospitalisation for a number of days following administration, according to national regulations. The decision to hospitalise or to release a patient should be determined on an individual basis, and the time of release judged by monitoring dose rate from the patient to assess the residual activity in the patient.

2.3.4. Radiation dose to staff and carers

(34) As with all procedures involving radiotherapeutics, standard precautions should be taken with the principle of ALARA. As patients are hospitalised, there are risks to different

groups of staff, including nurses, technologists, physicists and physicians, and staff doses should be monitored.

2.3.5. Patient organ dosimetry

(35) Fixed administration protocols result in the delivery of a very wide range of absorbed doses (Flux et al., 2010). The use of dosimetry in radioiodine treatment of thyroid cancer to develop personalised treatment planning is increasing.

(36) Of note, dosimetry was performed at the outset by Seidlin et al. (1946) to calculate the cumulative absorbed doses delivered to metastases. Further influential studies have included the establishment in 1962 of a blood absorbed dose of 2 Gy as a surrogate biomarker for marrow toxicity (Benua et al., 1962) and a figure of 300 Gy to ablate thyroid remnant tissue and 80 Gy to eradicate lymph node metastases (Maxon et al., 1992).

(37) Since that time, a number of dosimetry studies have been performed that, although giving some variation in absolute values, have nevertheless shown significant correlations between the absorbed doses delivered and response (Strigari et al., 2014) and dosimetry guidelines have been published by the EANM (Lassmann et al., 2008).

2.3.6. Risks to patients

(38) As with all therapy procedures, pregnancy/breastfeeding is a contraindication, and patients should avoid conception. A range of side effects can arise from administration of radioiodine, the most common being sialadenitis and gastritis (Luster et al., 2008). A single administration of radioiodine can induce permanent xerostomia and can increase the risk of salivary malignancies (Klubo-Gwiezdzinska et al., 2010; Lee, 2010). A decline in leucocytes and platelets may also be seen and there are risks of pulmonary fibrosis in patients with lung metastases (Haugen et al., 2016). Patients to be treated with radioactive iodine should not undergo tests with iodinated contrast media within two months prior to the therapy due to the risk of iodine blockage with low uptake of radioactive iodine (Luster at al., 2008).

(39) Children and young people treated with radioiodine for differentiated thyroid cancer are likely to have a significantly longer survival than is the case for adults, although 2% have long term cause-specific mortality. Many children with pulmonary metastases develop stable disease following administration of radioiodine (Vassilopoulou-Sellin et al., 1993; Pawelczak et al., 2010). Long term follow up of children treated with radioiodine for differentiated thyroid cancer has shown an increase in secondary malignancies (Rubino et al., 2003; Brown et al., 2008; Hay et al., 2010; Francis et al., 2015). The risk of leukaemia increases with increasing cumulative activity and patients are more likely to develop secondary malignancies in the bladder, colorectal system, breast and salivary glands. Decreased spermatogenesis can also result from increasing cumulative activities of radioiodine which can have long term consequences for survivors.

2.3.7. Recommendations

(40) The overall cause-specific survival for differentiated thyroid cancer is approximately 85% (Luster et al., 2008). However, it is possible that this figure is heavily influenced by the number of low risk patients (where risk may be generally defined according to a number of factors including age, volume of disease and metastatic spread) that may not in fact require an administration of radioiodine (Mallick et al., 2012a). Survival for high risk patients including

those with metastases is only 25 – 40 %, indicating the need for stratification in treatment planning. Also of note is that the recurrence rate can be as high as 10 – 30 %. Insufficient treatment will entail further therapy at the risk of continuing progression and the development of iodine negativity. Excess radiation delivered to normal tissues is associated with potential side effects and some risk of secondary malignancies.

(41) While it may be argued that the low mortality precludes the necessity to optimise treatments further, the obvious benefit of living without disease, and the need to minimise the potential for secondary malignancies are strong arguments for the consideration of dosimetry for each treatment following therapy. This is particularly relevant for children and young people, and for high risk patients. Further studies are needed to investigate the role of pre-therapy dosimetry planning, taking into account the possibility of stunning, whereby uptake of activity for therapy is reduced. Thyroid stunning is a clinical problem in which exposure of a patient to diagnostic amounts of ^{131}I has been described to alter the ability of differentiated thyroid carcinoma, or remnants of thyroid tissue after thyroidectomy, to take up therapeutic amounts of ^{131}I.

2.4. Treatment of Polycythaemia Vera and Essential Thrombocythaemia

(42) ^{32}P phosphate was first used to treat polycythaemia vera (PV) and essential thrombocythaemia (ET) about 70 years ago. PV and ET are chronic progressive myeloproliferative disorders characterised by an over-production of erythrocytes and thrombocytes, respectively. Other disease features include leucocytosis, splenomegaly, thrombohaemorrhagic complications, vasomotor disturbances, pruritus, and a risk of disease progression into acute myeloid leukaemia or myelofibrosis. With the introduction of agents such as hydroxycarbamide, interferon and anagrelide, the role of ^{32}P has diminished. Today, PV and ET remain the only myeloproliferative conditions in which ^{32}P is indicated.

2.4.1. Aim of treatment

(43) ^{32}P is actively incorporated into DNA of rapidly proliferating cells and the treatment supresses the blood cell production by irradiation of the bone marrow. The radiopharmaceutical is used to suppress hyper-proliferative cell lines rather than to eradicate them. In spite of there being a number of alternative treatments, there remains a subgroup of elderly patients with PV and ET for whom ^{32}P as orthophosphate is used orally or by intravenous injection (Tennvall and Brans, 2007).

2.4.2. Treatment protocols

(44) The radiopharmaceutical is administered intravenously or orally. The activity generally used is either 74–111 MBq m^{-2} body surface with a maximum upper activity limit of 185 MBq, or a slightly higher activity of 3.7 MBq kg^{-1} body weight with a maximum upper activity limit of 260 MBq. A decrease in activity of 25% in patients >80 years of age is recommended by some investigators. An alternative, dose-escalating approach is to administer a fixed lower activity of 111 MBq. In the absence of an “adequate response”, a second treatment is to be given after 3 months, this time with a 25% increase in activity. This procedure of increased activity may be repeated every 3 months until an adequate response is

obtained. The upper activity limit for a single administration is 260 MBq (Tennvall and Brans, 2007).

2.4.3. Radiation dose to friends and family

(45) For outpatient therapy, there is a need for instructions to patient and family indicating 1) the need to avoid prolonged, close contact with young children and pregnant women, 2) a recommendation to sleep in a separate bed from partner or children for a few days after return home, 3) the need for personal hygiene to avoid any external contamination (^{32}P is excreted in urine for a period of two to three weeks).

2.4.4. Radiation dose to staff and carers

(46) As ^{32}P is a high energy beta emitter, it is essential to shield with PMMA during dispensing and injection.

2.4.5. Patient organ dosimetry

(47) Organs with the highest radiation absorbed dose are bone endosteum and haematopoietically active bone marrow, receiving around 11 mGy per MBq administered. A typical administration of 100 MBq thus gives over 1 Gy to bone endosteum and active bone marrow.

2.4.6. Risks to patients

(48) Contraindications are pregnancy and breastfeeding, and patients should avoid conception. The radiopharmaceutical is not recommended for women of childbearing age. The incidence of acute myeloid leukaemia (AML) 10 years after ^{32}P treatment was approximately 10% (Brandt and Anderson, 1995). Treatment using ^{32}P is therefore usually reserved for patients over the age of 65 – 70 years.

2.4.7. Recommendations

(49) ^{32}P can be used in elderly patients and those for whom alternative treatments using e.g. hydroxyurea, busulphan, interferon-alpha or anagrelide are not suitable.

2.5. Treatment of Skeletal Metastases

(50) Treatment of pain that is derived from skeletal metastases is one of the important issues in the management of cancer patients who are in advanced stages and need palliative care. Painful bone metastases may impair quality of life through limitation of daily activity, restricted mobility, insomnia, and anxiety. Management of bone pain should be multidisciplinary, involving analgesia, radiation, hormones, chemotherapy, bisphosphonates, and surgery. Localised metastases can be treated with external beam radiation, or surgery, whereas more diffuse bone metastases are usually treated by radiopharmaceuticals, hormones, chemotherapy, and bisphosphonates (Pandit-Taskar et al., 2004).

(51) Radiopharmaceuticals that emit beta particles such as ^{89}Sr chloride and ^{153}Sm-EDTMP (ethylenediamine tetramethylene phosphonate) have been administered for pain

relief in patients with painful skeletal metastases as palliative therapy. ^{223}Ra-dichloride, an alpha-emitting bone-seeking radiopharmaceutical, has appeared as a curative radiopharmaceutical therapy agent for castration-resistant prostate cancer with symptomatic bone metastases and has been shown to prolong overall survival (by approximately 3 months) in comparison with a placebo (Parker et al., 2013; Pandit-Takar et al., 2014).

2.5.1. Aim of treatment

(52) The aim of treatment with beta emitting radiopharmaceuticals is to control bone pain due to metastases and to improve quality of life in patients suffering from malignancies. The aim is principally palliation and anticancer effects that produce survival benefits are usually not evident. ^{89}Sr-chloride and ^{153}Sm-EDTMP are approved in a number of nations for the palliation of pain due to skeletal metastases from solid cancers, while ^{186}Re-HEDP (hydroxyethyledinediphosphonate), ^{188}Re-HEDP, ^{117m}Sn-DTPA (diethylenetriaminepentaacetic acid), and ^{177}Lu-EDTMP are under investigation (Finlay et al., 2005; Liepe et al., 2005b, 2007; Shinto et al., 2014; Yousefnia et al., 2015). The mechanism of pain relief by these radiopharmaceuticals is not fully understood. The aim of treatment of ^{223}Ra-dichloride therapy is to provide prolonged overall survival in castration-resistant prostate cancer patients with bone metastases.

2.5.2. Treatment protocols

(53) ^{89}Sr-chloride and ^{153}Sm-EDTMP have approval in a number of nations and thus have well-established treatment protocols. ^{89}Sr-chloride at an activity per body weight of 1.5 - 2.2 MBq kg^{-1} body weight is administered at a single intravenous injection as compared to ^{153}Sm-EDTMP at an activity per body weight of 37 MBq kg^{-1}. For both radiopharmaceuticals, patients have to visit their doctors regularly to ensure that the treatments are working and to check for unwanted effects including leukocytopenia and thrombocytopenia. Treatment protocols are under study for ^{186}Re-HEDP, ^{188}Re-HEDP, ^{117m}Sn-DTPA, and ^{177}Lu-EDTMP (Pandit-Taskar et al., 2004; Liepe and Kotzerke, 2007; Bodei et al., 2008; D'Angelo et al, 2012; Jie et al., 2013; Thapa et al., 2015).

(54) The approved administered activity per body weight for ^{223}Ra-dichloride is 55 kBq kg^{-1} given intravenously as 6 administrations every 4 weeks.

2.5.3. Radiation dose to friends and family

(55) As activity is excreted mainly through urine for ^{89}Sr-chloride and ^{153}Sm-EDTMP and through faeces for ^{223}Ra-dichloride, care must be taken to ensure that all excreta are disposed of in the sanitary sewer system when a patient is at home. Patients may be hospitalised for longer time if mentally incompetent and/or incontinent and therefore incapable of following radiation safety instructions and precautions (ICRP, 2004).

2.5.4. Radiation dose to staff and carers

(56) For ^{89}Sr, ^{153}Sm-EDTMP and ^{223}Ra patients can receive treatment on an outpatient basis, which is advantageous for ensuring that exposures of staff remain within acceptable limits. Higher irradiation of ^{186}Re-HEDP and ^{188}Re-HEDP results from the gamma emissions. Staff doses should be carefully monitored in all cases. ^{223}Ra-dichloride has been evaluated as

safe and straightforward to administer using conventional nuclear medicine equipment (Dauer et al. 2014).

2.5.5. Patient organ dosimetry

(57) ^{89}Sr gives absorbed doses of 0.2 - 2 and 0.05 – 0.3 Gy MBq^{-1} to the metastatic sites and red marrow, respectively (Breen et al., 1992), while ^{153}Sm-EDTMP gives absorbed doses of 5.3-8.8 and 1.2-2.0 mGy MBq^{-1} to the bone surfaces and red marrow, respectively (Eary et al., 1993). Absorbed dose values may vary depending on dosimetric models and biodistribution data. Of particular interest is the uncertainty over radiation weighting values for alpha dosimetry that can vary from 3-5 for deterministic effects (as is the case for radiotherapy) and for stochastic effects is recommended as 20 by the ICRP (Sgouros et al., 2010; Lassmann and Nosske, 2013).

2.5.6. Risk to patients

(58) Radiopharmaceuticals used for therapy of bone metastases must be used carefully as they may cause bone marrow suppression, especially in patients with reduced bone marrow reserve who have previously been treated with repeated chemotherapy. A transient rise in bone pain (flare) a few days after administration is recorded in some patients but usually not severe. Patients with renal dysfunction must undergo a careful evaluation prior to treatment because adverse effects including bone marrow suppression may be more serious. Contraindications are pregnancy and breastfeeding, and patients should avoid conception.

(59) ^{223}Ra has the advantage of sparing much of the marrow from irradiation, given the short-range alpha emissions. Non-haematological toxicities are generally more common than haematologic toxicity and are mild to moderate in intensity. The most common side effects are diarrhoea, fatigue, nausea, vomiting, and bone pain, some of which are dose-related. These side effects are easy to manage, and treatment is symptomatic and supportive (Pandit-Taskar et al., 2014). The long-term effects of ^{223}Ra in patients with extended survival are not yet known.

2.5.7. Recommendations

(60) Bone seeking radiopharmaceuticals have important roles in the management of painful bone metastases by alleviating pain and improving quality of life. Pain relief may last several months after a single injection of radiopharmaceuticals. The widely different administration protocols for each agent, that may be fixed or weight-based and may be administered once or multiple times, indicates that optimal treatment protocols are not yet established and further studies are necessary to this end. In terms of adverse effects, haematological toxicity due to marrow exposure should be taken into account. An investigation of the optimal absorbed dose to deliver for ^{223}Ra would help to determine optimal treatment regimens and to identify patients in whom treatment is likely to have little or no benefit. The radiopharmaceuticals are administered usually on an outpatient basis and standard radiation protection precautions are required.

2.6. Treatment of Neuroblastoma in Children and Young Adults

(61) Metaiodobenzylguanidine (mIBG), introduced in the 1980s, is a guanethidine and noradrenaline analogue taken up by cells of the sympathetic nervous system by an active transport process involving the noradrenaline transporter molecule.

(62) Neuroblastoma arises from the neural crest cells involved in the development of the nervous system and other tissues. It commonly occurs in the adrenal glands or in the nerve tissue and can spread to bones and liver. It accounts for around 6% of childhood cancers with only 67% surviving 5 years. ^{131}I-mIBG is most commonly administered in chemo-refractory or relapsed patients. Outcome is variable with response varying from 30% - 58% (Hoefnagel et al., 1991; Garaventa et al., 1999; Matthay et al., 2007).

2.6.1. Aim of treatment

(63) The aim of treatment is predominantly palliative. A range of responses are seen, including complete responses and downstaging, which may permit further surgery or external beam radiotherapy (George et al., 2016).

2.6.2. Treatment protocols

(64) Treatment regimens for ^{131}I-mIBG therapy for neuroblastoma vary widely. There are currently no established guidelines to govern the levels of activity administered. Typically, empirical fixed activities have been administered, comprising multiples of 3.7 GBq (Hoefnagel et al., 1991; Tristam et al., 1996), although weight-based activities have also frequently been administered. There is evidence that short term toxicity is significantly correlated with the whole-body absorbed dose, which can therefore act as a surrogate for the absorbed dose delivered to the red marrow. This has led to an alternative approach to fixed activity administrations, whereby the activities are tailored to deliver a prescribed whole-body absorbed dose (Gaze et al., 2005; Buckley et al., 2009). This can entail two administrations of 555 – 666MBq kg^{-1} to deliver a total whole body absorbed dose of 4 Gy, with peripheral blood stem cell support (Giammarile et al., 2008). There is, similarly, no protocol to govern the number of treatments delivered, and although single treatments have been administered, these are typically repeated once or twice. However, as many as five administrations have been reported (George et al., 2016).

2.6.3. Radiation dose to friends and family

(65) Individual risk estimates must be performed for each patient, taking home circumstances into account. This is particularly relevant for children and young people that may have siblings at home. Excretion is predominantly via the urine, and care must be taken to ensure that all excreta are disposed of in the sanitary sewer system. Written instructions must be provided to patients and to their families/carers on discharge.

2.6.4. Radiation dose to staff and carers

(66) Careful protection procedures are required to minimise radiation from the source and the administered patient. Shielded syringes should be utilised during the intravenous administration to ensure that extremity doses are maintained below occupational dose constraints. The use of automatic injection system will significantly reduce the effective dose

to the staff members (Rushforth et al., 2017). Administration protocols must be carefully considered. Personalised protocols (Gaze et al., 2005; Buckley et al., 2009) can entail extremely high levels of radiation in comparison with other treatments and as patients may be very young, a high level of care is required. Nursing staff in particular require specific training. Valuable advice related to administration of high-dose ^{131}I-MIBG therapy to children is given by Chu et al. (2016).

2.6.5. Patient organ dosimetry

(67) In contrast to many therapy procedures with radiopharmaceuticals, a large number of dosimetry studies have been performed relative to the number of centres that offer this treatment (Tristam et al., 1996; Matthay et al., 2001; Sudbrock et al., 2010; Flux et al., 2011). The absorbed doses delivered to whole-body, critical organs and tumours have been reported to vary by an order of magnitude (Matthay et al., 2001; Flux et al., 2011).

2.6.6. Risks to patients

(68) Acute toxicity is primarily haematological, causing neutropenia, thrombocytopenia and leukocytopenia (Buckley et al., 2009). Thyroid blockade is essential, but hypothyroidism can nevertheless result in over 10% of cases and hepatic toxicity has been reported in 75% of patients (Quach et al., 2011). Secondary malignancies have been reported in up to 5% of cases (Weiss et al., 2003).

2.6.7. Recommendations

(69) Although patients frequently present with advanced disease, long-term survival is not uncommon. The probability of inducing acute myelotoxicity, the potential for longer-term secondary neoplasms and the need to justify administrations of high activity to children and young people emphasise the need for personalised dosimetry planning and verification for all.

2.7. Treatment with Radiolabelled Peptide Receptor

(70) Neuroendocrine tumours express somatostatin receptors (SSR). Radiolabelled analogues of somatostatin have been developed for therapeutic purposes including ^{90}Y-DOTATOC ([^{90}Y-DOTA^{0},Tyr^{3}]-octreotide) and ^{177}Lu-DOTATATE ([^{177}Lu-DOTA^{0},Tyr^{3},Thr^{8}]-octreotide or [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate) that target the somatostatin receptor subtype 2. To date, a lack of randomised clinical trials has precluded evidence-based guidelines, although limited guidelines have been produced (Ramage et al., 2012) and a guidance document has been published jointly by the IAEA, EANM and SNMMI based predominantly on expert opinion (Bodei et al., 2013).

(71) The ideal radionuclide has not been established and there are arguments to support both ^{90}Y and ^{177}Lu. ^{90}Y, with a substantially longer range of beta-particles, is more able to deposit a uniform distribution of energy at a multicellular scale in the event of heterogeneous uptake, whereas it has been argued that this can produce greater kidney toxicity due to irradiation of the cortex (Bodei et al., 2008). ^{177}Lu also has the advantage of quantitative imaging for dosimetry, whereas a ^{90}Y administration must be ‘spiked’ with a tracer level of ^{111}In. The physical half-lives of both radionuclides (64 hours and 6.7 days for ^{90}Y and ^{177}Lu respectively) are compatible with the biological retention following uptake and do not cause

unnecessary hospitalisation. Both ^{177}Lu DOTATATE and ^{90}Y DOTATATE are radiolabelled in house, necessitating the usual precautions for such procedures.

2.7.1. Aim of treatment

(72) Response is variable and the aims of treatment are predominantly palliative. Partial or complete objective responses have been reported in up to 30 % of patients; in particular complete responses have been reported in 2-6% of patients with gastroenteropancreatic tumours (Bodei et al., 2013). Treatments are administered to adults, although one clinical trial has investigated the potential of ^{177}Lu-DOTATATE treatment of children and young people with neuroblastoma (Gains et al., 2011).

