Strahlenschutzkommission

Geschäftsstelle der Strahlenschutzkommission
Postfach 12 06 29
D-53048 Bonn

http://www.ssk.de

Nuclear medicine therapy

Recommendation by the German Commission on Radiological Protection

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Therapeutische Verfahren in der Nuklearmedizin

Empfehlung der Strahlenschutzkommission

Preface

Major advancements are being made in the specialist field of nuclear medicine where radioactive substances are increasingly being used for imaging diagnostics and therapeutic applications. Today, radioactive iodine therapy for thyroid diseases is accompanied by a plethora of new options, including treatments for oncological diseases involving nuclear medical products that are manufactured in-house and exempt from authorisation under the direct professional responsibility of the attending physicians at the clinics where therapy is subsequently administered. Patient suitability for such therapies is often investigated on a case-by-case basis using an imaging procedure known as thera(g)nostics which involves an identical or very similar carrier substance with diagnostic radiolabelling. Conceptually, this approach is closer to highly selective, locally targeted internal radiotherapy than pharmacological therapy. Particularly with serious malignant disorders, some of these therapies have proven effective once other forms of treatment no longer provide the desired results.

On 5 February 2019, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) asked the German Commission on Radiological Protection (SSK) to prepare an overview of radioactive substances currently used on a regular basis for nuclear medicine therapies, along with their accompanying prerequisites, clinical standards and administration routes. Based on this request, the working group prepared a series of tables containing the therapies currently in use, all aspects relevant to radiation protection, any occurring concomitant nuclides, and activity levels for the therapy to be administered.

This recommendation was prepared by the following members of the ‘Nuclides in nuclear medicine’ working group formed from the ‘Radiological protection in medicine’ committee:

- Prof. Dr. Dr. Dr. h. c. Andreas Bockisch, Essen University Hospital
- Prof. Dr. Andreas Buck, University Hospital Würzburg
- Prof. Dr. Wolfgang Burchert, University Clinic at Ruhr University Bochum Bad Oeynhausen
- Prof. Dr. Alexander Drzezga, University Hospital Cologne
- Prof. Dr. Alexander Haug, Medical University of Vienna
- Prof. Dr. Ken Herrmann, Essen University Hospital
- Prof. Dr. Jörg Kotzerke, Carl Gustav Carus University Hospital in Dresden
- Dr. Jens Kurth, University Hospital of Rostock
- Prof. Dr. Marianne Patt, Leipzig University Hospital
- Prof. Dr. Kambiz Rahbar, Münster University Hospital

The working group was supported by Dr. Christine Klingele (representing the German Federal Office for Radiation Protection - BfS).

Prof. Dr. Alexander Drzezga	*Prof. Dr. Günter Layer*	*Prof. Dr. Werner Rühm*
Chair of the ‘Nuclides in nuclear medicine therapy’ working group	Chair of the ‘Radiological protection in medicine’ committee	Chair of the German Commission on Radiological Protection (SSK)

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1 Introduction

In nuclear medicine, unsealed radioactive substances are used for diagnostic and therapeutic applications. Growing clinical needs have seen a rapidly growing number of nuclear medicine therapies emerge in recent years, in turn requiring the systematic collection and review of questions surrounding these therapies from a radiation protection perspective.

For many years now, iodine-131 has been by far the most frequently administered radiopharmaceutical in nuclear medicine to treat benign and malignant thyroid diseases. Such therapies use pure iodine-131, meaning that no carrier substance is added, so the thyroid tissue absorbs the iodine specifically. Nuclear medicine therapies have developed at pace in recent years, with a number of new approaches emerging that involve the administration of isolated radionuclides or a process where specific carriers target the intended tissue with the therapeutically effective radionuclides. Recent therapies now include alpha emitters to complement existing therapies largely involving beta radiation.

As is the case with radioactive iodine therapy, many of the therapies administered at present are based on a principle known as thera(g)nostics. This means that the same mechanism of specific enrichment of a compound in a particular tissue is used for diagnostics as well as therapeutically. Before administering a radiopharmaceutical as radiation therapy, thera(g)nostics can be used diagnostically to predict the anticipated distribution and enrichment. The selected diagnostic test uses the same binding mechanism and carrier molecule, or a structurally similar carrier molecule with alternative radiolabelling. This concept permits reliable patient selection and targeted therapy approaches which, particularly with oncological disorders, are often associated with comparatively low side effects as the therapeutic activity is accumulated specifically in the diseased tissue. Therapeutic effectiveness is not achieved pharmacologically, but by targeting radiation at the cells accumulating the radiopharmaceutical, and at their neighbouring cells. Any subsequent side effects are the result of radiation and not of pharmaceutical origin.

Given the rapid pace of advancement in this field, several of these theragnostic approaches are yet to receive marketing authorisation or are used off-label. There are a number of reasons for this situation. First, many of the recent developments were devised by universities rather than the pharmaceutical industry. This poses the problem that universities are barely or fully unable to apply for marketing authorisation and conduct the requisite prospective randomised clinical studies, both from financial and organisational perspectives. Second, some of the approaches cannot be patented, in turn making it very difficult for universities to find industrial sponsors for such studies given that the approaches cannot be exploited commercially. Third, some of the approaches have already been submitted for marketing authorisation but have not yet reached approval, while others have only received marketing authorisation for certain possible indications. Without industrial sponsorship, marketing authorisation is inconceivable, at least for the foreseeable future.

By contrast, theragnostics have proven effective in several applications, in turn leading to their swift clinical adoption. As an example, theragnostic approaches have become commonplace after proving successful in treating prostate cancer once all other options have been exhausted. Given the lack of alternatives available, it would be medically unethical to deny patients access to such new approaches which have proven effective, even if the new approaches are yet to receive marketing authorisation. Some of these approaches have even already been added to the corresponding guidelines. In contrast to therapeutic procedures, the production of non-approved preparations for diagnostic radiopharmaceuticals can be carried out by radiochemists and radiopharmacists on the basis of a manufacturing license. The corresponding responsibilities for production, quality control and release are defined in the German Ordinance

on the Manufacture of Medicinal Products and Active Substances (AMWHV 2006), which is based on the Medicinal Products Act (AMG 2005). This option is currently unavailable for therapeutic radiopharmaceuticals because Section 2 of the Ordinance on Radioactive Medicinal Products or Medicinal Products treated with Ionising Radiation (AMRadV 2007) prohibits the sale of therapeutic radiopharmaceuticals while making an exception for diagnostic radiopharmaceuticals. This discrepancy between current clinical use and current state of marketing authorisation has led to nuclear medicine physicians using or being forced to use unauthorised radionuclide therapies at their own responsibility on a significantly regular basis. In such instances, attending physicians at nuclear medicine centres often manufacture radiopharmaceuticals in-house and exempt from authorisation, in compliance with the strict regulatory requirements provided in Section 13 (2b) of the Medicinal Products Act (AMG 2005).

This situation is not expected to change in the near future (or at all in the case of some therapies and indications), hence the aim of this recommendation is to provide a summary of the status quo, and to ascertain the applications already in use in clinics. This recommendation offers physicians, scientists and authorities an overview of therapies and their current state of marketing authorisation, approaches already in clinical use or currently being researched, typical methods to consider, anticipated effects and side effects, and consequences in terms of radiation protection. As a result, this recommendation should serve to standardise therapies across multiple locations, in turn simplifying handling and possibly also improving safety.

Given the rapid pace of development in this field, the present recommendation should not be deemed complete and likely in need of updates to remain valid and applicable in the future. It should also be noted that the effects and side effects are only outlined here to provide a general idea of the respective approach. This information should never be deemed complete and must not be used as a basis for further medical decisions or to inform patients. When compiling this information, the focus was not on collating all of the physical and radiological data on (concomitant) nuclides, such as half-lives, probabilities and transition energy, meaning that no assurance can be given as to the completeness and correctness of the information provided, thus requiring further research of the applicable sources and literature.

1.1 Advisory mandate

In nuclear medicine, radioactive substances are administered to patients for diagnostic and therapeutic purposes. New medical therapies are emerging at a rapid pace and include many ways of using specific ligands to accumulate radionuclides in tumour tissue.

Here, radioactive substances are used in medical research and for established therapies with marketing authorisation. In everyday clinical practice, these substances are also used off-label, and a number of more recent therapies without approved commercial alternatives (at present) are manufactured in-house and exempt from marketing authorisation within the purview of the Medicinal Products Act (AMG 2005) and under the direct professional responsibility of the attending physicians at the clinics where therapy is subsequently administered. One such example is [^{177}Lu]Lu-PSMA (prostate-specific membrane antigen) radioligand therapy for metastatic castration-resistant prostate cancer which is already established in a number of clinics. This in turn raises the question of which specific criteria must be followed when preparing and administering such therapies.

To determine this, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) asked the German Commission on Radiological Protection (SSK) to prepare an overview of radioactive substances currently used on a regular basis for nuclear medicine therapy with a focus on the following aspects:

- Information about the disease/tumour along with the type of therapy
- Information about the nuclide, including any concomitant nuclides, with regard to the physical characteristics of the radiation emitter, therapy specificity, biokinetic properties of the carrier substance and nuclide, and target volume
- Typical level of activity to be administered on a case-by-case basis
- Evaluation of the extent to which therapy is conducted as part of medical research
- Need to hospitalise patients or conditions under which therapy can be performed in an outpatient setting.

1.2 Methods

The following indications/therapies are covered in this recommendation:

- Thyroid diseases (radioactive iodine therapy)
- Prostate cancer (prostate-specific membrane antigen (PSMA) ligand therapy)
- Neuroendocrine tumours (peptide receptor radionuclide therapy – PRRT)
- Bone metastases (enossal pain therapy/radium-223 dichloride)
- Joint diseases (radiosynoviorthesis)
- Liver tumours (selective internal radiotherapy – SIRT)
- Haematological/oncological disorders (radioligands and radioimmunotherapy)

The working group adopted a systematic approach to prepare an overview of established approaches for administering such nuclear medicine therapies, along with their accompanying prerequisites, particularly in terms of radiation protection. Information is provided in the form of tables and text which serve as a guide for users, and for assessment and evaluation purposes by the responsible authorities. It also includes specific recommendations with a view to pre-requisites and practical administration in line with radiation protection requirements, and is structured as follows:

- SSK recommendation (Chapter 2)
- Explanation of the recommendations (Chapter 3)
- Scientific justification for each approach covered in this recommendation, including clinical justification scenarios, the status quo of the therapy, and an outlook. These descriptions are accompanied by tables that provide details of the respective therapy/radiopharmaceutical as the therapeutic nuclides administered differ in terms of biodistribution depending on whether and which carrier substances are involved. This leads to different therapeutic effects and, in turn, different application types and indications. These radiopharmaceuticals have properties relevant to radiation protection which are not only based on the physical characteristics of the corresponding isotopes, but also on biodistribution as well as retention and excretion from the body. The tables include details of therapies currently administered on a broad scale, along with information about the radiopharmaceuticals/carrier and accompanying substances, indications, effects and possible side effects, manufacture and procurement of radio-pharmaceuticals, marketing authorisation status, subsequent radioactive waste and its disposal, administration routes and typically administered activity, radiation exposure, radiation protection measures, therapy setting (in-patient or outpatient), discharge re-quirements and dosimetry.

- Therapy nuclides tables (see Annex A-1) for the therapy nuclides clinically relevant at present, including the nuclides' physical properties (half-life, radiation type, energy spectrums, etc.) as well as points to bear in mind during handling and disposal given that such information may apply to other radiotherapeutics.

Where possible, the consensus nomenclature rules for radiopharmaceutical chemistry have been followed (Coenen et al. 2017), although the designation for the carrier-added radiolabelled radiopharmaceutical has been used in certain instances where the status of the radionuclide used for radiolabelling is or could be unclear in terms of the presence of stable isotopes (carriers).

2 SSK recommendation

From a radiation protection perspective, the following main quality criteria should be applied when administering nuclear medicine therapies:

Recommendation 1 Infrastructural requirements

The SSK recommends ensuring that suitable specialist facilities are provided and maintained as prerequisites for approval to prepare and administer therapies. The SSK would like to point out that this recommendation applies to therapies involving commercially available and in-house-manufactured radiotherapeutics, and extends to sufficiently qualified staff and structural requirements.

Recommendation 2 Need for hospitalisation

Many of the approaches require an inpatient stay on a nuclear medicine ward to satisfy medical and radiation protection requirements. When planning a patient's discharge, the public exposure caused per calendar year must be taken into consideration (particularly with multiple therapy cycles). When assessing a patient's suitability for discharge and the necessary subsequent radiation protection measures, the attending physician should consult with the medical physics experts involved and decide on the basis of individual dosimetric assessments rather than general assumptions.

Recommendation 3 Quality assurance in the manufacture of nuclear medicine therapeutics

The licence holder is responsible for assuring the quality of commercially available radiopharmaceuticals, while the manufacturer is responsible for quality assurance during on-site production (pharmaceutical/chemical quality, radionuclide purity). From a clinical perspective, off-label therapies and therapeutic radiopharmaceuticals manufactured in-house have become established and are deemed medically necessary for a number of indications. The SSK recommends retaining such options. From a radiation protection viewpoint, the SSK considers it necessary to provide a clear legal framework for such forms of manufacturing and their accompanying authorisation studies.

Recommendation 4 Disposal of radioactive waste from nuclear medicine

Radioactive waste must be disposed of properly and is therefore governed by corresponding limits and legislation. The SSK notes that proper disposal is an integral part of a therapy and recommends that for each individual delivery, commercial providers should be required to supply accurate disposal information for commercially available radiopharmaceuticals (i. e. no general statements or mean values), including relevant concomitant nuclides. The cost of radioactive waste disposal is to be included in the cost of therapy.

3 Explanation of the recommendations

3.1 Infrastructural requirements for nuclear medicine therapies

Suitable specialist facilities for administering therapies must be provided and expanded where necessary. This applies both to the administration of commercially available therapeutics and, above all, to individual therapeutic radiopharmaceuticals manufactured and administered in-house and exempt from authorisation at present (AMG 2005).

Approval should be subject to the presence of qualified staff (nuclear medicine physicians, nuclear medicine assistants and care staff, medical physics experts, radiochemists/radiopharmacists) as well as structural requirements to ensure radiation protection when manufacturing, handling and administering radiopharmaceuticals, providing inpatient stays, disposing of radioactive waste, and for the decontamination plant. The requirements placed upon nuclear medicine centres in Germany must be observed, with updates made accordingly to keep pace with legislation and to ensure compliance in the future (AMG 2005, StrlSchG 2017). Expenses incurred to ensure radiation protection must be included when calculating the treatment costs to be covered.

3.2 Need for hospitalisation

Many forms of nuclear medicine therapy require hospitalisation for medical and radiation protection reasons, such as patient exposure, excretions, and waste treatment. The tables in the scientific justification section of this recommendation provide specific information about discharge criteria for each therapy. Section 122 (4) of the German Radiation Protection Ordinance (StrlSchV) only allows patients to be discharged from the radiation protection area of a nuclear medicine ward if it can be assumed that relatives and third parties will not receive an effective dose of more than 1 mSv. The Guidelines of Radiation Protection in Medicine of 26 May 2011 (GMBl. 2011, nos. 44-47, p. 867), last updated by circular of the Federal Ministry for the Environment, Nature Conservation, Buildings and Nuclear Safety (BMUB) of 11 July 2014) (GMBl. 2014, no. 49, p. 1,020) (BMUB 2011), Chapter 6.7,2, pp. 26-27) and based on the radiation protection law valid until 30 December 2018, require patients who have been treated with unsealed radioactive substances to spend at least 48 hours post-treatment in the ward's observation area designed to ensure radiation protection (structural radiation protection, waste water treatment plant, trained staff, etc.). This period of time is based on experience with radioactive iodine therapy, but also applies to other nuclides and approaches. After 48 hours, patients can be discharged subject to the criteria set out below. With multiple cycles of therapy, the total possible exposure from all therapy cycles within a calendar year is to be taken as a basis for assessment (see below). Outpatient treatment is an option if it can be reliably ruled out that relatives and third parties will receive an effective dose of more than 1 millisievert per calendar year (due to the surface dose rate and factors such as excretion, contaminated bandages and dressings, etc.), and if it can be ensured that radioactive body fluids will be disposed of properly. Section 6.7.3 of the Guidelines of Radiation Protection in Medicine lists several therapies which can be performed in an outpatient setting.

– The need for hospitalisation extends beyond radiation protection (dosimetry, medical patient observation). According to a ruling by the Federal Social Court (based on an example involving radioactive iodine therapy), hospitalisation should be considered part of the medical treatment and therefore subject to reimbursement by health insurance companies (Federal Social Court, ruling of 30 July 2019, B 1 KR 15/18 R).
– Section 122 (4) of the German Radiation Protection Ordinance (StrlSchV 2018) requires the radiation protection executive to only allow patients to be discharged from the radiation

protection area if it can be assumed that relatives and third parties will not receive an effective dose of more than 1 millisievert per calendar year.

– In addition, the radiation protection executive must ensure that discharges of radioactive substances with waste water from radionuclide wards and excretions as per Section 99 of the German Radiation Protection Ordinance (StrlSchV) are constantly monitored and comply with the prescribed limits. Other requirements laid down in Sections 100 to 102 of the German Radiation Protection Ordinance (StrlSchV) also apply.

– Some therapies are typically administered in multiple cycles to achieve the intended therapeutic effect. This leads to an accumulation of public exposure to radiation from patients over the course of a calendar year which must be taken into account when discharging every single patient, and may require prolonged inpatient stays as a result.

– When assessing whether a patient can be discharged from a radiation protection standpoint, along with whether and for how long radiation protection measures may be required post-discharge, the attending physician will consult with the medical physics experts involved and take a decision based on individual dosimetric assessments rather than general or average assumptions. Details of the different forms of therapy are provided in the tables in the respective chapters.

  Unlike therapies that only use beta and alpha emitters, therapies involving radionuclides which emit a significant level of gamma radiation require particular attention when considering a patient's discharge due to the resulting public exposure.

3.3 Quality assurance in the manufacture of nuclear medicine therapeutics

The licence holder is responsible for ensuring the quality of commercially available radiopharmaceuticals. From a clinical perspective, off-label therapies and therapeutic radiopharmaceuticals produced in-house have become established for a number of indications provided below in the scientific justification section of this recommendation and based on the status quo in 2022. These therapies must be retained where medically required to ensure patient care, at least until marketing authorisation can be extended or until authorised preparations of equal quality and effectiveness can be readily supplied.

To this end, patients in Germany have access to nuclear-medical diagnostics and treatment, including radiopharmaceuticals not approved for commercial distribution which can be produced on-site and by the attending physicians. Quality assurance for on-site production is performed by the manufacturer in accordance with current legislation and the state of the art in science and technology.

