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### Radiological Protection in Therapy with Radiopharmaceuticals

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## Aims and Scope

The International Commission on Radiological Protection (ICRP) is the primary body in protection against ionising radiation. ICRP is a registered charity and is thus an independent non-governmental organisation created at the 1928 International Congress of Radiology to advance for the public benefit the science of radiological protection. ICRP provides recommendations and guidance on protection against the risks associated with ionising radiation from artificial sources such as those widely used in medicine, general industry, and nuclear enterprises, and from naturally occurring sources. These are published approximately four times each year on behalf of ICRP as the journal *Annals of the ICRP*. Each issue provides in-depth coverage of a specific subject area.

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The Main Commission consists of a Chair and twelve other members. Committees typically comprise just over 15 members each. Task Groups are usually chaired by an ICRP Committee member and usually contain a number of specialists from beyond the Main Commission and Committees. They are assigned the responsibility for drafting reports on various subjects, which are reviewed and finally approved by the Main Commission. These reports are then published as *Annals of the ICRP*.

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## Radiological Protection in Therapy with Radiopharmaceuticals

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## Guest Editorial

### **RADIOLOGICAL PROTECTION IN THERAPY WITH RADIOPHARMACEUTICALS**

Nuclear medicine is the medical application of radioactive tracer technology invented by Hevesy and Paneth in 1913. Radiopharmaceuticals are chemical and biological substances labelled with a radioisotope and approved as drugs for human medical use by the national authority.

Pharmaceuticals that accumulate selectively in a tissue, organ, or lesion through physiological and metabolic processes are chosen to be labelled with radioisotopes. Due to the very small quantity of pharmaceutical labelled with a very large amount of radioactivity (high specific activity), radiopharmaceuticals do not reveal effects as drugs. Thus, radiopharmaceuticals are used to deliver radioisotopes to specific parts of the body for diagnostic and therapeutic purposes with radiation.

The distribution of a radioisotope and its temporal changes in the body can be traced by external measurement of emitted gamma radiation. The distribution can be displayed as images with quantified radioactivity, which are used for diagnosis, therapy planning, and evaluation of treatment effects. Beta- and alpha-radiation-emitting radioisotopes that accumulate in a lesion such as cancer can destroy cells by focused irradiation of the pathological tissues. This mechanism is used for therapy. The efficient use of radiopharmaceuticals for both diagnosis and therapy using alpha, beta, and gamma radionuclides is called ‘theranostics’.

In the 1940s, the first reports of the use of radioactive iodine to treat diseases of the thyroid, and radioactive phosphorus to treat leukaemia were greeted with great enthusiasm by the medical profession and the public. These classic findings were immediately recognised as forerunners of a whole series of similar uses of radioactive ‘magic bullets’ (Wagner, 2006). Even today, radioiodine therapy of hyperthyroidism and thyroid cancers is increasingly used in Japan and elsewhere. Bone-seeking agents labelled with  $^{89}\text{Sr}$  or  $^{153}\text{Sm}$  have been used for relief of intractable bone pain. Alpha-emitting  $^{223}\text{Ra}$ -dichloride has been shown to reduce pain and extend survival of patients with multiple bone metastases. The treatment of metastatic endocrine tumours using radiopharmaceuticals that bind to hormone receptors such as somatostatin receptors has been widely used in Europe, and is expected to be approved in Japan.

Radioimmunotherapy targeting cancer-related antigens, such as prostate-specific membrane antigen, has been investigated for clinical uses using antibodies labelled with beta emitters such as  $^{131}\text{I}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ , and  $^{177}\text{Lu}$ , as well as alpha emitters such as  $^{211}\text{At}$ ,  $^{213}\text{Bi}$ , and  $^{225}\text{Ac}$ . Theranostics is a new medical science that combines the diagnostic properties of antibodies labelled with photon-emitting radionuclides with therapeutic alpha- and beta-emitting radionuclides.

Medical use of technologies for radiopharmaceutical targeting of pathologic tissues in cancer treatment has been expanding worldwide. The number of patients who receive radiopharmaceutical therapy has doubled in the past 10 years in Japan.

Radiological protection in radiopharmaceutical therapy has unique aspects because unsealed radionuclides are used with much greater activities than commonly employed in diagnostic nuclear medicine. These greater activities may require hospitalisation of patients in wards specifically designed and equipped with special shielding and contamination control. The criteria for the release of patients or treatment as outpatients must be determined based on potential dose to family and friends.

Patients who receive radiopharmaceuticals for therapeutic purposes become radiation sources with larger doses and for longer periods compared with those who receive radiopharmaceuticals for diagnostic purposes. Special protective measures must be taken with regards to contact with other people, especially children and pregnant women. If these patients travel or pass by radiation monitors, alerts may be activated. Therefore, patients should carry relevant documents issued by the hospitals. Breast feeding must be stopped and conception should be avoided for certain periods of time. Special considerations for radiological protection are also necessary if radioactive patients are on dialysis.