2.7.2. Treatment protocols

(73) Treatment protocols have become to a limited extent standardised based on established practice. There are nevertheless variations. ^{90}Y-DOTATATE or ^{90}Y-DOTATOC is frequently administered as 3.7 GBq m^{-2} body surface for 2 cycles or with a fixed activity of 2.78 – 4.44 GBq for 2-4 cycles. ^{177}Lu-DOTATATE is commonly administered as a fixed activity of 5.55 - 7.4 GBq over 3-5 cycles. The interval between administrations varies from 6 – 12 weeks (Bodei et al., 2013). Patients with compromised renal function are recommended to be administered lower activities. Patients with compromised marrow reserves may require a stem cell harvest for subsequent reinfusion although haematological toxicity is generally very low. Combination therapies of ^{90}Y- and ^{177}Lu-DOTATATE administered alternately are currently under investigation (Kunikowska et al., 2011; Savolainen et al., 2012; Seregni et al., 2014). There have been no activity or absorbed dose escalation trials to establish optimal administration protocols, either at a population level or for individual patients.

(74) There are high levels of somatostatin receptors in children and young people with neuroendocrine tumours, although with few exceptions clinical trials exclude this patient population due to unknown safety profile (Menda et al., 2010; Schmidt et al., 2010; Gains et al., 2011).

2.7.3. Radiation dose to friends and family

(75) Activity is excreted through body fluids, primarily urine and perspiration. Care must therefore be taken when a patient is discharged, and home circumstances should be taken into account.

2.7.4. Radiation dose to staff and carers

(76) Patients are typically hospitalised for one or two nights only which entails risks of exposures of different groups of staff, including nurses, technologists, physicists and physicians. For the treatment of beta particle emitting radionuclides, including ^{90}Y and ^{177}Lu, particular attention should be taken for the staff working on preparation and handling of radiopharmaceuticals given to the patient. Shielded syringes should be utilised during the intravenous administration of radiopharmaceuticals as necessary to ensure that extremity doses are maintained below occupational dose constraints. Doses to the finger tips from preparation and administration are typically in the range 5-10 mSv from single administrations when protection is optimised, but can be over 100 mSv if precautions are inadequate. Monitoring the dose to the finger tips using finger stall dosimeters for the main

fingers carrying out manipulations is strongly recommended for radiological protection in order to give a realistic picture of staff dose levels (Cremonesi et al., 2006b; ICRP, 2008; Grassi et al, 2009; Vanhavere et al., 2012).

2.7.5. Patient organ dosimetry

(77) Internal dosimetry is employed routinely in only a minority of centres and may be applied to tumours and to organs-at-risk including kidney and liver. Active marrow absorbed doses per administered activity from ^{90}Y-DOTATATE have been reported ranging from 0.03 – 0.17 Gy GBq^{-1}, kidney absorbed doses from 1.71 – 2.73 Gy GBq^{-1} and liver absorbed doses from 0.27 – 0.92 Gy GBq^{-1} (Cremonesi et al., 2006a, 2010; Bodei et al., 2008). Absorbed doses per administered activity from ^{177}Lu-DOTATATE to active marrow, kidneys and liver have been reported as ranging from 0.02 – 0.07 Gy GBq^{-1}, 0.32 – 1.67 Gy GBq^{-1} and 0.05 – 0.21 Gy GBq^{-1} respectively. Although correlations between absorbed dose and effect have not been an endpoint of any clinical trial to date, there is increasing evidence of such correlations covering both response (Pauwels et al., 2005; Ilan et al., 2015) and toxicity (Barone et al., 2005; Walrand et al., 2011; Strigari et al., 2014). There is evidence that the intra-patient variation in absorbed doses is small, whereas the inter-patient variation is significant (Hindorf et al., 2007; Sundlöv et al., 2017).

2.7.6. Risks to patients

(78) As with all therapy procedures, pregnancy/breastfeeding is a contraindication, and patients should avoid conception. Excretion is predominantly urinary and, hence, amino acids are routinely co-administered to protect kidneys. Kidney toxicity is nevertheless seen (Barone, 2005; Imhof, 2011) and a biologically effective dose (BED) of < 28 Gy (see section 4.7) has been recommended for patients with higher risk factors treated with ^{90}Y-DOTATATE (Bodei et al., 2008). A corresponding value for patients treated with ^{177}Lu-DOTATATE has yet to be determined. Grade 3-4 myelotoxicity is observed in up to 10-13% of patients and cases of myelodysplastic syndrome or overt acute myelogenous leukaemia have been reported (Valkema et al., 2002; Barone et al., 2005; Kwekkeboom et al., 2005; Bushnell et al., 2010; Strosberg et al., 2017).

2.7.7. Recommendations

(79) The treatment of adult and paediatric neuroendocrine cancers with radiolabelled peptides continues to develop and expand. As yet, there are few data to inform long term risk estimates although there is abundant evidence for acute toxicity primarily to kidneys and to bone marrow. The inter-patient variation in absorbed doses delivered to tumours and the potential for acute radiation induced nephrotoxicity and myelosuppression mean that prospective patient–specific organ and tissue dosimetry should ideally be performed for all patients. This may not always be feasible in which case, as treatment is almost invariably administered in multiple cycles, an initial administration according to a fixed activity or body surface area can safely establish the biokinetics of the individual patient. Retrospective dosimetry should be performed before and following subsequent administrations which may then be modified according to the cumulative absorbed doses delivered to tumours and organs-at-risk. The prospect of personalised treatments based on carefully designed dosimetry protocols is quite feasible. There is some evidence that biological parameters such

as BED can be of benefit to calculate risks of toxicity to organs at risk (OARs) and these should be further investigated and considered (Barone et al., 2005; Wessels et al., 2008).

2.8. Radioimmunotherapy

(80) Radioimmunotherapy involves radiolabelled antibodies that recognise tumour-specific antigens and deliver therapeutic radiation to neoplasms (Barbet et al., 2012). Antibodies may be mouse monoclonal antibodies, or in many cases human/mouse chimeric or humanised antibodies that are obtained by genetic engineering technologies in order to reduce immunogenicity in humans. Mostly radionuclides are beta emitters such as ^{131}I, ^{90}Y, ^{186}Re, and ^{153}Sm, and lately alpha emitters such as ^{225}Ac and ^{213}Bi are also recognised as potentially useful, and have been used in humans in some preliminary clinical studies (Sgouros et al., 2010; Larson et al., 2015).

(81) Substantial efforts have focused on research for development of radioimmunotherapy although to date only two agents have been approved by health authorities as commercially available radioimmunotherapy agents; ^{131}I-tositumomab and ^{90}Y-ibritumomab tiuxetan (Goldsmith, 2010). Both are directed to CD-20 positive, relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma and provide high response rate, although sufficient long-term survival data have not yet been accumulated. ^{90}Y-ibritumomab tiuxetan is effectively applied also to consolidation therapy, that is, therapy for patients with previously untreated lymphoma who achieve a partial or complete response to first-line chemotherapy (Chatal et al., 2008). A number of radioimmunotherapy agents are currently in development or in early phase trials, targeting other indications including neuroblastoma (Kramer et al., 2007), leukaemia (Miederer et al., 2004) and ovarian carcinoma (Andersson et al., 2009).

(82) So far no radioimmunotherapy agent has proved to be effective for solid cancers, or has been approved by health authorities due to low tumour-to-normal tissue absorbed dose ratios, although many agents have been investigated in clinical studies. Research continues to enhance the efficacy of radioimmunotherapy by improving tumour-to-normal tissue ratios, for example, using pre-targeting methods (Goldenberg et al., 2012), and by applying new radionuclides including alpha emitters.

2.8.1. Aim of treatment

(83) As radioimmunotherapy encompasses a range of procedures, treatment aims are largely dependent on the radiopharmaceutical and the treatment itself, although the aim of treatment is generally to eradicate tumour tissues that express tumour-associated antigens.

2.8.2. Treatment protocols

(84) Treatment regimens vary widely for radioimmunotherapy procedures. ^{90}Y-ibritumomab tiuxetan therapy has well-established treatment protocols. Rituximab at 250 mg m^{-2} is infused over 4 hours, followed by an infusion per body weight of 14.8 MBq kg^{-1} of ^{90}Y-ibritumomab tiuxetan, not exceeding 1,184 MBq. In some countries and regions, prior to ^{90}Y-ibritumomab tiuxetan therapy, imaging with ^{111}In-ibritumomab tiuxetan is performed according to a therapy protocol implemented to verify the expected biodistribution and

exclude patients who show an altered biodistribution, such as the rapid clearance from the blood pool, with prominent liver, spleen, or marrow uptake (Hanaoka et al., 2015).

2.8.3. Radiation dose to friends and family

(85) Exposure of friends and family is dependent on the radionuclide administered and the relevant procedures should be followed accordingly. Activity is excreted through body fluids, primarily urine and perspiration. Care must therefore be taken when a patient is discharged, and home circumstances should be taken into account.

2.8.4. Radiation dose to staff and carers

(86) Careful attention should be taken for handling of beta emitting radiopharmaceuticals as similar to the previous section. Particularly attention should be taken to finger dose for preparation of ^{90}Y- ibritumomab tiuxetan because high radiation dose has been reported (ICRP, 2008; Vanhavere et al., 2012).

2.8.5. Patient organ dosimetry

(87) A large number of dosimetry studies have been performed related to radioimmunotherapy procedures. In Phase III trials of ^{90}Y-ibritumomab tiuxetan, the median estimated radiation absorbed doses were 0.71 and 14.84 Gy to the active bone marrow and tumour, respectively (Wiseman et al., 2001). In radioimmunotherapy, radiation dose to organs at risk including the liver, lung, intestine, and kidney in relation to given radiolabelled antibodies should be evaluated carefully using clinical tests and imaging modalities to prevent unexpected overdose delivery.

2.8.6. Risks to patients

(88) In cases of ^{131}I- and ^{90}Y-ibritumomab radiolabelled antibodies, acute toxicity is primarily haematologic, causing thrombocytopenia and leukocytopenia. This needs careful management in patients with less bone marrow reserves due to prior repeated chemotherapies. Immunogenic response against the antibody is also a potential concern and should be monitored carefully. As with all therapy procedures, pregnancy/breastfeeding is a contraindication, and patients should avoid conception.

2.8.7. Recommendations

(89) Individual absorbed dose estimates must be performed for treatment planning and post administration verification of dosimetry on an individualised basis. Due to the range of radionuclides used, this may in some cases entail the use of surrogate imaging agents (for example ^{111}In in place of ^{90}Y).

2.8.8. Emerging Technologies in Radioimmunotherapy

(90) A number of new radiotherapeutics are currently under development, some of which have already reached the stages of clinical studies to evaluate safety and efficacy in humans. Examples of new methods that have lately attracted worldwide attention include, but are not limited to, prostate-specific membrane antigen (PSMA) ligands for prostate cancer, and

radioimmunotherapy with alpha-emitters for haematological malignancies such as anti-CD33 antibody labelled with ^{213}Bi or ^{225}Ac for acute myeloid leukaemia. Another new approach to radiopharmaceutical therapy involves pre-targeting techniques, which can enhance tumour-to-normal tissue accumulation ratios, and therefore the anti-tumour effect of treatment. Pre-targeting techniques, which are more complex than conventional techniques, might require more tailored considerations in safe and efficacious usage. Radiological protection standards should be established for these new methods although it will take some time until sufficient data on radiation doses and risks, as well as on patient care, are accumulated in clinical studies.

2.8.8.1. Therapy with PSMA ligands

(91) PSMA is overexpressed in prostate cancer, especially in de-differentiated or castration-resistant cases. Radiolabelled ligands for radionuclide imaging aimed at PSMA have recently been the subject of a number of studies showing high diagnostic accuracy in detecting primary tumours, recurrence, and metastases with good detection rates. The intense PSMA expression in prostate cancer also provides a promising approach to develop new radiopharmaceuticals for therapy. Some PSMA ligands have advantages of high affinity that produce good tumour-to-normal tissue contrast as well as the ability to be labelled with ^{68}Ga for imaging and ^{177}Lu for therapy. Several studies have reported promising results for response rates and a favourable safety profile after therapy with ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (Rahbar et al., 2017). Another application of PSMA ligands in radiopharmaceutical therapy has been reported as an initial experience with targeted ^{225}Ac-PSMA-617 alpha-therapy in a limited number of patients (Kratochwil et al., 2016). Such alpha-emitter-labelled PSMA ligands may have high potential for treatment of prostate cancer.

2.8.8.2. Radioimmunotherapy with alpha-emitters

(92) Because alpha-particles have a short range and a high linear energy transfer, radioimmunotherapy with alpha-emitters offers the potential for efficient tumour cell killing while sparing surrounding normal cells (Jurcic and Rosenblat, 2014). To date, clinical studies of alpha-particle immunotherapy for acute myeloid leukaemia (AML) have focused on the myeloid cell surface antigen CD33 as a target using monoclonal antibodies. Clinical studies demonstrated safety, feasibility, and anti-leukaemic effects of ^{213}Bi-labelled anti-CD33 antibodies. A next-generation compound containing ^{225}Ac, half-life of 10 days, was developed because the use of ^{213}Bi is limited by its short half-life of 46 minutes (Jurcic and Rosenblat, 2014).

2.8.8.3. Pre-targeting techniques

(93) For the enhancement of efficacy of radionuclide therapy as well as radionuclide imaging, pre-targeting strategies have been introduced. An example of pre-targeting techniques is an approach of radioimmunotherapy in which the antibody is not labelled but used to provide binding sites to small molecular weight radioactivity vectors. Such techniques have been shown to increase tumour to non-target uptake ratios and anti-tumour efficacy has been demonstrated in clinical studies (Chatal et al., 1995; Kraeber-Bodere et al., 2006). Another example of pre-targeting techniques involves affibody (small proteins

engineered to bind to a high number of target proteins) molecule-based peptide nucleic acid (PNA)-mediated pre-targeting, which increased radionuclide uptake in tumours in preclinical studies (Honarvar et al., 2016).

2.9. Intra-arterial Treatment of Hepatocellular Carcinoma and Liver Metastases (Selective Internal Radiation Therapy: SIRT)

(94) Hepatocellular carcinoma (HCC) and liver metastases may be treated via direct infusion of a radiotherapeutic substance into the hepatic artery, by selectively catheterising the hepatic artery branches that supply the tumours. The underlying basis for this procedure is that liver tumours preferentially take their blood supply from the hepatic artery while normal liver is predominantly fed by the portal vein. In recent years two commercial products, both radiolabelled with ^{90}Y, have become the mainstay for these treatments. Glass microspheres (Therasphere® BTG, Ontario, Canada) and resin microspheres (SIR-Spheres®, SIRTex Medical Limited Sydney, Australia) have similar properties, although differ in terms of the size of the particles and the concentration of activity on each sphere (Giammarile et al., 2011). ^{166}Ho-microspheres are also currently under development (Smits et al., 2012). The procedure also involves initial angiography and embolisation of branches not supplying a tumour before microspheres are injected.

(95) This treatment offers the potential to deliver high absorbed doses to small and large liver lesions with precision targeting. Potential disadvantages include a relatively invasive procedure and the possibility of irradiation of normal tissue (primarily lungs, gut and normal liver) that can have fatal implications (Giammarile et al., 2011).

2.9.1. Aim of treatment

(96) The primary aim of treatment is palliative, although complete responses and long remissions have been reported.

2.9.2. Treatment protocols

(97) A number of formulae are employed to determine the level of activity to administer. Current treatment protocols for microspheres, including mono-compartmental and partition models, are predominantly based on levels of activity administered or on activity per body surface area. Lung shunting is considered the most serious risk. For this reason a pre-therapy whole-body ^{99m}Tc-MAA (macro-aggregated albumin) scan is performed and administered activities are modified accordingly. If the lung shunt is too great, ^{90}Y microsphere administration is contraindicated. The potential for redistribution to bowel, stomach or pancreas must also be considered (Lambert, 2010). Post therapy scanning is usually performed of the liver to ensure uptake. ^{90}Y bremsstrahlung imaging is most commonly used, although in recent years, PET imaging has been developed following successful investigation into the low positron yield of ^{90}Y, which is sufficient for the high concentrations of activity localised in tumour and normal liver (Lhommel et al., 2010).

(98) There are no standardised treatment protocols or guidelines for ^{131}I-lipiodol. This has not been considered an option for treatment of children and young people due to the concerns of protection (Giammarile et al., 2011).

2.9.3. Radiation dose to friends and family

(99) As full physical retention is assumed for the microsphere treatments and ^{90}Y is primarily a beta emitter, less stringent radiation protection issues are required and should be addressed according to national guidelines.

2.9.4. Radiation dose to staff and carers

(100) Although microspheres are not metabolised and are considered as medical devices, they must be treated as unsealed sources of radiation and standard precautions must be taken. Standard precautions should be taken for care and imaging. Treatment with ^{131}I-lipiodol must be subject to the usual restrictions involving this radionuclide.

2.9.5. Patient organ dosimetry

(101) Dosimetry is performed to guide treatment in few centres. Methods based on calculations of the absorbed doses delivered to tumours and to normal liver (partition or multi-compartmental modelling) have been developed although there are as yet no published standard methodologies (Cremonesi et al., 2014) and gross assumptions are frequently made. For example, the dosimetry method developed for glass spheres is used to calculate the mean absorbed doses to the whole liver, inclusive of any tumour involvement. In recent years post-therapy imaging and dosimetry have been developed using the low positron emission from ^{90}Y which enables the use of PET (Willowson et al., 2015).

2.9.6. Risks to patients

(102) Microspheres are considered as medical devices and are not subject to active uptake in normal organs. Irradiation of normal liver parenchyma, either from localisation within the liver or from cross irradiation from localisation in liver tumours, is always a risk factor that must be considered as this may cause radiation hepatitis. Radiation induced liver disease has not as yet been clearly defined. There is evidence that an initial state of cirrhosis affects the tolerability to radioembolisation (Chiesa et al., 2011). Delivery of radiation to the pancreas will cause abdominal pain, acute pancreatitis or peptic ulceration. Lung shunting occurs when administered activity passes into the pulmonary circulation and may result in radiation pneumonitis. Inadvertent delivery to the gall bladder may result in cholecystitis. Shunting to lungs, the GI tract or pancreas will vary from one procedure to the next and absorbed dose limiting toxicity is therefore not possible to predict without pre-therapy biodistribution scanning. Treatment verification is essential following therapy administration as infusion locations may not be guaranteed and indeed may be modified from the pre-therapy work up. As with all therapy procedures, pregnancy/breastfeeding is a contraindication, and patients should avoid conception.

2.9.7. Recommendations

(103) The potential to induce severe toxicity or even to cause death, combined with the probability of undertreating many patients, necessitates the use of personalised dosimetry for treatment planning. The lack of certainty regarding the ability of the pre-therapy ^{99m}Tc-MAA imaging study to predict the absorbed dose distribution delivered at therapy, exacerbated by

the possibility of administering the therapy to a different location from that used for the tracer study, render post-treatment verification essential if the effect of treatment is to be understood.

2.10. Treatment of Arthritis (Radionuclide Synovectomy)

(104) The administration of radiopharmaceuticals for the treatment of rheumatoid or osteoarthritis has been used for over 40 years (Ansell et al., 1963) and has become well established and widely used. It is also used for treatment of haemophilic synovitis. This is considered to be a cost effective and well tolerated option with significant advantages over surgery and intra-articular administrations of steroids or chemical synovectomy.

(105) Following initial administrations with ^{198}Au, radionuclides with higher beta-particle energies and with longer path length are now commonly used, including ^{90}Y and ^{32}P colloid for larger joints such as the knee, ^{186}Re-colloid for smaller joints including elbows and ankle, and ^{169}Er-citrate for metatarsophalangeal joint (Knut, 2015).

2.10.1. Aim of treatment

(106) The aim of radiosynovectomy is to reduce swelling and to provide pain relief. Reduction of knee joint swelling has been seen in over 40% of patients and pain relief in 88%. Wrist, elbow, shoulder, ankle and hip joints have shown significant improvement and restoration of normal function and long-term pain relief has been achieved in about 70% of small finger joints. In haemophilic arthropathies complete cessation of bleeding has been seen in 60% of patients and improved mobility in 75% (Das, 2007).

