5 Regulations and Requirements of Scientific Centers Performing Radiopeptide Therapies

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5.1 Introduction

Radiopeptide Therapy or Peptide Receptor Radionuclide Therapy (PRRT) is a multidisciplinary and technically demanding procedure, and many emerging centers underestimate the expertise required to perform safe and successful treatment with radionuclides or "byproduct material" such as with ^{111}In-Octreotide. First and foremost, a multidisciplinary treatment protocol should be well established for the patient treatment. This includes the structured interaction between diagnostic imaging, nuclear medicine, requirements and provisions for radiation safety, multidisciplinary care team, and surgical oncology nursing staff, release and follow-up procedures.

5.1.1 Multidisciplinary Approach

Scientific centers performing radiopeptide infusions should be ideally characterized by a multidisciplinary approach to the design, delivery, and reappraisal of primary or metastatic neuroendocrine tumor treatment, or by referral from a multidisciplinary team consisting of specialists such as surgeon, pathologist, oncologist, (interventional) radiologist, nuclear medicine physician, radiotherapist, and gastroenterologist [Appendix, Table 5.4 Multidisciplinary board (Limouris et al. 2008)] [1]. The primary purpose of this board is to study and decide the treatment plan; setting up priorities for each therapy step also includes several subcategories and alternative therapeutic modalities according to disease progression.

5.1.2 Radiopeptide Infusion Team

Once the eligibility criteria (Hicks et al. 2017) [2] are completed, then the PRRT protocol could be preceded. Complete clinical history as well as patient's consent should be obtained. At least 24 h prior the diagnostic angiography and the radiopeptide infusion procedure, patients' written consent should be documented. According to the recommendations by the radiopeptide therapy consortium (RPTC) [1] the team performing radiopeptide infusions should include staff having experience in the following:

1. Care for the overall medical treatment of the cancer patient
2. Perform vascular catheterization
3. Perform and interpret radiologic scans
4. Assume the responsibility of the delivery of the ^{111}In-Octreotide and be the authorized user
5. Establish radiation safety

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While the interventional radiologist is particularly responsible for the angiography procedure, further care for the treated patients is usually assumed by the referring clinician or another designated number of the multidisciplinary board.

Prior to the radiopeptide Infusion, the technical complexity, any potential consequences or difficulties, and possible risks during the therapy procedure should be explained analytically to the patient in a dedicated counseling interview.

Once the radiopeptide infusion has been completed, each case should be reviewed again by the multidisciplinary team to inform the team members with respect to subsequent treatment decisions. On discharge of the patient, recommendations and information leaflet on further hydration, nutrition, medication, radiation safety instructions, follow-up visits, and contact details in case of post procedural side effects should all be given in hand.

5.2 Legal Regulations of Scientific Centers Performing Radiopeptide Therapies

5.2.1 Licensing

Radioactive material for diagnosis or therapy should only be used and stored at medical institutions that have the license and the appropriate designed facilities. The administration of therapeutic doses of radionuclides must be under the responsibility of a physician who is licensed under national regulations to administer radioactive materials to humans. Medical physicists are also subject to licensing since they are responsible for the radiation protection and safety use of radionuclides. Of course, the licensing requirements for the nuclear therapy ward may vary from country to country and may even include a minimum design and construction requirements, the necessary facilities, and the equipment as well **(IAEA, Nuclear medicine resources manual, 2006)** [3].

Considering, however, the case of radiopeptide infusions a special license is needed additionally in most European Countries from the appropriate national authorities or professional bodies since such infusions are regarded as a "clinical trial" and moreover this license is individualized for each patient defining the number of therapy cycles and the quantity of administered radionuclide.

For the case of intra-arterial administration procedure, which is performed within the radiology catheterization room and not in the nuclear medicine department, a specific authorization is additionally requested in order to satisfy all the radiation protection requirements and avoid any contamination hazard. (Appendix, Table 5.5: Hospital requirements for initiating radiopeptide therapies).

5.2.2 Appropriate Facilities and Equipment

The instrumentation in nuclear medicine could be classified into four main sections:

(a) Single photon imaging equipment (including SPECT, SPECT/CT) and dual photon imaging equipment (combining the various approaches to PET such as PET/CT, PET/MRI)
(b) Some nonimaging instruments such as isotope dose calibrator, portable contamination monitor (acoustic dose rate meter), and survey radiation detectors for survey of photons and beta radiation
(c) Phantoms: ^{57}Co sheet for uniformity tests, resolution bar, and SPECT for quality control measurements.
(d) Tools for handling and storing radioactive materials. Radio wash liquids for decontamination procedures.