Hospital staff who deal with radiopharmaceutical therapy need special training and experience in safety measures, in addition to those for regular radiation workers, to avoid contamination from unsealed radiation sources. They also need to know how to decontaminate in case of contamination. Special care is required to contain contamination within controlled areas.

For decades, ICRP has developed dose coefficients and other guidance related to calculating doses to patients undergoing procedures using radiopharmaceuticals. Most recently, these have been summarised in *Publication 128* (ICRP, 2015a).

In the current publication, ICRP provides recommendations on radiological protection of patients, staff, and members of the public relating to radiopharmaceutical therapy. Nuclear medicine physicians who practice radiopharmaceutical therapy, doctors who prescribe it, and other hospital staff who are involved need to be familiar with radiological protection considerations for patients and workers.

In case of nuclear or radiological accidents or malicious acts, people with internal exposure to radioactive materials must be hospitalised for radiation dose estimation and treatment. The most appropriate facilities for these purposes are rooms designed specifically for radiopharmaceutical therapy. Medical personnel trained in the care of therapy patients may also be excellent specialists for dealing with other types of radiological emergencies. Staff should receive training with regular exercises to ensure that they are prepared for unanticipated nuclear or radiological medical emergencies.

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## RADIOLOGICAL PROTECTION IN THERAPY WITH RADIOPHARMACEUTICALS

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Approved by the Commission in November 2018

**Abstract**—Radiopharmaceuticals are increasingly used for the treatment of various cancers with novel radionuclides, compounds, tracer molecules, and administration techniques. The goal of radiation therapy, including therapy with radiopharmaceuticals, is to optimise the relationship between tumour control probability and potential complications in normal organs and tissues. Essential to this optimisation is the ability to quantify the radiation doses delivered to both tumours and normal tissues. This publication provides an overview of therapeutic procedures and a framework for calculating radiation doses for various treatment approaches. In radiopharmaceutical therapy, the absorbed dose to an organ or tissue is governed by radiopharmaceutical uptake, retention in and clearance from the various organs and tissues of the body, together with radionuclide physical half-life. Biokinetic parameters are determined by direct measurements made using techniques that vary in complexity. For treatment planning, absorbed dose calculations are usually performed prior to therapy using a trace-labelled diagnostic administration, or retrospective dosimetry may be performed on the basis of the activity already administered following each therapeutic 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 an approximate measure of lifetime risk of detriment attributable to the stochastic effects of radiation exposure, principally cancer, but effective dose does not predict future cancer incidence for an individual and 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. Minimisation 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 radiological protection. The decision to hold or release a patient after radiopharmaceutical therapy should account for potential radiation dose to members of the public and carers that may result from residual

radioactivity in the patient. In these situations, specific radiological protection guidance should be provided to patients and carers.

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

## MAIN POINTS

- Treatment with radiopharmaceuticals requires administration protocols that justify and optimise the treatment. Individual absorbed dose estimates should be performed for treatment planning and for postadministration verification of doses to tumours and normal tissues.
- Special consideration should be given to pregnant women and children exposed to ionising radiation. Pregnancy is usually contraindicated in radiopharmaceutical therapy. Breast feeding should be discontinued in patients receiving radiopharmaceutical therapy.
- Radiation sources used in radiopharmaceutical therapy can contribute to exposures to medical personnel and others who may spend time within or adjacent to rooms that contain such sources. Meaningful radiation 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 radiological protection. Accident prevention and review of safe practices 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 the radiological protection principles of justification and optimisation. Radiological protection actions should not prevent or delay life-saving medical procedures or surgery in the event that they may be required for medical care. Staff should be informed and trained with respect to patient radiation levels.
- 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's situation, considering factors such as the residual activity in the patient, the patient's wishes, and family considerations (particularly the presence of children or pregnant family members). Information to guide radiological protection at home should be provided to patients and carers.



# 1. INTRODUCTION

(1) In radiation therapy, cancer is treated to preserve life and to improve the quality of life of the patient. While radiation therapy focuses on treating the malignancy, absorbed doses delivered to normal organs and tissues should be minimised to limit adverse tissue reactions. Current ICRP recommendations related to therapy with radiopharmaceuticals are found in *Publications 73* (ICRP, 1996a), *94* (ICRP, 2004), *103* (ICRP, 2007a), and *105* (ICRP, 2007b).

(2) The medical community currently does not have adequate resources for the collection of useful biokinetic or dosimetric data for such procedures. However, quantitative imaging and dosimetry should be the basis for treatment planning for radiopharmaceutical therapy,<sup>1</sup> just as they are for external-beam radiotherapy.

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

(4) Many publications deal with absorbed doses delivered to critical organs and tumours. These include details on the biokinetics of uptake and retention. It would be valuable if a greater amount of biokinetic information could be provided from the increasing number of studies that are being performed. It would also be beneficial to assess the integrity of data gathered from descriptions of the methods used to acquire the data.

(5) This publication details a framework to perform individualised dosimetry to plan therapeutic procedures and to verify the absorbed dose delivered.