2.10.2. Treatment protocols

(107) Radiopharmaceuticals for synovectomy can be administered at intervals, typically 3 months apart, following a successful first treatment. Repeated treatments are more effective than single treatments with higher activity. Current levels of activity administered have little evidence base and are derived empirically (Johnson et al., 1995).

2.10.3. Radiation dose to friends and family

(108) Dose to friends and family are not likely to be higher than those from standard diagnostic examinations.

2.10.4. Radiation dose to staff and carers

(109) Procedures are standardised as for diagnostic administrations, and sensible precautions must be undertaken, with the use of syringe shields where necessary. Exposures of radiopharmacists and nurses were found to be within acceptable limits, although for the therapists working in centres with high number of patients, the effective dose was reported to be 21 μSv for six treatments (Lancelot et al., 2008).

2.10.5. Patient dosimetry

(110) Uncertainties in absorbed dose calculations were addressed almost 40 years ago (Bowring and Keeling, 1978) when it was considered that the challenges of uptake and target

localisation, quantification of the activity and monitoring the retention were scientifically and logistically prohibitive. A comprehensive approach to dosimetry for radiosynovectomy ideally requires a Monte Carlo approach which enables the production of depth dose profiles for any given radionuclide (Johnson et al., 1995).

2.10.6. Risks to patients

(111) The limited range of intra-articular injected radionuclides, while *in situ*, ensures little irradiation of adjacent tissues. Reported side effects are rare and are generally related to the administration procedure (comprising joint inflammation and skin necrosis from extra articular administrations). The radiation exposure of the whole body of patients is very low because the limited range of the beta emissions (10 mm for ^{90}Y and up to 1 mm for ^{169}Er). No genotoxic effects were found in peripheral blood following administration of ^{90}Y-citrate in children with haemophilic synovitis (Klett et al., 1999; Turkmen et al., 2007). Absorbed doses delivered to lymph nodes, liver, spleen and whole-body have been calculated as 619 (154-1644) mGy, 62 (15-165) mGy, 62 (15-165) mGy and 37 (9-99) mGy, and leakage rates from sequential imaging are reported to be > 2 % (Klett et al., 1999). In cases of 48 h immobilisation after therapy, the leakage rate of radio-colloids is > 2 % (Klett et al., 1999). A large Canadian study of patients receiving radiosynovectomy with ^{90}Y, no increase in the incidence of cancer was observed in a study of 2412 adult patients with a variety of underlying conditions although the study concluded that further investigation was needed for procedures for younger patients (Infante-Rivard et al., 2012). As with all therapy procedures, pregnancy/breastfeeding is a contraindication, and patients should avoid conception.

2.10.7. Recommendations

(112) Leakage of particulates has been demonstrated to be low in animal models with sequential gamma camera imaging and is expected to be low in humans (Noble et al., 1983). However, studies are needed to confirm the assumption.

3. BIOKINETIC DATA COLLECTION

- **In radiopharmaceutical therapy, the absorbed dose delivered to an organ or tissue is governed by the radiopharmaceutical uptake into and clearance from the source organ and surrounding organs, combined with the radionuclide physical half-life. Biokinetic data can be collected using techniques that vary in complexity. These should be chosen with regard to the accuracy required for the particular task.**
- **Acquisition should follow protocols (or Standard Operating Procedures) to assure consistency and allow for comparisons.**

3.1. Whole-body Activity

(113) Although radionuclides for therapy need to have short range emissions to focus dose delivery within target tissues, whole-body monitoring of organ/tissue uptake and retention rely on the radionuclide also having penetrating photon emissions. For radionuclides having penetrating photon or bremstrahlung emissions, the activity in the whole-body can be measured most easily and accurately with a detector at a distance larger than 2 m. The first data point is taken before the patient micturates so that this value can be used for normalizing the data set to 100%. All subsequent measurements must be performed in the same geometry. This procedure is correct only if the sensitivity of the probe is independent of the distribution of activity in the patient. This is normally the case, if the photons scattered by the patient are eliminated by spectroscopic measurements including only the photo-peak of the radionuclide in question (Lassmann et al., 2008).

(114) The determination of activity of the whole-body can alternatively be performed by repeated whole-body scans with a gamma camera. Post-therapeutically it has to be ascertained that the dead time correction of the camera is set up properly (Delpon et al., 2002; Hänscheid et al., 2006; Lassmann et al., 2008).

3.2. Activity in the Blood

(115) This method is typically applied for determining the absorbed dose to the blood (Lassmann et al., 2008; Hänscheid et al., 2009) or to the bone marrow (Hindorf et al., 2010). The kinetics of activity in blood is typically measured by serial sampling of heparinised blood and subsequent measurement in a calibrated well counter. In particular, dependent on the biokinetics of the compound considered, at least one blood sample needs to be withdrawn at a later stage (> 96 h) (Lassmann et al., 2008).

3.3. Organ and Tumour Activity

3.3.1. Quantitative imaging

(116) Quantitatively accurate imaging is required for treatment planning and evaluation of radiopharmaceutical therapy. Over the past years there has been a great deal of progress in

the development of methods for accurately quantifying nuclear medicine images. However, propagation of these methods into clinics has been slow.

(117) Achieving quantification requires appropriate equipment, software and human resources. The level of these requirements depends on the imaging task. For example, quantifying activity in a tumour in the lungs requires more sophisticated resources than quantifying whole-body activity. However, detailed knowledge about the requisite levels of resources is not widely available or appreciated.

(118) While, in general, multiple use of sophisticated imaging devices provide for better determination of the biokinetics of a radiopharmaceutical, this benefit must be weighed against what is practically achievable. On the one hand, a few probe measurements could provide valuable insights into whole-body retention in the individual patient. On the other hand, multiple SPECT/CT or PET/CT sessions might be needed for initial evaluation of efficiency and toxicity of novel therapeutic radiopharmaceuticals.

(119) The type and number of imaging sessions needed for a particular patient undergoing radiopharmaceutical treatment must thus be optimised. Consideration should include what personnel and equipment are available; the financial and logistical hurdles for using them; the expected accuracy of the quantification; any radiation protection concerns involved in the imaging sessions; and any possible patient discomfort.

(120) This section provides a brief overview of the technology involved in quantitatively accurate imaging. More thorough descriptions such as the IAEA Human Health Reports No. 9 (Quantitative Nuclear Medicine: Concepts, Requirements and Methods) can be consulted for more details (IAEA, 2014b).

3.3.2. Planar imaging

(121) Today, planar imaging with a gamma camera for dosimetric purposes is useful for determining organ uptake and clearance biokinetics, and individual organ overlap must be accurately assessed, taking into account attenuation, scatter, and background correction (Siegel at al., 1999).

(122) Planar images are most commonly used with dual-head cameras (Siegel et al., 1999; Glatting et al., 2005). For opposite heads the pixel-wise geometric mean is a first-order approximation for the activity in the corresponding pixel (conjugate view method). The dependency of the measured count-rate I_{PQ} [counts s^{-1}] of the activity A_{PQ} [MBq] of a point source PQ is

$$I_{PQ} = C \cdot A_{PQ} \cdot e^{-\mu_e x} \tag{3.1}$$

where C is the calibration coefficient [counts MBq^{-1} s^{-1}] of the camera head, μ_e [1 cm^{-1}] is the effective linear attenuation coefficient and x [cm] the depth of the point source in the body. The geometric mean of the count rates G [counts s^{-1}] for two opposite camera heads and the thickness of the body D [cm] is calculated as

$$G = \sqrt{I_a \cdot I_p} = A_{PQ} \cdot C \cdot \sqrt{e^{-\mu_e x} \cdot e^{-\mu_e (D-x)}} = A_{PQ} \cdot C \cdot e^{-\mu_e D/2} \tag{3.2}$$

where I_a and I_p are the measured anterior and posterior count rates and $C = \sqrt{C_a \cdot C_p}$ the calibration factor for the geometric man of both camera heads. Solving eq. (3.2) for the unknown activity A_{PQ} results in

$$A_{PQ} = \frac{\sqrt{I_a \cdot I_p}}{C} e^{\mu_e D/2} \tag{3.3}$$

(123) Thus, the thickness of the investigated object or patient and linear attenuation coefficient are required for determining the activity of a point source when using two opposite camera heads. This equation is only valid if the sensitivity of the camera head is not dependent on the distance from the source. As this is only approximately true, the error can be more than 100%, depending on the nuclide, the energy window and the collimator in comparison to the mid-position of the point source (Glatting and Lassmann, 2007).

3.3.3. SPECT/CT

(124) The market share of SPECT/CT systems, i.e. gamma cameras, which are coupled with a CT for attenuation correction, has grown in recent years. Today, to measure activity in the accumulating organs and tumours using imaging techniques, quantification by means of SPECT/CT for at least one data point is state-of-the-art. Due to the inclusion of scattering and attenuation correction, accuracies of better than 10% are achievable in phantom measurements (Dewaraja et al., 2012, 2013).

(125) The calibration of imaging systems is essential for patient-specific dosimetry in nuclear medicine therapy. Unfortunately, there is no universal calibration standardisation method published for the gamma cameras and radionuclides used in radiopharmaceutical therapy today. In addition, large calibration sources for nuclides which either are used pre-therapeutically as a substitute for ^{90}Y (^{111}In) or therapeutically used nuclides are not available (^{131}I, ^{177}Lu). Therefore the calibration relies on ‘in-house’ produced calibration phantoms, which are filled with the appropriate radionuclide solutions.

(126) For the calibration and for determining the optimal parameters for quantifying SPECT/CT a large calibration source in air and in water filled with the radioactive substances in question should be scanned and reconstructed, to obtain the appropriate values. For the best quantification, the following conditions should be met (Dewaraja et al., 2012, 2013; Fernández et al, 2012; Zimmerman et al., 2016):

- A finer angular grid with reduced scanning times is better than a course grid (Dewaraja et al., 2012).
- MIRD Pamphlet 26 (Ljungberg et al., 2016) states that iterative methods require a certain number of updates before reaching an acceptable image quality. MIRD Pamphlet 23 (Dewaraja et al., 2012) defines the convergence as when the 90% recovery has been reached, this is a level of ‘high reconstruction accuracy’. A general ‘rule-of-thumb’ is that more complex reconstruction problems (where more corrections are included in the algorithm) require a larger number of iterations to reach convergence. It is important to investigate this dependency and optimise reconstruction parameters using data from phantom studies and simulations but also sample patient data with representative activity distributions and counting statistics. Due to the limited spatial resolution of SPECT/CT it is advisable when using the CT volume or a fixed threshold for volume-of-interest

drawing to implement corrections for the partial-volume effect. For an empirical correction of the spill-out of the counts the volume-of-interest may be increased to account for the spatial resolution of the SPECT/CT system in comparison to the volume measured by CT.

- For ^{111}In and ^{177}Lu there is no difference in accuracy whether one or two photopeaks are chosen, provided that the energy windows for the photopeak and the adjacent scatter windows are chosen correctly. For ^{177}Lu, however, care has to be taken that, for an incorrect window setting of the scatter window for the 113 keV peak, the quantification might show a larger error than 10% (Ljungberg et al., 2016).

(127) In principle, the required organ volumes can be obtained from tomographic emission measurements. The accuracy of these methods, however, especially in smaller structures, is limited due to their relatively poor spatial resolution. In addition, motion artefacts can mask the true organ volume. Therefore, it seems useful to use high-resolution anatomical procedures such as CT scans or MRI for the determination of volumes.

3.3.4. PET/CT

(128) The role of PET/CT for therapeutic radiopharmaceuticals has mostly focused on using positron-emitting surrogates of the therapeutic radionuclides, such as ^{124}I for ^{131}I, and ^{86}Y for ^{90}Y treatments.

(129) The possibility of quantitative PET/CT imaging of ^{90}Y has, however, been demonstrated for SIRT (Carlier et al., 2015). A multicentre comparison of quantitative ^{90}Y PET/CT for dosimetric purposes after radioembolisation with resin microspheres showed that the current generation time-of-flight scanners can consistently reconstruct ^{90}Y activity concentrations, but they underestimate activity concentrations in small structures (≤37 mm diameter) within a warm background due to partial volume effects and constraints of the reconstruction algorithm (Willowson et al., 2015).

3.4. Quantitative Protocols

3.4.1. Quantitative Imaging Protocols

(130) Protocols (or Standard Operating Procedures) ensure consistency of data acquisition and processing. A protocol (or a set of protocols) should describe all the steps required to obtain satisfactory clinical data and measurements from them. A protocol should be written for any quantitative imaging task.

(131) The expertise required for designing protocols differs from that required to implement them and different personnel may be required. Typically, the protocol could be written by a trained medical physicist and the medical staff, while technologists can be trained to execute protocols.

(132) Quality assurance and quality control tasks (QA/QC) should be performed at a specified frequency to ensure that the equipment is operating as intended. The schedule for QA/QC procedures should be specified in the protocol. QA/QC results should be systematically provided along with all the data related to the protocol.

3.4.2. Pharmacokinetics and the Integration of the Time-activity-curve

(133) The choice of acquisition times for determining the uptake and retention of activity in an organ or structure of interest determines the reliability of the assessment of the number of decays in this organ/structure (Glatting and Lassmann, 2007). This value is calculated by integrating the respective time-activity curves. According to the MIRD Pamphlet 21 nomenclatures (Bolch et al., 2009) this quantity is called time-integrated activity in the source region (old term: 'cumulated activity'). The number of data points needed depends upon the biokinetics in the respective organ/tissue. As a rule of thumb, one needs at least three measurements for correctly fitting each of the exponential functions required for describing the biokinetics (Siegel et al., 1999). The determination of the number of exponential functions for an adequate description of the biokinetics is not trivial, as, in principle, for an exact representation an infinite number of functions are necessary. The number of functions used in reality depends strongly on the tolerated errors of the fitting process.

(134) For the integration of the time activity curves and calculation of the time-integrated activity coefficient, a software solution presented by Kletting et al. (2013) offers a range of possible functions by means of statistical criteria.

(135) As the number of scans in patients is limited MIRD Pamphlet 16 (Siegel et al., 1999) recommends five measurements at $T_e/3$, $2T_e/3$, $3T_e/2$, $3T_e$, $5T_e$; T_e, is the effective half-life in the organ/structure considered. However, in practice, the choice will depend also on the availability of the equipment and the clinical condition of the patient.

4. METHODS FOR ABSORBED DOSE CALCULATIONS

- **The use of radiopharmaceuticals for cancer treatment requires detailed, patient-specific dosimetry and dose planning for assesments of absorbed dose to both normal tissues and tumours based on the quantitative measurements of organ activity over time, and organ mass.**

(136) The use of radiopharmaceuticals for cancer treatment requires detailed, patient-specific dosimetry for assessments of absorbed dose to normal tissues and to tumour tissues. In therapy treatment planning, the calculation of radiation absorbed dose to internal organs, tissues, and the whole-body, is a fundamentally important aspect of successfully achieving clinical objectives. Since radiopharmaceuticals are usually administered systemically or orally, radionuclide therapy necessarily involves delivery of some radiation energy to normal organs and tissues. The amount of activity administered should be great enough to effectively treat the neoplasm while minimizing radiation dose to normal tissues. Therefore, the activity that may be safely administered can be determined by assessing the maximum absorbed doses to the most important, toxicity-limiting normal tissues.

(137) Quantitative measurements of organ activity over time, and organ mass, are essential to calculate absorbed doses. In radiopharmaceutical therapy treatment planning and for patient safety, it is usually more important to accurately assess normal organ dose than to assess tumour dose. The ratio of the target region (or tumour) dose to the limiting normal organ dose, or D_{tumour}/D_{normal}, is the therapeutic index. Therapeutic index provides an estimate of therapeutic efficacy and safety.

4.1. Purpose for Absorbed Dose Calculations

(138) Absorbed dose calculations are performed prior to therapy on the basis of measurements made following a trace-labelled diagnostic infusion, or post-therapy on the basis of measurements following a therapy infusion. Internal radiation dosimetry serves several fundamental purposes in radiopharmaceutical therapy and radiation protection, including:

- To evaluate the safety and efficacy of a therapeutic agent;
- To provide an information source for discussing anticipated radiation doses with patients:
- To plan an appropriate treatment for radiopharmaceutical therapy;
- To predict short-term and long-term radiation effects or dose-related biological endpoints associated with radiotherapy, and to correlate biological effects with radiation dose;
- To provide a required list of estimated radiation doses to internal organs from radiopharmaceuticals;
- To fulfil legal obligations and demonstrate regulatory compliance;
- To serve as a component of complete patient medical records.

4.2. Data for Absorbed Dose Calculations

(139) In radiopharmaceutical therapy, the time of intake and the amount of activity administered represent known or established quantities, determined by prescription, based on

prior estimates of the radiation dose that will be needed to achieve beneficial therapy outcomes.

(140) The major challenge in radiation dose assessment is to assess accurately the time-course of retention of radionuclide in organs and tumour tissue. The pharmacokinetic behaviour of radiolabelled drug products is analysed and determined by direct measurements (nuclear medicine imaging), direct bioassay (blood and excreta counting), and/or tissue biopsy counting (see Chapter 3). Direct measurements may be supplemented by pharmacokinetic modelling using population parametric values. For therapy treatment planning or post-infusion follow-up, individual patient measurements are more reliable than estimates based on population biokinetic models. Since the biodistribution and metabolic behaviour of radiopharmaceuticals usually vary from one patient to another, patient-specific measurements are needed to determine patient-specific biokinetic parameters.

(141) Direct measurements of organ or tissue radioactivity must account for the geometry and density of the source organ or tissue, organ size and mass, potential overlap, thickness of tissue between the organ and the detector, and the spatial distribution of activity within a tissue. Measurements are corrected for body and detector background, detector dead time, and photon attenuation and scatter that may influence the accuracy of direct counting.

(142) For any radionuclide, the information needed to calculate absorbed dose includes: the total activity administered to the patient and time of infusion, the fraction of the administered activity that is taken up by each major source organ or tissue, and the time-dependent retention and clearance of activity in each major source organ through complete radiological decay.

(143) In the medical setting, measurements of organ activity may be made using calibrated nuclear medicine systems; these include planar gamma camera (anterior/posterior) imaging, single-photon emission computed tomography (SPECT) imaging, positron emission tomography (PET), and single crystal (sodium iodide or other scintillator) photon detectors. The patient is placed within the field of view for quantitative imaging over thoracic or abdominal regions; alternatively, the patient may receive a whole-body scan for region-of-interest measurements. The imaging procedure is repeated at pre-determined time points following a base-line (pre-injection) count and a post-injection image immediately after radiopharmaceutical infusion (near time zero). Markers are used to correctly position the patient for repetitive measurements. The technician selects regions of interest by outlining the major organs or tissue regions. In addition to all regions of interest, it is important to measure whole-body radioactivity over time.

(144) Instrument counts in selected regions of interest are converted to units of activity (Bq) using radionuclide standards, patient-thickness measurements, background subtraction, attenuation correction, and scatter correction techniques. Such instrument counts require availability of photon emissions for quantitative counting. When it is not possible to determine precise activity concentrations in organs and tissues with time, estimates may be made using biokinetic or pharmacokinetic modelling. The quality of the assessment depends on the validity of the model parameters assumed. Modelling can provide important information where data are lacking, but the models are rarely patient-specific, and potential errors that are introduced must be taken into account.

4.3. Absorbed Dose

(145) Absorbed dose is the fundamental radiation quantity that describes energy deposition by ionising radiation in an absorbing medium (ICRU, 2016); absorbed dose applies to all radiation exposures, all types of ionising radiation, any absorbing medium, and all biological targets and geometries. Calculation of absorbed dose from intake of radionuclides requires information about the amount of radioactivity present over time periods through complete decay, the mass and geometry of the target tissue, and all physical factors governing energy deposition after radionuclide decay (ICRP, 2015a, 2015b).

(146) In radiopharmaceutical therapy, the time of intake and the amount of activity administered represent known or established quantities. The amounts of radioactivity present in organs and tissues after administration may be determined by direct quantitative imaging or by sample measurement and pharmacokinetic modelling. Methods that have been developed for medical internal radiation dosimetry greatly simplify the dose-assessment task without compromising on essential details. Nuclear medicine imaging, image rendering, and computational capabilities are evolving to meet the needs for accurate and reliable internal dosimetry. Current methods extend from the whole-organ to the cellular and multi-cellular levels, and may be applied to either uniform or non-uniform radionuclide distributions within organs and tissues. Patient-specific methods are preferred over generic model assumptions.