By permitting this, legislators acknowledge the various reasons why radiopharmaceuticals are of limited commercial availability. For example, some diagnostic radiopharmaceuticals cannot be transported or delivered from one centre to multiple recipients due to their extremely short half-lives ranging from just a few minutes to several hours. In other instances, patenting is not an option, in turn making it impossible to market the active substances used. This lack of opportunity for commercial exploitation prevents a product from reaching the market at all or only with a significant delay between its development and market availability for clinical applications. The carrier substance usually cannot be expected to have any pharmacological effect given the low quantity of carrier substances used for radiolabelling in diagnostic radiopharmaceuticals. Therapeutic radiopharmaceuticals do not achieve their intended effect pharmacologically, but by delivering radiation specifically to the target tissue. Consequently, these approaches cannot be compared with other pharmacological therapies, which is why established marketing authorisation processes also only appear to be of limited suitability.

For this reason, exception from the general obligation to obtain a marketing authorization (Section 21 (1) AMG (AMG 2005)) and from the ban on marketing (Section 7 (1) AMG) have already been created. The requirements for these exceptions are laid down in Section 2 (1) (3) of the Ordinance on Radioactive Medicinal Products or Medicinal Products treated with Ionising Radiation (AMRadV 2007). To date, these exceptions typically only applied to diagnostic radiopharmaceuticals, meaning that radiopharmaceuticals for therapeutic applications could not be manufactured and administered in compliance with this legislation.

In the event that such preparations are not available as authorised medicinal products, Section 13 (2b) (1) of the Medicinal Products Act (AMG) permits attending physicians to manufacture them in-house and exempt from authorisation. When doing so, physicians can, but are not obliged to, request assistance from correspondingly qualified experts such as radiochemists/radiopharmacists. As a result, these therapies are still assessed in the same way as pharmacologically active substances under the Medicinal Products Act (AMG 2005), but they do not account for the fact that both the effects and side effects of the therapies are due to targeted radiotherapy and not the result of pharmacological effects.

In general, the effects and risks of new nuclear medical therapies need to be assessed specifically. Given the empirically low frequency of side effects, (central) registers could be used to build up a catalogue of cases covering the effects and side effects of such therapies that is large enough to be able to apply for marketing authorisation.

Needs-based in-house manufacture and administration of commercially unavailable radiopharmaceuticals have proven safe and reliable over the course of several decades. In view of this, the common practice in Germany is considered to be highly successful, both in Germany and internationally. It is essential to maintain this reputation in the future, not least due to the fundamental importance of early clinical introduction of innovative treatment methods and their associated benefits for patients requiring treatment.

In view of this, and particularly from a radiation protection perspective, legislation should be updated, especially medicinal product-related regulations, to adequately accommodate aspects particular to radiopharmaceuticals. The obvious option here would be to include a provision on nuclear medicine therapies in the Ordinance on Radioactive Medicinal Products or Medicinal Products treated with Ionising Radiation (AMRadV) (AMRadV 2007), similar to the one for diagnostic nuclear medicine procedures. Adding such a provision would ensure sufficient regulation of radiopharmaceutical manufacturing in terms of medicinal product safety, while also facilitating individualised patient care (Patt et al. 2021).

3.4 Disposal of radioactive waste from nuclear medicine

Radioactive waste from nuclear medicine therapies must be disposed of correctly in accordance with corresponding statutory limits and legislation. The cost of radioactive waste disposal is to be included in the cost of therapy.

When short-lived radionuclides (main nuclides with a half-life of hours to days) are produced as required for nuclear medicine, there is a risk of contamination with small quantities of (long-lived) radioactive isotopes (concomitant nuclides) in some cases which may be relevant for clearance in individual cases. Each individual delivery of commercially available radiopharmaceuticals should be supplied with accurate disposal information (i. e. no general statements or mean values), particularly when it comes to relevant contaminations (Freudenberg et al. 2022, Gehr et al. 2022).

Radioactive waste from nuclear medicine is largely disposed of according to the requirements for an unrestricted clearance, as provided for in Section 35 of the German Radiation Protection

Ordinance (StrlSchV 2018) where the main criterion is compliance with the limits for surface contamination in Annex 4, Table 1, Column 3 of the German Radiation Protection Ordinance (StrlSchV). The requirements for this are provided in Section 42 (2) of the German Radiation Protection Ordinance (StrlSchV 2018) which states that measurements of the specific activity (clearance measurements) are required to determine agreement with the content of the clearance notice. For radionuclides with a sufficiently short half-life, proof of compliance with clearance levels can also be demonstrated by providing a corresponding decay period based on the given initial activity and half-life (decay storage). Consequently, every object contaminated when preparing and carrying out examinations and therapy must be collected separately from other non-contaminated waste and then also disposed of separately. Contaminated objects include transport containers and materials used during each respective step, such as swabs, syringes, cannulas, patient bed pads and gloves, since they may be contaminated as well. Any remaining liquids, e. g. in vials or syringes, should not be removed and then disposed of separately so as to minimise any additional exposure and, above all, contamination risk. Waste arising in connection with radiotherapy must be collected and disposed of in a special collection container. This step differs from other waste management procedures followed by health services (hospitals or doctors' practices) where the primary focus is hygiene, injury avoidance (from handling glass or cannulas) and separation of waste by material. For this particular step, unrestricted clearance depends upon the specific activity, which is determined by calculating the quotient of the activity of the waste to be cleared and its mass. Depending on the amount of waste present, activity can be measured using an activimeter (dose calibrator), semiconductor spectrometer, contamination monitor or other suitable measuring equipment (Wanke und Geworski 2014). Activity from known contaminations by concomitant nuclides must be measured and taken into consideration.

The waste mass is measured by weighing the empty collection container designated for clearance, then filling it with radioactive waste and subtracting the empty mass of the container.

Clearance may be issued if the respective levels in Annex 4, Table 1 of the German Radiation Protection Ordinance (StrlSchV) are complied with when applying the sum formulae from Annex 8 of the German Radiation Protection Ordinance (StrlSchV 2018) to mixtures containing several radionuclides. Here, it is important to include any contaminations and to ensure that the proportion of the nuclides that are not considered does not exceed 10 % of the sum formula (Annex 8, Part A, No. 1e of the German Radiation Protection Ordinance (StrlSchV)). Particular emphasis is to be placed on the relevance of concomitant nuclides with a half-life that far exceeds that of the main nuclide as its proportion of total activity will increase over time.

As well as unrestricted clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV), radioactive substances can be disposed of by way of specific clearance as provided for in Section 36 the German Radiation Protection Ordinance (StrlSchV), clearance in individual cases as defined in Section 37 of the German Radiation Protection Ordinance (StrlSchV), or at a federal state collecting depot.

Disposal can incur considerable expense, particularly when unrestricted clearance is not an option and waste must be disposed of at a federal state collecting depot. This situation needs to be accounted for in cost calculations. Reimbursement of all incurred costs should be ensured in the interests of upholding radiation protection.

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Patt et al. 2021 Patt M, Kuwert T, Luster M, Krause BJ, Solbach C. Regulatorische Anforderungen an Radiopharmaka in Deutschland: die Fachgesellschaft im behördlichen Dialog. Nuklearmedizin. 2021 Feb;60(1):55-8, doi: 10.1055/a-1288-6725, Epub 2021/02/04

StrlSchG 2017 Gesetz zum Schutz vor der schädlichen Wirkung ionisierender Strahlung (Strahlenschutzgesetz - StrlSchG) vom 27. Juni 2017 (BGBl. I S. 1966), das zuletzt durch Artikel 11 des Gesetzes vom 12. Dezember 2019 (BGBl. I S. 2510) geändert worden ist

StrlSchV 2018 Verordnung zum Schutz vor der schädlichen Wirkung ionisierender Strahlung (Strahlenschutzverordnung - StrlSchV) vom 29. November 2018. BGBl. I S. 2034, 2036, die durch Artikel 1 der Verordnung vom 27. März 2020 (BGBl. I S. 748) geändert worden ist

Wanke und Geworski 2014 Wanke C, Geworski L. [Conservative calibration of a clearance monitor system for waste material from nuclear medicine]. Z Med Phys. 2014 Sep;24(3):252-60, doi: 10.1016/j.zemedi.2014.01.001, Epub 18. 02. 2014

Specific descriptions of the individual therapies

Scientific justification

1 Radionuclide therapy for thyroid diseases involving radioactive iodine (radioiodine)iodine-131 therapy (RAI)

Within the context of radioactive iodine therapy, the term radioactive iodine is used to describe the isotope iodine-131. Radioactive iodine therapy has been well established since the 1950s as a means of treating benign and malignant thyroid diseases.

1.1 Indications and therapy goals

1.) Benign thyroid diseases (focal or disseminated functional thyroid autonomy, Graves' disease (hyperthyroidism), hypertrophy/struma requiring treatment) with the aim of eliminating autonomous parts of the thyroid gland tissue (autonomy) or performing ablation of thyroid gland tissue (Graves' disease) or to reduce tissue volume.

2.) Malignant thyroid diseases (differentiated thyroid cancer – DTC) and PDTC (poorly differentiated thyroid carcinoma – PDTC) as adjuvant therapy with the aim of eradicating occult metastases or remaining thyroid tumour tissue and as a positive side effect of remnant ablation of post-operative thyroid tissue. Radioactive iodine therapy is also used successfully in the treatment of locally persistent primary cancer and in relapse cases.

1.2 Implementation

1.2.1 Preparation and therapy planning

Re: 1.) Stable thyroid function is preferable before administering radioactive iodine therapy (RAI) for benign disorders. Iodine excess, such as administering iodinated contrast media or medication with a high iodine content, can prevent radioactive iodine therapy from being successfully performed for prolonged periods. Therapeutic target doses have been stipulated for the given disease (Recommendation for Action, German Society of Nuclear Medicine (DGN) 2015). To determine the activity to be administered to achieve the necessary target dose (depending on the target volume, iodine uptake and duration in the thyroid gland), an individual radioactive iodine test is performed with a low level of iodine-131 activity (reference activity) compared to that administered during therapy. Both the radioactive iodine test and the subsequent RAI should be performed in a stable baseline iodine metabolism. If therapeutic thyrostatic medication is required to pharmacologically inhibit the thyroid function, a brief break from taking the medication pre-therapy typically leads to improved iodine uptake and significantly reduces the level of iodine-131 activity needed during therapy.

As the organ equivalent dose achieved with RAI depends on intrathyroidal metabolism and, to some extent, on general metabolism, individual cases can occur where achieved dose significantly deviates from the planned dose without there being an underlying error in the application. However, minor deviations typically have no impact on the success of the treatment as RAI has a very broad therapeutic effect.

With benign thyroid diseases, RAI sometimes is considered in competition with operative therapy options. The extremely low risk of radiation-induced secondary malignancies, which only occur years later (if at all), is comparable with that of perioperative lethality. The benefit of RAI is that it avoids any potential complications from operations (hypoparathyroidism, vocal cord paresis, general complications arising after an operation, rare complications such as paralysis of the shoulder muscle by damaging the accessory nerve, or a lymphatic fistula by damaging the thoracic duct) as well as scars and a potentially extended healing period. In contrast to operations, however, RAI only starts to have an effect several days to a few weeks after being administered. Decisions on whether to operate or to administer radioactive iodine

therapy should be based on individual clinical and subjective criteria. Clinical situations may arise where both options make sense from a medical perspective.

Re: 2.) Radioactive iodine is largely administered as an adjuvant therapy for differentiated thyroid cancer after undergoing a thyroidectomy. Here, RAI serves to eliminate any remaining tumour cells and occult metastases, and to prevent relapses. With this indication, RAI has proven to be effective and, unlike many other adjuvant oncological therapies, is associated with a very positive side-effect profile (see below). As a consequence, post-operative RAI has established itself as a safe and well-tolerated form of therapy in Germany. In addition, radioactive iodine therapy has high curative potential in case ofo initially persistent remaining tumour cells or metastases, and in the event of relapses (DGN 2015). Therapy is administered with standard activity doses (typically 1 GBq to 4 GBq per cycle, also up to 7 GBq per cycle in the event of a higher risk status and up to 18 GBq per cycle for targeted metastasis therapy). Pre-therapy dosimetry is generally of little use with adjuvant therapy given that the aim of therapy is to target any occult metastases not detectable during imaging. Radioactive iodine therapy for thyroid cancer involves TSH (thyroid-stimulating hormone) stimulation by pausing thyroxine treatment for several weeks or by administering rhTSH (recombinant human thyroid-stimulating hormone). rhTSH is not formally approved for metastasis therapy, but can be justified in individual cases, e. g. if pausing thyroxine treatment is not or barely feasible/clinically justifiable, after explaining the intended off-label use to the patient. Alimentary consumption of iodine should be reduced insofar as possible, along with any other iodine uptake before and during therapy as this will compete with the radioactive iodine, in turn reducing the radiation dose in the target tissue (tumour). Mandatory follow-up after adjuvant radioactive iodine therapy, after treating metastases, or in the event of relapses can only be performed with one nuclide suited to detecting low iodine-absorbing tissue. This excludes the use of technetium -99m and iodine-123 due to their respective half-life being too short. Such diagnostics are typically performed six to twelve months after the final cycle of iodine-131 therapy and involve activity of 0.4 GBq to 1.0 GBq. The same rules apply to both radiation protection and therapy.

1.2.2 General course of therapy

Before radioactive iodine therapy is administered, patients are informed about their disease and the aim of therapy. Information covered during such conversations includes potential side effects and the risk of radiation-induced neoplasm, while putting this into the context of leaving the illness untreated. Alternative therapies are also discussed with a view to their advantages and disadvantages compared to RAI.

Here, RAI is typically administered orally by way of a capsule containing the prescribed activity which may vary by +/- 10 %. Administration of the prescribed activity intravenously or as an oral solution is only performed in exceptional cases for radiation protection reasons (e. g. to avoid the risk of contamination). Radioactive iodine therapy must be performed as an inpatient treatment, with a minimum stay of 48 hours. During this time, the majority of the unbound activity is excreted renally, with some unbound activity exhaled (typically 30 % to 70 % when treating ‘benign diseases’, > 90 % when treating ‘malignant diseases after a thyroidectomy’). Any activity remaining in the body after 48 hours is typically organically bound. Dose rate measurements are taken at predefined intervals during an inpatient stay to determine the therapy dose and earliest possible time of discharge from a radiation protection perspective. Additional measurements are also taken when treating benign thyroid diseases to determine the therapy dose accumulated in the target tissue.

Therapy is administered as an inpatient treatment, with patients discharged after a minimum of 48 hours in line with (SSK 1996) and Section 9.1 of the Guidelines of Radiation Protection in

Medicine. During this time, the majority of the unbound activity is excreted renally, thus requiring an adequate treatment plant for radioactive waste water as stipulated in DIN 6844-2. Upon discharge, patients must not expose relatives and third parties to an effective dose of more than 1 mSv (Section 80 (1) of the German Radiation Protection Act (StrlSchG 2017) and Section 122 (4) of the German Radiation Protection Ordinance (StrlSchV 2018)). This ensures that upon discharge, the dose rate measured at a distance of 2 metres from the surface of the patient is below the threshold of 3.5 $\mu Sv\ h^{-1}$ (SSK 1996).

1.2.3 Contraindications and side effects

Side effects from radioactive iodine therapy may occur depending on the activity administered and include, for instance, temporary nausea (only) after thyroid cancer therapy, and temporary low to medium pain after therapy for any remaining thyroid tissue. Reduced function of the parotid glands (Jentzen et al. 2006, Riachy et al. 2020) and sometimes the tear glands eventually occurs primarily (and rarely also persistently) during therapy involving high activity levels. The likelihood of radiation-induced secondary malignancies depends on the total activity administered, which in turn is determined by the individual risk and thus of secondary importance overall. Contraindications include, in particular, pregnancy and breastfeeding.

Table 1.1: Radioactive iodine therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	-	-	-
Known pharmacological effects of unlabelled carrier/accompanying substances in administered quantity	**-**	-	-
Known side effects of unlabelled carrier/accompanying substances in administered quantity	**-**	-	-
Typically administered quantity	**-**	-	-

Procurement/preparation of [^{131}I]iodine	
Name	[^{131}I]iodine
Commercially available radiopharmaceutical	Yes
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	2116 (Capsule) 0281 (Solution) 0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	-

Active waste from manufacture/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	-	-
Radiation type (%α, %β, %γ)	-	See Table A-1.2
Energy spectrums (α, β, γ)	-	See Table A-1.2
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	-	-
Disposal of residual substances and waste water		Potentially contaminated material is stored until decayed and disposed of conventionally after clearance. Patient excretions are collected in a waste water treatment plant (decontamination plant) and discharged to the sewerage system once the activity concentration is low enough.