(6) Therapeutic radiopharmaceuticals typically exhibit large differences in biokinetics from one patient to another. Personalised dosimetry is essential to ascertain individual radiopharmaceutical biokinetics to ensure that a subsequent therapy administration does not exceed organ or tissue tolerance levels. The practice and optimisation of radiopharmaceutical therapy practice and optimisation requires different competencies, including medical physicists, nuclear medicine technologists, nuclear medicine physicians, endocrinologists, and oncologists.

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

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<sup>1</sup>Therapy with radiopharmaceuticals is referred to by many synonymous terms, including 'targeted radionuclide therapy', 'unsealed source therapy', 'systemic radiation therapy', and 'molecular radiotherapy'. In this publication, the generic term 'radiopharmaceutical therapy' is used for consistency with other ICRP and ICRU publications.



## 2. RADIOPHARMACEUTICAL THERAPY METHODS: JUSTIFICATION AND OPTIMISATION

### 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 dosimetric calculations, related to quantitative imaging, absorbed dose calculations, and considerations of normal tissue detriment. The 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) The objectives of treatment with radiopharmaceuticals are often palliative, as in the case of beta emitters for bone metastases. Complete responses are common only in limited cases, such as for the ablation of thyroid remnants following thyroidectomy. In the majority of treatments, a range of responses are seen.

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

(11) Clinical introduction of a new radiotherapeutic method involves the development of administration protocols that justify and optimise the treatment.

(12) Many new radiopharmaceuticals are being developed. Each new agent must be considered separately, and the potential benefits and risks involved must be considered in relation to safety and efficacy, individual patient status, and the aim of treatment.

(13) Records of the specifics of therapy with unsealed radionuclides should be maintained. Data concerned with absorbed dose planning and activities of administered radiopharmaceuticals should always be included in the patient's medical records.

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

### 2.2. Treatment of hyperthyroidism and other benign thyroid conditions

(15)  $^{131}\text{I}$ -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  $^{131}\text{I}$ -iodide, but  $^{131}\text{I}$  solution is also used for individualised administration of the activity. Radioactive iodine accumulates in the thyroid gland, and beta particles emitted by  $^{131}\text{I}$  destroy the cells of the thyroid gland. Although this is established as a first-line treatment, there is little consensus concerning treatment regimens, and there is ongoing controversy over the aims of treatment.

### 2.2.1. Aim of treatment

(16) The aim of treatment is to destroy the cells of the thyroid gland and to suppress the hyperactive thyroid function to render the patient euthyroid or hypothyroid.

### 2.2.2. Treatment protocols

(17) Treatment protocols fall into three categories according to the treatment objective.

- An administration of a fixed activity with the aim to render patients hypothyroid within a short period of time, whereupon patients continue on life-long thyroid replacement hormones (RCP, 2007).
- A personalised approach to inducing hypothyroidism to achieve a prompt response albeit with the minimal administered activity necessary (Kobe et al., 2008; Stokkel et al., 2010; Schiavo et al., 2011).
- A personalised approach with the aim of rendering patients euthyroid where possible, and 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,b). The mean effective half-time for excretion of  $^{131}\text{I}$  from the thyroid is approximately 5 days, although this has been shown to vary widely. Radiation dose assessments should be performed for individual treatments, taking into account patient-specific factors. Detailed written guidance for reducing exposure from the patient should be provided to the patient and their family.

### 2.2.4. Radiation dose to staff

(19) The levels of activity administered for treatment of benign thyroid conditions are substantially less than those administered for ablation or therapeutic procedures, and greater than those administered for diagnostic studies. Occupational doses should be determined for staff members who work with  $^{131}\text{I}$ , and it may be important to track thyroid doses for radiopharmacists who handle  $^{131}\text{I}$ .

### 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, activities are administered without dosimetric consideration, while in other cases, dosimetry is performed to guide treatment (Stokkel et al., 2010). Advances in quantitative imaging and dosimetry enable more precise dosimetric calculations that may take into account volume and sequential retention measurements acquired from  $^{131}\text{I}$  or  $^{123}\text{I}$  single-photon emission computed tomography (SPECT), and  $^{124}\text{I}$  positron emission tomography (PET) (Merrill et al., 2011). Dosimetric 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 breast feeding are contraindicated for treatment, and patients should avoid conception for 4–6 months (see Sections 5.3.3 and 5.3.4). Identification of any patient who may be pregnant is crucial as  $^{131}\text{I}$ -iodide is taken up by the fetal thyroid from 8–10 weeks post conception, and doses to the fetal thyroid can result in permanent hypothyroidism and a risk for severe physical and mental retardation due to deficiency of thyroid hormones (Berg et al., 1998). Patients to be treated with radioactive iodine should not undergo tests with iodinated contrast media within 2 months prior to the therapy, due to the risk of iodine blockage and low uptake of radioactive iodine (Luster et al., 2008).

### 2.2.7. Recommendations

(22) At present, there are no standardised protocols for thyroid disease treatment, which reflects the lack of evidence base for best practice. A fixed activity administration, without dosimetric calculations, while convenient for many centres, results in the administration of higher activities than is necessary for effective treatment of benign thyroid disease (Jönsson and Mattsson, 2004; Sisson et al., 2007).