Reliability of imaging instrumentation is critical to the practice of nuclear medicine and even more they are extremely sensitive to environmental conditions and consequently strict control of temperature and humidity is a must, as well as a

continuous and stable power supply by the help of UPS unit. Regular assessment is required to confirm the equipment's performance and quality control protocols must be organized according the NEMA standards to ensure stable practice.

In the case of interventional nuclear medicine additional care must be taken in the angiography room, in order to exclude the problem of contamination. Several factors should be cared of such as e.g. the following:

- Controllable access to angiography room
- Floors impervious to liquids
- Special care for the angiography unit so as case of contamination could be avoided (pedals should be draped with plastic covers placed as a precautionary measure)
- Staff should have passive personnel dosimeters as well as active personnel dosimeters for direct reading during the isotope administration.
- Protective clothing (e.g. appropriate lab gown) is necessary to prevent the transfer of contamination hazard. Overshoes, caps, masks and thick gloves for protection of external beta radiation hazard must be in hand.
- The delivery catheter and all other contamination material that are potentially radioactive should be disposed according the radiation protection regulations.

5.3 Quality Control and Documentation of Radionuclides Applied

5.3.1 Introduction

All radiopharmaceuticals administered to patients should be checked and recorded down carefully before the administration procedure in order to ensure the correct amount of activity, the quality and efficacy of the product so as safety is under warranty in all subjects. Since testing is not possible in order to cover all the required control testing procedures, it is good to develop at least a quick quality control protocol and documentation of the product. This chapter outlines the necessary steps and techniques that should be considered.

5.3.2 Documentation

Documentation is required in order to set out all the necessary standards and requirements into which radiopharmacy operates. Four areas to take care are the following:

(a) Storage conditions: Once the product has been introduced to the hospital, special storage conditions are required to be satisfied, such as the suitable temperature, so as the product remains stable up to the administration time.
(b) Full records and receipts of all the administered radionuclides relating to the activity, calibration, and expiration time must be carefully double checked.
(c) Definition of the standards to which the radiopharmacy operates: control checks of dose calibrators and safety cabinets.
(d) Records of disposal material: Disposal materials should be checked and disposed according the national legislation.

5.3.2.1 Radionuclide Activity

It is necessary to ensure that the correct activity is administered to the patient and thus requirement of measurement is needed by the help of dose calibrator. For this case, special care should be considered in the measurement of activity before and after dispensing the radiopharmaceutical keeping the same measurement conditions in order to have a more reliable measurement.

5.3.2.2 Radiochemical Purity

The radiochemical purity is defined as the proportion of the total radioactivity of the nuclide concerned present in the stated chemical form. For most radiopharmaceuticals the radiochemical purity will be expected to be greater than 95%, in order to proceed for administration.

For radiopharmaceuticals purchased in their final form, such as ^{111}In, manufacturers will normally declare the radiochemical purity, and the radiopharmacy need not perform any further determinations.

However, for the case of radiopharmaceuticals prepared "in-house," either totally from original materials or purchased kits, radiochemical purity should be established prior to the administration, in order to check the suitability of the final product. Low radiochemical purities may lead to an unintended biodistribution of the radiopharmaceutical. For diagnostic cases, this may lead to a false diagnostic result but for therapeutic radiopharmaceuticals it can produce significant dosimetry problems.

A range of techniques are available for such determinations, but it is preferable to choose a technique which is simple, fast, and reliable to catch the timing of administration.

The simplest and most widely used technique is that of planar chromatography, which employs suitable stationary material (e.g. porous paper or thin layers of silica gel) and readily available mobile phases (e.g. saline, acetone, and butanone). **IAEA-TECDOCs 649 and 805** [4, 5].

5.3.2.3 Disposal of Radioactive Waste

Radioactive waste from nuclear medicine procedures could be hazardous and a good management is needed in order to ensure that the radiation exposure to an individual (general public, radiation worker, patient) and the environment does not exceed the prescribed safe dose limits (Table 5.1).