Administration of radiopharmaceutical			
	Type and quantity used to treat benign diseases	**Type and quantity used to diagnose malignant diseases**	**Type and quantity used to treat malignant diseases**
Typically administered activity per therapy cycle	200 MBq to 1,200 MBq (up to 1,800 MBq in individual cases)	400 MBq to 1,000 MBq	2 GBq to 11 GBq (1 GBq to 18 GBq in individual cases)
Administration routes	Typically oral	Typically oral	Typically oral
Typical number of administrations/therapy cycles	1	1	1 to 2
Typical time between therapy cycles	-	-	3 to 6 months
Limiting factors for repeating therapy (e. g. dose-limiting organ)			Bone marrow function, lungs Limit only reached in exceptional cases

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{131}I]iodine	Thyroid hormones
Biological action of the radiopharmaceutical	Elimination of functioning thyroid gland (tumour) tissue after internalisation via sodium/iodide (NIS) symporter	-
Biodistribution/specific accumulation in	Thyroid gland, incl. differentiated thyroid cancer	-
Non-specific/non-target accumulation dominant in	Salivary glands, stomach, bladder (urine); active thymus gland, lactating woman	-
Known common side effects (> 10 %)	During therapy for benign diseases: Hypothyroidism, temporary feeling of pressure for a few hours with no pathological significance During therapy for malignant diseases: Reduced salivary gland function, not always subjectively deemed limiting. Minor nausea for a few hours (radiation-induced gastritis)	-
Rare severe side effects	-	-

Dose/dosimetry			
	Therapy for benign diseases	**Adjuvant therapy for malignant diseases**	**Therapy for malignant diseases with an active tumour**
Typical effective dose per therapy session per patient (per administration)	Variable	Variable	Variable
Typical effective dose (total for all patient cycles)	Variable	Variable	Variable
Dose-limiting organ	-	Bone marrow is hardly ever reached	Bone marrow Lung only reached in exceptional circumstances
Intended dose target region	100 Gy to 400 Gy depending on the disease	Risk-dependent standard activity	Typically standard activity The maximum therapy activity can be measured with blood dosimetry. >> 100 Gy is aimed for with lesion dosimetry
Required pre-therapy dosimetry and imaging	Probe measurement or scintigraphy with iodine-131	Scintigraphy of remaining thyroid tissue No dosimetry	Imaging in event of relapse (local or metastases), possibly PET/CT imaging and dosimetry with iodine-124
Required post-therapy dosimetry and imaging	Post-therapy radiotracer scintigraphy required Intratherapeutic dosimetry. Determination of the dose rate upon discharge	Imaging (radiotracer scintigraphy); dosimetry of target volume generally not possible and should not be required as a rule Determination of the dose rate upon discharge	Imaging (radiotracer scintigraphy); dosimetry of target volume generally not possible and should not be required as a rule Determination of the dose rate upon discharge

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	[^{131}I]iodine
Excretion modes	Renal/urine; gastrointestinal/faecal; pulmonal/airborne
Excretion route most relevant for radiation protection	Renal
Typical duration of excretion relevant for radiation protection	2 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital)
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	γ
Type(s) of radiation emitted by patient most relevant to radiation protection	γ
Anatomic focal points of radiation (where present)	Thyroid gland
Typical duration of radiation relevant for radiation protection emitted by patient	Benign: typically 2 to 5 days Malignant: typically 2 days
Required radiation protection measures in hospital and post-hospital	Therapy ward with waste water treatment plant (decontamination plant) Post-hospital: Primarily hygiene, possibly keeping distance from relatives

Surroundings (other persons in same household)	
Typical dose to other persons in same household per therapy session	< 1 mSv[1]
Total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv[2]
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stays where required	Upon discharge, all envisaged therapy cycles within a calendar year must comply with the limit. Calculation of exposure is only required under certain circumstances, e. g. a patient requiring care who needs to be discharged as soon as possible

Hospitalisation concept	
Inpatient setting necessary	Yes
Reasons why hospitalisation is needed to administer therapy safely	Collect excretions Protect the public from radiation Administer intratherapeutic dosimetry
Reasons why outpatient care is possible, but hospitalisation may be required	Not applicable, hospitalisation required

Therapeutic indication(s)	
Approved indications	Benign: Therapy for hyperthyroidism (possibly compensated or latent with medication), e. g. thyroid autonomy for or after Graves' disease (hyperthyroidism), struma reduction, ablation of residual tissue for Graves' disease Malignant: Adjuvant therapy (ablation therapy), relapse or metastasis therapy
Current typical indications for therapy as an individual curative treatment	Not applicable
New indications arising from studies/research	Not applicable
Therapy already added to guidelines	Yes

Reimbursement	
Inpatient	DRG
Outpatient	Not applicable, as prohibited
Reimbursement issues	-

2 Radionuclide therapy involving PSMA ligands

Prostate-specific membrane antigen (PSMA) is located in the cytosol in normal prostate cells and switches to a membrane-bound protein in prostatic carcinoma and its metastases, particularly at the castration-resistant stage. The radiopharmaceutical localises PSMA-positive prostate tumour tissue and can detect both bone metastases and soft-tissue metastases. Therapy involves the administration of a radiopharmaceutical (PSMA ligand) labelled with, for instance, lutetium-177. The aim of therapy is to eliminate, or at least inhibit or slow the growth of tumour cells, e. g. in bone metastases and soft-tissue metastases.

[1] Section 81 of the German Radiation Protection Act (StrlSchG)

[2] Section 81 of the German Radiation Protection Act (StrlSchG)

2.1 Indications and therapy goals

PSMA radioligand therapy is currently administered to patients with castration-resistant prostate cancer with soft-tissue metastases and/or bone metastases.

For indication of therapy, all of the following preconditioins have to be met:

1. Histopathologically diagnosed prostate cancer
2. PSMA-positive metastases (PSMA-PET or PSMA scintigraphy)
3. Progression during therapy

Indication is determined by reviewing all clinical information and, in particular, alternative therapy options for each individual patient. Clinical case presentation in the context of an interdisciplinary tumour board is an established procedure in such instances. PSMA radioligand therapy is now used in addition to previously administered forms of therapy. [^{177}Lu]Lu-PSMA-617 (trade name PLUVICTO^{TM}) received FDA approval in the USA in March 2022 following the positive results of a phase III study (VISION) and having achieved the primary endpoints (Sartor et al. 2021). European marketing authorisation by the EMA is expected to be granted in the near future. The phase III study involved patients with metastatic castration-resistant prostate cancer treated with at least one round of chemotherapy (docetaxel) and at least one round of new-generation androgen deprivation therapy (ADT) (abiraterone/enzalutamide) (Rahbar et al. 2019). If prior [^{177}Lu]Lu-PSMA-617 therapy fails, some treatment centres perform additional alpha-emitting actinium-225 targeted PSMA-radioligand therapy (Feuerecker et al. 2021). Standalone use of this therapy would need to be evaluated in prospective studies. The Australian phase II study (Hofman et al. 2021) compared the effectiveness of [^{177}Lu]Lu-PSMA-617 with cabazitaxel in men with metastatic castration-resistant prostate cancer. [^{177}Lu]Lu-PSMA-617 therapy was shown to have a higher biochemical (PSA) response with fewer side effects (Hofman et al. 2021). In view of this, second-line chemotherapy is not considered mandatory before [^{177}Lu]Lu-PSMA-617 therapy.

2.2 Implementation

2.2.1 Preparation and therapy planning

After indication, patients are informed about the aim of therapy, how it will be administered, the potential side effects and alternatives before arriving at a mutual decision on the course of therapy. A number of tests are performed pre-therapy, including a renal function scintigraph to exclude any obstructions. In the event of obstructive uropathy, a urethral catheter or ureteric stent should be inserted where possible to provide relief.

2.2.2 General course of therapy

In general, [^{177}Lu]Lu-PSMA radioligand therapy is administered in a series of up to six cycles, each six to eight weeks apart. In individual cases, additional cycles in one or more series may be performed after a break in therapy and upon repeat presentation for tumour treatment.

Typical courses of therapy include 6.0 GBq or 7.4 GBq of [^{177}Lu]Lu-PSMA radioligand therapy (PSMA-617 or PSMA-I&T (imaging & therapy)). After two cycles of therapy, PSMA imaging is performed to monitor the progress and determine early on whether the therapy is working or not so it can be changed if necessary.

Therapy is administered on an inpatient basis, with the majority of the unbound activity (up to 80 %) excreted renally within 48 hours (Kurth et al. 2018). As a result, patients are required to spend at least 48 hours in a nuclear medicine ward with a waste water treatment plant

(decontamination plant) for radioactive waste water as stipulated in DIN 6844-2 (DIN 6844-2 2020). Upon discharge, patients must not expose relatives and third parties to an effective dose of more than 1 mSv of ionising radiation (Section 80 (1) of the German Radiation Protection Act (StrlSchG 2017), Section 122 (4) German Radiation Protection Ordinance (StrlSchV 2018)). As is the case with radioactive iodine therapy, this is ensured by not discharging the patient until the dose rate measured at a distance of 2 metres from the surface of the patient is below a threshold of 1 mSv when applying the integral dose (SSK 1996). When determining the threshold, it must be taken into consideration that PSMA-targeted therapy consists/may consist of multiple cycles administered within a calendar year. As a result, the discharge limit must take into consideration the number of therapy cycles. Table 2.1 summarises the various thresholds as given by Stoll, accounting for the physical half-life of lutetium-177 (Stoll 2018).

Table 2.1: Dose rate not to be exceeded at a distance of 2 metres from the surface of the patient depending on the number of therapy cycles per calendar year

Number of cycles per calendar year	1	2	3	4
Dose rate upon discharge	4.3 µSv h^{-1}	2.2 µSv h^{-1}	1.4 µSv h^{-1}	1.1 µSv h^{-1}

Alternatively, several dose rate measurements can be taken per cycle to determine the effective half-life for a given patient which is then used in the integral dose rather than the physical half-life (Kurth et al. 2018). However, the anticipated dose to relatives and third parties must be calculated per cycle and summed for all subsequent cycles, meaning that the time of discharge will vary accordingly.

Alpha-emitting actinium-225 targeted radioligand therapy can be administered as an experimental alternative or complement to [^{177}Lu]Lu-PSMA radioligand therapy. Actinium-225 targeted radioligand therapy has proven effective in patients for whom [^{177}Lu]Lu-PSMA radioligand therapy failed to have any (more) effect (Feuerecker et al. 2021). The time of discharge does not need to be adjusted by individual dosimetry for actinium-225 targeted radioligand therapy because the emitted radiation measurable outside of the patient's body does not contribute significantly to the dose to relatives and third parties. However, hospitalisation is highly recommended for at least 48 hours given that up to 80 % of renal excretion takes place during this time and must be collected as contaminated waste water.

2.2.3 Contraindications and side effects

Side effects

By and large, patients tolerate PSMA radioligand therapy well. However, side effects specific to both PSMA radioligand therapy and to radiotherapy in general may occur.

- Pain at the point of injection
- In rare cases: Discomfort, nausea and vomiting after an injection
- Weight loss, exhaustion (also possible due to the underlying disease)
- Acute (reversible) change in blood count (leukopenia, thrombocytopenia and erythropenia, with a reduction in erythrocytes also possible due to the tumour infiltrating the bone marrow
- Impaired liver and renal function
- Chronic damage to the salivary glands, in rare cases also to tear glands.

Contraindications

- Life expectancy < 6 months (ECOG (Eastern Cooperative Oncology Group) >2) unless therapy serves to alleviate symptoms
- Unacceptable medical risk or inpatient stay at a nuclear ward contraindicated for radiation protection reasons, e. g. dementia, risk of contamination due to incontinence
- Impaired renal function: Obstruction or hydronephrosis with impaired function, glomerular filtration rate (GFR) < 30 ml min^{-1} or creatinine more than twice the normal level
- Myelosuppression:
    - Leukocytes < $2.5 \cdot 10^9$ l^{-1}
    - Thrombocytes < $75 \cdot 10^9$ l^{-1}
- Active infection including active or symptomatic viral hepatitis

Relative contraindications (for discussion, e. g. during a tumour board)

- Myocardial infarction or arterial thromboembolism in the past 3 months
- Cardiac insufficiency NYHA (New York Heart Association) III - IV
- Brain metastases (patient should present for consultation in department for radioation oncology)
- Secondary malignancy with rapid progression
- Diseases or medications impairing renal function
- Untreatable hydronephrosis (sonography, renal scintigraphy – Rsz) (relative contraindication)

Table 2.2: [^{177}Lu]Lu-PSMA radioligand therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	PSMA ligands (prostate-specific membrane antigen) PSMA-617, PSMA-I&T, etc.	None	Anti-emetic drugs
Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Typically administered quantity	Approx. 100 µg to 200 µg (radiolabelling with no-carrier-added lutetium-177)	-	Please refer to the product information for the effects, side effects and typical dosages

Procurement/manufacture of radiopharmaceuticals used		
	[^{177}Lu]Lu-PSMA-617	**[^{177}Lu]Lu-PSMA I&T**
Name	[^{177}Lu]Lu-PSMA-617	[^{177}Lu]Lu-PSMA I&T
Commercially available radiopharmaceutical	No Phase III study complete (Sartor et al. 2021); FDA approved in the USA in March 2022; EMA marketing authorisation pending	No
Approved components used during in-house preparation	[^{177}Lu]$LuCl_3$ for radiolabelling	[^{177}Lu]$LuCl_3$ for radiolabelling
Existing monographs (Ph. Eur.)	2798 [^{177}Lu]$LuCl_3$ for radiolabelling 0125 (Radiopharmaceutical preparations)	2798 [^{177}Lu]$LuCl_3$ for radiolabelling 0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	PSMA-617	PSMA-I&T

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	A: Lutetium-177 B: Lutetium-177m (for carrier-added lutetium-177)	A: Lutetium-177 B: Lutetium-177m (for carrier-added lutetium-177)
Radiation type (%α, %β, %γ)	See Table A-1.6	See Table A-1.6
Energy spectrums (α, β, γ)	See Table A-1.6	See Table A-1.6
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	Approx. 600 MBq lutetium-177 (remaining in vial)	Approx. 200 MBq (remaining in vial)
Disposal of residual substances and waste water	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal In the event of residual lutetium-177m, possibly also disposal via federal state collecting depot	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal In the event of residual lutetium-177m, possibly also disposal via federal state collecting depot

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	6,000 MBq – 7,400 MBq lutetium-177 per therapy cycle
Administration routes	IV
Typical number of administrations/therapy cycles	Typically 6 therapy cycles; resumption of therapy possible in the event of renewed progression
Typical time between therapy cycles	6 to 8 weeks
Limiting factors for repeating therapy (e. g. dose-limiting organ)	Blood count (bone marrow), renal function (kidney), salivary glands

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{177}Lu]Lu-PSMA-617; [^{177}Lu]Lu-PSMA-I&T	-
Biological action of the radiopharmaceutical	Binds with the PSMA-bearing extracellular vesicles, followed by internalisation	-
Biodistribution/specific accumulation in	Prostate cancer cells and their metastases	-
Non-specific/non-target accumulation dominant in	Kidneys, liver, salivary glands, tear glands, proximal duodenum	-
Known common side effects (> 10 %)	Nausea/vomiting, haemototoxicity, fatigue	-
Rare severe side effects	-	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	0.44 Gy at 7.4 GBq
Typical effective dose (total for all patient cycles)	2.64 Gy after 6 cycles
Dose-limiting organ	Bone marrow, sometimes also kidney (both are potentially dose-limiting)
Intended dose target region	Unknown
Required pre-therapy dosimetry and imaging	Target identification required (PSMA-targeted PET/CT, PET/MRI or SPECT/CT)
Required post-therapy dosimetry and imaging	Determination of the dose rate upon discharge, post-therapy radiotracer scintigraphy, additional imaging optional between therapy cycles, quantification optional, dosimetry during 1st cycle for approx. seven days (variable protocols)

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	Lutetium-177
Excretion modes	Renal/urine; low gastrointestinal/faecal
Excretion route most relevant for radiation protection	Renal
Typical duration of excretion relevant for radiation protection	2 to 3 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital) Post-hospital: Advise patients to collect pads or similar for several days; ideally flush the toilet multiple times after use
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	Patient emits almost exclusively γ
Type(s) of radiation emitted by patient most relevant to radiation protection	γ
Anatomic focal points of radiation (where present)	Metastases; kidneys during first few days
Typical duration of radiation relevant for radiation protection emitted by patient	Approx. 3 days
Necessary radiation protection measures in hospital and post-hospital	Therapy ward with waste water treatment plant (decontamination plant) Post-hospital: Toilet hygiene, keeping distance from vulnerable persons

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	0.07 mSv – 0.26 mSv
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv[3] (Note: Time of discharge may need to be adjusted depending on the number of cycles per calendar year)
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stays where required	Yes, if early discharge is required given the patient's social surroundings: the anticipated doses to other persons in the same household as the patient should be calculated based on the patient's respective discharge dose rates if more than four to six cycles are administered in a calendar year

Hospitalisation concept	
Inpatient setting necessary	Yes
Typically recommended hospitalisation period	Approx. 3 nights
Possible reasons for extended period of hospitalisation	Dosimetry, domestic situation, general state
Reasons why hospitalisation is needed to administer therapy safely	Dosimetry, radiation protection, frequently limited general state, in turn requiring palliative care
Reasons why outpatient care is possible, but hospitalisation may be required	Not applicable, as prohibited
Specific factors influencing number and duration of inpatient stays	No

Therapeutic indication(s)	
Approved indications	None at present
Current typical indications for therapy as an individual curative treatment	Patients with mCRPC after exploring all other meaningful options provided in the guidelines
New indications arising from studies/research	Clinical studies are currently investigating PSMA-targeted radioligand therapy for use at every stage of the illness
Therapy already added to guidelines	Yes (e. g. German S3 guidelines prostate cancer)

Reimbursement	
Inpatient	DRG (M10B at present)
Outpatient	Not applicable, as prohibited
Reimbursement issues	Cost of dosimetry and imaging not covered

[3] Section 81 of the German Radiation Protection Act (StrlSchG)

Table 2.3: [^{225}Ac]Ac-PSMA radioligand therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	PSMA ligands (prostate-specific membrane antigen) PSMA-617	None	Anti-emetic drugs
Known pharmacological effects of unlabelled carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Known side effects of unlabelled carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Typically administered quantity	10 µg to 20 µg per MBq	-	Please refer to the product information for the effects, side effects and typical dosages

Procurement/preparation of [^{225}Ac]Ac-PSMA-617	
Name	[^{225}Ac]Ac-PSMA-617
Commercially available radiopharmaceutical	No
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	PSMA-617 [^{225}Ac]$AcCl_3$ for radiolabelling [^{225}Ac]$Ac(NO_3)_3$ for radiolabelling

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	Actinium-225	-
Radiation type (%α, %β, %γ)	See Table A-1.10	-
Energy spectrums (α, β, γ)	See Table A-1.10	-
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	Less than 1 MBq Actinium-225 (remaining in vial)	-
Disposal of residual substances and waste water	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal	-

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	100 kBq kg^{-1} KG
Administration routes	IV
Typical number of administrations/therapy cycles	3 to 4 cycles
Typical time between therapy cycles	6 to 8 weeks
Limiting factors for repeating therapy (e. g.e. g. dose-limiting organ)	Salivary glands, blood count (bone marrow), renal function (kidney),

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{225}Ac]Ac-PSMA-617	-
Biological action of the radiopharmaceutical	Binds with the PSMA-bearing extracellular vesicles, followed by internalisation	-
Biodistribution/specific accumulation in	Prostate cancer cells and their metastases	-
Non-specific/non-target accumulation dominant in	Kidneys, liver, salivary glands, tear glands, proximal duodenum	-
Known common side effects (> 10 %)	**Xerostomia**, nausea/vomiting, haemototoxicity, fatigue, xerophthalmia	-
Rare severe side effects		-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	329 mGy at 7 MBq (Kratochwil et al. 2016, Kratochwil et al. 2017)
Typical effective dose (total for all patient cycles)	1.97 Gy after 6 cycles (Kratochwil et al. 2016)
Dose-limiting organ	Bone marrow, salivary glands, kidneys (in rare cases) (all are potentially dose-limiting)
Intended dose target region	Unknown
Required pre-therapy dosimetry and imaging	Target identification required (PSMA-targeted PET/CT, PET/MRI or SPECT/CT)
Required post-therapy dosimetry and imaging	Post-therapy radiotracer scintigraphy, additional imaging optional between therapy cycles, quantification optional Dosimetry during 1st cycle for approx. 7 days (variable protocols)

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	Actinium-225 Bismuth-213 Lead-209
Excretion modes	Renal/urine; low gastrointestinal/faecal
Excretion route most relevant for radiation protection	Renal
Typical duration of excretion relevant for radiation protection	2 to 3 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital) Post-hospital: Advise patients to collect pads or similar for several days; ideally flush the toilet multiple times after use
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	Patient emits only γ
Type(s) of radiation emitted by patient most relevant to radiation protection	γ
Anatomic focal points of radiation (where present)	Target tissue; initially the kidneys
Typical duration of radiation relevant for radiation protection emitted by patient	Approx. 3 days
Necessary radiation protection measures in hospital and post-hospital	Therapy ward with waste water treatment plant (decontamination plant) Post-hospital: Toilet hygiene, keeping distance from vulnerable groups of people

Dose to other persons in same household	
Potential dose to other persons in same household per therapy session	Low dose expected with inpatients
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	Low dose expected with inpatients

Hospitalisation concept	
Inpatient setting necessary	Yes
Typically recommended hospitalisation period	48 h (2 nights)
Possible reasons for extended period of hospitalisation	General state, comorbidities
Reasons why hospitalisation is needed to administer therapy safely	Dosimetry, radiation protection, frequently limited general state, in turn requiring palliative care
Reasons why outpatient care is possible, but hospitalisation may be required	Not applicable
Specific factors influencing number and duration of inpatient stays	None

Therapeutic indication(s)	
Approved indications	None at present
Current typical indications for therapy as an individual curative treatment	Patients with mCRPC after exploring all other meaningful options provided in the guidelines, incl. [^{177}Lu]Lu-PSMA-617; following a decision by the interdisciplinary tumour board
New indications arising from studies/research	Anticipated, but no known major clinical trials ongoing at present to explore further indications
Therapy already added to guidelines	No

Reimbursement	
Inpatient	No general provision
Outpatient	Not applicable

3 Peptide receptor radionuclide therapy (PRRT) involving lutetium-177- and yttrium-90-labelled somatostatin analogues for neuroendocrine tumours

Peptide receptor radionuclide therapy (PRRT) describes therapy for neuroendocrine tumours where the somatostatin analogues used are typically radiolabelled with lutetium-177, but sometimes with yttrium-90 instead.