(23) In principle, a personalised approach based on patient-specific measurements can ensure the administration of minimal effective activity, thereby minimising the potential for long-term risks and the radiation doses delivered to staff, family, and comforters and carers. A personalised dosimetric approach may provide the potential to render patients euthyroid where this may be desired. 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 normal organs and outcome. Such trials should be stratified according to the volume of the thyroid, initial uptake, and retention (Howarth et al., 2001; Reinhardt et al., 2002).

## 2.3. Treatment of differentiated thyroid cancer

(24)  $^{131}\text{I}$ -iodide 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 (Thyrogen, Genzyme Corp., Cambridge, MA, USA) 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 a therapeutic response.

(25) Management guidelines have been published for adult patients with thyroid nodules and differentiated thyroid cancer (Silberstein et al., 2012; Haugen et al., 2016), and for the diagnosis and management of thyroid disease during pregnancy and the postpartum period (Alexander et al., 2017).

### 2.3.1. Aim of treatment

(26) For ablation, the aim of treatment is to eradicate residual normal thyroid tissue and malignant tissue. 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, opinions differ regarding the therapeutic effectiveness of radioiodine (Perros et al., 2014). In some cases, 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 low (Luster et al., 2008). No multi-centre trials have been conducted to date to establish the optimal activity to administer for ablation or subsequent therapeutic procedures. Consequently, guidelines do not give strong recommendations regarding optimised levels of administration.

(28) In recent years, the UK HiLo trial and the French ESTIMABL trial demonstrated that 1.1 GBq  $^{131}\text{I}$  is as effective as 3.7 GBq for ablation in low- or intermediate-risk patients, although the interpretation of these results is debated. An ongoing discussion concerns whether radioiodine should be administered at all in low-risk patients (Mallick et al., 2012b; Schlumberger et al., 2012; Haugen et al., 2016).

(29) In the absence of trial-based evidence, activity schedules have been proposed to maximise therapy effectiveness and to minimise the likelihood of secondary malignancies.

(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 has been written (Francis et al., 2015). Administrations for radioiodine ablation in children vary widely. Activity may be adjusted by body weight (usually  $1.85\text{--}7.4\text{ MBq kg}^{-1}$ ), by body surface area, or by age (Jarzab et al., 2005; Luster et al., 2008). A hybrid approach of combining 24-h-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  $1.1\text{--}11.0\text{ GBq}$  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) Retention and excretion of radioiodine vary among patients. The mean effective half-time for  $^{131}\text{I}$  excretion after total thyroidectomy is less than that for hyperthyroidism (Hänscheid et al., 2006; Remy et al., 2008). Written guidance should be provided to the patient, taking into account their family circumstances, and comfort and carer consent is required if in close contact with the patient.

(33) Patients undergoing treatment may require hospitalisation following administration, according to national patient release regulations. The decision to hospitalise or to release a patient should be determined on an individual basis according to calculations of potential radiation doses to family and members of the public.

### 2.3.4. Radiation dose to staff

(34) As with all procedures involving radiotherapeutics, standard precautions should be taken with the principle of dose limitation. 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 to target thyroid tissues (Flux et al., 2010).

(36) Seidlin et al. (1946) calculated the cumulative absorbed doses to metastases. Further studies have used a blood absorbed dose of  $2\text{ Gy}$  as a surrogate biomarker for marrow toxicity (Benua et al., 1962),  $300\text{ Gy}$  to ablate thyroid remnant tissue, and  $80\text{ Gy}$  to eradicate lymph node metastases (Maxon et al., 1992).

(37) Dosimetric studies show significant correlations between the absorbed doses delivered and therapeutic response (Strigari et al., 2014), and dosimetric guidelines have been published by EANM (Lassmann et al., 2008).

### 2.3.6. Risks to patients

(38) As with all therapeutic procedures, pregnancy and breast feeding are contra-indicated. Conception advice is given according to national guidelines (see Section 5.3.6). 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-Gwiedzinska et al., 2010; Lee, 2010). A decline in leukocytes and platelets may also be seen. Pulmonary fibrosis has been observed in patients with thyroid-origin lung metastases (Haugen et al., 2016). Patients to be treated with radioactive iodine should not undergo tests with iodinated contrast media within 2 months prior to therapy due to the risk of iodine blockage with low uptake of radioactive iodine (Luster et 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. Children with pulmonary metastases may 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.

### 2.3.7. Recommendations

(40) The 10-year overall cause-specific survival for differentiated thyroid cancer is approximately 85% (Luster et al., 2008), depending on age, volume of disease, and metastatic spread (Mallick et al., 2012a). On the other hand, the 10-year survival in cases with distant metastases is only 25–40%, indicating the need for stratification in treatment planning. The recurrence rate can be as high as 10–30%. Insufficient treatment may necessitate 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) The obvious benefit of complete cure and the need to minimise the potential for secondary malignancies show the importance of dosimetry for each treatment. This is particularly relevant for children and young people, and for high-risk patients. Further studies are needed to investigate the role of pretherapy dosimetry planning, taking into account the possibility of stunning, whereby uptake of activity for therapy may be reduced. Thyroid stunning is a clinical observation in which exposure of a patient to diagnostic amounts of  $^{131}\text{I}$  has been described to alter the

ability of differentiated thyroid carcinoma or remnants of thyroid tissue after thyroidectomy to assimilate administered  $^{131}\text{I}$ .