(147) For radionuclide therapy, the relevant dosimetric quantity associated with immediate deterministic effects in radiopharmaceutical therapy is the absorbed dose, in units of J kg^{-1}. The absorbed dose, D, to an organ or tissue is the energy imparted, ε, per unit mass of tissue, m, from all ionising radiation components that contribute energy to the target tissue mass.

$$D = \varepsilon/m \qquad \text{Gy (J kg}^{-1}\text{)} \tag{4.1}$$

(148) When applied to radionuclides administered to a living biological system, where the source region is the same as the target region, the general absorbed dose equation includes a biological retention function to account for radionuclide metabolism and clearance, as well as the fraction of energy that is captured or absorbed in the target region.

$$D = \left(\frac{AEY\phi}{m}\right)\int_0^t B(t)\,dt \quad \text{Gy (J kg}^{-1}\text{)} \tag{4.2}$$

where D is the mean absorbed dose, A is the activity of the radionuclide (Bq), EY is the total energy emitted (joule) by activity in the organ or tissue (product of the particle energy and yield), ϕ is the fraction of that energy that is absorbed, m is the mass of the target region (kg), and $\int_0^t B(t)\,dt$ is the biological retention of the activity integrated from time t = 0 (injection) through complete decay (t = ∞), or for any specific time period, t (seconds or hours). The mass of the target organ should be determined from medical imaging; but standard model values for organ mass may be used if precise data are not available. Equation (4.2) rearranged is:

$$D = A\int_0^t B(t)\,dt\left(\frac{EY\phi}{m}\right) \quad \text{Gy (J kg}^{-1}\text{)} \tag{4.3}$$

(149) The patient comprises multiple source and target organs or tissues. The radiation absorbed dose to any organ or tissue includes all energy deposition event contributions from (a) radioactivity contained within the organ (the self-organ dose), and from (b) all energy depositions originating from radioactivity contained in all other organs and tissues of the whole body (the cross-organ dose). The mean absorbed dose is calculated by accounting for the physical half-life, biological retention, all radioactive emissions by a given radionuclide, and the individual absorbed fractions for all radioactive emissions from that radionuclide for any specified source-target geometry in the human body. The complex geometries represented by the human body for any age, sex, height, weight, variations in organ size, and differences in tissue density (skeleton, soft tissue, lungs), taken together, present formidable challenges for a comprehensive calculation that can account for all important determinants of ε/m for any specified target region. The dose calculation must account for differences in radionuclide biokinetics (uptake, retention, and clearance) unique to each organ or tissue for the radiopharmaceutical of interest, together with factors that may determine unique metabolic rates and health status of individual patients and which render differences in pharmacokinetics from one patient to another.

(150) The medical internal radiation dose (MIRD) schema (Loevinger and Berman, 1968) was developed to account for all physical, biological, and geometric factors for all energy contributions to absorbed dose for any target tissue from radionuclides in multiple source organs and remainder tissues. Since 1968, the MIRD schema has evolved to accommodate modern anatomical views by CT or MRI, voxel-level activity distributions, Monte-Carlo energy transport codes, pharmacokinetic compartment models, and radiobiological response parameters.

(151) After administration of a radiopharmaceutical via intravenous injection, the drug product redistributes quickly throughout the organs and tissues of the body, and all organs and tissues receive some amount of radiation dose. However, by definition in the MIRD schema, the source organ or region, r_S, is defined as any tissue mass, organ, tumour, or the whole body for which data are available to determine a time-activity curve. The target organ or region r_T, is defined as any organ or tissue for which an absorbed dose can be calculated.

(152) Using the updated MIRD/ICRP formalism and nomenclature (Bolch et al., 2009; ICRP, 2015b), the mean absorbed dose $D(r_T, \tau)$ to a target tissue r_T over a defined dose-integration period τ (infinity for short-lived radionuclides) following administration of a radioactive material to the medical patient is:

$$D(r_T, \tau) = \sum_{r_S} \int_0^{\tau} A(r_S, t)\, S(r_T \leftarrow r_S, t)\, dt \quad \text{Gy (J kg}^{-1}\text{)} \qquad (4.4)$$

where the quantity $S(r_T \leftarrow r_S, t)$ is the radionuclide-specific quantity representing the mean absorbed dose rate to target region r_T at time t after administration, per activity present in source region r_S (Snyder et al., 1969; Bolch et al., 2009). For a specific radionuclide and for a well-defined geometry representing the source-target pair,

$$S(r_T \leftarrow r_S, t) = \frac{1}{m(r_T,t)} \sum_i E_i Y_i\, \phi(r_T \leftarrow r_S, E_i, t) = \frac{1}{m(r_T,t)} \sum_i \Delta_i \phi(r_T \leftarrow r_S, E_i, t) \qquad (4.5)$$

where E_i and Y_i are the energy and yield (number per nuclear transition), respectively, of each radiation particle or photon i emitted by the radionuclide; Δ_i is their product (or mean energy emitted per nuclear transition); and the quantity $\phi(r_T \leftarrow r_S, E_i, t)$ is the absorbed fraction of

radiation energy E_i emitted by the source region r_S at time t that is absorbed in the target tissue r_T.

(153) If the quantity $A(r_s, t)$ is normalised to a unit administered activity A_0 and is designated as the quantity $a(r_s, t)$, then the absorbed dose coefficient $d(r_T, \tau)$ in target tissue r_T is (Bolch et al., 2009):

$$d(r_T, \tau) = \sum_{r_S} \int_0^{\tau} a(r_s, t)\, S(r_T \leftarrow r_S, t)\, dt \quad \text{Gy Bq}^{-1} \tag{4.6}$$

where $a(r_s, t) = A(r_s, t)/A_0$ is the fraction of the administered radioactivity remaining in the source tissue r_S at any time t post-infusion. The fraction $a(r_s, t)$ is the quantity that is measured for radiation dosimetry in the patient by region-of-interest quantitative imaging using clinical nuclear medicine instruments.

(154) Equation (4.4) may be simplified, when time dependence of S is neglected, using the time-independent expression:

$$D(r_T, \tau) = \sum_{r_S} \tilde{A}(r_s, \tau)\, S(r_T \leftarrow r_S) \text{ Gy} \tag{4.7}$$

where the quantity $\tilde{A}(r_s, \tau)$ represents the time-integrated activity (or total number of nuclear decay transitions) in source region r_s for the dose-integration period τ, and where:

$$\tilde{A}(r_s, \tau) = \int_0^{\tau} A(r_s, t)\, dt \quad \text{Bq s} \tag{4.8}$$

(155) Fully implemented, the MIRD/ICRP formalism represented by equation (4.7) accounts for all source regions, all target organs, respectively all source-target geometries, and all radioactive emissions contributing to absorbed dose. Tabulated values of S have been published to simplify internal dose calculations for simple source-target geometries. For all other cases, the specific absorbed fractions for a radionuclide and computational phantom-model must be calculated individually using a Monte Carlo nuclear transport code that accounts for geometry, tissue compositions, and absorber densities. Dosimetry calculations may be performed with a number of commercially available software packages or software developed in-house (Guy et al., 2003; McKay, 2003; Glatting et al., 2005; Stabin et al., 2005). Software used for calculation of organ doses and effective doses by ICRP is available (Andersson et al., 2014; ICRP, 2015a; www.idac-dose.org).

4.4. Time-integrated Activity Coefficient in a Source Region

(156) The time-integrated activity coefficient $\tilde{a}(r_s, \tau)$ is the area under the time-activity curve representing the integral quantity $\int_0^{\tau} a(r_s, t)\, dt$ in equation (4.6). This quantity was previously known as the residence time in earlier MIRD publications; it is equal to the ratio of the time-integrated activity and the total administered activity, A_0:

$$\tilde{a}(r_s, \tau) = \int_0^{\tau} a(r_s, t)\, dt = \tilde{A}(r_s, \tau) / A_0 \quad \text{Bq s Bq}^{-1}\text{, or s} \tag{4.9}$$

(157) The time-integrated activity coefficient is a common input value for software programmes that implement the MIRD/ICRP schema for absorbed dose calculations. The time-integrated activity coefficient for a source region may be determined by plotting the

fraction of administered activity in that source region over time and evaluating the area under the curve. Several measurement data points, depending on the form of the mathematical function, are needed to establish a time-activity curve best represented by the plotted data (Siegel et al., 1999).

(158) The counts obtained in an organ or tissue region of interest must be converted to units of radioactivity using appropriate measurement methods and calibration standards, including: daily quality assurance, patient positioning, patient-thickness measurements, background subtraction, attenuation correction, and scatter correction. In planar imaging, the geometric mean of counts obtained from anterior and posterior views is determined. The fraction of administered activity measured in the source region may be plotted as a function of time post-infusion. A mathematical function or time-activity curve should then be fitted to the plotted data using linear least-squares regression analysis. Physical decay is exponential, and biological uptake and clearance usually follow exponential patterns; therefore, an exponential function with one or more terms is usually an appropriate function to represent the plotted data. The fitted function is integrated numerically or analytically to yield the time-integrated activity coefficient.

(159) Alternatively, the time-integrated activity coefficient for a source region may be calculated using dynamic modelling if the pharmacokinetic parameters associated with model compartments (source regions) and their associated transfer coefficients are known or can be determined iteratively. When combined with dosimetry subroutines, and following the general MIRD/ICRP schema, biokinetic models may also be used to calculate radiation absorbed doses to target regions directly.

4.5. Uncertainties in Absorbed Dose Calculations

(160) Uncertainty analyses provides information about the sources of bias (accuracy) and random variation (precision), respectively, and their magnitudes, that show the reliability and quality of absorbed dose calculations. Internal dose calculations involve many different measurements, complex anatomical geometries, and highly variable biological factors when applied to administered radiopharmaceuticals. Uncertainty propagation is therefore challenging and perhaps intractable when all details of measurements and sources of modelling errors must be accounted for. Nonetheless, the major sources of uncertainty should be recognised, acknowledged, and minimised as much as possible, to improve confidence in the estimated absorbed dose.

(161) The total uncertainty in an estimate of the mean absorbed dose to an organ or tissue from a therapeutic radiopharmaceutical administered to a patient reflects different sources of uncertainty: (a) measurement uncertainties associated with quantitative imaging methods used to determine absolute activities in major source regions, (b) uncertainties in estimating integrated activity in organs/tissues and (c) the application of mathematical phantoms or standard reference models used to represent the anatomical organ geometries of live subjects.

(162) With modern activity measurement instruments (“dose calibrators”), administered activities may be known to accuracies within a few percent. Differences between planned and actual administered activity are only minor contributors to the total uncertainty if regular quality control is performed (IAEA, 2006a). Uncertainties associated with variances in assumed mass of the target organ may be minimised with use of patient CT and 3-dimensional volumetric reconstructions.

(163) Variations in estimated time-integrated activities for major source organs arise from inherent difficulties in measuring and quantifying organ uptake, retention, and redistribution of the radiopharmaceutical in tissues (Norrgren et al., 2003; Jönsson et al., 2005). Uncertainties associated with the shape of the time-activity curve may be minimised by obtaining sufficient data points to establish the time-activity function and optimise statistical fitting to the data. The most important data points are the initial organ uptake near time zero after administration or completion of the infusion, and the last time point that weighs heavily toward helping one to determine the slope of the long-term retention. Typically, a minimum of four or five data points are needed at properly spaced collection times to minimise uncertainty associated with area-under-curve analyses.

(164) Variations in estimates of photon cross-organ contributions to a source region dose, dependent on assumed distances between the source and target organs, contribute to uncertainties in tabulated *S* values. Physical data, such as the radionuclide emission energies and yields applicable to absorbed fraction calculations for target organs are well characterised and do not contribute significantly to overall uncertainty.

(165) Experimental measurement validation of calculated absorbed doses using reference anthropomorphic phantoms and mathematical models have indicated agreement within 20 to 60%, depending on the degree to which subjects compare with the body size and shape assumed in the calculations (Roedler, 1980).

4.6. Biologically Effective Dose (BED)

(166) When an absorbed dose is delivered by low-LET radiation at a low absorbed-dose rate, the radiobiological effects are known to decrease as compared to those obtained for the same absorbed dose delivered with a high dose rate. The decrease is associated with repair of DNA damage during irradiation, and depends on the tissue repair capacity and the rate of repair in relation to the time of radiation delivery. There are also other time-dependent factors that may modify the cellular response, such as proliferation (repopulation), redistribution in the cell cycle, and reoxygenation (Joiner and van der Kogel, 2015).

(167) In radiopharmaceuticl therapy the absorbed-dose rate in an organ or tissue is governed by the radiopharmaceutical uptake and retention in the organ itself and surrounding organs, combined with the radionuclide physical half-life. The radiation delivery can extend over long times (days or even weeks) (Gleisner at al., 2015), the absorbed-dose rate varies over time, and the mean absorbed-dose rate is considerably lower than in most other forms of radiotherapy. There are also spatial heterogeneities, governed mainly by the molecular mechanisms for radiopharmaceutical accumulation and the range of the particles that are emitted at radioactive decay.

(168) Applications of the linear-quadratic (LQ) radiobiological model were early described for radiopharmaceutical therapy (Millar, 1991; Howell et al., 1994; Dale, 1996) to estimate the fraction of cell surviving the irradiation, *SF*, as

$$SF = \mathrm{e}^{-(\alpha D + G(T)\,\beta D^2)} \qquad (4.10)$$

(169) where *D* is the absorbed dose delivered from the start of irradiation until time *T*, and α and β are radiobiological parameters that characterise the shape of the cell survival curve. The first term in the exponent, linear in *D*, dominates the cell-survival curve at low absorbed doses and has been interpreted to be associated with lethal DNA damage induced by single-

particle tracks (Dale, 1996). The second, quadratic, term describes the increasingly downward curvature for *SF* at higher absorbed doses and has been interpreted as effects from pairwise interaction of sub-lethal lesions induced by two particle tracks. The function G, called the Lea-Catcheside factor, acts as a damping of the second term, and is deduced from the perspective that there is a probability that the first sub-lethal DNA lesion is repaired before the second is induced. *G* is formally defined as (Lea and Catcheside, 1942; Kellerer and Rossi, 1974).

$$G(T) = \frac{2}{D^2}\int_0^T R(t)\left[\int_0^t R(w)\varphi(t-w)\mathrm{d}w\right]\mathrm{d}t \qquad (4.11)$$

where $R(t)$ is the absorbed-dose rate as function of time. The function $\varphi(t)$ describes the loss of sub-lethal lesions due to repair and is often assumed to be a single-phase process with a repair half time, T_{rep}, and rate constant $\mu = \ln(2) / T_{\mathrm{rep}}$, such that

$$\varphi(t) = \mathrm{e}^{-\mu t} \qquad (4.12)$$

although multi-phase repair processes have also been reported (Joiner and van der Kogel, 2009). The function *G(T)* takes values between zero and one depending on the rate of repair in relation to the rate of cell-lesion induction, in turn proportional to the absorbed-dose rate.

(170) For most radionuclide therapies, irradiation continues until the radionuclide has decayed or has been excreted. For an absorbed-dose rate function described by an effective decay constant, λ, combined with equation (4.12) and integration in equation (4.11) to infinity, *G(T)* takes the form

$$\lim_{T\to\infty} G(T) = \frac{\lambda}{\lambda+\mu} \qquad (4.13)$$

Analytic solution of equation (4.11) for more complicated absorbed-dose rate patterns or repair functions can become quite cumbersome. It was noted that the integral within brackets in equation (4.10) can be described as a convolution (Gustafsson et al., 2013a). This formulation allows for numerical implementation, which opens for application of more complex absorbed-dose rate functions and repair functions other than mono-exponential functions (Gustafsson et al., 2013b).

(171) The biologically effective dose (BED) is a concept within the framework of the LQ model (Barendsen, 1982; Fowler, 1989; Dale, 1996; Joiner and van der Kogel, 2009). It relies on the idea of equieffective treatments, i.e. treatments that produce the same probability of inducing a specific clinical (biological) endpoint (Bentzen et al., 2012). The main use of BED is in external-beam radiotherapy and brachytherapy where it is a clinically accepted method for conversion between different fractionation schemes and absorbed-dose rate patterns. In radiopharmaceutical therapy its usefulness for describing clinically observed effects has been demonstrated (Barone et al., 2005; Wessels et al., 2008; Strigari et al., 2010). Barone et al. (2005) found that kidney toxicity correlated better to BED than to absorbed dose, and in MIRD Pamphlet No. 20 (Wessels et al, 2008) these and other data were combined to find that the relationship between BED and the incidence of renal complications was comparable to that obtained for external-beam radiotherapy. Strigari et al. (2010) described a relationship between BED and the normal tissue complication probability of liver.

(172) For organs and tissue, the biologic effect is described in a functional form that is equivalent to the logarithm of the cell killing in equation (4.10), i.e. – ln(*S*). The BED is then calculated according to

$$BED = D + \frac{G(T)}{\alpha/\beta} D^2 = D\left(1 + \frac{G(T)\cdot D}{\alpha/\beta}\right) = D \cdot RE \qquad (4.14)$$

where the α/β value is characteristic for the organ or tissue and the endpoint, i.e. an observed effect. The formulation of BED as the product of *D* and the relative effectiveness, *RE*, has been given by Barendsen (1982) and Dale (1996). In this notation *RE* is the ratio of absorbed doses required to yield a given equieffect, where the BED is the absorbed dose when given at infinitesimally small fraction doses or infinitesimally low dose rate. The BED is higher or equal to *D*, so *RE* is larger than, or equal to unity.

(173) Figure 4.1 shows the value of *RE* for selected values of the different parameters in equations (4.14) and (4.13). For short effective half-lives, *G* approaches unity and *RE* goes towards a value valid for an instant delivery of the absorbed dose. For long effective half-lives, *G* becomes small and *RE* approaches unity. Changes in *D* or α/β both result in variations of *RE* along the vertical axis, whereas changes in the repair half-life induce shifts along the horizontal direction.

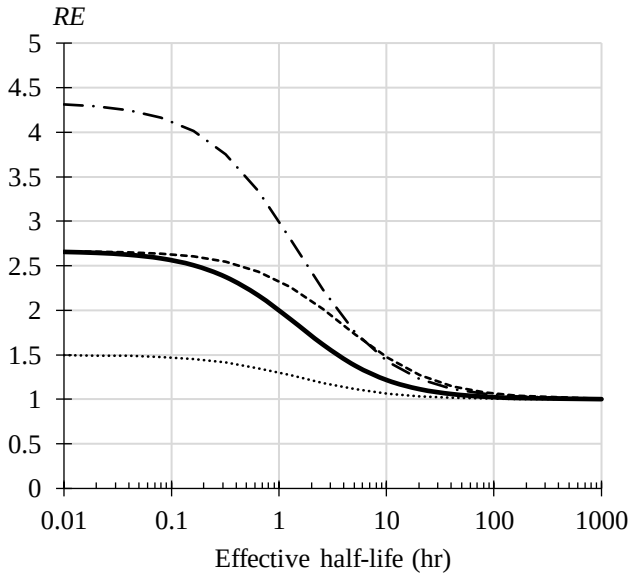

Fig. 4.1. The relative effectiveness, *RE*, obtained from equations (4.14) and (4.13). As baseline values, shown by the solid line, parameters used are D=5 Gy, α/β=3 Gy, and T_{rep} = 1.5 h. The dash-dotted line is obtained when the absorbed dose is changed to 10 Gy, and dotted line when α/β is changed to 10 Gy. The dashed line is obtained when the repair half-life is changed to 4 hr.