3.1 Indications and therapy goals

PRRT involving [^{177}Lu]Lu-DOTATATE (Lutathera^{TM}) has been approved and is used for the treatment of inoperable or metastatic, progressive, well-differentiated (G1 and G2) SSTR-positive gastroenteropancreatic neuroendocrine tumours (GET NETs) in adults. Non-approved uses include, but are not limited to, neuroendocrine neoplasms (NEN) of the lung, G3 NET, neuroendocrine carcinoma (NEC) meningioma, mixed neuroendocrine non-neuroendocrine neoplasms (MINEN), and G1/G2 NET CUP (cancer of unknown primary). Current German and international guidelines recommend PRRT as second-line treatment for ileum NET after treatment with somatostatin analogues, and sometimes as second-line treatment for pancreatic NET after treatment with somatostatin analogues, but sometimes only after performing chemotherapy for pancreatic NET. PRRT has relatively low side effects as compared to other possible therapies (chemotherapy, everolimus, sunitinib; exception: somatostatin analogues), is well tolerated, and improves affected patients' quality of life.

3.2 Implementation

3.2.1 Preparation and therapy planning

Somatostatin receptor expression, ideally demonstrated in all NET lesions, is a requirement for performing PRRT. This is typically demonstrated by demonstrating somatostatin receptor expression of all lesions in a positron emission tomography (PET) scan using gallium-68-labelled somatostatin analogues, e. g. DOTATATE, DOTATOC, with PET-tracer retention in the liver usually used as a reference to confirm sufficient uptake of the lesions. In most cases, progression of the disease is a prerequisite. However, PRRT is also sometimes used in the event of a poor prognosis, such as the presence of a high hepatic tumour burden. Obstructive hydronephrosis should be ruled out prior to commencing therapy.

3.2.2 General course of therapy

PRRT is performed as a short infusion, typically involving four cycles of 7.4 GBq, each eight to twelve weeks apart. During the first cycle of therapy, dosimetry should be performed to determine the dose of relevant organs. Dose-limiting organs include the kidneys and bone marrow, although no dose-response relationship or reliable toxicity limits have been established to date. To reduce the equivalent dose to the kidneys by 40 % to 50 %, an infusion of arginine and lysine (25 g of each) is administered 30 minutes before commencing therapy. As this infusion can cause nausea, anti-emetic drugs such as ondansetron are also often administered prophylactically. Corticosteroids are administered in the event of a high hepatic tumour burden, brain metastases, or bone metastases with a risk of complication due to swelling. As is the case

with lutetium-177-PSMA therapy, the dose rate measured at a distance of 2 metres from the surface of the patient must be below the discharge limit, depending on the number of therapy cycles per calendar year, as shown in Table 2.1, before patients can be released from inpatient treatment. The dose rate should be measured 48 hours after commencing therapy at the earliest. Therapy is administered on an inpatient basis, with the majority of the [^{177}Lu]Lu-DOTATATE (approx. 80 %) excreted renally within 48 hours (Esser et al. 2006). As a result, patients are required to spend at least 48 hours in a nuclear medicine ward with a waste water treatment plant (decontamination plant) for radioactive waste water. Upon discharge, patients must not expose relatives and third parties to an effective dose of more than 1 mSv of ionising radiation (Section 80 (1) of the German Radiation Protection Act (StrlSchG 2017) and Section 122 (4) German Radiation Protection Ordinance (StrlSchV 2018)). This is ensured by not discharging the patient until the dose rate measured at a distance of 2 metres from the surface of the patient is below a threshold of 1 mSv when applying the integral dose (SSK 1996). It should be noted that metastable lutetium-177m with a half-life of 160.4 days may be present depending on the nuclide production process. Therapy is administered with approved [^{177}Lu]Lu-DOTATATE as well as other somatostatin analogues such as lutetium-177-labelled DOTATOC and HA-DOTATATE. In addition, somatostatin receptor antagonists are used which are currently undergoing evaluation in a study (^{177}Lu-OPS201 = satoreotide tetraxetan). The benefit of these antagonists appears to be an increased binding capacity to somatostatin receptors with subsequent higher uptake by the tumour. This benefit may be offset by a higher equivalent dose to the bone marrow and kidneys. Both lutetium-177 and yttrium-90 are used, with the latter only used rarely due to its higher nephrotoxicity (Bodei et al. 2008).

3.2.3 Contraindications and side effects

Pregnancy and breast-feeding are absolute contraindications. Sufficient renal function and bone marrow reserve are required to perform PRRT. There are no evidence-based limits available for this. The current guideline from NANETS/SNMMI (Hope et al. 2020) provides a GFR of 30 ml min^{-1} as the lower renal function limit. There are also no evidence-based limits for haemoglobin, platelets and leucocytes. The aforementioned guideline provides the following values for reference: Haemoglobin 8 g dl^{-1}, leucocytes 2 T ml^{-1}, platelets 70 T ml^{-1} (Hope et al. 2019).

Possible acute side effects include nausea and vomiting (depending on the amino acid infusions), abdominal pain, diarrhoea, exhaustion, mild hair loss and taste disturbance.

Relevant side effects largely apply to the kidneys and the haematopoietic bone marrow. Higher-grade thrombocytopenia (Grade 3/4) occurs in 2 % of patients, lymphocytopenia in 9 %, leukopenia in 1 %, and neutropenia in 1 % (Strosberg et al. 2017). Myelodysplastic syndrome occurs in approx. 2 % to 3 % of patients after around two years, while higher-grade nephrotoxicity is observed in fewer than 2 % of patients.

Table 3.1: Radionuclide therapy involving ^{177}Lu- and ^{90}Y-labelled somatostatin analogues

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	DOTATATE HA-DOTATATE DOTATOC	-	Solution containing 25 g of lysine and 25 g of arginine

Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	For the effects, side effects and typical dosages, please refer to the product information for the additionally administered substances
Typically administered quantity	250 µg	-	Please refer to the product information for the effects, side effects and typical dosages

Procurement/manufacture of radiopharmaceuticals used				
Name	[^{177}Lu]Lu-DOTATATE	[^{177}Lu]Lu-HA-DOTATATE	[^{177}Lu]Lu-DOTATOC	[^{90}Y]Y-DOTATOC
Commercially available radiopharmaceutical (yes/no)	Yes	No	No	No
Approved components used during in-house preparation	[^{177}Lu]$LuCl_3$ for radiolabelling	[^{177}Lu]$LuCl_3$ for radiolabelling	[^{177}Lu]$LuCl_3$ for radiolabelling	[^{90}Y]YCl_3 for radiolabelling
Existing monographs (Ph. Eur.)	2798 [^{177}Lu]$LuCl_3$ for radiolabelling 0125 (Radiopharmaceutical preparations)	2798 [^{177}Lu]$LuCl_3$ for radiolabelling 0125 (Radiopharmaceutical preparations)	2798 [^{177}Lu]$LuCl_3$ for radiolabelling 0125 (Radiopharmaceutical preparations)	2803: [^{90}Y]YCl_3 for radiolabelling 0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	DOTATATE	HA-DOTATATE	DOTATOC	DOTATOC

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	Lutetium-177/yttrium-90, possibly lutetium-177m (depending on the manufacturer)	[^{177}Lu]Lu-DOTATATE Lutetium-177m
Radiation type (%α, %β, %γ)	See Tables A-1.1 and A-1.6	See Tables A-1.1 and A-1.6
Energy spectrums (α, β, γ)	See Tables A-1.1 and A-1.6	See Tables A-1.1 and A-1.6
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	Approx. 800 MBq lutetium-177 (remaining in vial)	Typically low (< 5 %, approx. 370 MBq)
Disposal of residual substances and waste water	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal In the event of residual lutetium-177m, possibly also disposal via federal state collecting depot	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal In the event of residual lutetium--177m, possibly also disposal via federal state collecting depot

Administration of radiopharmaceutical	
Typically administered activity per therapy cycle	7,400 MBq lutetium-177 (3,700 MBq Yttrium-90) per therapy cycle
Administration routes	IV
Typical number of administrations/therapy cycles	4 cycles
Typical time between therapy cycles	8 to 12 weeks
Limiting factors for repeating therapy (e. g.e. g. dose-limiting organ)	Blood count (bone marrow), renal function (kidney)

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{177}Lu]Lu-DOTATATE, [^{177}Lu]Lu-HA-DOTATATE, [^{177}Lu]Lu-DOTATOC, [^{90}Y]Y-DOTATOC	-
Biological action of the radiopharmaceutical	Binding to somatostatin receptor 2, subsequent internalisation	-
Biodistribution/specific accumulation in	Neuroendocrine system tumours	-
Non-specific/non-target accumulation dominant in	Kidney, liver, spleen	-
Known common side effects (> 10 %)	Nausea, vomiting, haemotoxicity, fatigue	-
Rare severe side effects		-

Dose/dosimetry	
Typical effective dose per therapy session per patient (typical number of cycles: 4)	370 mGy (from marketing authorisation study [^{177}Lu]Lu-DOTATATE)
Typical effective dose (total for all patient cycles)	1,480 mGy
Dose-limiting organ	Bone marrow, sometimes also kidney (both are potentially dose-limiting)
Intended dose target region	Unknown
Required pre-therapy dosimetry and imaging	Scintigraph necessary for target identification
Required post-therapy dosimetry and imaging	Post-therapy radiotracer scintigraphy, additional imaging optional between therapy cycles, quantification optional Dosimetry during 1st cycle for approx. 5 days (variable protocols)

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	Lutetium-177/ Yttrium-90
Excretion modes	Renal/urine; low gastrointestinal/faecal
Excretion route most relevant for radiation protection	Renal
Typical duration of excretion relevant for radiation protection	2 to 3 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital) Post-hospital: Advise patients to collect pads or similar for several days; ideally flush the toilet multiple times after use
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	Patient emits almost 100 % γ
Type(s) of radiation emitted by patient most relevant to radiation protection	γ (bremsstrahlung)
Anatomic focal points of radiation (where present)	Metastases (often of the liver)
Typical duration of excretion relevant for radiation protection emitted by patient	Approx. 2 to 3 days
Necessary radiation protection measures in hospital and post-hospital	Inpatient: Therapy ward with waste water treatment plant (decontamination plant), post-hospital toilet hygiene, keeping distance from vulnerable persons

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	Max. 0.37 mSv (for lutetium-177)
Potential total dose from all cycles to other persons in same household after a typical number of cycles (4)	< 1 mSv (Note: Time of discharge may need to be adjusted depending on the number of cycles per calendar year)
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stays where required	Yes, if early discharge is required given the patient's social surroundings: the anticipated doses to other persons in the same household as the patient should be calculated based on the patient's respective discharge dose rates if 4 cycles are administered in a calendar year

Hospitalisation concept	
Inpatient setting necessary	Yes
Typically recommended hospitalisation period	2 to 5 days
Possible reasons for extended period of hospitalisation	Dosimetry, side effects (e. g. diarrhoea), domestic situation, comorbidities
Reasons why hospitalisation is needed to administer therapy safely	Dosimetry, radiation protection
Reasons why outpatient care is possible, but hospitalisation may be required	Prohibited
Specific factors influencing number and duration of inpatient stays	No

Therapeutic indication(s)	
Approved indications	Treatment of inoperable or metastatic, progressive, well-differentiated (G1 and G2) SSTR-positive gastroenteropancreatic neuroendocrine tumours (GET NETs) in adults
Current typical indications for therapy as an individual curative treatment	NET in the lung, G3 NET, meningioma, paraganglioma, G1/G2 NET CUP
New indications arising from studies/research	Yes (ongoing studies on pheochromocytoma, small-cell lung cancer, breast cancer)

Therapy already added to guidelines	Yes (e. g. German S2k guideline NET, and ESMO, ENETS, NCCI guidelines)

Reimbursement	
Inpatient	DRG variable post-tumour localisation plus additional fee
Outpatient	Not applicable
Reimbursement issues	No general provision

4 Radionuclide therapy involving [^{153}Sm]Sm-EDTMP or [^{223}Ra]radium dichloride for bone pain and bone metastases in metastatic castration-resistant prostate cancer (mCRPC)

For cancer patients with bone metastases, the bone pain associated with metastases frequently has a considerable impact on quality of life. While chemotherapy, bisphosphonate and hormone therapy are used at the systemic level, local radiotherapy may also be indicated for local pain management. Palliative pain relief with radionuclides has been used successfully for more than 50 years and is evaluated positively in a systematic literature review according to evidence-based criteria (Bauman et al. 2005). Of numerous radiopharmaceuticals, [^{153}Sm]samarium-ethylene diamine tetramethylene phosphonate ([^{153}Sm]Sm-EDTMP) and [^{223}Ra]radium dichloride currently remain the only commercially available radiopharmaceutical agents. In Germany, therapy with [^{153}Sm]Sm-EDTMP has been approved since 1998.

Therapy with the alpha-particle emitter [^{223}Ra]radium dichloride (Alpharadin, Xofigo) for castration-resistant metastatic prostate cancer (mCRPC) was first approved in Germany in 2013.

4.1 Indications and therapy goals

Radionuclide therapy of bone metastases has two objectives: 1) Systemic pain management ([^{153}Sm]Sm-EDTMP, [^{223}Ra]radium dichloride (Alpharadin, Xofigo)) and 2) anticancer therapy ([^{223}Ra]radium dichloride (Alpharadin, Xofigo)). The most relevant indication for [^{153}Sm]Sm-EDTMP is refractory pain secondary to skeletal metastases with osteoblastic activity confirmed by bone scintigraphy (in prostate, lung or breast cancer) and a markedly impaired quality of life (Fischer 1999, Handkiewicz-Junak et al. 2018).

4.2 Implementation

4.2.1 Preparation and therapy planning

For therapy planning purposes, current evidence of bone metastases (bone scintigraphy) is a prerequisite for therapy involving [^{153}Sm]Sm-EDTMP and [^{223}Ra]radium dichloride. There is no need to interrupt ongoing bisphosphonate therapy as long as increased accumulation is demonstrated in bone scans during the treatment. Prerequisites include sufficient function of the bone marrow, kidneys and liver as well as a life expectancy of at least three months and a Karnofsky performance status of > 40 %. Extensive radiation should have been completed at least two to three months prior.

4.2.2 General course of therapy

A standard activity of 37 MBq kg^{-1} body weight [^{153}Sm]Sm-EDTMP is injected strictly intravenously; the therapy can be administered on an outpatient basis. Subsequent to that, radiotracer scintigraphy is carried out to verify a regular distribution of activity. If the first cycle

of therapy proves unsuccessful, a second cycle can be carried out at the earliest six weeks after the first; in this case, the response rate is still around 50 % (Fischer 1999).

Therapy with [^{223}Ra]radium chloride is also administered by intravenous injection of six individual doses every four weeks at a dose of 55 kBq kg^{-1} radium-223 per body weight. Due to the possibility of haemotoxocity (particularly thrombocytopenia), controls of the differential blood count are indicated prior to each dose administration. The therapy can be administered on an outpatient basis; no radiotracer scintigrams are intended post-therapy (Pandit-Taskar et al. 2014, Poppel et al. 2016).

To prevent complications from bone metastases, the German S3 Guideline on Prostate Cancer recommends the administration of the anti-RANKL antibody (receptor activator of nuclear factor-kappaB ligand) denosumab or the bisphosphonate zoledronic acid as add-on to mCRPC therapy (Konig et al. 2020). Both active substances inhibit osteoclast activity and also reduce pathologically increased bone resorption in osteoblastic bone metastases as well as the release of tumour-promoting growth factors by the osteoclasts.

4.2.3 Contraindications and side effects

Contraindications for palliative pain management include imminent or extant bone marrow compression due to vertebral metastases or unstable fractures. As outlined above, [^{223}Ra]radium dichloride therapy is contraindicated particularly in combination with abiraterone acetate plus prednisone/prednisolone, and the therapy is not recommended in patients with a low level of osteoblastic bone metastases ($n < 6$) or in patients with only asymptomatic bone metastases and in combination with other systemic cancer therapies other than LHRH analogues. Side effects that are more commonly reported for both forms of therapy include decreased leucocyte and platelet counts, as well as nausea, diarrhoea and vomiting, an increased incidence of bone fractures ([^{223}Ra]radium dichloride) and a transient initial increase in bone pain ([^{153}Sm]Sm-EDTMP).