## 2.4. Treatment of polycythaemia vera and essential thrombocythaemia

(42)  $^{32}\text{P}$ -phosphate was first used to treat polycythaemia vera and essential thrombocythaemia approximately 70 years ago. Polycythaemia vera and essential thrombocythaemia are chronic progressive myeloproliferative disorders characterised by overproduction of erythrocytes and thrombocytes, respectively. Other disease features include leukocytosis, 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  $^{32}\text{P}$  has diminished. Today, polycythaemia vera and essential thrombocythaemia remain the only myeloproliferative conditions treated by  $^{32}\text{P}$ -phosphate.

### 2.4.1. Aim of treatment

(43)  $^{32}\text{P}$  is actively incorporated into DNA of rapidly proliferating cells. Treatment suppresses blood cell production by irradiating bone marrow. Beta radiation from  $^{32}\text{P}$  suppresses hyperproliferative cell lines. Despite alternative treatments, elderly patients with polycythaemia vera and essential thrombocythaemia respond to oral or intravenous administration of  $^{32}\text{P}$ -phosphate (Tennvall and Brans, 2007).

### 2.4.2. Treatment protocols

(44)  $^{32}\text{P}$ -phosphate is administered intravenously or orally. The administered activity is  $74\text{--}111\text{ MBq m}^{-2}$  body surface with a maximum upper activity limit of  $185\text{ MBq}$ , or a slightly higher activity of  $3.7\text{ MBq kg}^{-1}$  body weight with a maximum upper activity limit of  $260\text{ MBq}$ . A decrease in activity of 25% in patients aged  $>80$  years is recommended by some investigators. An alternative, dose-escalating approach is to administer a fixed lower activity of  $111\text{ MBq}$ . In the absence of an 'adequate response', a second treatment may be given after 3 months with a 25% increase in activity. This procedure of increased activity may be repeated every 3 months until an adequate therapeutic response is obtained. The upper activity limit for a single administration is  $260\text{ MBq}$  (Tennvall and Brans, 2007).

### 2.4.3. Radiation dose to friends and family

(45) For outpatient therapy, the patient and family should be instructed to: (1) avoid prolonged, close contact with young children and pregnant women; (2) sleep in

a separate bed from a partner or children for a few days after return home; and (3) practice good personal hygiene to avoid any external contamination as  $^{32}\text{P}$  is excreted in urine for 2–3 weeks after treatment.

#### **2.4.4. Radiation dose to staff**

(46) As  $^{32}\text{P}$  is a high-energy beta emitter, it is essential to employ plastic and metal shielding during dispensing and injection.

#### **2.4.5. Patient organ dosimetry**

(47) Organs with the highest radiation dose are bone endosteum and haematopoietically active bone marrow, which receive approximately 11 mGy per MBq administered (ICRP, 1987). A typical administration of 100 MBq may impart more than 1 Gy to bone endosteum and active bone marrow.

#### **2.4.6. Risks to patients**

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

#### **2.4.7. Recommendations**

(49)  $^{32}\text{P}$ -phosphate can be used in elderly patients and those for whom alternative treatments such as hydroxyurea, busulphan, interferon-alpha, or anagrelide are not suitable.

### **2.5. Treatment of skeletal metastases**

(50) Treatment of painful skeletal metastases is important for 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 is multi-disciplinary, and may include analgesia, radiation, hormones, chemotherapy, bisphosphonates, and surgery. Localised metastases can be treated with external-beam radiation or surgery. Diffuse bone metastases are usually treated by radiopharmaceuticals, hormones, chemotherapy, and bisphosphonates (Pandit-Taskar et al., 2004).

(51) Beta-emitting radiopharmaceuticals such as  $^{89}\text{Sr}$ -chloride and  $^{153}\text{Sm}$ -EDTMP (ethylenediamine tetramethylene phosphonate) have been administered for pain relief

in patients with painful skeletal metastases as palliative therapy.  $^{223}\text{Ra}$ -dichloride, an alpha-emitting bone-seeking radiopharmaceutical, has emerged as a radiopharmaceutical therapy agent for castration-resistant prostate cancer with symptomatic bone metastases, and has been shown to prolong overall survival (3–6 months) (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 skeletal metastases. These agents are rarely curative.  $^{89}\text{Sr}$ -chloride and  $^{153}\text{Sm}$ -EDTMP are approved in some countries for relief of painful skeletal metastases from solid cancers, while  $^{186}\text{Re}$ -HEDP (hydroxyethylenediphosphonate),  $^{188}\text{Re}$ -HEDP,  $^{117\text{m}}\text{Sn}$ -DTPA (diethylenetriamine pentaacetic acid), and  $^{177}\text{Lu}$ -EDTMP are under investigation (Finlay et al., 2005; Liepe et al., 2005b; Liepe and Kotzerke, 2007; Shinto et al., 2014; Yousefnia et al., 2015). The mechanism of pain relief by these radiopharmaceuticals is believed to be due to reduction of pressure on neurons. The aim of treatment of  $^{223}\text{Ra}$ -dichloride therapy in prostate cancer patients with bone metastases is to improve quality of life by mitigating pain without use of addictive pain killers while prolonging overall survival.