5. SPECIFIC RADIATION PROTECTION ISSUES

- **The need for guidance on radiation protection for people at risk of exposure include hospital staff, members of the patient's family including children, and carers, neighbours, visitors to the household, co-workers, those encountered in public places, on public transport or at public events, and the general public. These risks can be effectively managed and mitigated with well-trained staff, appropriate facilities, and the use of patient-specific radiation safety precaution instructions.**
- **Special consideration should be given to pregnant women exposed to ionising radiation. Pregnancy is a contraindication to radiopharmaceutical therapy, unless the therapy is life-saving. Breastfeeding should be discontinued in radiopharmaceutical therapy patients.**
- **Accident prevention in radiation therapy should be an integral part of the design of facilities, equipment, and administration procedures.**
- **Optimisation of staff exposures include consideration of education and training, equipment design, proper shielding and handling of sources, personal protective equipment and tools as well as awareness and engagement in radiation protection.**
- **Individual monitoring of the whole body and extremities must be considered for staff during the management of radiopharmaceutical therapy patients and in the preparation and administration of radiopharmaceuticals.**
- **Radiation sources used in radiopharmaceutical therapy can contribute significant doses to medical personnel and others who may spend time within or adjacent to rooms that contain such sources. Meaningful dose reduction and contamination control can be achieved through the use of appropriate procedures, and facility and room design, including shielding where appropriate.**
- **Medical practitioners should provide all necessary medical care consistent with patient safety and appropriate medical management. Radiation protection considerations should not prevent or delay life-saving operations in the event that surgery is required. Staff should be informed when a patient may pose a radioactive hazard, and advice and training should be provided prior to administrations.**
- **The decision to hospitalise or release a patient after therapy should be made on an individual basis considering factors such as the residual activity in the patient, the patient's wishes, family considerations (particularly the presence of children), environmental factors, and existing guidance and regulations. Advice on specific radiation protection precautions should be provided to patients and carers.**

5.1. Introduction

(174) The use of radiation for radiopharmaceutical therapy is a planned exposure situation – it needs to be under regulatory control, with an appropriate authorisation in place from the regulatory body before operation can commence (ICRP, 2007a). Misadministration, spills and other such incidents or accidents can give rise to potential exposure, but these remain part of the planned exposure situation as their occurrence is considered in the granting of an authorisation (Carlsson and LeHeron, 2014). Each of the categories of exposure of individuals (medical, occupational, and public) need to be considered in radiopharmaceutical therapy. In addition, the three fundamental principles of radiological protection (justification,

optimisation, and limitation) (ICRP, 2007a) are applicable. In a nuclear medicine facility, occupational and public exposures are subject to all three principles, whereas medical exposure of patients is subject to the first two only (ICRP, 2007b).

(175) Implementation of radiological protection for radiopharmaceutical therapy is an essential part of the system for implementing quality medical practice in a facility. The most important aspect is to establish a safety culture among staff, such that protection and accident prevention are regarded as inherent to daily activities. Several guidelines for implementation of radiation protection in a nuclear medicine facility have been developed (IAEA, 2005a; 2005b, 2009, 2014; Sisson et al 2011) that address: programme elements, responsibilities, education and training, facility design, monitoring, waste, and health surveillance. These should be consulted as applicable in addition to the considerations given in subsequent sections of this publication.

5.2. Requirements for Radiopharmaceutical Therapy Treatment Rooms and Wards

(176) The following aims should be considered in the design of radiopharmaceutical therapy treatment rooms and wards: optimising protection to reduce the exposure to external radiation and contamination, maintaining low radiation background levels to avoid interference with imaging equipment, meeting pharmaceutical requirements, sequestering waste appropriately, and ensuring safety and security of sources (locks and controlled access).

(177) Typically, rooms for high-activity patients should have separate toilet and washing facilities. The design of safe and comfortable accommodation for visitors is important. Floors and other surfaces should be covered with smooth, continuous, non-absorbent, and non-porous surfaces that can be easily cleaned and decontaminated. The walls should be finished in a smooth and washable surface, for example, painted with washable, non-porous paint. Secure areas should be provided with bins for the temporary storage of linen and waste contaminated with radioactivity.

(178) Proper shielding and ventilation is required for storage of bulk radioiodine containers. Preparation of activity for administration of radioiodine should be performed in hoods with adequate airflow to protect staff and extraction systems capable of adsorbing contaminants prior to emission. Adequate containment and exhaust should be provided for the storage of radioiodine waste and articles with residual contamination.

(179) Radiopharmaceutical therapy patients in unshielded hospital rooms may expose persons in adjacent areas to levels of radiation that might cause dose constraints to be exceeded. Vacating adjacent rooms or areas or installing shielding (e.g. permanent poured concrete, solid concrete block, steel plates, lead sheets or portable shielding devices) may be necessary to ensure dose constraints are maintained in adjacent areas (Chu et al., 2016). Areas on floors immediately above and below such patient's rooms as well as on the same floor must be considered. Table 5.1 gives typical shielding effectiveness values for ^{131}I which requires the most intensive shielding. Exposure or dose rates should be measured after each radiopharmaceutical administration, or worst-case scenario evaluations documented to confirm that these are below levels that could cause a dose constraint to be exceeded.

Table 5.1. Typical shielding effectiveness values for ^{131}I.

	Half value layer	Tenth value layer
Lead (Delacroix et al, 2002)	3.0 mm	11 mm
Concrete (Schleien et al, 1998)	5.5 mm	18 mm

(180) A monitoring system should be established in facilities, considering protection of the public and staff. For permanent shielding evaluations, it is important to properly design structural shielding, considering anticipated dose rates in controlled and supervised areas (IAEA, 2006b). Dose rates in occupied areas adjacent to the radionuclide treatment room should be monitored and results recorded to ensure that dose constraints are not exceeded and protection is optimised.

(181) It is preferable that patient treatment rooms be for individual patients and adjacent to each other. If this is not possible, appropriate shielding is required between the treated patient and a neighbouring patient. When required, shielding should be provided for nurses and visitors of radiopharmaceutical therapy patients; movable shields may be used within patient rooms. When required, prior to each treatment, movable shields should be placed close to the patient's bed in such a way that exposure of the nurses caring for the patient is minimised. This is achieved by anticipating the nurse's tasks, positions and movements throughout the room.

5.3. Patients (Medical Exposure)

5.3.1. Justification and optimisation of protection

(182) In radiation therapy, the aim is to eradicate neoplastic (or otherwise diseased) target tissue or to palliate the patient's symptoms. Some deterministic damage (tissue reactions) to surrounding tissue and some risk of stochastic effects in exposed non-target tissues are inevitable, but the goal of all radiation therapy is to optimise the relationship between the probability of tumour control and normal tissue complications. If the dose to the target tissue is too low, the therapy will be ineffective and the exposures will not have been justified (ICRP, 2007b). However, the protection of tissues outside the target volume is an integral part of dose planning. Thus, the principle of optimisation of protection is applied to nuclear medicine therapy procedures that have been justified with an emphasis that the appropriate radiopharmaceutical and activity are selected, correctly calculated, measured and administered so that the activity is primarily localised in the organ(s) of interest, while the activity in the rest of the body is maintained ALARA (ICRP, 2001b).

5.3.2. Considerations prior to therapy

(183) A risk assessment must be performed prior to radiopharmaceutical therapy to ensure that the patient is self-caring, able to tolerate isolation (if appropriate), and able to comply with radiation precautions (when necessary).

5.3.3. Pregnancy

(184) Pregnancy is a contraindication to radiopharmceutical therapy, unless the therapy is life-saving. This advice is all the more valid for radioiodine therapy and for other radionuclides with the potential to accumulate in fetal tissues. Beyond 10-13 weeks of gestation, the foetal thyroid may receive extremely high doses in cases of therapy using ^{131}I-iodide (Watson et al., 1989; Berg et al., 1998; ICRP, 2008). The possibility of pregnancy should be carefully excluded before administration. Therefore, where treatment is likely or anticipated, the patient should also be advised to take appropriate contraceptive measures in the time prior to therapy.

(185) Before any procedure using ionising radiation, it is important to determine whether a female patient is pregnant with a blood pregnancy test performed before time (usually within 72 hours) of treatment in all women, from menarche to 2 years after menopause, who could become pregnant. There may be exceptions to the requirement for a pregnancy test, but there must be incontrovertible evidence that pregnancy is impossible, for example, surgical hysterectomy (Sisson et al, 2011).

(186) The feasibility and performance of medical exposures during pregnancy require specific consideration owing to the radiation sensitivity of the developing embryo/foetus (ICRP, 2001a, 2007a). The ICRP has given detailed guidance in *Publications 84* (ICRP, 2000) and *105* (ICRP, 2007b). Radiation risks after prenatal radiation exposure are discussed in detail in ICRP *Publication 90* (ICRP, 2003).

(187) A major problem occurs when a female, who is not thought to be pregnant, is treated for thyroid carcinoma and is found to be pregnant after the administration of radioiodine. If a patient is discovered to be pregnant shortly after a therapeutic radio-iodine administration, maternal hydration and frequent voiding should be encouraged to help eliminate maternal radioactivity and to reduce radioiodine residence time in the bladder. If the pregnancy is discovered within several hours of the radioiodine administration and the fetus is old enough to have a functional thyroid, one should consider thyroid-blocking using potassium iodide. If the pregnancy is discovered later, the placental transfer of radioiodine can result in very high absorbed doses to the fetal thyroid that may cause significant damage. Since the fetal whole-body dose is usually below 100 mGy, there is no reason to terminate the pregnancy (ICRP, 2000); however, the mother should be given usual levels of replacement thyroid hormone.

5.3.4. Breastfeeding

(188) Female patients should be advised that breastfeeding is absolutely contraindicated after therapeutic administration of radionuclides. Any therapeutic radiopharmaceutical administered orally, intravenously or arterially is potentially hazardous to the child, and breast feeding must cease. Intracavitary administrations of suspended particles such as yttrium-90 silicate represent little hazard; however, it would still be wise to cease feeding. Breastfeeding should be discontinued in radiopharmaceutical therapy patients for two reasons. The first and most critical is to prevent radionuclides in milk from reaching the infant (and in particular the infant's thyroid gland in radioiodine therapies) (Azizi and Smyth, 2009) in addition to the external radiation from the patient to the infant. The second reason is to limit radiation of the breast tissue, which may concentrate certain radionuclides during lactation. The restriction period depends on the radionuclide administered for therapy. In case of ^{131}I treatment, the patient should stop breastfeeding 6 weeks before the treatment (Sisson et al., 2011) and should not resume it after the treatment for her current child.

5.3.5. Radioactive patients on dialysis

(189) The care of patients receiving radiopharmaceutical therapy and who are on dialysis may require additional consideration and radiation protection/medical physics experts should be consulted. In general, for systemic treatments, these patients will not biologically clear radioactive materials in the same manner as typical patients since the clearance is highly dependent on the schedule of dialysis sessions.

5.3.6. Conception

(190) Conception should be avoided in both males and females, with clear advice from 4-12 months following radiopharmaceutical therapy. Table 5.2 obtained from *Publication 106* (ICRP, 2004) gives additional information on precaution times for female avoidance of conception for specific radionuclide therapies. Pregnancy should also be delayed based on the need to normalise hormonal responses (e.g. in the case of thyroid therapy) for a successful pregnancy and healthy infant development, and to ensure that additional radiation treatment is not imminent (Sisson et al., 2011).

(191) It is widely recommended, on the basis of prudence, that male patients take steps to avoid fathering children during the months immediately following therapy. However, there is no strong evidence base to support this view (Sawka et al., 2008a, 2008b).

Table 5.2. Periods for avoiding pregnancy after radiopharmaceutical therapy to ensure that the dose to the fetus will not exceed 1 mGy*

Radionuclide and form	For treatment of:	All activities up to: (MBq)	Avoid pregnancy (months)
^{131}I-iodide	Hyperthyroidism	800	4
^{131}I-iodide	Thyroid cancer	6,000	4
^{131}I-mIBG	Neuroendocrine tumours	7,500	3
^{32}P-phosphate	Myeloproliferative disease	200	3
^{89}Sr-chloride	Bone metastases	150	24
^{90}Y-colloid	Arthritic joints	400	0
^{90}Y-colloid	Malignancies	4,000	1

* Selected data from Table 13.3 of ICRP *Publication 94* (ICRP, 2004).

5.3.7. Prevention of medical errors with radiopharmaceuticals

(192) Accident prevention in radiation therapy should be an integral part of the design of equipment and premises and of the working procedures (ICRP, 2007b). A key feature of accident prevention has long been the use of multiple safeguards against the consequences of failures through design of equipment and facilities as well as the use of working procedures. Working procedures should require key decisions, especially in radiation therapy, to be subject to independent confirmation. Effective communication between all the staff and the patient is a vital part of the process. Remedial actions in emergency situations associated with

the use of radioactive materials in therapy need to be identified prior to any programme launch (e.g. the dose from an excessive or erroneous administration of radioiodine in therapy may be reduced by the early administration of stable iodine as potassium iodide or iodate to reduce the uptake of radioiodine by the thyroid).

(193) Care should be exercised in avoiding administration of a therapeutic radiopharmaceutical to the wrong patient. In addition, prior to administration, the following should be verified to match the prescription:

- Identification of the patient by two independent means;
- Identity of the radionuclide;
- Identity of the radiopharmaceutical;
- Total activity;
- Date and time of administration;
- Patients have been given information about their own safety.

(194) Records of the therapeutic radiopharmaceutical, data from dose planning, administered activity, the date and time of administration, and verification of the initial and residual assay should be entered in some form in the patient's medical record (ICRP 2007b) together with the activity at the time of discharge. It should be maintained at the hospital and given to the patient along with written precautionary instructions.

5.4. Staff (Occupational Exposure)

(195) Exposure of workers may arise from unsealed sources either through external irradiation of the body or through entry of radioactive substances into the body. The principles for the protection of workers from ionising radiation, including those in medicine, are discussed in *Publication 75* (ICRP, 1997) and in *Publication 103* (ICRP, 2007a). Generally, the yearly effective dose to staff working full time in nuclear medicine with optimised protection should be well below 5 mSv. Besides facility and equipment design, proper shielding and handling of sources as well as personal protective equipment and tools are important in such optimisation (ICRP, 2008; Carlsson and LeHeron, 2014). Optimisation is also achieved through education and training (ICRP, 2009), resulting in awareness and engagement in radiological protection. Detailed requirements for protection against occupational exposure for nuclear medicine facilities are given in several documents (ICRP, 2007a, 2007b; IAEA, 2011, 2014a) and recommendations on how to meet these requirements are given in IAEA Safety Guides (IAEA, 1999) and in particular IAEA Safety Reports Series No. 40 (IAEA, 2005a).

(196) Pregnant women and persons under the age of 18 y should not be involved in procedures with therapeutic levels of radiopharmaceuticals.

5.4.1. Protective equipment and tools

(197) Protective clothing should be used in radiopharmaceutical therapy areas where there is a likelihood of contamination. The clothing serves both to protect the body of the wearer and to help to prevent the transfer of contamination to other areas. Protective clothing should be removed prior to going to other areas such as staff rooms. The protective clothing may include laboratory gowns, waterproof gloves, overshoes ('booties'), and caps and masks for aseptic work. Radiation safety glasses should be worn to protect the eyes from beta radiation and contamination of the eye. When beta emitters are handled, two layers of gloves should be

worn to avoid contamination of the skin. There should be emphasis on use of shielding, tools and work practices that minimise exposure by preventing direct handling of vials, syringes and contaminated articles.

(198) In radiopharmaceutical therapy, most of the occupational exposures come from ^{131}I, which emits 364-keV photons. The attenuation by a lead apron at this energy is minimal (less than a factor of two) and is unlikely to result in significant dose reduction and may not justify the additional weight and discomfort of wearing such protective equipment. Typically, thicker permanent or mobile lead shielding may be more effectively applied for those situations that warrant its use. Radiation protection experts/medical physicists should determine the need and types of shielding required for each situation. The use of automatic injection systems will significantly reduce the absorbed dose to the staff members (Rushforth et al., 2017).

(199) Administration is normally by the oral route, intravenous injection (systemic), intra-articular injection or instillation of colloidal suspensions into closed body cavities (intracavitary). Shielded syringes should be utilised during the intravenous administration of radiopharmaceuticals as necessary to ensure that extremity doses are maintained below occupational dose constraints. Absorbent materials or pads should be placed underneath an injection or infusion site. The facility Radiation Protection Officer (RPO) should be consulted to determine the necessity of other protective equipment (e.g. shoe covers etc.) for particular radiopharmaceutical therapies.

(200) For oral administrations of therapeutic radiopharmaceuticals, the radioactive material should be placed in a shielded, spill-proof container. Care should be taken to minimise the chance for splashing liquid or for dropping capsules. Appropriate long-handled tools should be utilised when handling unshielded radioactive materials. For intravenous administrations by bolus injections, when dose rates warrant, the syringe should be placed within a syringe shield (plastic for beta emitting radionuclides to minimise bremsstrahlung, high Z materials for photon-emitting radionuclides) with a transparent window to allow for visualisation of the material in the syringe. For intravenous administrations by slower drip or infusions, the activity container should be placed within a suitable shield. For high-energy photons, a significant thickness of lead or other high-Z material may need to be evaluated. In addition, consideration should be given for shielding pumps and lines.

(201) Procedures for administering a therapeutic radiopharmaceutical shall include considerations to ensure as complete a delivery as possible of the prescribed therapeutic activity. Any residual activity in syringes, tubing, filters or other equipment utilised for administration should be assayed. Where appropriate, equipment should be flushed or rinsed with isotonic saline (or another physiological buffer) for parenteral administration or water for oral administrations. All materials utilised in administrations shall be considered as medical and radioactive waste, and should be labelled with the radionuclide, a radiation precaution sticker, and stored and or disposed of in a manner consistent with local regulations.

5.4.2. Individual monitoring

(202) Regular individual monitoring of external exposure should be performed during the management of radiopharmaceutical therapy patients and in the preparation and administration of radiopharmaceuticals. Extremity monitoring should also be carried out for handling of radiopharmaceuticals taking into account the potential differences between exposure of the dosimeter and the location of the extremity where the highest dose is likely to be received (Rimpler et al., 2011; Sans-Merce et al., 2011).

(203) Significant doses to the hands can be received during the administration of radionuclides which emit high-energy beta-radiation. If adequate protection measures are not in place, the exposure of the fingers will be high, and doses of many tens and even hundreds of mSv have been reported from single patient administrations for a number of different ^{90}Y therapies (Barth and Mielcarek, 2002; Liepe et al., 2005a; Rimpler et al., 2007; Rimpler and Barth, 2007). The use of grasp forceps to hold the needle significantly reduces the dose to the hands (ICRP, 2008). Training and educational materials are provided by ICRP (http://www.icrp.org/page.asp?id=35) and other organisations (http://www.oramed-fp7.eu/en/Training%20material).

(204) Staff to be monitored in a nuclear medicine facility should include all those who work routinely with radionuclides or nursing or other staff who spend time with therapy patients. Monitoring for internal contamination is rarely necessary in general nuclear medicine procedures on radiological protection grounds, but it may be useful in providing reassurance to staff (Carlsson and LeHeron, 2014). The circumstances in which internal monitoring becomes advisable are those where staff use significant quantities of ^{131}I for therapy. These staff should be included in a programme of regular thyroid uptake measurements.

5.4.3. Contamination control procedures

(205) In the event of a large-volume spill of radiopharmaceuticals, blood, urine or vomitus, medical practitioners or staff should cover the spill with an absorbent material and immediately contact the radiation protection/medical physics experts for appropriate clean-up assistance and specific instructions. After such a spillage, the following actions should be taken:

- The RPO should immediately be informed and directly supervise the clean-up;
- Absorbent pads should be placed over the spill to prevent further spread of contamination;
- All people not involved in the spill should leave the area immediately;
- Access to the contaminated area should be restricted;
- All people involved in the spill should be monitored for contamination when leaving the room;
- If clothing is contaminated, it should be removed and placed in a plastic bag labelled 'radioactive';
- If contamination of skin occurs, the area should be washed immediately;
- If contamination of an eye occurs, it should be flushed with large quantities of water.

(206) Upon discharge and release of the patient, all remaining waste and contaminated items should be removed and segregated into bags for disposable items and launderable items.

5.4.4. Surveys and monitoring

(207) For area monitoring, the operational quantity for assessing effective dose is the ambient dose equivalent, $H^*(10)$ (ICRU, 1993; ICRP, 1996b, 2010). The ambient dose equivalent rate from the patient should be determined. This information will assist in deriving appropriate arrangements for entry by visitors and staff and for patient release. Rooms with radiotherapy patients should be controlled areas.

5.4.5. Emergency patient care

(208) Medical practitioners should provide all necessary medical care consistent with patient safety and appropriate medical management. Unless otherwise specified by the facility RPO, nurses, physicians and other health care personnel are to perform all routine duties, including those requiring direct patient contact, in a normal manner.

(209) Ward nurses should be informed when a patient may pose a radioactive hazard, and advice and training should be provided regularly.