Table 4.1: Samarium-153 radionuclide therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	EDTMP	-	-
Known pharmacological effects of unlabelled carrier/accompanying substances in administered quantity	None	-	-
Known side effects of unlabelled carrier/accompanying substances in administered quantity	None	-	-
Typically administered quantity	15.4 µg GBq^{-1} – 35.7 µg GBq^{-1}	-	-

Procurement/preparation of Quadramet	
Name	Quadramet (^{153}Sm)
Commercially available radiopharmaceutical	Yes
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	-

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	-	Contamination with long-lived Europium nuclides possible, e. g. ^{154}Eu (HL: 8.6 a) (Loebe et al. 2014), for more details see Table A-1.3
Radiation type (%α, %β, %γ)	-	See Table A-1.30
Energy spectrums (α, β, γ)	-	See Table A-1.3
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	-	10 MBq to 200 MBq in vial, No measurement results of preparation or administration accessories available
Disposal of residual substances and waste water	-	Unrestricted clearance not possible, delivery to federal state collecting depot

Administration of radiopharmaceutical	
Typically administered activity per therapy cycle	37 MBq kg^{-1}
Administration routes	IV
Typical number of administrations/therapy cycles	One-time administration
Typical time between therapy cycles	> 4 to 6 months
Limiting factors for repeating therapy (e. g. dose-limiting organ)	Bone marrow function

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{153}Sm]Sm-EDTMP	Not applicable
Biological action of the radiopharmaceutical	Affinity to areas with active bone turnover due to phosphonic acid bonds	-
Biodistribution/specific accumulation in	Growth zones of the bone matrix	-
Non-specific/non-target accumulation dominant in	Not known	-
Known common side effects (> 10 %)	Increase in bone pain (flare reaction) shortly after injection (≤ two days), decrease in platelets and leucocytes.	-
Rare severe side effects	-	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	800 mSv
Typical effective dose (total for all patient cycles)	800 mSv
Dose-limiting organ	Healthy bone surface, red bone marrow, bladder wall, kidneys
Intended dose target region	-
Required pre-therapy dosimetry and imaging	Metastases confirmed by skeletal scintigraphy, determination of the administered activity based on body weight, no prior dose determination
Required post-therapy dosimetry and imaging	Radiotracer scintigraphy required, no dose determination necessary

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	^{153}Sm
Excretion modes	Renal/urine (approx. 35 % of the activity administered)
Excretion route most relevant for radiological protection	Renal
Typical duration of excretion relevant for radiation protection	4 h to 6 h
Handling of excrement in hospital and post-hospital	Outpatient therapy, for inpatients collect in waste water treatment plant (decontamination plant)
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	γ
Type(s) of radiation emitted by patient most relevant to radiation protection	γ
Anatomic focal points of radiation (where present)	Bone, distribution dependent on metastatic spread
Typical duration of radiation relevant for radiation protection emitted by patient	-
Required radiation protection measures in hospital and post-hospital	Hygiene due to urinary excretion in the first 6 to 12 hours, also recommendation to keep distance from other persons (at least 1 m)

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	< 0.8 mSv
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 0.8 mSv
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	No
Typically recommended hospitalisation period	Not necessary
Possible reasons for extended period of hospitalisation	Not applicable
Reasons why hospitalisation is needed to administer therapy safely	Not applicable
Reasons why outpatient care is possible, but hospitalisation may be required	Not applicable
Specific factors influencing number and duration of inpatient stays	Not applicable

Therapeutic indication(s)	
Approved indications	Palliative pain management of osteoblastic bone metastases
Currently typical indications for therapy as an individual curative treatment	Metastatic spread in osteosarcoma, bone marrow ablation prior to stem cell therapy
New indications arising from studies/research	-
Therapy already added to guidelines	025-005l_S1_Osteosarkome_2011043- (S1 Guideline Osteosarcoma) 022OLl_S3_Prostatakarzinom_2019-06 (S3 Guideline Prostate Cancer) 032-054OLl_S3_Supportiv_2019-11 (S3 Guideline Supportive Therapy) 032-045OLl_S3_Mammakarzinom_2020-02 (S3 Guideline Breast Cancer)

Reimbursement	
Inpatient	8 530x (radionuclide therapy, other)
Outpatient	EBM 17372, 40562
Reimbursement issues	Post-therapy imaging included, waste disposal also not reimbursed separately

Table 4.2: Radium-223 radionuclide therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Not applicable	-	-
Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	-
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	-
Typically administered quantity		-	-

Procurement/preparation of Xofigo	
Name	[^{223}Ra]radium chloride (Xofigo)
Commercially available radiopharmaceutical	Yes
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	-

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	-	Contamination with long-lived ^{227}Ac (HL: 21.8 a) and ^{227}Th (HL: 18.7 days) possible
Radiation type (%α, %β, %γ)	-	See Table A-1.9
Energy spectrums (α, β, γ)	-	See Table A-1.9
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	-	2 MBq in vial[4]
Disposal of residual substances and waste water	-	Unrestricted clearance not possible, delivery to federal state collecting depot

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	55 kBq kg^{-1}
Administration routes	IV
Typical number of administrations/therapy cycles	6
Typical time between therapy cycles	4 weeks
Limiting factors for repeating therapy (e. g. dose-limiting organ)	Myelosuppression

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{223}Ra]radium chloride	-
Biological action of the radiopharmaceutical	Affinity to regions with active bone turnover due to the similar chemical behaviour of calcium and radium	-
Biodistribution/specific accumulation in (where does it accumulate specifically)	Bone metastases	-
Non-specific/non-target accumulation dominant in	Intestinal tract	-
Known common side effects (> 10 %)	Diarrhoea, nausea, vomiting, thrombocytopenia and bone fractures	-
Rare severe side effects	-	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per dose)	30 mGy MBq^{-1} · 4 MBq = 120 mGy (Chittenden et al. 2015)
Typical effective dose (total for all patient cycles)	120 mGy · 6 cycles = 720 mGy
Dose-limiting organ	-
Intended dose target region	No fixed target dose specified
Required pre-therapy dosimetry and imaging	Skeletal scintigraphy with evidence of bone metastases
Required post-therapy dosimetry and imaging	-

[4] Assumption: Full vial: 6.6 MBq minus 70 kg · 55 kBq kg^{-1}

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patients	
Excreted nuclides	^{223}Ra ^{219}Rn
Excretion modes	Gastrointestinal/stool, pulmonary/breath (^{219}Rn)
Excretion route most relevant for radiological protection	Gastrointestinal
Typical duration of excretion relevant for radiation protection	24 h
Handling of excrement in hospital and post-hospital	-
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	-
Type(s) of radiation emitted by patient most relevant to radiation protection	-
Anatomic focal points of radiation (where present)	Bone, distribution dependent on metastatic spread
Typical duration of radiation relevant for radiation protection emitted by patient	None
Required radiation protection measures in hospital and post-hospital	None

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	< 80 µSv
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 0.5 mSv
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	No
Typically recommended hospitalisation period	Not necessary
Possible reasons for extended period of hospitalisation	Not applicable
Reasons why hospitalisation is needed to administer therapy safely	Not applicable
Reasons why outpatient care is possible, but hospitalisation may be required	Not applicable
Specific factors influencing number and duration of inpatient stays	Not applicable

Therapeutic indication(s)	
Approved indications	Bony metastatic, castration-resistant prostate cancer (mCRPC) with symptomatic bone metastases with no known visceral metastases
Currently typical indications for therapy as an individual curative treatment	Bone metastases of other tumour entities
New indications arising from studies/research	-
Therapy already added to guidelines	S3 Guideline PCA: AWMF registry number: 043/022OL

Reimbursement	
Inpatient	-
Outpatient	EBM 17372, 40582
Reimbursement issues	-

5 Radionuclide therapy of synovitis (radiosynoviorthesis) involving [^{169}Er]erbium citrate, [^{186}Re]rhenium sulfide and [^{90}Y]yttrium citrate

The term synoviorthesis is derived from the Greek words ‘synovialis’ (mucosa) and ‘orthosis’ (correction). Radiosynoviorthesis (RSO) refers to a treatment method to restore the synovial membrane and thus its function through the use of local radiation following intra-articular administration of radionuclides (Beil und Ruther 2015, Linke et al. 2011, Seidel und Kommission Pharmakotherapie der DGRh 2006). It is a local and minimally invasive alternative to surgical measures or intra-articular administration of chemical substances. RSO is an appropriate pain relief option, especially in older patients in whom surgical procedures are more frequently associated with higher complication rates (from the surgery itself and the risks of anaesthesia).

Even though synovitis is a benign condition per se, it can exhibit aggressive and locally destructive behaviour in the presence of various rheumatic diseases, so that the treatment concepts are absolutely comparable with anti-cancer therapy. Radiosynoviorthesis has been used as an adjuvant, local anti-inflammatory and pain-relieving measure for more than 50 years (Deutsch et al. 1993). After intra-articular injection of an appropriate beta-emitter, the latter is phagocytosed by the hyperplastic synovial membrane, from where the inflammatory changes are irradiated and the superficial, hypertrophic layers of the synovial membrane are destroyed. Due to the low penetration depth of the beta radiation, the cartilage and the bone are, for the most part, spared.

5.1 Indications and therapy goals

RSO is normally used in the context of rheumatoid arthritis (RA) and seronegative spondyloarthropathy. The primary indication is the treatment of chronic (multifocal) synovial hyperplasia where —despite being regressive under systemic therapy— one or a few joints fail to respond sufficiently to the treatment, or the local treatment of monoarthritis with or without prior systemic therapy (Beil und Ruther 2015, Gabriel et al. 2021, Linke et al. 2011, Seidel und Kommission Pharmakotherapie der DGRh 2006). In this respect, the indication for RSO must be established by an interdisciplinary team with the treating rheumatologists and orthopaedic surgeons. In pigmented villonodular synovitis, RSO is used as adjuvant therapy after synovectomy and in haemophilic arthropathy to prevent bleeding. Good results are also achieved in activated osteoarthritis, crystalline arthropathy or following prosthetic joint arthroplasty. The goals of RSO therapy include pain relief and an improved function of the affected joints (decreased effusion and increased mobility). Even if RSO has no impact, for example, on osteoarthritis, it can significantly improve the accompanying inflammation and thus enhance the therapeutic management.

5.2 Implementation

Synovitis can be confirmed by multiphase bone scintigraphy through visualisation of the inflammation in the ‘soft tissue scan’ (early phase) and evidence of bony transformation in the ‘mineralisation phase’ (late phase) using technetium-99m-labelled phosphonic acids. Prior to RSO of the knee joint, a synovial popliteal cyst, also known as a Baker’s cyst, should be ruled out. Both the patient’s complaints and the scintigraphy findings must be taken into account when establishing the indication.

After establishing the indication, informing the patient and obtaining his/her consent for the procedure, and after confirming an intra-articular position of the needle by X-ray (where

applicable following administration of a contrast agent for medium-sized or large joints), an appropriate beta-emitting radiocolloid is injected, followed by an injection of cortisone to facilitate a rapid decrease in the inflammation and to avoid reflux of the radioactivity into the puncture canal. The beta energy is adapted to the size of the joints: [^{169}Er]erbium citrate is used for finger and ankle joints, [^{186}Re]rhenium sulfide for medium-sized joints, and [^{90}Y]yttrium citrate for knee joints. The administered activity of the radiopharmaceutical is based on the size of the joint and the thickness of the synovial membrane; an exact dosimetry is not possible. For rhenium-186 and yttrium-90, post-therapy radiotracer scintigraphy by gamma radiation and/or bremsstrahlung is stipulated. Immobilisation for a period of 48 hours is meant to prevent increased lymphatic drainage. If the knee joint is immobilised, thromboembolic prophylaxis, e. g. with low-molecular heparin, is performed. To make immobilisation possible, the treatment is limited to one extremity per session. The success of the therapy can be reliably evaluated after three to four months; if pain relief is only temporary, RSO can be repeated. Even if the improvement lasts several years and a relapse occurs, RSO can be repeated and has high chances of success (Kresnik et al. 2002). RSO can be carried out on an outpatient basis.

5.2.1 Contraindications and side effects

Overall, complications or side effects following RSO are rare. Side effects include post-therapeutic inflammation. If bandaging is too tight or if there is increasing swelling of the extremity, pressure sores may develop over the course of the day. If the injection is not administered strictly into the joint, a radiation ulcer can develop in rare cases. As long as the hygienic measures are strictly observed, the risk of joint infection remains more theoretical. If a lower extremity is immobilised, the risk of thrombosis is generally managed by administration of an anticoagulant. There are relatively few contraindications for RSO. Absolute contraindications include pregnancy and breastfeeding, massive haemathrosis or acute trauma, local infections and a ruptured Baker's cyst or rotator cuff defects. Relative contraindications include joint instability with bone destruction. In addition, use of RSO requires a particular careful indication in young patients.

Table 5.1: Erbium-169 radionuclide therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Erbium citrate colloid	-	-
Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	-
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	-
Typically administered quantity	-	-	-

Procurement/preparation of [^{169}Er] erbium citrate	
Name	[^{169}Er]erbium citrate
Commercially available radiopharmaceutical	Yes
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	Not applicable

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	-	^{169}Yb (HL 32 days), max. proportion 1.4 %
Radiation type (%α, %β, %γ)	-	See Tables A-1.5 and A-1.9
Energy spectrums (α, β, γ)	-	See Tables A-1.5 and A-1.9
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	-	Few MBq, empty syringes, swabs
Disposal of residual substances and waste water	-	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	15 MBq – 40 MBq, depending on joint size
Administration routes	Intra-articular
Typical number of administrations/therapy cycles	1
Typical time between therapy cycles	6 months
Limiting factors for repeating therapy (e. g. dose-limiting organ)	None

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{169}Er]erbium citrate	-
Biological action of the radiopharmaceutical	Phagocytosis of the pharmaceutical by superficial synovial cells	-
Biodistribution/specific accumulation in (where does it accumulate specifically)	Synovial cells	-
Non-specific/non-target accumulation dominant in	-	-
Known common side effects (> 10 %)	No	-
Rare severe side effects	No	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	0.0082 mSv/MBq/% outflow
Typical effective dose (total for all patient cycles)	-
Dose-limiting organ	-
Intended dose target region	-
Required pre-therapy dosimetry and imaging	-
Required post-therapy dosimetry and imaging	No dosimetry

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	-
Excretion modes	-
Excretion route most relevant for radiological protection	-
Typical duration of excretion relevant for radiation protection	-
Handling of excrement in hospital and post-hospital	-
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	-
Type(s) of radiation emitted by patient most relevant to radiation protection	-
Anatomic focal points of radiation (where present)	Treated joint
Typical duration of radiation relevant for radiation protection emitted by patient	-
Required radiation protection measures in hospital and post-hospital	-

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	-
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	No, unless medically justified
Typically recommended hospitalisation period	-
Possible reasons for extended period of hospitalisation	-
Reasons why hospitalisation is needed to administer therapy safely	-
Reasons why outpatient care is possible, but hospitalisation may be required	-
Specific factors influencing number and duration of inpatient stays	-

Therapeutic indication(s)	
Approved indications	Septic arthritis, activated osteoarthritis, synovitis
Currently typical indications for therapy as an individual curative treatment	Not applicable
New indications arising from studies/research	Not applicable
Therapy already added to guidelines	Yes (“Guideline for radiosynoviorthesis”)

Reimbursement	
Inpatient	Billing code: 8-503.3
Outpatient	EBM
Reimbursement issues	-

Table 5.2: Rhenium-186 radionuclide therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Rhenium sulfide colloid	-	-
Known pharmacological effects of unlabelled carrier/accompanying substances in administered quantity	Not applicable	-	-
Known side effects of unlabelled carrier/accompanying substances in administered quantity	Not applicable	-	-
Typically administered quantity	Not applicable	-	-

Procurement/preparation of [^{186}Re] rhenium sulfide	
Name	[^{186}Re]rhenium sulfide
Commercially available radiopharmaceutical	Yes
Approved components used during in-house preparation	Not applicable
Existing monographs (Ph. Eur.)	0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	Not applicable

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	-	A: ^{186}Re B: ^{184}Re proportion < 1 % C: ^{188}Re proportion < 1 %
Radiation type (%α, %β, %γ)	-	See Table A-1.7 and A-1.8
Energy spectrums (α, β, γ)	-	See Table A-1.7 and A-1.8
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	-	Few MBq, empty syringes, swabs
Disposal of residual substances and waste water	-	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal

Administration of radiopharmaceutical	
Typically administered activity per therapy cycle	37 MBq – 185 MBq, depending on joint size
Administration routes	Intra-articular
Typical number of administrations/therapy cycles	1
Typical time between therapy cycles	6 months
Limiting factors for repeating therapy (e. g. dose-limiting organ)	Not applicable

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{186}Re]rhenium sulfide	-
Biological action of the radiopharmaceutical	Phagocytosis of the pharmaceutical by superficial synovial cells	-
Biodistribution/specific accumulation in	Synovial cells	-
Non-specific/non-target accumulation dominant in	-	-
Known common side effects (> 10 %)	Not applicable	-
Rare severe side effects	Not applicable	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	0.0102 mSv/MBq/% outflow
Typical effective dose (total for all patient cycles)	-
Dose-limiting organ	-
Intended dose target region	-
Required pre-therapy dosimetry and imaging	-
Required post-therapy dosimetry and imaging	Radiotracer scintigraphy

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	-
Excretion modes	-
Excretion route most relevant for radiological protection	-
Typical duration of excretion relevant for radiation protection	-
Handling of excrement in hospital and post-hospital	-
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	γ
Type(s) of radiation emitted by patient most relevant to radiation protection	-
Anatomic focal points of radiation (where present)	Treated joint
Typical duration of radiation relevant for radiation protection emitted by patient	-
Required radiation protection measures in hospital and post-hospital	-

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	-
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	No
Typically recommended hospitalisation period	-
Possible reasons for extended period of hospitalisation	-
Reasons why hospitalisation is needed to administer therapy safely	-
Reasons why outpatient care is possible, but hospitalisation may be required	-
Specific factors influencing number and duration of inpatient stays	-

Therapeutic indication(s)	
Approved indications	Septic arthritis, activated osteoarthritis, synovitis
Currently typical indications for therapy as an individual curative treatment	Not applicable
New indications arising from studies/research	Not applicable
Therapy already added to guidelines	Yes (“Guideline for radiosynoviorthesis”)

Reimbursement	
Inpatient	Billing code: 8-503.3
Outpatient	EBM
Reimbursement issues	-

Table 5.3: Yttrium-90 radionuclide therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Yttrium citrate colloid	-	-
Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	-	-	-
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	-	-	-
Typically administered quantity	-	-	-

Procurement/preparation of [^{90}Y] yttrium citrate	
Name	[^{90}Y]yttrium citrate
Commercially available radiopharmaceutical	Yes
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	0125 (Radiopharmaceutical preparations)
Unapproved components used during in-house preparation	-

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	-	^{90}Y
Radiation type (%α, %β, %γ)	-	See Table A-1.1
Energy spectrums (α, β, γ)	-	See Table A-1.1
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	-	Few MBq, empty syringes, swabs
Disposal of residual substances and waste water	-	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	185 MBq – 222 MBq
Administration routes	Intra-articular
Typical number of administrations/therapy cycles	1
Typical time between therapy cycles	6 months
Limiting factors for repeating therapy (e. g. dose-limiting organ)	None known

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{90}Y]yttrium citrate	-
Biological action of the radiopharmaceutical	Phagocytosis of the pharmaceutical by superficial synovial cells	-
Biodistribution/specific accumulation in	Synovial cells	-
Non-specific/non-target accumulation dominant in	-	-
Known common side effects (> 10 %)	-	-
Rare severe side effects	-	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	0.038 mSv MBq^{-1} 8.44 mSv for 222 MBq and low removal
Typical effective dose (total for all patient cycles)	-
Dose-limiting organ	-
Intended dose target region	-
Required pre-therapy dosimetry and imaging	-
Required post-therapy dosimetry and imaging	Radiotracer scintigraphy to verify administration, no dosimetry

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	-
Excretion modes	-
Excretion route most relevant for radiological protection	-
Typical duration of excretion relevant for radiation protection	-
Handling of excrement in hospital and post-hospital	-
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	γ
Type(s) of radiation emitted by patient most relevant to radiation protection	-
Anatomic focal points of radiation (where present)	Treated joint
Typical duration of radiation relevant for radiation protection emitted by patient	-
Required radiation protection measures in hospital and post-hospital	-

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	-
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	No
Typically recommended hospitalisation period	-
Possible reasons for extended period of hospitalisation	-
Reasons why hospitalisation is needed to administer therapy safely	-
Reasons why outpatient care is possible, but hospitalisation may be required	-
Specific factors influencing number and duration of inpatient stays	-

Therapeutic indication(s)	
Approved indications	Septic arthritis, activated osteoarthritis, synovitis
Currently typical indications for therapy as an individual curative treatment	Not applicable
New indications arising from studies/research	Not applicable
Therapy already added to guidelines	Yes (“Guideline for radiosynoviorthesis”)

Reimbursement	
Inpatient	Billing code: 8-503.3
Outpatient	EBM
Reimbursement issues	-

6 Selective internal radiotherapy (SIRT) of liver tumours with yttrium-90 and holmium-166

Selective internal radiotherapy (SIRT), also termed transarterial radioembolisation (TARE), is an established therapy for the treatment of malignant liver tumours. In this method, tiny tissue-compatible beads of resin, glass or poly-L-lactic acid —approved as medical devices— are administered directly into the hepatic arteries. Their small diameter causes the beads to get

lodged inside tumour vessels (embolisation), where they can deliver their effect locally via radiation (not pharmacologically). The therapeutic rationale behind the intra-arterial administration is based on the fact that healthy hepatic tissue derives its blood supply primarily via the veins (portal vein), while liver tumours are perfused especially via the hepatic artery.