### 2.5.2. Treatment protocols

(53)  $^{89}\text{Sr}$ -chloride and  $^{153}\text{Sm}$ -EDTMP are approved in several countries and thus have well-established treatment protocols. The recommended dosage of  $^{89}\text{Sr}$ -chloride is 148 MBq. Alternatively, a dosage of 1.5–2.2 MBq  $\text{kg}^{-1}$  body weight may be administered as a single intravenous injection, compared with  $^{153}\text{Sm}$ -EDTMP at an activity per body weight of 37 MBq  $\text{kg}^{-1}$ . For both radiopharmaceuticals, patients must visit their doctors regularly to ensure that the treatments are having a beneficial effect and to check for unwanted effects including leukocytopenia and thrombocytopenia. Treatment protocols are under study for  $^{186}\text{Re}$ -HEDP,  $^{188}\text{Re}$ -HEDP,  $^{117\text{m}}\text{Sn}$ -DTPA, and  $^{177}\text{Lu}$ -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  $^{223}\text{Ra}$ -dichloride is 55 kBq  $\text{kg}^{-1}$  given intravenously as one administration every 4 weeks over a period of 6 months.

### 2.5.3. Radiation dose to friends and family

(55) As activity is excreted mainly through urine for  $^{89}\text{Sr}$ -chloride and  $^{153}\text{Sm}$ -EDTMP, and through faeces for  $^{223}\text{Ra}$ -dichloride, care must be taken to ensure that all excreta are disposed of in the sanitary sewer system when a patient is at home. Nappies and other potentially contaminated material should be collected in

specified bags for waste disposal. The specified rubbish bags must be leak proof, and bags containing waste could be returned to the treating facility, as determined by the respective treatment personnel (Sisson et al., 2011). Patients may be hospitalised for a longer period 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

(56) For  $^{89}\text{Sr}$ ,  $^{153}\text{Sm-EDTMP}$ , and  $^{223}\text{Ra}$ , patients can receive treatment on an outpatient basis, which is advantageous for ensuring that exposures of staff remain low. Higher irradiation of  $^{186}\text{Re-HEDP}$  and  $^{188}\text{Re-HEDP}$  results from the gamma emissions. Staff doses should be monitored carefully in all cases.  $^{223}\text{Ra-dichloride}$  has been evaluated as safe and straightforward to handle and administer using conventional nuclear medicine equipment (Dauer et al., 2014).

#### 2.5.5. Patient organ dosimetry

(57)  $^{89}\text{Sr}$  delivers absorbed doses of 0.2–2 and 0.05–0.3 Gy MBq<sup>-1</sup> to the bone surfaces adjacent to metastatic sites and to red marrow, respectively (Breen et al., 1992), while  $^{153}\text{Sm-EDTMP}$  imparts absorbed doses of 5.3–8.8 and 1.2–2.0 mGy MBq<sup>-1</sup> to the bone surfaces and red marrow, respectively (Eary et al., 1993). Absorbed dose values may vary depending on individual patient biokinetics and metabolism. The range of absorbed doses of  $^{223}\text{Ra-dichloride}$  calculated from Phase 1 study data were 2–13 Gy MBq<sup>-1</sup> for bone surfaces, while absorbed doses to red marrow were 177–994 and 1–5 mGy MBq<sup>-1</sup> from bone surfaces and blood activity, respectively (Chittenden et al., 2015).

#### 2.5.6. Risk to patients

(58) Radiopharmaceuticals used for therapy of bone metastases 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 a few days after administration may occur in some patients. Patients with renal dysfunction must undergo careful evaluation prior to treatment because adverse effects including bone marrow suppression may be more serious. Contraindications are pregnancy and breast feeding.

(59)  $^{223}\text{Ra}$  has the advantage of sparing much of the marrow from irradiation by virtue of its short-range alpha emissions. Non-haematological toxicities are generally more common than haematologic toxicity and are mild to moderate in intensity; they include diarrhoea, fatigue, nausea, vomiting, and bone pain, some of which are dose-related (Pandit-Taskar et al., 2014). The long-term adverse effects of  $^{223}\text{Ra}$  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 for several months after a single injection. The widely different administration protocols for each agent, that may be fixed or weight-based and may be administered once or multiple times, indicate that optimal treatment protocols are not yet established and that 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  $^{223}\text{Ra}$  would help to determine optimal treatment regimens and identify patients in whom treatment is likely to have little or no benefit. The radiopharmaceuticals are usually administered on an outpatient basis, and standard radiological 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 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. Neuroblastoma accounts for approximately 6% of childhood cancers, with only 67% surviving for  $\geq 5$  years.  $^{131}\text{I}$ -mIBG is most commonly administered in chemorefractory or relapsed patients. Outcomes vary from 30% to 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  $^{131}\text{I}$ -mIBG 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; Tristram et al., 1996), although weight-based activities have also frequently been administered. Short-term toxicity may correlate 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 555–666 MBq kg<sup>-1</sup> 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, administrations are sometimes repeated and as many as five administrations have been reported (George et al., 2016).