(210) Radiation protection considerations should not prevent or delay life-saving operations in the event that surgery is required. The following precautions should be observed:

- The operating room staff should be notified;
- Operating procedures should be modified under the supervision of the RPO to minimise exposure and the spread of contamination;
- Protective equipment may be used as long as efficiency and speed are not affected;
- Rotation of personnel may be necessary if the surgical procedure is lengthy;
- The RPO should monitor all individuals involved;
- Doses to members of staff should be measured as required.

(211) If the medical condition of a patient deteriorates such that intensive nursing care becomes necessary, such care is a priority and should not be delayed. However, the advice of the RPO should be sought immediately. In the event of deterioration in the patient's medical condition, frequent or continual monitoring of the patient may be necessary (e.g. septic shock, pulmonary oedema, stroke or myocardial infarction).

(212) Life-saving efforts shall take precedence over consideration of radiation exposures received by medical personnel. This is particularly important for therapy patients containing large amounts of radionuclides. Medical personnel should, therefore, proceed with emergency care (e.g. when a patient has suffered a stroke), while taking precautions against the spread of contamination and minimising external exposure. The staff should avoid direct contact with the patient's mouth, and all members of the emergency team should wear protective gloves. Medical staff should be informed and trained on how to deal with radioactive patients. Rehearsals of the procedures should be held periodically.

5.4.6. Transfer of patients to another healthcare facility

(213) Some patients may need to be transferred to another healthcare facility (i.e. another hospital, skilled nursing facility, nursing home or hospice, etc.) following therapy treatments. In such a case, care must be taken that, in addition to practical measures and advice to ensure safety of other staff, compliance with any legal requirements relevant to the second institution is assured (IAEA, 2009) Patients transferred to another healthcare facility should meet the criteria for unrestricted clearance. However, the possibility for the generation of low-level radioactive waste should be examined by the RPO of the treating facility and any issues should be discussed with the facility accepting the patient transfer. In the rare event that a patient being transferred to another healthcare facility does not meet the criteria for unrestricted clearance, the RPO shall ensure that the facility accepting the patient transfer has an appropriate registration or licence that would allow acceptance of the patient with therapeutic amounts of radioactive materials on board. The RPO should provide radiation safety information and precautions, if any, for the patient and for the receiving healthcare facility.

5.4.7. Death of the patient following radiopharmaceutical therapy

(214) In the event that a patient dies within the treating healthcare facility while still containing a therapeutic quantity of radioactive material, the treating medical practitioner and the RPO shall be notified immediately.

(215) In cases where the death occurs in a hospital, access to the room occupied by the deceased should be controlled until the room has been decontaminated and surveyed. Radioactive bodies should be identified as potential hazards by a specified form of identifier. Identification of the possibility that a body may contain radioactive substances relies on information provided in the patient records, the information card or information gleaned from relatives or others. A body bag may need to be used to contain leakage of radioactive substances. To minimise external radiation, the body may need to be retained in a controlled area.

(216) The dose constraints applying to pathology staff responsible for the conduct of autopsy examinations will be either those for the general public or those for radiation workers, depending on the training and classification of the staff concerned. These constraints and the radiation safety procedures to be applied in practice should be determined in close consultation with the RPO from the department in which the therapy was administered.

(217) Unsealed radioactive substances may be present in a particular body cavity or organ, or they may have concentrated after systemic administration (e.g. ^{131}I in the thyroid gland). Drainage of the cavity or excision of the organ will reduce exposure if undertaken at the start of the autopsy. In addition, care should be given with respect to organs with significant activity. In cases where the patient had received a dose of beta-emitting colloid or spheres (e.g. ^{32}P chromic phosphate into a body cavity or ^{90}Y microspheres into the liver), significant activity may be present in the cavity fluid or in the embolised organ. Beta radiation sources may provide significant dose to the hands because they will be in close contact with body tissues and fluids (NCRP, 2006). Autopsy and pathology staff should wear standard protective clothing (i.e. gloves, lab coats, eye protection, etc.) and personnel monitoring should be considered. For beta emitters, double surgical gloves may be helpful in reducing skin exposures. An intake of airborne material inadvertently released during cutting or movement of radioactive tissue or organs can be prevented by wearing eye protection and a face mask.

(218) A proportion of the activity retained will appear in cremated remains and may be sufficient, particularly in the case of long lived radionuclides, to require controls to be specified. The main concern is in respect to the scattering of ashes, although contact dose rates with the container may have to be considered if cremation takes place shortly after administration.

(219) Crematorium employees may receive external exposure from the radioactive body or from contamination of the crematorium or internal exposure from inhalation of radioactive particles while handling the ashes (Wallace and Bush, 1991). Bodies that contain gamma emitting radionuclides will result in some external exposure to employees of the crematorium. No precautions are necessary as long as there is minimal time required to handle the body at the crematorium (a likely assumption). Cremation of non-volatile radionuclides might result in contamination of the furnace. As the most significant hazard from this contamination is inhalation of ash particles during cleaning of the furnace, it is appropriate for workers who clean the furnace to wear dust masks and protective garments.

(220) The most likely hazard to the general population in the vicinity of the crematorium is the inhalation of radioactive material emitted with the stack gases. Each crematorium should maintain records of the type and activity in bodies cremated, when known.

5.5. Comforters and Carers (Medical Exposure), and Members of the Public (Public Exposure)

(221) *Publication 94* (ICRP, 2004) recommends that young children and infants as well as visitors not engaged in direct care or comforting should be treated as members of the public (i.e., be subject to the public dose limit of 1 mSv/y). The registrant or licensee is responsible for controlling public exposure resulting from a nuclear medicine practice (IAEA, 2011). The presence of members of the public in or near the nuclear medicine facility shall be considered when designing the shielding and flow of persons in the facility. The sources of exposure to the public are primarily the same as for workers. The use of structural shielding and the control of sources, waste and contamination are thus fundamental to controlling exposure to the public.

(222) While medical exposures are predominantly delivered to individuals (patients), other individuals caring for and comforting patients are also exposed to radiation. These individuals include parents and others, normally family or close friends, who may come close to patients following administration of radiopharmaceuticals. These exposures are considered medical exposures (ICRP, 2007a). *Publication 94* (ICRP, 2004) recommends that for individuals directly involved in comforting and caring (other than young children and infants) a dose constraint of 5 mSv per episode (i.e., for the duration of a given release from hospital after therapy) is reasonable. The constraint needs to be used flexibly. For example higher doses may well be appropriate for parents of very sick children.

5.5.1. Release of the patient

(223) A patient who has undergone a therapeutic nuclear medicine procedure is a source of radiation that can lead to the exposure of other persons who come into the proximity of the patient. External irradiation of the persons close to the patient is related to the radionuclide used, its emissions, half-life and biokinetics, and can be important for some radionuclides. Excretion and vomitus result in the possibility of contamination of the patient's environment and other persons.

(224) If a non-occupationally exposed person is knowingly and voluntarily providing care, comfort and support to the patient, then their exposure is considered part of medical exposure, and they are subject to dose constraints (ICRP, 2007b). If the person is simply a member of the public, including persons whose work in the nuclear medicine facility does not involve working with radiation, then their exposure is part of public exposure.

(225) Patients do not need to be hospitalised automatically after all radionuclide therapies. Relevant national dose limits must be met and the principle of optimisation of protection must be applied, including the use of relevant dose constraints. The decision to hospitalise or to release a patient should be determined on an individual basis considering factors such as radiation level of the patient measured by dose rate monitoring, the residual activity in the patient, the patient's wishes, family considerations (particularly the presence of children), environmental factors, and existing guidance and regulations. Hospitalisation will reduce exposure to the public and relatives, but will increase exposure to hospital staff. Hospitalisation often involves a significant psychological burden as well as monetary and other costs that should be analysed and justified. ICRP (2004) has given detailed recommendations related to release of patients after therapy with unsealed radionuclides in its *Publication 94* (ICRP, 2004).

(226) Current recommendations regarding release of patients after therapy with unsealed radionuclides vary widely around the world. However, the decision to release a patient is based on the assumption that the risk can be controlled when the patient returns to their home. This is generally achieved by combining an appropriate release criterion with well-tailored instructions and information for the patient that will allow them to deal effectively with the potential risks.

(227) When appropriate, the patient or legal guardian shall be provided with written and verbal instructions with a view to the restriction of doses to persons in contact with the patient as far as reasonably achievable, and information on the risks of ionising radiation. It is important to develop effective communication methods. Specific instructions should include: minimisation of the spread of contamination, minimisation of exposure to family members, cessation of breast-feeding, and delaying conception after therapy. The amount of time that each precaution should be implemented should be determined based upon an estimate of the activity in the patient prior to discharge and an assessment of the dose likely to be received by carers and comforters or members of the public under various precaution formulations as compared to the appropriate dose constraints. Procedures for advising carers and comforters should be in place, developed in consultation with the RPO. Registrants and licensees should ensure that carers and comforters of patients during the course of treatment with radionuclides receive sufficient written instructions on relevant radiation protection precautions (e.g. time and proximity to the patient). Example methodologies for evaluating precaution time requirements have been published (Zanzonico et al., 2000; NCRP, 2006; IAEA, 2009; Sisson et al., 2011).

(228) Travel following therapy should be within certain restrictions and patients should carry relevant documentation in case of a medical emergency. If travelling, radiation detectors used for security purposes, for example in airports, are sufficiently sensitive to detect low levels of radiation.

5.5.2. Visitors to patients

(229) Arrangements should be made to control access of visitors (with special emphasis on controlling access of pregnant visitors and children) to patients undergoing radiopharmaceutical therapy and to provide adequate information and instruction to these persons before they enter the patient's room, so as to ensure appropriate protection. Licensees should also take measures for restricting public exposure to contamination in areas accessible to the public.

5.5.3. Travel

(230) Optimally, when there is no physical or other impairment, the patient should drive alone in a private car. If the patient must ride or drive with another person, then time and distance constraints apply. Use of a larger vehicle, such as a van, would permit further separation and consequently a reduction in exposure to others. The ICRP has previously evaluated the potential doses to others during patient travel and have published recommendations that allow use of public transportation by some patients treated by nuclear medicine therapy (ICRP, 2004 – see Table 10.7). Radionuclide characteristics and activity administered should be considered. For example, for patients treated for hyperthyroidism, the patient may use public transportation for up to 0.5 h if treated with 800 MBq or up to 3.5 h if treated with 200 MBq (ICRP, 2004).

(231) Patients travelling after radioiodine therapy rarely present a hazard to other passengers if travel times are limited to a few hours. Travel for 1–2 h immediately post-treatment in a private automobile large enough for the patient to maintain a distance of 1 m or greater from the other vehicle occupant(s) is generally permissible. A case-by-case analysis is necessary to determine the actual travel restrictions for each patient, especially for longer trips and for travel by public transport. A stay in a hotel or motel is not recommended after treatment with nuclear medicine therapy without specific environmental assessments and dose-rate evaluations. Exposure of those immediately involved with the patient and the general population can occur through environmental pathways including sewerage, discharges to water, incinerated sludge or cremation of bodies. From the point of view of the individual doses involved, this is of relatively minor significance (IAEA, 2009).

(232) Current international security measures, such as those in place at airports and border crossing points, can include extremely sensitive radiation detectors. It is quite possible that patients treated with gamma-emitting radionuclides could trigger these alarms, particularly in the period immediately following discharge. With current technology, it is possible to detect ^{131}I activity as little as 0.01 MBq at 2 to 3 m (Dauer et al., 2007a). It is possible that patients treated with radionuclides could trigger alarms for 95 days or longer (Dauer et al., 2007b, 2007c). Triggering of an alarm does not mean that a patient is emitting dangerous levels of radiation, as the detectors are designed to detect levels of radioactivity far below those of concern to human health. The security authorities are well aware of this possibility, and if a patient is likely to travel soon after discharge, the hospital or the patient's doctor should provide a written statement of the therapy and radionuclide used for the patient to carry. Personnel operating such detectors should be specifically trained to identify and deal with nuclear medicine patients. Records of the specific details of therapy with unsealed radionuclides should be maintained at the hospital and given to the patient along with written precautionary instructions (ICRP, 2008).

(233) If travel is planned within 4 months of receiving radiopharmaceutical therapy, particularly across international borders or via airports, tunnels, and/or over bridges or whenever inspection is likely, a form or card should be provided to the patient (Sisson et al., 2011). The form should specify the date of treatment, the radionuclide activity administered, the treating facility, and the name and telephone number of a contact individual knowledgeable about the case.

5.5.4. Radioactive waste

(234) Licensees are responsible for ensuring that the optimisation process for measures to control the discharge of radioactive substances from a source to the environment is subject to dose constraints established or approved by the regulatory body (IAEA, 2000, 2004, 2005a). This is particularly relevant for facilities where exhaust systems are required for radioiodine storage and handling. The need for containment and/or ventilation for accumulated or stored ^{131}I waste should be evaluated where appropriate. While for diagnostic patients there is no need for collection of excreta and ordinary toilets can be used, for therapy patients, there are very different policies in different countries, but, in principle, the clearance criteria should follow a dilution and decay methodology. Much of the activity initially administered is eventually discharged to sewers. Storing a patient's urine after therapy appears to have minimal benefit as radionuclides released into modern sewage systems are likely to result in doses to sewer workers and the public that are well below public dose limits (ICRP, 2004). However, local restrictions regarding the discharge of activity may apply. Once a patient has

been released from hospital, the excreted radioactivity levels are low enough to be discharged through the toilet in their home without exceeding public dose limits.

6. SUMMARY OF RECOMMENDATIONS

(235) Increasing use of radiopharmaceuticals for therapy is of benefit for the patient. The goal of radiation therapy, including therapy with radiopharmaceuticals, is to optimise the relationship between the probability of tumour control and the probability of normal tissue complications.

(236) In radiopharmaceutical therapy, the absorbed dose in an organ or tissue is governed by the radiopharmaceutical uptake and retention in the organ itself and surrounding organs, combined with the radionuclide physical half-life. Biokinetic data are collected using techniques that vary in complexity and chosen with regard to the accuracy required for the particular task.

(237) Individual dose estimates must be performed for each patient. In principle, a fully personalised approach based on patient-specific measurements can ensure the administration of appropriate activity for treatment with minimal effects in surrounding normal tissue, thereby minimising the radiation doses delivered to staff, family and comforters and carers and will further minimise the long-term risks.

(238) Special consideration should be given to pregnant women exposed to ionising radiation. Pregnancy is a strong contraindication to radiopharmaceutical therapy, unless the therapy is life-saving. Female patients should be advised that breastfeeding is contraindicated after therapeutic administration of radionuclides. Breastfeeding should be discontinued in radiopharmaceutical therapy patients.

(239) In addition to the patients treated with radiopharmaceutical therapy, the people at risk of exposure include hospital staff, members of the patient's family, including children, and carers, neighbours, and the general public. These risks can be effectively managed and mitigated with well-trained staff, appropriate facilities, and the use of patient-specific radiation safety precaution instructions.

(240) Optimisation of staff exposures include consideration of equipment design, proper shielding and handling of sources as well as personal protective equipment and tools as well as education and training resulting in awareness and engagement in radiation protection. Individual monitoring of the whole body and extremities must be considered during the management of radiopharmaceutical therapy patients and in the preparation and administration of radiopharmaceuticals.

(241) Medical practitioners should provide all necessary medical care consistent with patient safety and appropriate medical management. Radiological protection considerations should not prevent or delay life-saving operations in the event that surgery is required. Staff should be informed when a patient may pose a radioactive hazard, and advice and training should be provided prior to administrations.

(242) The decision to hospitalise or release a patient after therapy should be made on an individual basis considering factors such as the residual activity in the patient, the patient's wishes, family considerations (particularly the presence of children), environmental factors, and existing guidance and regulations. Specific radiation protection precautions should be provided to patients and carers.

REFERENCES

Alexander, E.K., Pearce, E.N., Brent, G.A., et al., 2017. 2016 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum, Thyroid. doi: 10.1089/thy.2016.0457.

Andersson, H., Cederkrantz, E., Bäck, T, et al., 2009. Intraperitoneal alpha-particle radioimmunotherapy of ovarian cancer patients: pharmacokinetics and dosimetry of ^{211}At-MX35 F(ab')2 - a phase I study. J. Nucl. Med. 50 (7), 1153-1160.

Andersson, M., Johansson, L., Minarik, D., et al., 2014. An internal radiation dosimetry computer program, IDAC 2.0, for estimation of patient doses from radiopharmaceuticals. Rad. Prot. Dosim. 162 (3), 299–305.

Ansell, B.M., Crook, A., Mallard, J.R., et al., 1963. Evaluation of intra-articular colloidal gold Au 198 in the treatment of presistent knee effusions. Ann. Rheum. Dis. 22, 435-439.

Azizi, F., Smyth, P., 2009. Breastfeeding and maternal and infant iodine nutrition. Clin. Endocrinol. 70, 803–809.

Barbet, J., Bardies, M., Bourgeois, M., et al. 2012. Radiolabeled antibodies for cancer imaging and therapy. Methods Mol. Biol. 907, 681-697.

Barendsen, G.W., 1982. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int. J. Radiat. Oncol. Biol. Phys. 8, 1981-1997.

Barone, R., Borson-Chazot, F.O., Valkerna, R., et al., 2005. Patient-specific Dosimetry in predicting renal toxicity with Y-90-DOTATOC: Relevance of kidney volume and dose rate in finding a dose-effect relationship. J. Nucl. Med. 46 (Suppl. 1), 99S-106S.

Barth, I., Mielcarek, J., 2002. Occupational beta radiation exposure during radiosynoviorthesis. Sixth European ALARA Network Workshop in Occupational Exposure Optimization in Medical Field and Radiophamaceutical Industry, Madrid, 43-46. (http://www.eu-alara.net/images/stories/pdf/program6/Session%20B/I_Barth.pdf).

Benua, R.S., Cicale, N.R., Sonenberg, M., et al., 1962. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. Am. J. Roentgenol. Radium Ther. Nucl. Med. 87, 171-182.

Bentzen, S.M., Dorr, W., Gahbauer, R., et al., 2012. Bioeffect modeling and equieffective dose concepts in radiation oncology--terminology, quantities and units. Radiother. Oncol. 105, 266-268.

Berg, G., Nystrom, E., Jacobsson, L., et al., 1998. Radioiodine treatment of hyperthyroidism in a pregnant woman. J. Nucl. Med. 39, 357–361.

Bodei, L., Cremonesi, M., Ferrari, M., et al., 2008. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with Y-90-DOTATOC and Lu-177-DOTATATE: the role of associated risk factors. Eur. J. Nucl. Med. Mol. Imaging 35 (10), 1847-1856.

Bodei, L., Mueller-Brand, J., Baum, R.P., et al., 2013. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur. J. Nucl. Med. Mol. Imaging 40 (5), 800-816.

Bolch, W.E., Eckerman, K.F., Sgouros. G. et al., 2009. MIRD Pamphlet No. 21: a generalized schema for radiopharmaceutical dosimetry – standardization of nomenclature. J. Nucl. Med., 50 (3), 477-484.

Bowring, C.S., Keeling, D.H., 1978. Absorbed radiation dose in radiation synovectomy. Brit. J. Radiol. 51, 836-837.

Brandt, L., Anderson, H., 1995. Survival and risk of leukaemia in polycythemia vera and essential thrombocythemia treated with oral radiophosphorus. Eur. J. Haematol. 54 (1), 21–26.

Breen, S.L., Powe, J.E., Porter, A.T., 1992. Dose estimation in strontium-89 radiotherapy of metastatic prostatic carcinoma. J. Nucl. Med. 33 (7), 1316-1323.

Brown, A.P., Chen, J., Hitchcock, Y.J. et al., 2008. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J. Clin. Endocrinol. Metabol. 93 (2), 504-515.

Buckley, S.E., Chittenden, S.J., Saran, F.H.,et al., 2009. Whole-body dosimetry for individualized treatment planning of ^{131}I-MIBG radionuclide therapy for neuroblastoma. J. Nucl. Med. 50 (9), 1518-1524.

Bushnell, D.L., Jr., O'Dorisio, T.M., O'Dorisio, M.S., et al., 2010. ^{90}Y-edotreotide for metastatic carcinoid refractory to octreotide. J. Clin. Oncol. 28 (10), 1652-1659.

Carlier, T., Willowson, K.P., Fourkal, E., et al., 2015. ^{90}Y -PET imaging: Exploring limitations and accuracy under conditions of low counts and high random fraction. Med. Phys. 42, 4295-4309.