Two commercial yttrium-90-labelled preparations with different microspheres (SIR-Spheres®, resin; Thera-Sphere™, glass) are currently CE-certified for the treatment of primary or secondary malignant tumours. A further treatment option, labelled with holmium-166 (Quirem-Spheres™, also CE-certified), is also available. The topic of dosimetry in SIRT is playing an increasingly important role. The current status of clinical experience is provided in the tables, whereby new data are continuously being published. With regard to the currently included dosimetry figures, we refer to the works of Salem et al. and Konijnenberg et al., as well as the current EANM guideline (Konijnenberg et al. 2021, Salem et al. 2019, Weber et al. 2022).

6.1 Indications and therapy goals

Indications for SIRT include primary liver malignancies such as hepatocellular carcinoma and intrahepatic cholangiocarcinoma, as well as liver metastases from extrahepatic primary tumours such as colorectal cancer, breast cancer and neuroendocrine tumours. In the majority of patients, the primary goal of therapy is to prolong survival without a curative approach. However, an ongoing prospective phase 3 study in patients with colorectal cancer and liver metastases showed that the adjunctive use of SIRT in second-line chemotherapy led to a significant increase in progression-free survival (PFS) and hepatic PFS (Mulcahy et al. 2021). This is the first prospective, randomised phase 3 study with SIRT where the primary endpoint was reached and an increase in PFS was achieved. Furthermore, SIRT can also be used in isolated cases with a curative intention within the scope of bridging a patient to transplantation, i. e. to achieve temporary local stabilisation.

6.2 Implementation

6.2.1 Preparation and therapy planning

The indication for SIRT should be made beforehand in a multidisciplinary tumour board review taking the guidelines and alternative therapies into account. In addition, it must be ensured that the tumour burden is limited to the liver or that the hepatic tumour burden is key to the patient's prognosis, as the treatment can only deliver its therapeutic effects inside the liver due to its mode of action.

To ensure that SIRT can be carried out with as few side effects as possible, the microspheres must remain securely in the liver after administration and must not travel with the blood to the lungs via a bypass (known as a shunt) or to other organs (e. g. the stomach, gall bladder, duodenum, pancreas) via small side branches. Because the radiation also partly affects healthy hepatic tissue, the function of the liver must for the most part be preserved (e. g. bilirubin within the normal range or only marginally elevated, liver enzymes only marginally elevated). Portal vein thrombosis does not present a contraindication.

For SIRT to be technically feasible, it must be possible to access and probe the hepatic arteries with a catheter, there must be no significant anomalies in vascularisation, and any branches supplying other organs must be embolised risk-free prior to the therapy.

6.2.2 General course of therapy

After establishing the indication for SIRT, therapy is initiated and normally comprises two inpatient stays. During the first inpatient stay, angiography of the hepatic vessels is performed,

followed by administration of a radioactive tracer to detect any unwanted microsphere distribution. If necessary, small branches are embolised and any relevant shunting is quantified. Following the first intervention it is again assessed whether SIRT is technically feasible, and the corresponding radioactivity to be administered is calculated. During the second inpatient stay, angiography is repeated and the radioactive substance is then administered. After both interventions, the patient should remain in bed for about five to six hours in order to prevent secondary bleeding from the inguinal area. During the further course, whole- or partial-body imaging is performed to document the therapy.

Prior to administration of the actual therapy, the patient receives pre-medication consisting of a glucocorticoid (usually Fortecortin) and a gastroprotective drug. Sufficient hydration must also be ensured. Analgesics and medicines against nausea/vomiting can be administered as needed. In addition, antibiotics are administered to prevent infections.

In Germany, treatment is followed by an inpatient stay. According to the 2009 SSK recommendation (SSK 2009), patients should be isolated for at least 48 hours on a nuclear medicine ward due to the possibility of contamination and possible active excretions (Drescher et al. 2020). If patients are transferred to/placed in a different ward, e. g. for medical reasons, radiation protection commissioners of a nuclear medicine department must be involved in the patients' care and in ensuring radiation protection in the first 48 hours. This concerns excretions and materials (e. g. bandages) that potentially came into contact with body fluids, that were assessed with regard to absence of contamination and that may have to be disposed of as radioactive waste (SSK 2009). In addition, the patients must be monitored with regard to medical complications (vascular access, pain, incorrect administration). Radiotracer scintigraphy to verify correct administration of the therapy is also required. At the time of hospital discharge it must be ensured that the ionising radiation emitted by the patients does not exceed an effective dose of 1 mSv for relatives and third parties (Section 80 (1) of the German Radiation Protection Act (StrlSchG 2017), Section 122 (4) of the German Radiation Protection Ordinance (StrlSchV 2018)). This is ensured if the dose rate measured at a distance of 2 metres from the patient's surface at the time of discharge is below a threshold that guarantees a value smaller than 1 mSv when applying the integral dose (SSK 1996). Due to the above restrictions, it is not practicable to administer the therapy on an outpatient basis.

6.2.3 Contraindications and side effects

Generally speaking, if prepared properly, the therapy is well tolerated. The most common side effects include short-term pain in the upper abdomen (possibly already during the treatment), nausea and fever. Corresponding symptoms usually resolve within one to two days. Very rare, severe side effects can occur if microspheres travel to healthy organs (e. g. stomach, pancreas, lungs) despite taking adequate precautions during the preparation. A flow of microspheres into healthy liver tissue can lead to a temporary or permanent deterioration in liver function (radiation-induced liver disease). The frequency of this side effect can be significantly reduced by delivering the therapy in two phases and administering cortisone, provided there are no contraindications for this.

Table 6.1*: Radionuclide therapy SIRT with yttrium-90*

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Microspheres made of synthetic resin and glass	-	Proton pump inhibitors (e. g. pantoprazole) Anti-emetic drugs (e. g. ondansetron, granisetron) Steroids (e. g. 20 mg dexamethasone IV, followed by 10 mg prednisone/day orally) Extended-release opioids, if necessary
Known pharmacological effects of unlabelled carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Known side effects of unlabelled carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Typically administered quantity	Glass microspheres: 1.2 million – 8 million microspheres per vial in 0.6 ml water (22,000–73,000 per mg) Synthetic resin microspheres: 40 million – 80 million microspheres per vial in 5 ml water	-	Please refer to the product information for the effects, side effects and typical dosages

Procurement/preparation of radiopharmaceuticals used	
Name	^{90}Y-TheraSphere ^{90}Y-SIR-Spheres
Commercially available radiopharmaceutical/medical device	Yes (medical device)
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	None, because medical device
Unapproved components used during in-house preparation	-

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	Not applicable	^{90}Y-TheraSphere (Freudenberg et al. 2022, Metyko et al. 2012): ^{91}Y, ^{88}Y, ^{51}Cr ^{90}Y-SIR-Spheres (Freudenberg et al. 2022, Metyko et al. 2012): none
Radiation type (%α, %β, %γ)	Not applicable	See Table A-1.1
Energy spectrums (α, β, γ)	Not applicable	See Table A-1.1
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	Not applicable	Typically minimal (< 5 %), higher residual quantities if partial quantities are withdrawn in the clinical setting
Disposal of residual substances and waste water	Not applicable	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal Contamination with ^{88}Y is critical. At the time of calibration, this is approx. 3 orders of magnitude above the limit for unrestricted clearance for 1 kg of waste matter. If nearly the full activity is administered, the activity in the waste falls below the limit after a decay period of about 1 year. For unused preparations contaminated with ^{88}Y, a return to the manufacturer or disposal via the federal state collecting depot is recommended.

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	^{90}Y-TheraSphere: 3 GBq – 20 GBq, calculated according to formula or dosimetry $A_{Therapy}=D_{PTV}*m_{PTV}/(50x(1-shunt_{Lungs}))$ ^{90}Y-SIR-Spheres: Calculated according to formula or dosimetry $A_{Therapy}=(BSA-0.2)+ m_{Tumour}/(m_{Liver}+m_{Tumour})$ Dose reduction of 20 % for lung shunt ≥ 10 % and < 15 %, and of 40 % for lung shunt ≥ 15 % and < 20 % (Weber et al. 2022)
Administration routes	IA via catheter
Typical number of administrations/therapy cycles	1 to 2
Typical time between therapy cycles	4 to 6 weeks
Limiting factors for repeating therapy (e. g. dose-limiting organ)	Lung shunting, technical feasibility, REILD (adioembolization-induced liver disease), extrahepatic flow

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	^{90}Y-TheraSphere ^{90}Y-SIR-Spheres	-
Biological action of the radiopharmaceutical	Elimination of the liver tumour tissue or liver metastases	-
Biodistribution/specific accumulation in	Around areas with hyperperfusion, depending on position of catheter	-
Non-specific/non-target accumulation dominant in	Outflow area, especially lungs, stomach	-
Known common side effects (> 10 %)	Fatigue, malaise, fever (all very common, > 10 %) Nausea, vomiting, post-embolization syndrome (common, 1-10 %)	-
Rare severe side effects	REILD	-

Dose/dosimetry (Konijnenberg et al. 2021, Salem et al. 2019, Weber et al. 2022)	
Typical effective dose per therapy session per patient (per administration)	Variable, negligible in comparison with liver dose
Typical effective dose (total for all patient cycles)	Target liver: 100 Gy – 120 Gy, depending on calculation using single- or multi-compartment model
Dose-limiting organ	Lungs and liver
Intended dose target region	Liver: 100 Gy – 120 Gy, possibly 150 Gy; for segmentation therapy > 500 Gy
Required pre-therapy dosimetry and imaging	Calculation of lung shunting, therapy planning for hepatic tissue
Required post-therapy dosimetry and imaging	Intra-therapeutic dosimetry normally not possible, post-therapy SPECT(/CT) or PET/CT to confirm distribution

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	^{90}Y
Excretion modes	Minimal renal/urine (between 0.01 % and 0.20 %), also gastrointestinal/stool (very minimal) (Drescher et al. 2020)
Excretion route most relevant for radiological protection	Renal, to a lesser extent also gastrointestinal. Potentially also contaminated access routes/dressings.
Typical duration of excretion relevant for radiation protection	2 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital)
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	γ (nearly 100 %) (bremsstrahlung)
Type(s) of radiation emitted by patient most relevant to radiation protection	γ (bremsstrahlung)
Anatomic focal points of radiation (where present)	Liver
Typical duration of radiation relevant for radiation protection emitted by patient	2 days
Required radiation protection measures in hospital and post-hospital	In hospital: Therapy ward with waste water treatment plant (decontamination plant)

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	< 1 mSv[5]
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv[6]
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	Yes
Typically recommended hospitalisation period	Based on the radiation protection recommendation: at least 2 days (SSK 2009)
Possible reasons for extended period of hospitalisation	Care dependency, co-morbidities, domestic situation
Reasons why hospitalisation is needed to administer therapy safely	Dosimetry, radiation protection, monitoring
Reasons why outpatient care is possible, but hospitalisation may be required	Not applicable
Specific factors influencing number and duration of inpatient stays	No

Therapeutic indication(s)	
Approved indications	Treatment of primary liver tumours (HCC) and liver metastases
Currently typical indications for therapy as an individual curative treatment	Not applicable
New indications arising from studies/research	In combination with immunotherapy
Therapy already added to guidelines	Yes (e. g. S3 Guideline HCC)

Reimbursement	
Inpatient	DRG, ZE, NUB isolated case
Outpatient	No
Reimbursement issues	MD

[5] Section 80 (1) of the German Radiation Protection Act (StrlSchG)

[6] Section 81 of the German Radiation Protection Act (StrlSchG)

Table 6.2: Radionuclide therapy SIRT with holmium-166

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Poly(L-lactic acid) – PLLA	-	-
Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	Embolisation	-	-
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	-	-	-
Typically administered quantity	30 million particles for therapy, 3 million particles for diagnostics	-	-

Procurement/preparation of radiopharmaceuticals used	
Name	QuiremSpheres, QuiremScout
Commercially available radiopharmaceutical/medical device	Yes (medical device)
Approved components used during in-house preparation	-
Existing monographs (Ph. Eur.)	None, because medical device
Unapproved components used during in-house preparation	-

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	-	A: ^{166}Ho B: ^{166m}Ho
Radiation type (%α, %β, %γ)	-	See Table A-1.4
Energy spectrums (α, β, γ)	-	See Table A-1.4
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	-	≈ 200 MBq
Disposal of residual substances and waste water	-	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	≈ 5 GBq to 7 GBq
Administration routes	Intra-arterial
Typical number of administrations/therapy cycles	2 (left and right hepatic lobes separately)
Typical time between therapy cycles	4 to 5 weeks
Limiting factors for repeating therapy (e. g. dose-limiting organ)	**-**

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	PLLA	-
Biological action of the radiopharmaceutical	Embolisation	-
Biodistribution/specific accumulation in	apillary bed of the tumour	-
Non-specific/non-target accumulation dominant in	Lungs	-
Known common side effects (> 10 %)	-	-
Rare severe side effects	-	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	No information
Typical effective dose (total for all patient cycles)	No information
Dose-limiting organ	Liver
Intended dose target region	-
Required pre-therapy dosimetry and imaging	Radiotracer scintigraphy with [^{99m}Tc]Tc-MAA or QuiremScout, determination of hepatopulmonary shunting, determination of liver mass
Required post-therapy dosimetry and imaging	Radiotracer scintigraphy

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	^{166}Ho
Excretion modes	Minimal renal/urine, also gastrointestinal/stool (very minimal) (Drescher et al. 2020)
Excretion route most relevant for radiological protection	Renal, to a lesser extent also gastrointestinal. Potentially also contaminated access routes/dressings.
Typical duration of excretion relevant for radiation protection	2 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital)
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	γ
Type(s) of radiation emitted by patient most relevant to radiation protection	γ
Anatomic focal points of radiation (where present)	Liver
Typical duration of radiation relevant for radiation protection emitted by patient	2 days
Required radiation protection measures in hospital and post-hospital	Inpatient admission

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	< 1 mSv[7]
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv[8]
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	Yes
Typically recommended hospitalisation period	2 days
Possible reasons for extended period of hospitalisation	Care dependency, co-morbidities, domestic situation
Reasons why hospitalisation is needed to administer therapy safely	Dosimetry, radiation protection, monitoring
Reasons why outpatient care is possible, but hospitalisation may be required	Not applicable, as prohibited
Specific factors influencing number and duration of inpatient stays	No

Therapeutic indication(s)	
Approved indications	Analogous to SIRT with ^{90}Y particles
Currently typical indications for therapy as an individual curative treatment	-
New indications arising from studies/research	Not applicable
Therapy already added to guidelines	-

Reimbursement	
Inpatient	DRG
Outpatient	No
Reimbursement issues	MD

7 Radionuclide therapy of haematological/oncological disorders involving lutetium-177 and yttrium-90 (CXCR4-directed endoradiotherapy)

CXCR4-directed (CXC motif chemokine receptor 4) radioreceptor therapy is a novel method that is currently used after the established treatment methods have been exhausted. Chemokine receptors play a significant role in cell migration and represent important homing factors for haematopoietic stem cells in the bone marrow and for the dissemination of tumour cells to different tissues. [^{68}Ga]Ga-CXCR4 is used as a PET-tracer for directed in-vivo diagnostics, while [^{90}Y]Y-CXCR4 and [^{177}Lu]Lu-CXCR4 are used within the scope of radioligand therapy (RLT) of CXCR4-expressing malignant tumours (Buck et al. 2017, Buck et al. 2022).

7.1 Indications and therapy goals

1.) Multiple myeloma: Progressive disease after prior treatment with conventional chemotherapeutics, immunomodulators and glucocorticoids. The therapy can be used as

[7] Section 81 of the German Radiation Protection Act (StrlSchG)

[8] Section 81 of the German Radiation Protection Act (StrlSchG)

part of a conditioning regimen in patients scheduled to undergo autologous or allogeneic stem cell transplantation.

2.) Acute leukaemia (acute myeloid leukaemia, acute lymphocytic leukaemia): The therapy can be used to treat early relapses after prior allogeneic stem cell transplantation or refractory primary cancers following standard protocols.

3.) Malignant lymphoma: Progressive disease after the conventional established therapy options have been exhausted.

4.) Solid tumours: Progressive disease after the conventional established therapy options have been exhausted.

7.2 Implementation

7.2.1 Preparation and therapy planning

As a general rule, the indication is established in close collaboration with the haematology/ oncology specialists. The indication must be established on the basis of histological or cytological findings confirming the underlying malignancy.

Sufficient CXCR4 expression of tumour manifestations is ensured within the scope of pre-therapeutic PET/CT imaging using [^{68}Ga]Ga-CXCR4. Prior to administering the therapy, pre-therapeutic dosimetry is obligatory due to numerous individual kinetic parameters of the radiopharmaceutical. This is done with a standard activity of [^{177}Lu]Lu-CXCR4 (200 MBq), followed by whole-body scintigraphy scans at five minutes, one hour, four hours, 24 hours, 48 hours, 72 hours and, where necessary, 96 hours after administration of the test dose (Hanscheid et al. 2022).

Possible therapeutic radionuclides include lutetium-177 and yttrium-90. Due to the shorter half-life, use of yttrium-90 can enable stem cell transplantation as soon as 14 days after implementation of the CXCR4-RLT. When using lutetium-177 as a therapeutic radionuclide, a longer phase of aplasia of up to four weeks can be expected. A higher complication rate must be taken into account, particularly due to the high propensity to infections.

Patients are not required to be in a fasted state for dosimetry and therapy. The radiopharmaceutical is administered via an indwelling peripheral cannula; strictly intravenous administration must be ensured.