### **2.6.3. Radiation dose to friends and family**

(65) Precautions must be considered for each patient, taking home circumstances into account. This is particularly relevant for children and young people who 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 their families and carers on discharge from hospital.

### **2.6.4. Radiation dose to staff**

(66) Careful protection procedures are required to minimise radiation from the source and the administered patient. Shielded syringes should be employed during intravenous administration to ensure that extremity doses to medical staff and radiopharmacists are maintained as low as possible. The use of an automatic injection system will significantly reduce the radiation exposure of 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. Nursing staff, in particular, require specific training in radiological protection. Valuable advice related to administration of high-dose <sup>131</sup>I-MIBG therapy to children is given by Chu et al. (2016).

### **2.6.5. Patient organ dosimetry**

(67) In contrast to many therapeutic procedures with radiopharmaceuticals, a large number of dosimetric studies have been performed relative to the number of centres that offer <sup>131</sup>I-MIBG therapy (Tristram et al., 1996; Matthay et al., 2001; Sudbrock et al., 2010; Flux et al., 2011). The absorbed doses delivered to the whole body, critical organs, and tumours have been reported to vary by an order of magnitude (Matthay et al., 2001; Flux et al., 2011), indicating the important role of personalised dosimetry.

### **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 occur in >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 dosimetric planning and verification for all.

## 2.7. Treatment with radiolabelled peptide receptor

(70) Neuroendocrine tumours express somatostatin receptors. Radiolabelled analogues of somatostatin have been developed for therapeutic purposes including  $^{90}\text{Y}$ -DOTATOC ( $[^{90}\text{Y}\text{-DOTA}^0, \text{Tyr}^3]\text{-octreotide}$ ) and  $^{177}\text{Lu}$ -DOTATATE ( $[^{177}\text{Lu}\text{-DOTA}^0, \text{Tyr}^3, \text{Thr}^8]\text{-octreotide}$  or  $[^{177}\text{Lu}\text{-DOTA}^0, \text{Tyr}^3]\text{-octreotate}$ ) which 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 International Atomic Energy Agency (IAEA), EANM, and the Society of Nuclear Medicine and Molecular Imaging based predominantly on expert opinion (Bodei et al., 2013).

(71) The ideal radionuclide has not been established and there are arguments to support both  $^{90}\text{Y}$  and  $^{177}\text{Lu}$ .  $^{90}\text{Y}$ , with a substantially longer range of beta particles, is more able to deposit a uniform distribution of energy at a multi-cellular 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).  $^{177}\text{Lu}$  also has the advantage of photon emissions useful for quantitative imaging for dosimetry, whereas  $^{90}\text{Y}$  is often tagged with a tracer level of  $^{111}\text{In}$ . The physical half-lives of both radionuclides (64 h and 6.7 days for  $^{90}\text{Y}$  and  $^{177}\text{Lu}$ , respectively) are compatible with biological retention following uptake. Both  $^{177}\text{Lu}$ -DOTATATE and  $^{90}\text{Y}$ -DOTATATE are radiolabelled in house, necessitating the usual precautions for the staff at such procedures.

### 2.7.1. Aim of treatment

(72) Response is variable and the aim of treatment is predominantly palliative. Partial or complete objective responses have been reported in up to 30% of patients; in particular, complete responses have been reported in 26% of patients with gastroenteropancreatic tumours (Bodei et al., 2013). Treatments are usually administered to adults, although one clinical trial has investigated the potential of  $^{177}\text{Lu}$ -DOTATATE treatment of children and young people with neuroblastoma (Gains et al., 2011).

### 2.7.2. Treatment protocols

(73) Treatment protocols have been standardised with some variations.  $^{90}\text{Y}$ -DOTATATE or  $^{90}\text{Y}$ -DOTATOC is administered as  $3.7 \text{ GBq m}^{-2}$  body surface for two cycles or with a fixed activity of 2.78–4.44 GBq for two to four cycles.  $^{177}\text{Lu}$ -DOTATATE is commonly administered as a fixed activity of 5.55–7.4 GBq over three to five cycles. The interval between administrations varies from 6 to 12 weeks (Bodei et al., 2013). Patients with compromised renal function are given lower activities. Patients with compromised marrow reserves may require a stem cell harvest for subsequent re-infusion, although haematological toxicity is generally low. Combination therapies of  $^{90}\text{Y}$ - and  $^{177}\text{Lu}$ -DOTATATE administered alternately are currently under investigation (Kunikowska et al., 2011; Savolainen et al., 2012; Seregini et al., 2014). Dose escalation trials have not established optimal administration protocols.