Carlsson, S., LeHeron, J., 2014. Radiation protection. In: Bailey, D., Humm, J., Todd-Pokropek, A., et al. (Eds.), *Nuclear Medicine Physics: A Handbook for Teachers and Students*. IAEA, Vienna.

Chatal, J.F., Faivre-Chauvet, A., Bardies, M., et al., 1995. Bifunctional antibodies for radioimmunotherapy. Hybridoma 14 (2), 125-128.

Chatal, J.F., Kraeber-Bodere, F., Barbet, J., 2008. Consolidation radioimmunotherapy of follicular lymphoma: a step towards cure? Eur. J. Nucl. Med. Mol. Imaging 35 (7), 1236-1239.

Chiesa, C., Maccauro, M., Romito, R., et al., 2011. 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. Q. J. Nucl. Med. Mol. Imaging 55 (2), 168-197.

Chu, B.P., Horan, C., Basu, E., et l., 2016. Feasibility of administering high-dose ^{131}I-MIBG therapy to children with high-risk neurobastoma without lead-lined rooms. Pediatr. Blood Cancer 63 (5), 801-807.

Cremonesi, M., Ferrari, M., Bodei, L., et al., 2006a. Dosimetry in peptide radionuclide receptor therapy: A review. J. Nucl. Med. 47 (9), 1467-1475.

Cremonesi, M., Ferrari, M., Paganelli, G., et al., 2006b. Radiation protection in radionuclide therapies with ^{90}Y-conjugates: risk and safety. Eur. J. Nucl. Med. Mol. Imaging 33 (11), 1321-1327.

Cremonesi, M., Botta, F., Di Dia, A., et al., 2010. Dosimetry for treatment with radiolabelled somatostatin analogues. A review. Q. J. Nucl. Med. Mol. Imaging 54 (1), 37-51.

Cremonesi, M., Chiesa, C., Strigari, L., et al., 2014. Radioembolization of hepatic lesions from a radiobiology and dosimetric perspective. Front. Oncol. 4, 210.

Dale, R.G., 1996. Dose-rate effects in targeted radiotherapy. Phys. Med. Biol. 41, 1871-1884.

D'angelo, G., Sciuto, R., Salvatori, M., et al., 2012. Targeted "bone-seeking" radiopharmaceuticals for palliative treatment of bone metastases: a systematic review and meta-analysis. Q. J. Nucl. Med. Mol. Imaging 56 (6), 538-543.

Das, B., 2007. Role of radiosynovectomy in the treatment of rheumatoid arthritis and hemophilic arthropathies. Biomed. Imaging Interv. J. 3 (4), e45.

Dauer, L.T., St. Germain, J., Williamson, M.J., et al., 2007a. Whole-body clearance kinetics and external dosimetry of ^{131}I-3F8 monoclonal antibody for radioimmunotherapy of neuroblastoma. Health Phys. 92 (1), 33–39.

Dauer, L.T., Williamson, M.J., St. Germain, J., et al, 2007b. Tl-201 stress tests and homeland security. J. Nucl. Cardiol. 14, 582–588.

Dauer, L.T., Strauss, H.W., St. Germain, J., 2007c. Responding to nuclear granny, J. Nucl. Cardiol. 14, 904–905.

Dauer, L.T., Williamson, M.J., Humm, J., et al., 2014. Radiation safety considerations for the use of $^{223}RaCl_2$ in men with castration-resistant prostate cancer. Health Phys. 106 (4), 494-504.

Delacroix, D., Guerre, J.P., Leblanc, P., et al., 2002. *Radionuclide and Radiation Protection Data Handbook*, Oxford University Press, Oxford.

Delpon, G., Ferrer, L., Lisbona, A., et al., 2002. Correction of count losses due to deadtime on a DST-XLi (SMVi-GE) camera during dosimetric studies in patients injected with iodine-131. Phys. Med. Biol. 47 (7).

Dewaraja, Y.K., Frey, E.C., Sgouros, G., et al., 2012. MIRD Pamphlet No. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. J. Nucl. Med. 53, 1310-1325.

Dewaraja, Y.K., Ljungberg, M., Green, A.J., et al., 2013. MIRD Pamphlet No. 24: Guidelines for quantitative ^{131}I SPECT in dosimetry applications. J. Nucl. Med. 54, 2182-2188.

Eary, J.F., Collins, C., Stabin, M., et al., 1993. Samarium-153-EDTMP biodistribution and dosimetry estimation. J. Nucl. Med. 34 (7), 1031-1036.

Fernández Tomás, M., Preylowski, V., Schlögl, S., et al., 2012. Influence of the reconstruction parameters on image quantification with SPECT/CT. Eur. J. Nucl. Med. Mol. Imaging 39, S254.

Finlay, I.G., Mason, M.D., Shelley, M., 2005. Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol. 6 (6), 392-400.

Flower, M.A., Al-Saadi, A., Harmer, C.L., et al., 1994. Dose-response study on thyrotoxic patients undergoing positron emission tomography and radioiodine therapy. Eur. J. Nucl. Med. Mol. Imaging 21 (6), 531-536.

Flux, G.D., Haq, M., Chittenden, S.J., et al., 2010. A dose-effect correlation for radioiodine ablation in differentiated thyroid cancer. Eur. J. Nucl. Med. Mol. Imaging 37 (2), 270-275.

Flux, G.D., Chittenden, S.J., Saran, F., et al., 2011. Clinical applications of dosimetry for mIBG therapy. Q. J. Nucl. Med. Mol. Imaging 55 (2), 116-125.

Fowler, J.F., 1989. The linear-quadratic formula and progress in fractionated radiotherapy. Br. J. Radiol. 62, 679-694.

Francis, G.L., Waguespack, S.G., Bauer, A.J., et al., 2015. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid 25 (7), 716-759.

Franzius, C., Dietlein, M., Biermann, M., et al., 2007. [Procedure guideline for radioiodine therapy and ^{131}iodine whole-body scintigraphy in paediatric patients with differentiated thyroid cancer]. Nuklearmedizin 46 (5), 224-231.

Gains, J.E., Bomanji, J.B., Fersht, N.L., et al., 2011. ^{177}Lu-DOTATATE molecular radiotherapy for childhood neuroblastoma. J. Nucl. Med. 52 (7), 1041-1047.

Gustafsson, J., Nilsson, P., Gleisner, K.S., 2013a. On the biologically effective dose (BED)-using convolution for calculating the effects of repair: I. Analytical considerations. Phys. Med. Biol. 58, 1507-1527.

Gustafsson, J., Nilsson, P., Gleisner, K.S., 2013b. On the biologically effective dose (BED)-using convolution for calculating the effects of repair: II. Numerical considerations. Phys. Med. Biol. 58, 1529-1548.

Garaventa, A., Bellagamba, O., Lo Piccolo, M.S., et al., 1999. I-131-metaiodobenzylguanidine (I-131-MIBG) therapy for residual neuroblastoma: a mono-institutional experience with 43 patients. Brit. J. Cancer 81 (8), 1378-1384.

Gaze, M.N., Chang, Y.C., Flux, G.D., et al., 2005. Feasibility of dosimetry-based high-dose ^{131}I-meta-iodobenzylguanidine with topotecan as a radiosensitizer in children with metastatic neuroblastoma. Cancer Biother. Radiopharm. 20 (2), 195-199.

George, S.L., Falzone, N., Chittenden, S., et al., 2016. Individualized ^{131}I-mIBG therapy in the management of refractory and relapsed neuroblastoma. Nucl. Med. Commun. 37 (5), 466-472.

Giammarile, F., Chiti, A., Lassmann, M., et al., 2008. EANM procedure guideline for ^{131}I-meta-iodobenzylguanidine (^{131}I-mIBG) therapy. Eur. J. Nucl. Med. Mol. Imaging 38 (7), 1393-1406.

Giammarile, F., Bodei, L., Chiesa, C., et al., 2011. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur. J. Nucl. Med. Mol. Imaging 38 (7), 1393-1406.

Glatting, G., Landmann, M., Kull, T., et al., 2005. UlmDos - a software tool for voxelbased dosimetry before radionuclide therapy. Biomed. Tech. 50, 94-95.

Glatting, G., Lassmann, M., 2007. Nuklearmedizinische Dosimetrie. In: Krause, B.-J., Schwaiger, M., Buck, A.K. (Eds.), *Nuklearmedizinische Onkologie*. 1. ed. Hüthig Jehle Rehm. Landsberg, Germany.

Gleisner, K.S., Brolin, G., Sundlov, A., et al., 2015. Long-term retention of ^{177}Lu/^{177m}Lu-dotatate in patients investigated by gamma-spectrometry and gamma-camera imaging. J. Nucl. Med. 56, 976-984.

Goldenberg, D.M., Chang, C.H., Rossi, E.A., et al., 2012. Pretargeted molecular imaging and radioimmunotherapy. Theranostics 2 (5), 523-540.

Goldsmith, S.J., 2010. Radioimmunotherapy of lymphoma: Bexxar and Zevalin. Semin. Nucl. Med. 40 (2), 122-135.

Grassi, E., Sghedoni, R., Asti, M., et al., 2009. Radiation protection in ^{90}Y-labelled DOTA-D-Phe1-Tyr$_3$-octreotide preparations. Nucl. Med. Commun., 30 (2), 176-182.

Guy, M.J., Flux, G.D., Papavasileiou, P., et al., 2003. A dedicated package for ^{131}I SPECT quantification, registration and patient-specific dosimetry. Cancer Biother. Radiopharm. 18 (1), 61-69.

Hanaoka, K., Hosono, M., Tatsumi, Y., et al., 2015. Heterogeneity of intratumoral ^{111}In-ibritumomab tiuxetan and ^{18}F-FDG distribution in association with therapeutic response in radioimmunotherapy for B-cell non-Hodgkin's lymphoma. EJNMI Res. 5, 10. doi: 10.1186/s13550-015-0093-3.

Haugen, B.R., Alexander, E.K., Bible, K.C., et al., 2016. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 26 (1), 1-133.

Hay, I.D., Gonzalez-Losada, T., Reinalda, M.S., et al., 2010. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J. Surg. 34 (6), 1192-1202.

Hindorf, C., Chittenden, S., Causer, L., et al., 2007. Dosimetry for ^{90}Y-DOTATOC therapies in patients with neuroendocrine tumors. Cancer Biotherapy & Radiopharmaceuticals 22 (1), 130-135.

Hindorf, C., Glatting, G., Chiesa, C., et al., 2010. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. Eur. J. Nucl. Med. Mol. Imaging 37, 1238-1250.
Hoefnagel, C.A., Voute, P.A., De Kraker, J., et al., 1991. [^{131}I]metaiodobenzylguanidine therapy after conventional therapy for neuroblastoma. J. Nucl. Biol. Med. 35 (4), 202-206.
Honarvar, H., Westerlund, K, Altai, A., et al., 2016. Feasibility of affibody molecule-based PNA-mediated radionuclide pretargeting of malignant tumors. Theranostics 6 (1), 93-103.
Howarth, D., Epstein, M., Lan, L., et al., 2001. Determination of the optimal minimum radioiodine dose in patients with Graves' disease: a clinical outcome study. Eur. J. Nucl. Med. 28 (10), 1489-1495.
Howell, R.W., Goddu, S.M., Dandamundi, V.R., 1994. Application of the linear-quadratic model to radioimmunotherapy: Further support for the advantage of longer-lived radionuclides. J. Nucl. Med. 35, 1861-1869.
Hänscheid, H., Lassmann, M., Luster, M., et al., 2006. Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: Procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J. Nucl. Med. 47 (4), 648-654.
Hänscheid, H., Lassmann, M., Luster, M., et al., 2009. Blood dosimetry from a single measurement of the whole body radioiodine retention in patients with differentiated thyroid carcinoma. Endocr. Relat. Cancer. 16 (4), 1283-1289. doi: ERC-09-0076.
Hänscheid, H., Canzi, C., Eschner, W., et al., 2013. 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 40, 1126-1134.
IAEA, 1999a. Occupational Protection, IAEA Safety Standards Series No. RS-G-1.1, IAEA, Vienna, Austria.
IAEA, 1999b. Assessment of Occupational Exposure Due to Intakes of Radionuclides, IAEA Safety Standards Series No. RS-G-1.2, Vienna, Austria.
IAEA, 1999c. , Assessment of Occupational Exposure Due to External Sources of Radiation, IAEA Safety Standards Series No. RS-G-1.3, IAEA, Vienna, Austria.
IAEA, 2000. Regulatory Control of Radioactive Discharges to the Environment, IAEA Safety Standards Series No. WS-G-2.3, IAEA, Vienna, Austria.
IAEA, 2004. Applications of the Concepts of Exclusion, Exemption and Clearance, IAEA Safety Standards Series No. RS-G-1.7. IAEA, Vienna, Austria.
IAEA, 2005a. Applying Radiation Safety Standards in Nuclear Medicine, Safety Reports Series No. 40, IAEA, Vienna, Austria.
IAEA, 2005b. Management of Waste from the Use of Radioactive Material in Medicine, Industry, Agriculture, Research and Education, IAEA Safety Standards Series No. WS-G-2.7, IAEA, Vienna, Austria.
IAEA, 2006a. Application of the Management System for Facilities and Activities: Safety Guide, IAEA Safety Standards Series No. GS-G-3.1, IAEA, Vienna, Austria.
IAEA, 2006b. Radiation Protection in the Design of Radiotherapy Facilities, Safety Report Series No. 47, IAEA, Vienna, Austria.
IAEA, 2009. Release of Patients After Radionuclide Therapy, Safety Reports Series No. 63, IAEA, Vienna, Austria.
IAEA, 2011. Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards — Interim Edition, IAEA Safety Standards Series No. GSR Part 3 (Interim), IAEA, Vienna, Austria.

IAEA, 2014a. Nuclear Medicine Physics: A handbook for teachers and students, IAEA, Vienna, Austria.
IAEA, 2014b. Quantitative Nuclear Medicine Imaging: Concepts, Requirements and Methods. IAEA Human Health Reports No. 9, IAEA, Vienna, Austria.
ICRP, 1987. Radiation dose to patients from radiopharmaceuticals. ICRP Publication 53. Ann. ICRP 18 (1-4).
ICRP, 1996a. Radiological Protection and Safety in Medicine. ICRP Publication 73, Ann. ICRP 26 (2).
ICRP, 1996b. Conversion coefficients for use in radiological protection against external radiation. ICRP Publication 74. Ann. ICRP 26 (3/4).
ICRP, 1997. General principles for the radiation protection of workers. ICRP Publication 75, Ann. ICRP 27 (1).
ICRP, 1998. Radiation dose to patients from radiopharmaceuticals (Addendum 2 to ICRP Publication 53). ICRP Publication 80. Ann. ICRP 28 (3).
ICRP, 2000. Pregnancy and medical radiation. ICRP Publication 84, Ann. ICRP 30 (1).
ICRP, 2001a. Doses to the Embryo and Fetus from Intakes of Radionuclide by the Mother. ICRP Publication 88, Ann. ICRP 31 (1-3).
ICRP, 2001b. Radiation and your patient - A Guide for Medical Practitioners. ICRP Supporting Guidance 2, Ann. ICRP 31 (4).
ICRP, 2003. Biological Effects after Prenatal Irradiation (Embryo and Fetus), ICRP Publication 90, Ann. ICRP 33 (1-2).
ICRP, 2004. Release of patients after therapy with unsealed radionuclides. ICRP Publication 94, Ann. ICRP 34 (2).
ICRP, 2007a. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103, Ann. ICRP 37 (2-4).
ICRP, 2007b. Radiological Protection in Medicine. ICRP Publication 105, Ann. ICRP 37 (6).
ICRP, 2008. Radiation Dose to Patients from Radiopharmaceuticals - Addendum 3 to ICRP Publication 53. ICRP Publication 106, Ann. ICRP 38 (1-2).
ICRP, 2009. Education and training in radiological protection for diagnostic and interventional procedures. ICRP Publication 113. Ann. ICRP 39 (5).
ICRP, 2010. Conversion coefficients for radiological protection quantities for external radiation exposures. ICRP Publication 116. Ann. ICRP 40 (2-5).
ICRP, 2015a. Radiation dose to patients from radiopharmaceuticals: A Compendium of current information related to frequently used Substances. ICRP Publication 128, Ann. ICRP 44 (2S).
ICRP, 2015b. Occupational intakes of radionuclides: Part 1. ICRP Publication 130. Ann. ICRP 44 (2).
ICRU, 1993. Quantities and Units in Radiation Protection Dosimetry. ICRU Report 51. ICRU, Bethesda, MD, USA,
ICRU, 2016. Key data for ionizing-radiation dosimetry: Measurement standards and applications. ICRU Report No.90. J. ICRU 14 (1). doi: 10.1093/jicru/ndw043.
International Organization for Standardization (ISO), 1975. Basic Ionizing Radiation Symbol, ISO 361, Geneva.
Ilan, E., Sandstrom, M., Wassberg, C., et al., 2015. Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using ^{177}Lu-DOTATATE. J. Nucl. Med. 56 (2), 177-182.

Imhof, A., Brunner, P., Marincek, N., et al., 2011. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [^{90}Y-DOTA]-TOC in metastasized neuroendocrine cancers. J. Clin. Oncol. 29 (17), 2416-2423.

Infante-Rivard, C., Rivard, G.E., Derome, F., et al., 2012. A retrospective cohort study of cancer incidence among patients treated with radiosynoviorthesis. Haemophilia 18 (5), 805-809.

Jarzab, B., Handkiewicz-Junak, D., Wloch, J., 2005. Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. Endocr-Relat. Cancer 12 (4), 773-803.

Jie, Y., Congjin, L., Xingdang, L., et al., 2013. Efficacy and safety of ^{177}Lu-EDTMP in bone metastatic pain palliation in breast cancer and hormone rfractory prostate cancer: a phase II study. Clin. Nucl. Med. 38 (2), 88-92.

Joiner, M.C., van der Kogel, A., 2009. *Basic clinical radiobiology*. CRC Press: Boca Raton.

Johnson, L.S., Yanch, J.C., Shortkroff, S., et al., 1995. Beta-particle dosimetry in radiation synovectomy. Eur. J. Nucl. Med. 22 (9), 977-988.

Jönsson, H., Mattsson, S., 2004. Excess radiation absorbed doses from non-optimised radioiodine treatment of hyperthyroidism. Rad. Prot. Dosim. 108 (2), 107-111.

Jönsson, L., Ljungberg, M., Strand, S.E., 2005. Evaluation of accuracy in activity calculations for the conjugate view method from Monte Carlo simulated scintillation camera images using experimental data in an anthropomorphic phantom. J. Nucl. Med. 46, 1679–1686.

Jurcic, J.G. and Rosenblat, T.L., 2014. Targeted alpha-particle immunotherapy for acute myeloid leukemia. Am. Soc. Clin. Oncol. Educ. Book. e126-131.

Kellerer, A.M.; Rossi, H.H., 1974. The theory of dual radiation action. In: *Current Topics in Radiation Research*, Ebert, M., Howard, A., Eds. North Holland publishing company, Amsterdam, 1974; Vol. VIII, pp 85-158.

Klett, R., Puille, M., Matter, H.P.,et al., 1999. Activity leakage and radiation exposure in radiation synovectomy of the knee: influence of different therapeutic modalities. Z. Rheumatol. 58 (4), 207-212.

Kletting, P., Schimmel, S., Kestler, H.A., et al., 2013. Molecular radiotherapy: the NUKFIT software for calculating the time-integrated activity coefficient. Med. Phys. 40, 102504.

Klubo-Gwiezdzinska, J., Van Nostrand, D., Burman, K.D., et al., 2010. Salivary gland malignancy and radioiodine therapy for thyroid cancer. Thyroid 20 (6), 647-651.

Knut, L., 2015. Radiosynovectomy in the therapeutic management of arthritis. World J. Nucl. Med. 14 (1), 10-15.

Kobe, C., Eschner, W., Sudbrock, F., et al., 2008. Graves' disease and radioiodine therapy. Is success of ablation dependent on the achieved dose above 200 Gy? Nuklearmedizin 47 (1), 13-17.

Kraeber-Bodere, F., Rousseau, C., Bodet-Milin, C., et al., 2006. Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and ^{131}I-labeled bivalent hapten in a phase I optimization clinical trial. J. Nucl. Med. 47 (2), 247-255.

Kramer, K., Humm, J.L., Souweidane, M.M., et al., 2007. Phase I study of targeted radioimmunotherapy for leptomeningeal cancer using intra-Ommaya ^{131}I-3FB. J. Clin. Oncol. 25 (34), 5465-5470.