Sufficient hydration must also be ensured prior to commencing the therapy. On the day of therapy, pre-medication with anti-emetic drugs (5-HT3 antagonists) is recommended. An amino acid solution (25 g lysine and 25 g arginine in 2 l NaCl) is administered to ensure kidney protection. The infusion is first administered over 30 minutes to 60 minutes and then stopped during RLT. After administration of the therapeutic agent, infusion of the arginine-lysine solution is continued for another two to two and a half hours.

7.2.2 General course of therapy

Close monitoring of vital signs (pulse, blood pressure) is required before and after RLT.

The therapy is administered in the inpatient setting. A large proportion of the unbound activity is eliminated via the kidneys within 48 hours. For this reason, patients must be isolated on a nuclear medicine therapy ward equipped with an adequate retention and waste water treatment plant (decontamination plant) for at least 48 hours. Thereafter, at the time of hospital discharge/transfer to an oncology department administering the further therapy it must be ensured that the ionising radiation emitted by the patients does not exceed an effective dose of 1 mSv for relatives and third parties (Section 80 (1) of the German Radiation Protection Act

(StrlSchG 2017) and Section 122 (4) of the German Radiation Protection Ordinance (StrlSchV 2018)). This is ensured if the dose rate measured at a distance of 2 metres from the patient's surface at the time of hospital discharge is below a threshold that guarantees a value smaller than 1 mSv when applying the integral dose (SSK 1996). Because the patients are partly critically ill, regular physical examinations and laboratory analyses are indicated.

For patients with a higher tumour burden, the occurrence of tumour lysis syndrome must be considered and adequate fluid intake ensured (2 l d^{-1} to 3 l d^{-1} in the first days post-therapy).

7.2.3 Contraindications and side effects

CXCR4-directed RLT is tolerated very well (Maurer et al. 2019). Early experience has shown no significant acute side effects and toxicities or intolerances. Allergic reactions have not been observed to date. Due to the usually complex medical histories, patients should be monitored for general internal complications such as haemorrhages due to thrombocytopenia and infections.

Table 7.1: Pentixather [^{90}Y]Y-CXCR4 radionuclide therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Pentixather[9]	-	Arginine-lysine preparation 2 l/2.5–4 h Proton pump inhibitors (e. g. pantoprazole) Anti-emetic drugs (e. g. ondansetron, granisetron)
Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	None	-	Please refer to the product information for the effects, side effects and typical dosages
Typically administered quantity	100 µg – 200 µg	-	Please refer to the product information for the effects, side effects and typical dosages

Procurement/preparation of radiopharmaceuticals used	
Name	[^{90}Y]Y-CXCR4 [^{177}Lu]Lu-CXCR4
Commercially available radiopharmaceutical	No
Approved components used during in-house preparation	[^{90}Y]YCl_3 for radiolabelling [^{177}Lu]$LuCl_3$ for radiolabelling
Existing monographs (Ph. Eur.)	2803 ([^{90}Y]YCl_3 for radiolabelling)

[9] Chemical notation: Cyclo(D-3-iodo-Tyr[1]-[NMe]-D-Orn[2](AMBS-DOTA)-Arg[3]-2-Nal[4]-Gly[5]

	2798 ([^{177}Lu]LuCl$_3$ for radiolabelling)
Unapproved components used during in-house preparation	CXCR4

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	^{90}Y ^{177}Lu	Not applicable
Radiation type (%α, %β, %γ)	See Tables A-1.1 and A-1.6	
Energy spectrums (α, β, γ)	See Tables A-1.1 and A-1.6	
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	Typically minimal (< 5 %), higher residual quantities if partial quantities are withdrawn in the clinical setting	
Disposal of residual substances and waste water	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal	

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	[^{90}Y]Y-CXCR4: 3 GBq – 30 GBq, according to individual dosimetry Dose adjustment in renal failure
Administration routes	IV via central venous catheter or peripheral venous catheter (over 0.5 h to 1 h)
Typical number of administrations/therapy cycles	1
Typical time between therapy cycles	Not applicable
Limiting factors for repeating therapy (e. g. dose-limiting organ)	Bone marrow function, availability of haematopoietic stem cells

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	[^{90}Y]Y-CXCR4	-
Biological action of the radiopharmaceutical	Myeloablation (stem cells) Irradiation of CXCR4-expressing tumour cells Crossfire effect	-
Biodistribution/specific accumulation in	Haematopoietic bone marrow, CXCR4-expressing tumour cell compartment	-
Non-specific/non-target accumulation dominant in	Renal and hepatic excretion	-
Known common side effects (> 10 %)	Pancytopenia, fatigue	-
Rare severe side effects	-	-

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	^{90}Y ^{177}Lu
Excretion modes	Renal/urine, to a lesser extent gastrointestinal/stool
Excretion route most relevant for radiological protection	Renal
Typical duration of excretion relevant for radiation protection	2 days
Handling of excrement in hospital and post-hospital	Waste water treatment plant (decontamination plant) (in hospital) Post-hospital: Advise patients to collect pads or similar for several days; ideally flush the toilet multiple times after use
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	Bremsstrahlung (nearly 100 %)
Type(s) of radiation emitted by patient most relevant to radiation protection	Bremsstrahlung (nearly 100 %)
Anatomic focal points of radiation (where present)	Kidneys, bladder
Typical duration of radiation relevant for radiation protection emitted by patient	2 days
Required radiation protection measures in hospital and post-hospital	In hospital: Therapy ward with waste water treatment plant (decontamination plant); thereafter transfer of patient to haematology/oncology department for stem cell transplantation (autologous/allogeneic PBSCT)

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	2 Gy
Typical effective dose (total for all patient cycles)	2 Gy
Dose-limiting organ	Kidneys and bladder
Intended dose target region	Bone marrow: 2 Gy Tumour compartment: > 30 Gy Haematological disorders: > 30 Gy Solid tumours: > 20 Gy
Required pre-therapy dosimetry and imaging	[^{68}Ga]Ga-CXCR4-PET/CT, [^{177}Lu]Lu-CXCR4 scintigraphy, Calculation of bone marrow activity, kidney/liver dose
Required post-therapy dosimetry and imaging	Post-therapy SPECT/CT to estimate the dose achieved in the bone marrow or tumour

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	< 1 mSv[10]
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv[11]
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

[10] Section 81 of the German Radiation Protection Act (StrlSchG)

[11] Section 81 of the German Radiation Protection Act (StrlSchG)

Hospitalisation concept	
Inpatient setting necessary	Yes
Typically recommended hospitalisation period	48 hours
Reasons why hospitalisation is needed to administer therapy safely	Dosimetry, radiation protection with regard to excretions, monitoring

Therapeutic indication(s)	
Approved indications	None yet
Currently typical indications for therapy as an individual curative treatment	Myeloablation within the scope of conditioning prior to autologous/allogeneic PBSCT (Multiple myeloma, acute myeloid leukaemia, aggressive lymphoma)
New indications arising from studies/research	Not applicable
Therapy already added to guidelines	No

Reimbursement	
Inpatient	NUB, isolated case
Outpatient	Not applicable
Reimbursement issues	No

8 Radionuclide therapy of B-cell non-Hodgkin's lymphoma involving [^{90}Y]Y-CD20 ibritumomab tiuxetan (Zevalin)

The radiopharmaceutical [^{90}Y]Y-CD20 ibritumomab tiuxetan is used within the scope of radioimmunotherapy. CD20 is an antigen that is expressed on the surface of B-lymphocytes.

8.1 Indications and therapy goals

The indication for radioimmunotherapy is established in collaboration with the haematology/oncology specialists. [^{90}Y]Y-CD20 ibritumomab tiuxetan (Zevalin) is approved for the treatment of CD20-positive follicular B-cell non-Hodgkin's lymphoma refractory to treatment with other CD20-specific immunoconjugates (rituximab) or relapsed after induction therapy.

8.2 Implementation

8.2.1 Preparation and therapy planning

Pre-therapy dosimetry is not required; whole-body scintigraphy with indium-111-labelled anti-CD20 antibodies may provide indicators of increased complication rates. In addition, pre-therapy whole-body imaging to detect and identify all lymphoma manifestations is also advisable. [^{18}F]FDG-PET/CT or PET-MRI appear to be particularly suitable methods.

A control of the blood count is necessary within one week prior to administering radioimmunotherapy. As the therapy is associated with changes in the blood count, the leucocyte count should be above 1,500 μl^{-1} and the platelet count above 100,000 μl^{-1} prior to therapy. The degree of bone marrow infiltration should not be greater than 25 %, while life expectancy should not be less than three months.

8.2.2 General course of therapy

To achieve saturation of non-specific CD20 antigens, the non-radioactive antibody (rituximab) is administered one week prior to radioimmunotherapy (day 1) at a dose of 250 mg m^{-2} body

surface area. This infusion is repeated one week later (day 8) using the same dose level. After that, the radioimmunoconjugate can be administered. The infusion is generally administered as a short infusion (e. g. over ten minutes). Patients are not required to be in a fasted state prior to administration of the therapy (Tennvall et al. 2007).

For platelet counts > 150,000, a dose of 15 MBq [^{90}Y]Y-CD20 mAB kg^{-1} body weight is administered on day 8. In the presence of thrombocytopenia (100,000–149,000) the dose is reduced to 11 MBq kg^{-1} body weight. The maximum dose is 1.2 GBq.

8.2.3 Contraindications and side effects

Acute side effects following administration of yttrium-90 Zevalin are generally not expected.

Inpatient admission is not mandatory.

The most common side effect is a decrease in leucocyte and platelet counts by 30 % to 70 % relative to baseline values. The strongest decrease normally occurs seven to nine weeks after administration of the therapy. For this reason, regular controls of the blood count, at least in weekly intervals, are advisable until bone marrow function has fully recovered. Following radioimmunotherapy there is an increased risk of secondary myelodysplastic syndromes (MDS) or acute myeloid leukaemia.

Extravasation must be strictly avoided, as this may lead to local soft tissue radionecrosis.

Table 8.1: Zevalin® ^{90}Y ibritumomab tiuxetan radionuclide therapy

Pharmacological effects of unlabelled carrier/accompanying substances			
	Pharmacological API and/or carrier substance(s) to be radiolabelled (where applicable)	**Accompanying substance(s) in administered preparation (where applicable)**	**Other substances typically administered during therapy**
Name	Anti-CD20 monoclonal antibody (ibritumomab tiuxetan)	-	HAMA test required prior to therapy
Known pharmacological effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	B-cell depletion	-	-
Known side effects of <u>unlabelled</u> carrier/accompanying substances in administered quantity	Propensity to infections, nausea, vomiting, fever, headache, cough, dizziness	-	-
Typically administered quantity	3 mg mAB 250 mg m^{-2} BSA unlabelled antibody as co-medication (rituximab)	-	-

Procurement/preparation of Zevalin	
Name	[^{90}Y]Y-CD20 ibritumomab tiuxetan (Zevalin)
Commercially available radiopharmaceutical	Individual components are commercially available as approved medicinal products within the meaning of pharmaceutical legislation
Approved components used during in-house preparation	[^{90}Y]YCl_3 for radiolabelling and ibritumomab tiuxetan (Zevalin)
Existing monographs (Ph. Eur.)	2 803 ([^{90}Y]YCl_3 for radiolabelling)
Unapproved components used during in-house preparation	-

Active waste from preparation/supply		
	From in-house preparation	**From supplied preparation (long-lived concomitant nuclides in the preparation)**
Name	Not applicable	[^{90}Y]Y-CD20 ibritumomab tiuxetan (Zevalin)
Radiation type (%α, %β, %γ)	Not applicable	See Table A-1.1
Energy spectrums (α, β, γ)	Not applicable	See Table A-1.1
Amount of activity typically remaining in waste per therapy (α, β, γ MBq)	Not applicable	Minimal (< 5 %)
Disposal of residual substances and waste water	Not applicable	Storage until decay, then clearance as per Section 35 of the German Radiation Protection Ordinance (StrlSchV) and conventional disposal

Administration of radiopharmaceutical	
	Type and quantity of administered therapy
Typically administered activity per therapy cycle	^{90}Y ibritumomab tiuxetan (Zevalin): Max. 1.2 GBq 15 MBq kg^{-1} BW (platelets > 150,000) 11 MBq kg^{-1} BW (platelets 100,000–150,000)
Administration routes	Slow IV via central venous catheter or peripheral venous catheter
Typical number of administrations/therapy cycles	1
Typical time between therapy cycles	Not applicable
Limiting factors for repeating therapy (e. g. dose-limiting organ)	Bone marrow function

Effect		
	Radiopharmaceutical	**Metabolites**
Name of radiopharmaceutical	^{90}Y	-
Biological action of the radiopharmaceutical	Irradiation of CD20-positive malignant (but also benign) B-lymphocytes or CD20-positive lymphoma	-
Biodistribution/specific accumulation in	Bone marrow, CD20-positive lymphoma	-
Non-specific/non-target accumulation dominant in	Renal and hepatic excretion	-
Known common side effects (> 10 %)	Leucocytopenia, fatigue, asthenia, nausea, vomiting, headache, cough, dizziness, shortness of breath	-
Rare severe side effects	-	-

Dose/dosimetry	
Typical effective dose per therapy session per patient (per administration)	2 Gy
Typical effective dose (total for all patient cycles)	2 Gy
Dose-limiting organ	Kidneys, bladder and bone marrow
Intended dose target region	Tumour compartment: >30 Gy
Required pre-therapy dosimetry and imaging	Standard activities according to bone marrow function
Required post-therapy dosimetry and imaging	-

Exposure of surroundings/employees/environment by patient	
Radioactive excretion by patient	
Excreted nuclides	^{90}Y
Excretion modes	Renal, to a lesser extent gastrointestinal/stool
Excretion route most relevant for radiological protection	Renal
Typical duration of excretion relevant for radiation protection	Proportion of excreted activity relatively low, majority excreted within the first 48 h (approx. 4 %) (Geworski et al. 2006)
Handling of excrement in hospital and post-hospital	Outpatient therapy (SSK 2005), if inpatient then waste water treatment plant (decontamination plant)
Radiation emitted by patient post-treatment	
Emitted radiation type (%α, %β, %γ)	Bremsstrahlung (nearly 100 %)
Type(s) of radiation emitted by patient most relevant to radiation protection	Bremsstrahlung (nearly 100 %)
Anatomic focal points of radiation (where present)	Kidneys, bladder
Typical duration of radiation relevant for radiation protection emitted by patient	2 days
Required radiation protection measures in hospital and post-hospital	Outpatient setting possible

Surroundings (other persons in same household)	
Potential dose to other persons in same household per therapy session	< 1 mSv[12]
Potential total dose from all cycles to other persons in same household after a typical number of cycles (</> 1 mSv)	< 1 mSv[13]
Calculation of exposure of other persons in same household per year for total of all cycles, with adjustment of inpatient stay where required	No

Hospitalisation concept	
Inpatient setting necessary	No
Typically recommended hospitalisation period	48 h
Possible reasons for extended period of hospitalisation	-
Reasons why hospitalisation is needed to administer therapy safely	-
Reasons why outpatient care is possible, but hospitalisation may be required	Poor overall health
Specific factors influencing number and duration of inpatient stays	No

[12] Section 81 of the German Radiation Protection Act (StrlSchG)

[13] Section 81 of the German Radiation Protection Act (StrlSchG)

Therapeutic indication(s)	
Approved indications	CD20-positive follicular lymphoma (refractory to rituximab)
Currently typical indications for therapy as an individual curative treatment	Other low-grade lymphomas; DLBCL
New indications arising from studies/research	Not applicable
Therapy already added to guidelines	Yes (S3 Guideline Diagnosis, treatment and follow-up care of patients with follicular lymphoma, dated 07/2020)

Reimbursement	
Inpatient	DRG, isolated case
Outpatient	Assumption of costs
Reimbursement issues	No

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Annex

A-1 Radionuclide tables

The tables below provide a concise overview of the most important distinguishing characteristics of the nuclides used within the scope of radiotherapy (radiation types, energies and half-lives), of any accompanying nuclides and of the decay nuclides that occur during the decay process. For additional information relating to radiation protection when handling these nuclides, please refer to relevant advice and reports from the BfS for handling beta emitters (BfS 2013), from the SSK for basic principles of determining effective dose limits as a result of external radiation exposure (SSK 2018) and to the 'Radionuclide and Radiation Protection Data Handbook' (Delacroix et al. 2002).