(74) High levels of somatostatin receptors are observed in children and young people with neuroendocrine tumours, although, with few exceptions, clinical trials exclude this patient population due to an 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 from hospital, and home circumstances should be taken into account. An individual risk assessment may be required to determine any restrictions on close contact with friends and family when the patient returns home.

### 2.7.4. Radiation dose to staff

(76) For beta-emitting radionuclides, including  $^{90}\text{Y}$  and  $^{177}\text{Lu}$ , particular attention should be given to protect staff who prepare and handle the radiopharmaceuticals. Shielded syringes should be used during the intravenous administration of radiopharmaceuticals as necessary to ensure that extremity doses are maintained below occupational dose limits. Equivalent doses to the finger tips from preparation and administration are typically in the range of 5–10 mSv from single administrations when protection is optimised, but can be >100 mSv if precautions are inadequate. Monitoring the equivalent dose to the finger tips using finger stall dosimeters for the main fingers carrying out manipulations is advised for radiological protection to give a reliable indication of finger dose (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 the kidneys and liver.

Absorbed doses per administered activity from  $^{90}\text{Y}$ -DOTATATE to active marrow, kidneys, and liver have been reported as  $0.03\text{--}0.17\text{ Gy GBq}^{-1}$ ,  $1.71\text{--}2.73\text{ Gy GBq}^{-1}$ , and  $0.27\text{--}0.92\text{ Gy GBq}^{-1}$ , respectively (Cremonesi et al., 2006a, 2010; Bodei et al., 2008). Absorbed doses per administered activity from  $^{177}\text{Lu}$ -DOTATATE to active marrow, kidneys, and liver have been reported as  $0.02\text{--}0.07\text{ Gy GBq}^{-1}$ ,  $0.32\text{--}1.67\text{ Gy GBq}^{-1}$ , and  $0.05\text{--}0.21\text{ Gy GBq}^{-1}$ , 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). Absorbed dose varies significantly from one patient to another (Hindorf et al., 2007; Sundlöv et al., 2017).

### 2.7.6. Risks to patients

(78) As with all therapeutic procedures, pregnancy/breast feeding is a contraindication, and patients should avoid conception. Excretion is predominantly urinary and, hence, amino acids are routinely co-administered to protect the kidneys. Kidney toxicity is observed in some patients (Barone et al., 2005; Imhof et al., 2011), and a biologically effective dose (BED) not to exceed 28 Gy (see Section 4.7) has been recommended for patients with higher risk factors treated with  $^{90}\text{Y}$ -DOTATATE (Bodei et al., 2008). 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) Data show evidence for acute toxicity primarily to the kidneys and bone marrow. The 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 be performed for all patients. The prospect of personalised treatments based on carefully designed dosimetric protocols is quite feasible. There is some evidence that biological parameters such as BED can be of benefit to estimate risks of toxicity to organs at risk, and these should be investigated further (Barone et al., 2005; Wessels et al., 2008).

## 2.8. Radioimmunotherapy

(80) Radioimmunotherapy involves radiolabelled antibodies that target and bind to tumour-specific antigens, and deliver enhanced 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. Common

radionuclides include beta emitters such as  $^{131}\text{I}$ ,  $^{90}\text{Y}$ ,  $^{186}\text{Re}$ , and  $^{153}\text{Sm}$ , and alpha emitters such as  $^{225}\text{Ac}$  and  $^{213}\text{Bi}$  (Sgouros et al., 2010; Larson et al., 2015).

(81) Agents approved by health authorities for general use include  $^{131}\text{I}$ -tositumomab and  $^{90}\text{Y}$ -ibritumomab tiuxetan (Goldsmith, 2010). Both are directed to CD20-positive, relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma. Both agents have a high response rate, with many patients experiencing long-term cancer-free survival.  $^{90}\text{Y}$ -ibritumomab tiuxetan is effectively applied to 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) To date, no radioimmunotherapeutic agent has proved to be effective in achieving sufficiently high absorbed dose to treat solid cancers. Research continues to investigate the efficacy of radioimmunotherapy, with efforts to improve therapeutic ratios with pretargeting (Goldenberg et al., 2012) and increased use of alpha emitters.

### 2.8.1. Aim of treatment

(83) As radioimmunotherapy encompasses a range of procedures, 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 radioimmunotherapeutic procedures.  $^{90}\text{Y}$ -ibritumomab tiuxetan therapy has well-established treatment protocols. Rituximab at  $250\text{ mg m}^{-2}$  is infused over 4 h, followed by an infusion per body weight of  $14.8\text{ MBq kg}^{-1}$  of  $^{90}\text{Y}$ -ibritumomab tiuxetan, not exceeding  $1184\text{ MBq}$ . In some countries and regions, prior to  $^{90}\text{Y}$ -ibritumomab tiuxetan therapy, imaging with  $^{111}\text{In}$ -ibritumomab tiuxetan is performed according to a therapeutic protocol implemented to verify the expected biodistribution and exclude patients who show an altered biodistribution, such as 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.