Kratochwil, C., Bruchertseifer, F., Giesel, F.L., et al., 2016. ^{225}Ac-PSMA-617 for PSMA-targeted alpha-radiation therapy of metastatic castration-resistant prostate cancer. J. Nucl. Med. 5 (12), 1941-1944

Kunikowska, J., Krolicki, L., Hubalewska-Dydejczyk, A., et al., 2011. Clinical results of radionuclide therapy of neuroendocrine tumours with ^{90}Y-DOTATATE and tandem ^{90}Y/^{177}Lu-DOTATATE: which is a better therapy option? Eur. J. Nucl. Med. Mol. Imaging 38 (10), 1788-1797

Kwekkeboom, D.J., Mueller-Brand, J., Paganelli, G., et al., 2005. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. J. Nucl. Med., 46 (Suppl. 1), 62S-66S.

Lambert, B., Mertens, J., Sturm, E.J.,et al., 2010. ^{99m}Tc-labelled macroaggregated albumin (MAA) scintigraphy for planning treatment with ^{90}Y microspheres. Eur. J. Nucl. Med. Mol. Imaging 37 (12), 2328-2333.

Lancelot, S., Guillet, B., Sigrist, S., et al., 2008. Exposure of medical personnel to radiation during radionuclide therapy practices. Nuclear Medicine Communications 29 (4), 405-410.

Larson, S.M., Carrasquillo, J.A., Cheung, N-K., et al., 2015. Radioimmunotherapy of human tumours. Nat. Rev. Cancer 15 (8), 347-360.

Lassmann, M., Hanscheid, H., Chiesa, C., et al., 2008. 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 35 (7), 1405-1412.

Lassmann, M., Nosske, D., 2013. Dosimetry of ^{223}Ra-chloride: dose to normal organs and tissues, Eur. J. Nucl. Med. Mol. Imaging 40 (2), 207-212.

Lea, D.E., Catcheside, D.G., 1942. The mechanism of the induction by radiation of chromosome aberrations in tradescantia. J. Genet. 44, 216-245.

Lee, S.L., 2010. Complications of radioactive iodine treatment of thyroid carcinoma. J.Natl. Compr. Canc. Netw. 8 (11), 1277-1286; quiz 1287.

Leiter, L., Seidlin SM, Marinelli, L.D., 1946. Adenocarcinoma of the thyroid with hyperthyroidism and functional metastases; studies with thiouracil and radioiodine. J. Clin. Endocrinol. Metab. 6, 247-261.

Leslie, W.D., Ward, L., Salamon, E.A., et al., 2003. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J. Clin. Endocrinol. Metab. 88 (3), 978-983.

Lhommel, R., van Elmbt, L., Goffette, P., et al., 2010. Feasibility of ^{90}Y TOF PET-based dosimetry in liver metastasis therapy using SIR-spheres. Eur. J. Nucl. Med. Mol. Imaging 37 (9), 1654-1962.

Liepe, K., Andreeff, M., Wunderlich, G., et al., 2005a. Radiation protection in radiosynovectomy of the knee. Health Phys. 89, 151–154.

Liepe, K., Runge, R., Kotzerk, J., 2005b. The benefit radiopharmaceuticals in the treatment of metastatic bone pain. Journal of Cancer Research and Clinical Oncology 131 (1), 60-66.

Liepe, K., and Kotzerke, J., 2007. A comparative study of ^{188}Re-HEDP, ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{89}Sr in the treatment of painful skeletal metastases. Nucl. Med. Commun, 28 (8), 623-630.

Ljungberg, M., Celler, A., Konijnenberg, M.W., et al., 2016. MIRD Pamphlet No. 26: Joint EANM/MIRD guidelines for quantitative ^{177}Lu SPECT applied for dosimetry of radiopharmaceutical therapy. J. Nucl. Med. 57 (1), 151-162.

Loevinger, R., Berman, M., 1968. A schema for absorbed-dose calculations for biologically distributed radionuclides. MIRD Pamphlet No. 1. J. Nucl. Med. 9 (Suppl. 1), 7–14.

Luster, M., Clarke, Clarke, S.E., Dietlein, M., et al., 2008. Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur. J. Nucl. Med. Mol. Imaging 35 (10), 1941-1959.

Mallick, U., Harmer, C., Hackshaw, A., et al., 2012a. Iodine or Not (IoN) for low-risk differentiated thyroid cancer: the next UK National Cancer Research Network randomised trial following HiLo. Clin. Oncol. 24 (3), 159-161.

Mallick, U., Harmer, C., Yap, B., et al., 2012b. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N. Engl. J. Med. 366, 1674-1685.

Matthay, K.K., Panina, C., Huberty, J., et al., 2001. Correlation of tumor and whole-body dosimetry with tumor response and toxicity in refractory neuroblastoma treated with ^{131}I-MIBG. J. Nucl. Med. 42, 1713-1721.

Matthay, K.K., Yanik, G., Messina, J., et al., 2007. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. J. Clin. Oncol. 25 (9), 1054-1060.

Maxon, H.R.,3rd., Englaro, E.E., Thomas, S.R., et al., 1992. Radioiodine-131 therapy for well-differentiated thyroid cancer--a quantitative radiation dosimetric approach: outcome and validation in 85 patients. J. Nucl. Med. 33 (6), 1132-1136.

McKay, E., 2003. A software tool for specifying voxel models for dosimetry estimation. Cancer Biother. Radiopharm. 18, 61-69.

Menda, Y., O'Dorisio, M.S., Kao, S., et al., 2010. Phase I trial of ^{90}Y-DOTATOC therapy in children and young adults with refractory solid tumors that express somatostatin receptors. J. Nucl. Med. 51 (10), 1524-1531.

Merrill, S., Horowitz, J., Traino, A.C., et al., 2011. Accuracy and optimal timing of activity measurements in estimating the absorbed dose of radioiodine in the treatment of Graves' disease. Phys. Med. Biol. 56 (3), 557-571.

Metso, S., Jaatinen, P., Huhtala, H.,et al., 2007. Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. J. Clin. Endocrinol. Metab. 92 (6), 2190-2196.

Miederer, M., McDevitt, M.R., Sgouros, G., et al., 2004. Pharmacokinetics, dosimetry, and toxicity of the targetable atomic generator, ^{225}Ac-HuM195, in nonhuman primates. J. Nucl. Med. 45 (1), 129-137.

Millar, W.T., 1991. Application of the linear-quadratic model with incomplete repair to radionuclide directed therapy. Br. J. Radiol. 64, 242-251.

NCRP, 2006. Management of Radionuclide Therapy Patients, *NCRP Report No. 155*, Bethesda, USA.

Noble, J., Jones, A.G., Davies, M.A., et al., 1983. Leakage of radioactive particle systems from a synovial joint studied with a gamma camera: its application to radiation synovectomy. J. Bone Joint Surg. Am. 65 (3), 381-389.

Norrgren, K., Svegborn, S.L., Areberg, J., Mattsson, S., 2003. Accuracy of the quantification of organ acticity from planar gamma camera images. Cancer Biother. Radiopharm, 18 (1), 125-131,

Pandit-Taskar, N., Batraki, M., Divgi, C.R., 2004. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. J. Nucl. Med. 45 (8), 1358-1365.

Pandit-Taskar, N., Larson, S.M., Carrasquillo, J.A., 2014. Bone-seeking radiopharmaceuticals for treatment of osseous metastases, Part 1: alpha therapy with ^{223}Ra-dichloride. J. Nucl. Med. 55 (2), 268-274.

Parker, C., Nilsson, S., Heinrich, D., et al., 2013. Alpha emitter radium-223 and survival in metastatic prostate cancer. New Engl. J. Med. 369 (3), 213-223.

Pauwels, S., Barone, R., Walrand, S., et al., 2005. Practical dosimetry of peptide receptor radionuclide therapy with Y-90-labeled somatostatin analogs. J. Nucl. Med. 46, 92S-98S.

Pawelczak, M., David, R., Franklin, B., et al., 2010. Outcomes of children and adolescents with well-differentiated thyroid carcinoma and pulmonary metastases following I-131 treatment: A systematic review. Thyroid 20 (10), 1095-1101.

Perros, P., Boelaert, K., Colley, S., et al., 2014. Guidelines for the management of thyroid cancer. Clin. Endocrinol. 81 (Suppl. 1), 1-122.

Quach, A., Ji, L., Mishra, V., et al., 2011. Thyroid and hepatic function after high-dose ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) therapy for neuroblastoma. Pediatr. Blood Cancer 56 (2), 191-201.

Rahbar, K., Ahmadzadehfar, H., Kratochwil, C., et al., 2017. German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J. Nucl. Med. 58 (1), 85-90.

Ramage, J.K., Ahmed, A., Ardill, J., et al., 2012. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 61 (1), 6-32.

Reinhardt, M.J., Brink, I., Joe, A.Y., et al., 2002. Radioiodine therapy in Graves' disease based on tissue-absorbed dose calculations: effect of pre-treatment thyroid volume on clinical outcome. Eur. J. Nucl. Med. Mol. Imaging 29 (9), 1118-1124.

Remy, H.1., Borget, I,, Leboulleux, S,, et al., 2008. ^{131}I effective half-life and dosimetry in thyroid cancer patients. J. Nucl. Med. 49 (9):1445-1450.

Rimpler, A., Barth, I., 2007. Beta radiation exposure of medical staff and implications for extremity dose monitoring. Rad. Prot. Dosim. 125, 335–339.

Rimpler, A., Barth, I., Senftleben, S., et al., 2007. Beta radiation exposure of staff during therapies with Y-90 labeled substances. Beta-Days in Capri (Italy), 20–22 Sept. 2007 (http://www.uznuclear.rug.ac.be/betadayscapri/).

Rimpler, A., Barth, I., Ferrari, O., et al., 2011. Extremity exposure in nuclear medicine therapy with 90Y-labelled substances – results of the ORAMED project. Radiat. Meas. 46 (11), 1283-1286.

Roedler, H.D., 1980. Accuracy of internal dose calculations with special consideration of radiopharmaceutical biokinetics, in: Third International Radiopharmaceutical Symposium, Watson, E.E., Schlafke-Stelson, A.T., Coffey, J.L., et al., (Eds.), Oak Ridge: U.S. Department of Human Services, pp. 1−20.

Royal College of Physicians, 2007. Radioiodine in the Management of Benign Thyroid Disease: Clinical guidelines. *RCP Report of a Working Party*, London, UK.

Rubino, C., de Vathaire, F., Dottorini, M.E., et al., 2003 Second primary malignancies in thyroid cancer patients. Brit. J. Cancer 89 (9), 1638-1644.

Rushforth, D.P., Pratt, B.E., Chittenden, S.J., et al., 2017, InfuShield: a shielded enclosure for administering therapeutic radioisotope treatments using standard syringe pumps. Nucl. Med. Commun. 38, 266-252.

Sans-Merce, M, Ruiz, N., Barth, I., et al., 2011. Recommendations to reduce hand exposure for standard nuclear medicine procedures. Radiat. Meas. 46 (11), 1330-1333.

Savolainen, S., Konijnenberg, M., Bardies, M., et al., 2012. Radiation dosimetry is a necessary ingredient for a perfectly mixed molecular radiotherapy cocktail. Eur. J. Nucl. Med. Mol. Imaging 39 (3), 548-549.

Sawka, A.M., Lea, J., Alshehri, B., et al., 2008a. A systematic review of the gonadal effects of therapeutic radioactive iodine in male thyroid cancer survivors. Clin. Endocrinol. (Oxf) 68 (4), 610-617.

Sawka, A.M., Lakra, D.C., Lea, J., et al., 2008b. A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. Clin. Endocrinol. (Oxf) 69 (3), 479-490.

Schiavo, M., Bagnara, M.C., Calamia, I., et al., 2011. A study of the efficacy of radioiodine therapy with individualized dosimetry in Graves' disease: need to retarget the radiation committed dose to the thyroid. J. Endocrinol. Invest. 34 (3), 201-205.

Schleien, B., Birky, B., Slaback, L., 1998. Handbook of Health Physics and Radiological Health, 3rd edn. Williams and Wilkins, Baltimore, MD.

Schlumberger, M., Catargi, B., Borget, I., et al., 2012. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. The New England Journal of Medicine 366 (18), 1663-1673.

Schmidt, M., Baum, R.P., Simon, T., et al., 2010. Therapeutic nuclear medicine in pediatric malignancy. Q. J. Nucl. Med. Mol. Imaging 54 (4), 411-428.

Seidlin, S.M., Marinelli, L.D., Oshry, E., 1946. Radioactive iodine therapy; effect on functioning metastases of adenocarcinoma of the thyroid. JAMA 132 (14), 838-847.

Seregni, E., Maccauro, M., Chiesa, C., et al., 2014. Treatment with tandem [^{90}Y]DOTA-TATE and [^{177}Lu]DOTA-TATE of neuroendocrine tumours refractory to conventional therapy. Eur. J. Nucl. Med. Mol. Imaging 41 (2), 223-230.

Shinto, A.S., Shibu, D., Kamaleshwaran, K.K., et al., 2014. ^{177}Lu-EDTMP for Treatment of Bone Pain in Patients with Disseminated Skeletal Metastases J Nucl Med Technol 42, 55–61.

Siegel, J.A., Thomas, R., Stubbs, J.R., et al., 1999. MIRD Pamphlet No. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. J. Nucl. Med. 40, 37S-61S.

Sgouros, G., Roeske, J.C., McDevitt, M.R., et al., 2010. MIRD Pamphlet No. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. J. Nucl. Med. 51 (2), 311-328.

Silberstein, E.B., Alavi, A., Balon, H.R., et al., 2012. The SNM practice guideline for therapy of thyroid disease with ^{131}I 3.0. J. Nucl. Med. 53 (10), 1633-1651.

Sisson, J.C., Avram, A.M., Rubello, D., et al., 2007. Radioiodine treatment of hyperthyroidism: fixed or calculated doses; intelligent design or science? Eur. J. Nucl. Med. Mol. Imaging 34 (7), 1129-1130.

Sisson, J.C., Freitas, J., McDougall, I.R., et al., 2011. Radiation safety in the treatment of patients with thyroid diseases by radioiodine ^{131}I: Practice. Recommendations of the American Thyroid Association. The American Thyroid Association Taskforce on Radioiodine Safety. Thyroid 21 (4), 335-346.

Smits, M.L., Nijsen, J.F., van den Bosch, M.A., et al., 2012 Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. Lancet Oncol. 13 (10), 1025-1034.

Snyder, W.S., Ford, M.R., Warner, G.G., et al., 1969. Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogeneous phantom. MIRD Pamphlet No. 5. J. Nucl. Med. 10 (Suppl. 3).

Stabin, M.G., Sparks, R.B., Crowe, E, 2005. OLINDA/EXM: The second-generation personal computer software for internal dose assessment in nuclear medicine. J. Nucl. Med. 46 (3), 1023-1027.

Stokkel, M.P., Handkiewicz, J.D., Lassmann, M., et al., 2010. EANM procedure guidelines for therapy of benign thyroid disease. Eur. J. Nucl. Med. Mol. Imaging 37 (11), 2218-2228.

Strigari, L., Sciuto, R., Rea, S., et al., 2010. Efficacy and toxicity related to treatment of hepatocellular carcinoma with Y-90-SIR spheres: radiobiologic considerations. J. Nucl. Med. 51, 1377-1385.

Strigari, L., Konijnenberg, M., Chiesa, C., et al., 2014. The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. Eur. J. Nucl. Med. Mol. Imaging 41 (10), 1976-1988.

Strosberg, J., El-Haddad, G., Wolin, E., et al, 2017. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. N. Engl. J. Med. 376 (2):125-135.

Sudbrock, F., Schmidt, M., Simon, T.,et al., 2010. Dosimetry for ^{131}I-MIBG therapies in metastatic neuroblastoma, phaeochromocytoma and paraganglioma. Eur. J. Nucl. Med. Mol. Imaging 37 (7), 1279-1290.

Sundlöv, A., Sjögreen-Gleisner, K., Svensson, J., et al., 2017. Individualised ^{177}Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry. Eur. J. Nucl. Med. Mol. Imaging 22 Mar 2017. doi: 10.1007/s00259-017-3678-4. [Epub ahead of print]

Tennvall, J., Brans, B., 2007. EANM procedure guideline for ^{32}P phosphate treatment of myeloproliferative diseases. Eur. J. Nucl. Med. Mol. Imaging 34, 1324–1327.

Thapa, P., Nikam, D., Das, T., et al., 2015. Clinical efficacy and safety comparison of ^{177}Lu-EDTMP with ^{153}Sm-EDTMP on an equidose basis in patients with painful skeletal metastases. J. Nucl. Med. 56, 1513-1519.

Tristam, M., Alaamer, A.S., Fleming, J.S., et al., 1996. Iodine-131-metaiodobenzylguanidine dosimetry in cancer therapy: risk versus benefit. J. Nucl. Med. 37 (6), 1058-1063.

Turkmen, C., Ozturk, S., Unal, S.N., et al., 2007. The genotoxic effects in lymphocyte cultures of children treated with radiosynovectomy by using yttrium-90 citrate colloid. Cancer Biother. Radiopharm. 22 (3), 393-399.

Valkema, R., De Jong, M., Bakker, W.H., et al., 2002. Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: the Rotterdam experience. Semin. Nucl. Med. 32 (2), 110-122.

Vanhavere, F., Carinon, E., Gualdrini, G., et al., 2012. ORAMED: Optimisation of Radiation Protection for Medical Staff. EURADOS Report 2012-02, http://www.eurados.org./en/Documents_Publications

Vassilopoulou-Sellin, R., Klein, M.J., Smith, T.H., et al., 1993. Pulmonary metastases in children and young adults with differentiated thyroid cancer. Cancer 71 (4), 1348-1352.

Verburg, F.A., Biko, J., Diessl, S., et al., 2011. I-131 activities as high as safely administrable (AHASA) for the treatment of children and adolescents with advanced differentiated thyroid cancer. J. Clin. Endocrinol. Metab., 96 (8), E1268-1271. doi:10.1210/jc.2011-0520.

Wallace, A.B., Bush, V., 1991. Management and autopsy of a radioactive cadaver, Austlaras. Phys. Eng. Sci. Med. 14, 119–124.

Walrand, S., Barone, R., Pauwels, S., et al., 2011. Experimental facts supporting a red marrow uptake due to radiometal transchelation in ^{90}Y-DOTATOC therapy and relationship to the decrease of platelet counts. Eur. J. Nucl. Med. Mol. Imaging 38 (7), 1270-1280.

Watson, E.E., Stabin, M.G., Eckerman, K.F., 1989. A model of the peritoneal cavity for use in internal dosimetry. J. Nucl. Med. 30, 2002–2011.

Weiss, B, Vora, A., Huberty, J., et al., 2003. Secondary myelodysplastic syndrome and leukemia following ^{131}I-metaiodobenzylguanidine therapy for relapsed neuroblastoma. J. Pediatr. Hematol. Oncol. 25 (7), 543-547.

Wessels, B.W., Konijnenberg, M.W., Dale, R.G., et. al., 2008. MIRD pamphlet No. 20: The effect of model assumptions on kidney dosimetry and response--implications for radionuclide therapy. J. Nucl. Med. 49, 1884-1899.

Willowson, K.P., Tapner, M., Team, Q.I., et al., 2015. 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 42 (8), 1202-1222.

Wiseman, G.A., White, C.A., Sparks, R.B., et al., 2001. Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. Crit. Rev. Oncol. Hematol. 39 (1-2), 181-194.

Yousefnia, H., Zolghadri, S., Jalilian, A.R., 2015. Absorbed dose assessment of ^{177}Lu-zoledronate and ^{177}Lu-EDTMP for human based on biodistribution data in rats. J. Med. Phys. 40 (2), 102–108.

Zanzonico, P.B., Siegel, J.A., St. Germain, J., 2000. A generalized algorithm for determining the time of release and the duration of post-release radiation precautions following radionuclide therapy, Health Phys. 78, 648–659.

Zimmerman, B.E., Grosev, D., Buvat, I., et al., 2016. Multi-centre evaluation of accuracy and reproducibility of planar and SPECT image quantification: An IAEA phantom study. Z. Med. Phys. 19 April 2016. doi:10.1016/j.zemedi.2016.03.008. [Epub ahead of print]