A-1.1 Yttrium-90

Nuclide(s) administered	**Name**	**Radiation type (%α, %β, %γ)**	**Important transformation energies (α, β, γ)**	**Half-life/-lives**
(Active) nuclide used for labelling or pure	Yttrium-90	β^- (100 %)	β^-: 2,280.1 keV (99.98 %) ($^{90}Y \rightarrow {}^{90}Zr$) β^+: (0.0032 %)	64 h (2.7 d)
Accompanying nuclides in administered preparation (proportion %)	None ^{90}Y-TheraSphere: A: Yttrium-91 B: Yttrium-88 C: Chromium-51	A: β^- (100 %) B: EC β^+ (100 %) C: EC (100 %)	A: β^-: 1,544.8 keV (100 %) ($^{91}Y \rightarrow {}^{91}Zr$) (stable) B: γ: 898.0 keV (93.7 %) γ: 1,836.1 keV (99.2 %) ($^{88}Y \rightarrow {}^{88}Sr$) (stable) C: EC: 752.7 keV (90.02 %) γ: 320.1 keV (10 %) ($^{51}Cr \rightarrow {}^{51}V$) (stable)	A: 58.5 d B: 106.7 d C: 27.7 d
Decay nuclides in the body (A/B/C..)	Zirconium-90 (stable)			

A-1.2 Iodine-131

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Iodine-131	β^- (100 %) γ (100 %)	β^-: 606.3 keV (89.9 %) β^-: 333.8 keV (7.3 %) β^-: 247.9 keV (2.1 %) : γ: 364 keV (81.7 %) γ: 637 keV (7.2 %)	192.6 h (8.0 d)
Accompanying nuclides in administered preparation (proportion %)	None			
Decay nuclides in the body (A/B/C..)	A: Xenon-131 (stable) B: Xenon-131m	B: IT (100 %)	B: γ: 163.9 keV (1.9 %) (^{131m}Xe→ ^{131}Xe) (stable)	B: 11.8 d

A-1.3 Samarium-153

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Samarium-153	β^- (100 %)	β^-: 808.2 keV (17.5 %) β^-: 705.0 keV (49.6 %) β^-: 635.4 keV (32.2 %) γ: 103.2 keV (30 %)	46.3 h (1.9 d)
Accompanying nuclides in administered preparation (proportion %)	A: Europium-152 B: Europium-154 C: Europium-155 D: Europium-156	A: EC (72.1 %) β^+ (< 1 %) β^- (27.9 %) B: β^- (99.98 %) EC β^+ (0.02 %) C: β^- (100 %) D: β^- (100 %)	A: EC: 344.5 keV (24.9 %) EC 640.5 keV (17.4 %) EC 788.4 keV (21.7 %) β^-: 695.6 keV (13.8 %) B: β^-: 570.9 keV (36.3 %) 840.6 keV (16.8 %) 1,845.3 keV (10 %) C: β^-: 146.8 keV (47 %) β^- 165.6 keV (25 %) β^- 192.1 keV (8.1 %) β^- 252.1 keV (17.6 %) (^{154}Eu→ ^{154}Gd) (stable) D: β^- 485.0 keV (29 %) β^- 2451.0 keV (32 %) β 264.2 keV (10.3 %)	A: 13.5 a B: 8.6 a C: 4.7 a D: 15.2 d
Decay nuclides in the body (A/B/C..)	Europium-153 (stable)			

A-1.4 Holmium-166

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Holmium-166	β^- (100 %)	β^-: 1,854.9 keV (50.0 %) β^-: 1,774.3 keV (48.7 %) γ: 80.6 keV (6.7 %)	26.8 h (1.1 d)
Accompanying nuclides in administered preparation (proportion %)	Holmium-166m	β^- (100 %)	β^-: 1,315.4 keV (3.0 %) β^-: 73.9 keV (76.4 %) β^-: 33.3 keV (17.7 %) γ: 184.4 keV (72.6 %) 280.4 keV (29.7 %)	$4.38 \cdot 10^5$ d (1,200 a)
Decay nuclides in the body (A/B/C..)	Erbium-166 (stable)			

A-1.5 Erbium-169

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Erbium-169	β^- (92.5 %) EC (7.5 %)	β^-: 351.1 keV (55.0 %) β^-: 342.69 keV (45.0 %)	225.4 hs (9.4 d)
Accompanying nuclides in administered preparation (proportion %)	Ytterbium-169 (1.4 %)	EC (100 %)	β^-: 592.8 keV (3.7 %) β^-: 529.7 keV (83.2 %) γ: 307.7 keV (10.05 %) 198.0 keV (35.8 %) 130.5 keV (11.3 %) 109.8 keV (17.5 %)	768.6 h (32.0 d)
Decay nuclides in the body (A/B/C..)	Thulium-169 (stable)			

A-1.6 Lutetium-177

Nuclide(s) administered	**Name**	**Radiation type (%α, %β, %γ)**	**Important transformation energies (α, β, γ)**	**Half-life/-lives**
(Active) nuclide used for labelling or pure	Lutetium-177	β^- (100 %)	β^-: 498.3 keV (78.6 %) γ: 208.36 keV (11 %) 112.9 keV (6.4 %)	159.5 h (6.7 d)
Accompanying nuclides in administered preparation (proportion %) Note: occur only when prepared using the following method: $^{176}Lu(n, \gamma)^{177}Lu$ No occurrence during indirect production: ^{176}Yb (n, γ)$^{177}Yb \rightarrow {}^{177}Lu$	Lutetium-177m (approx. 0.02 % for carrier-added ^{177}Lu)	β^- (78.3 %) IT (21.7 %)	β^-: 153.0 keV (61.3 %) γ: 208.4 keV (57.7 %) 228.5 keV (37.0 %) 113.0 keV (20.4 %) 378.5 keV (29.7 %) 418 keV (21.3 %)	160.4 d
Decay nuclides in the body (A/B/C..)	Hafnium-177 (stable)			

A-1.7 Rhenium-186

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Rhenium-186	β^- (92.5 %) EC (7.5 %)	β^-: 1,069.5 keV (71.0 %) β^-: 932.3 keV (21.5 %) β^-: 581.6 keV (5.8 %) γ: 137.2 keV (9.42 %)	89.2 h (3.7 d)
Accompanying nuclides in administered preparation (proportion %)	A: Rhenium-184 B: Rhenium-188	A: EC β^+ (100 %) B: See Table A-1.8	EC: 579.7 keV (76.1 %) 477.0 keV (17.6 %) $^{184}Re \rightarrow {}^{184}W$ (stable) B: See Table A-1.8	A: 38.2 d
Decay nuclides in the body (A/B/C..)	A: Osmium-186 (virtually stable) B: Wolfram-186 (stable)			A: 10^{15} a

A-1.8 Rhenium-188

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Rhenium-188	β^- (100 %)	β^-: 2,120.4 keV (71.1 %) β^-: 1,965.4 keV (25.6 %) γ: 155.0 keV (15.1 %)	17.005 h (0.7 d)
Accompanying nuclides in administered preparation (proportion %)	-[14]			
Decay nuclides in the body (A/B/C..)	A: Osmium-188 (stable)			

[14] Contamination with Wolfram-188 is possible, as it is eluted using the $^{188}W/^{188}Re$ generator; relevant details are not available in the literature.

A-1.9 Radium-223

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Radium-223	α (100 %)	α: 5,979.3 keV (100 %) $^{223}Ra \rightarrow {}^{219}Rn$ α: 6,946.1 keV (100 %) $^{219}Rn \rightarrow {}^{215}Po$ α: 7,526.4 keV (100 %) $^{215}Po \rightarrow {}^{211}Pb$ α: 6,750.5 keV (99.7 %) $^{211}Bi \rightarrow {}^{207}Tl$ β^-: 1,423.0 keV (100 %) $^{207}Tl \rightarrow {}^{207}Pb$ β^-: 1,370.0 keV (100 %) $^{211}Pb \rightarrow {}^{211}Bi$ γ: 154 keV (5.6 %) γ: 269 keV (13.7 %) X-ray quanta 81.1 keV (15.2 %) 83.7 keV (25.6 %)	273.6 h (11.4 d) 4.0 s 1.8 ms 2.1 min 4.8 min 36.1 min
Accompanying nuclides in administered preparation (proportion %)	A: Thorium-227 B: Actinium-227	A: α (100 %) B: β^- (98.6 %) B: α (1.4 %)	A: α: 6,446.4 keV (100 %) $^{227}Th \rightarrow {}^{223}Ra$ B: β^-: 44.8 keV (98.6 %) $^{227}Ac \rightarrow {}^{227}Th$ β^-: 44.8 keV (99.9 %) $^{223}Fr \rightarrow {}^{223}Ra$ α: 5,042.2 keV (1.4 %) $^{227}Ac \rightarrow {}^{223}Fr$	A: 449.28 h (18.7 d) B: 21.7 a
Decay nuclides in the body (A/B/C..)	Lead-207 (stable)			

A-1.10 Actinium-225

Nuclide(s) administered	Name	Radiation type (%α, %β, %γ)	Important transformation energies (α, β, γ)	Half-life/-lives
(Active) nuclide used for labelling or pure	Actinium-225	α (100 %)	α: 5,935.2 keV (100 %) $^{225}Ac \rightarrow {}^{221}Fr$ α: 6,457.9 keV (100 %) $^{221}Fr \rightarrow {}^{217}At$ α: 7,201.9 keV (99.9 %) $^{217}At \rightarrow {}^{213}Bi$ α: 5,982.0 keV (2.1 %) $^{213}Bi \dashrightarrow {}^{209}Tl$ α: 8,537.0 keV (100 %) $^{213}Po \rightarrow {}^{209}Pb$ β^-: 1,427.0 keV (97.9 %) $^{213}Bi \rightarrow {}^{213}Po$ β^-: 3,982.0 keV (100 %) $^{209}Tl \rightarrow {}^{209}Pb$ β^-: 644.2 keV (100 %) $^{209}Pb \rightarrow {}^{209}Bi$ γ: 440 keV (25.9 %) → ^{213}Bi 218 keV (11.4 %) → ^{221}Fr	237.6 h (9.9 d) 4.9 min 32.3 ms 45.6 min 4.3 µs 45.6 min 2.2 min 3.3 h
Accompanying nuclides in administered preparation (proportion %)	-[15]			
Decay nuclides in the body (A/B/C..)	Bismuth-209 (virtually stable)			$1.9 \cdot 10^{19}$ a

[15] No relevant details in the literature; thorium-229 possible but not confirmed to date; see also: Hesse L. Bestimmung der Radionuklidreinheit nuklearmedizinischer Präparate. [Master's thesis]. Dresden University. 2020; daughters stable, as short-lived, time to stability: ^{221}Fr → 21 mins; 213Bi → 201 mins

All data according to ‘The Lund/LBNL Nuclear Data Search’ (Table of Radioactive Isotopes) (http://nucleardata.nuclear.lu.se/toi/).

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A-2 Abbreviations

ALSYMPCA study	Alpharadin in symptomatic prostate cancer study
AMG	Medicinal Products Act (German: *Arzneimittelgesetz*)
BfS	Federal Office for Radiation Protection (German: *Bundesamt für Strahlenschutz*)
CT	Computed tomography
CUP	Cancer of unknown primary (unknown primary tumour)
CXCR4	CXC motif chemokine receptor 4
DGN	German Society of Nuclear Medicine (German: *Deutsche Gesellschaft für Nuklearmedizin e.V.*)
DOTANOC	DOTA-[Nal^3]-octreotide
DOTATATE	DOTA-(Tyr^3)-octreotate
DOTATOC	DOTA(0)-Phe(1)-Tyr(3)) octreotide, edotreotide
DRG	Diagnosis-related group
DTC	Differentiated thyroid cancer
EANM	European Association of Nuclear Medicine
EBM	Uniform Assessment Standard (German: *Einheitlicher Bewertungsmaßstab*)
ECOG	Eastern Cooperative Oncology Group
EDTMP	Ethylenediamine tetra(methylene phosphonic acid)
FDG	Fluorodeoxyglucose
GEP-NET	Gastroenteropancreatic neuroendocrine tumour
GFR	Glomerular filtration rate
HA-DOTATATE	DOTA-3-iodo-Tyr3-octreotate
HL	Half-life
LHRH	Luteinising hormone-releasing hormone
LSS	Federal state collecting depot (German: *Landessammelstelle*)

MAA	Labelled macroaggregated albumin
mCRPC	Metastatic castration-resistant prostate cancer
MD	Medical Service of the Health Funds (German: *Medizinischer Dienst der Krankenkassen*)
MDS	Myelodysplastic syndrome
MiNEN	Mixed neuroendocrine non-neuroendocrine neoplasms
MRI	Magnetic resonance imaging
NANETS	North American Neuroendocrine Tumor Society
NET	Neuroendocrine tumour
NUB	New examination and treatment methods (German: *Neue Untersuchungs- und Behandlungsmethoden*)
NYHA	New York Heart Association
PDTC	Poorly differentiated thyroid carcinoma
PET	Positron emission tomography
PFS	Progression-free survival
PRRT	Peptide receptor radionuclide therapy
PSMA	Prostate-specific membrane antigen
PSMA-I&T	PSMA for imaging & therapy
RA	Rheumatoid arthritis
RAI	Radioactive iodine therapy
RANKL	Receptor activator of nuclear factor-kappaB ligand
REILD	Radioembolization-induced liver disease
rhTSH	Recombinant human thyroid-stimulating hormone
RI	Radioiodine
RLT	Radioligand therapy
RSc	Renal scintigraphy
RSO	Radiosynoviorthesis
SIR-spheres	Selective internal radio-spheres

SIRT	Selective internal radiotherapy
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	Single-photon emission computed tomography
StrlSchG	German Radiation Protection Act (German: *Strahlenschutzgesetz*)
StrlSchV	German Radiation Protection Ordinance (German: *Strahlenschutzverordnung*)
TARE	Transarterial radioembolization
TSH	Thyroid-stimulating hormone – thyrotropine
ULN	Upper Limit of Normal
WHO	World Health Organization
ZE	Additional Fee (German: *Zusatzentgelt*)
Zevalin	Ibritumomab tiuxetan

A-3 Glossary

Activity	Activity refers to the number of atomic nuclei in a radioactive substance that decay per time unit. The unit for activity is the reciprocal second with the special unit name becquerel, abbreviated: Bq. 1 becquerel corresponds to the decay of one nucleus per second. This unit supersedes the former unit for activity, Curie, abbreviated: Ci. 1 Ci corresponds to $3.7 \cdot 10^{10}$ Bq. **Note** 'Activity' refers to the physical quantity of the number of decays per time unit, 'radioactivity' to the characteristic of certain nuclides to undergo transformation. According to: (Koelzer 2019)
Becquerel	Becquerel (Bq) is the SI unit for activity. The unit symbol is Bq. Definition: 1 Bq = $^{-1}$. The former unit for activity is Curie (Ci). The conversion factor for the two units is as follows: 1 Ci = $3.7 \cdot 10^{10}$ Bq.
CT	Computed tomography is an imaging technique that uses the absorption values of X-rays passing through the body to produce cross-sectional images. It involves the reconstruction of a large volume of projection data of an object captured from different angles to create digital cross-sections of the body. To this end, the body is moved longitudinally in order to generate stepwise or continuous three-dimensional image data of a particular region of the body. CT is the imaging procedure with the highest collective radiation exposure.
Clearance	Clearance refers to the administrative act effecting the release of low-level radioactive material and low-level radioactive movable objects, buildings, surfaces, facilities or facility parts from regulatory control under nuclear or radiation protection legislation **(**BfS 2019).
Clearance measurements	Clearance measurements of radioactive hospital waste serve to provide metrological evidence for clearance of the waste by the authority. Clearance measurements are taken of radioactive waste when its radioactivity is so low that it can be assigned to other types of hospital waste and can then be treated or disposed of accordingly. Clearance measurements may require a preceding interim storage period during which waste with short half-lives can lose its activity during interim storage – this is also referred to as decay time. According to (BfS n.d.)

Dosimetry	The term dosimetry refers to different methods, such as measurement and calculation methods or processes to determine the dosage of radiation emitted by ionising radiation (Rühle et al. 2009**).**
Half-life, physical	The half-life t_R is the period of time in which the activity of a radionuclide *R* decreases to half of its original value. $$t_R = \frac{\ln 2}{\lambda_R}$$ In this context, λ_R is the decay constant of the radionuclide *R*. After three half-lives have elapsed, approx. 10 % of the original activity remains, which further decreases to approx. 1 % after seven half-lives and to approx. 0.1 % after ten half-lives. The half-lives of radionuclides range from less than 10^{-12} s to more than 10^{12} a (Rühle et al. 2009).
In-house preparation	In-house preparation of radiopharmaceuticals refers to the manufacture of radioactive medicinal products within the own facility. This may take place, for example, in nuclear medicine departments of university hospitals, research facilities, private practices, etc.
In-house manufacture	Synonym for in-house preparation.
Nuclear medicine	The field of nuclear medicine comprises the use of radioactive substances, sonographic and nuclear procedures for the diagnosis of the function and localisation of organs, tissues and systems, for the recognition and evaluation of disease progression as well as the treatment with unsealed radionuclides and the interests of radiation protection (Bundesärztekammer 2018).
Organ dose	The organ dose H_T is the product of the mean absorbed dose in an organ, tissue or body part and the radiation weighting factor w_R according to ICRP. The values of the radiation weighting factor w_R according to ICRP are based on the type and quality of the radiation (photons, electrons, neutrons, protons, alpha particles).
PET (scan)	Positron emission tomography (PET). An imaging procedure in nuclear medicine that measures the distribution of low-level radioactive substances to generate images of biochemical and physiological functions. In modern medical diagnostics, PET is used almost exclusively in combination with CT as PET-/CT.
Preparation exempt from authorisation	This is the preparation of a radiopharmaceutical by the treating physician or directly under his/her professional responsibility under the legal basis set forth in Section 13 (2b) of the AMG (AMG 2005).

Radioactive substance	For the purposes of this Act, ‘radioactive substances’ (nuclear fuels and other radioactive materials) means all substances containing one or more radionuclides the activity or specific activity of which precludes their being disregarded under the provisions contained in this Act or in a statutory ordinance issued by the Federal Government with the consent of the Bundesrat on the basis of this Act (StrlSchG 2017, Section 3 (1)).
Radioligand therapy	The term radioligand refers to a radionuclide-labelled substance which can bind as a ligand to a target protein, for example a receptor, of the target cell. In radioligand therapy, this enables targeted transportation of the radioactivity to its target site.
Radionuclide	A radionuclide is a radioactive nuclide in the ground state or metastable state. Its designation contains the element symbol and the corresponding mass number, e. g. ^{90}Sr, ^{99m}Tc (Rühle et al. 2009).
Radionuclide therapy	Therapy involving the use of unsealed radionuclides.
Radiopharmaceutical	Radiopharmaceutical is a synonym for ‘radioactive medicinal product’ (from the Greek pharmakon drug, medicine). Radiopharmaceuticals are medicinal products that are or contain radioactive substances and spontaneously emit ionizing radiation and are intended to be used on account of these properties. By law, radiopharmaceuticals are medicinal products. As a general rule, they have no pharmacological activity. According to: (AMG 2005, Section 4 (8))
Radiopharmacy	Radiopharmacy or nuclear pharmacy refers to the development, preparation and quality testing of radiopharmaceuticals.
Sievert	Sievert is the SI unit of equivalent dose, organ dose and effective dose. The unit symbol is Sv. Definition: 1 Sv = 1 J kg^{-1} The former unit for equivalent dose is Rem (rem). The conversion factor for the two units is as follows: 1 Sv = 100 rem The following applies for the equivalent dose rate: 1 Sv s^{-1} = 100 rem s^{-1} According to: (Rühle et al. 2009)

Sponsor (medical research)	The sponsor of a clinical trial is a natural or legal person who assumes the responsibility for initiating, managing and financing a clinical trial in humans. This also includes the correct implementation of clinical trials in accordance with the radiation protection provisions set forth in Sections 31–37 of the German Radiation Protection Act 2017 (StrlSchG 2017).
Theragnostics (also: theranostics, radiotheranostics)	The concept behind thera(g)nostics is based on the use of a specific mechanism to promote the accumulation of an active substance/radiopharmaceutical, not only for the diagnosis and choice of therapy, but also for the therapy itself. The same binding mechanism and where applicable the same carrier is used both for the respective diagnostic test and for delivering the therapy, but partly with a different radionuclide labelling. Before a therapeutic radiopharmaceutical is administered, the expected distribution and accumulation can be verified by means of the diagnostic procedure.
Therapy cycle	Nuclear medicine therapy is frequently administered in intervals referred to as cycles where treatment phases alternate with treatment breaks. The radiopharmaceutical is administered in a cycle, which is followed by a treatment break lasting several days, weeks or months. The treatment break gives healthy tissue that was affected by the treatment the opportunity to regenerate, as healthy tissue can usually recover faster from nuclear medicine therapy than tumour tissue. According to: (Deutsche Krebsgesellschaft n.d.)
Tumour	The term tumour refers to uncontrolled tissue growth that can occur in many tissues in the body. There are genetic factors that can promote the formation of a tumour. Ionising radiation can increase the probability of tumour formation. In the event of a neoplasm (growth of body tissue), it is graded according to its biological growth behaviour and the original tissue. Depending on its ability to metastasise, a distinction is made between benign, malignant and semi-malignant tumours. Malignant tumours are often called cancer.
Unsealed radioactive material	Unsealed radioactive substances means all radioactive substances except sealed radioactive substances (StrlSchG 2017, Section 5 (34)).
Waste, radioactive	Radioactive substances that are designated for disposal or must be disposed of in a controlled way for reasons of radiation protection (Koelzer 2019**).**

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