When disposing of waste, attention should be paid to the following points:

- Once the surface dose rate in any individual bag of waste is below of 5 mGy/h or ≤5 μ Sv/h (**European Directive 2011/70 EURATOM, 19-7-2011)** [6] it can be disposed of. (Check with the local regulatory authority).
- Radioactive waste could be disposed according **(European Directive 2013/59 EURATOM, 5-12-2013)** [7] whenever the radioactive concentration (KBq/Kgr) reaches a certain amount for each different radionuclide, e.g. for the case of In-111 it is 100 KBq/Kgr.
- Always disposable gloves should be worn and caution exercised when handling sharp items such as syringes.
- Before disposure, any labels and radiation symbols should be removed.
- Waste should be placed in a locally appropriate waste disposal container, such as a biological waste bag; two bags is always advisable to minimize the risk of spillage

Table 5.1 Recommended dose limits in planned exposure situations

Type of limit	Occupational	Public
Effective dose[a]	20 mSv/year, averaged over defined periods of 5 years[e]	1 mSv/ year[f]
Annual equivalent dose in:		
Lens of the eye[b]	**20 mSv**	**15 mSv**
Skin[c,d]	500 mSv	50 mSv
Hands and feet	500 mSv	–
Effective dose to the foetus[g]	1 mSv	1 mSv

[a]Limits on effective dose are for the sum of the relevant effective doses from external exposure in the specified time period and the committed effective dose from intakes of radionuclides in the same period. For adults, the committed effective dose is computed for a 50-year period after intake, whereas for children it is computed for the period up to age 70 years

[b]**This limit is a 2011 ICRP recommendation** [9]

[c]The limitation on effective dose provides sufficient protection for the skin against stochastic effects

[d]Averaged over 1 cm^2 area of skin regardless of the area exposed

[e]With the further provision that the effective dose should not exceed 50 mSv in any single year. Additional restrictions apply to the occupational exposure of pregnant women

[f]In special circumstances, a higher value of effective dose could be allowed in a single year, provided that the average over 5 years does not exceed 1 mSv per year

[g]The dose to pregnant women is limited up to 1 mSv/year, based on which the fetus is regarded as a member of the public

5.4 Release of the Patient

5.4.1 Radiation Safety Issues, General Principles

When the patient is hospitalized following radionuclide therapy, the people at risk of exposure may include hospital staff who may be radiation workers (occupational exposure) or not. Of course, radiation workers are effectively trained with radiation and they know how to work in order to avoid contamination and minimized the radiation hazard by the help of suitable facilities. But concerning the public at large, a significant problem may be arising once the patient has been released. According to the current radiation protection regulations (ICRP and IAEA) no dose limits for patients have been established, but for staff and members of the public, dose constraints have been provided and accepted by law in most of the European countries. Examples of the dose limits according the **ICRP 103**, **European Directive 2013/59/05-12-2013, EURATOM** [8] are presented in Table 5.1: Recommended dose limits in planned exposure situations.

5.4.2 Discharge Limits (ICRP Recommendations)

Patients may be discharged from hospital or clinic following radionuclide therapy treatment when an estimate of the effective dose to any member of the general public should not exceed 1 millisievert (mSv) in a year. This dose limit applies to adults and children, including the unborn child as well as to persons who may contact the patient, for example, through work, travel, social, or domestic activities. Adult family members or persons who care for the patient are not necessarily subject to the 1 mSv dose limit for members of the public. The effective dose for those persons helping the patient or living with them should not exceed the dose constraint of 5 mSv.

Mind that recommendations regarding release of patients after therapy with unsealed radionuclides many vary widely around the world. Hospitalization or release, in-patient or outpatient, has been based on one or more of the following reasons:

(a) A requirement for regulatory compliance, based on the following:
- Dose limits or constraints from the ICRP, international, or national bodies as prescribed in the previous paragraph.
- The residual activity in the patient.
- The dose rate at a specified distance from the patient.

(b) Isolation of the patient to reduce dose to the public and family.

(c) Issues associated with the patient:
- A medical condition that requires hospitalization.
- A mental condition that might reduce compliance.
- Their home circumstances.

5.4.2.1 Guidance Based on Retained Activity

Many countries and regulatory authorities use an approach to patient release after radionuclide therapy based on the activity retained in the patient. This can be in addition to the dose limit/constraint approach described by ICRP, but in some cases, retained activity could be used in parallel **(IAEA, Safety reports series No 63)** [10]. Limits for retained activity are not provided for all the therapeutic radionuclides; most of the recommendations, are relating with I-131 therapies **(European Commission: Radiation Protection 97, 1998)** [11] since it is the oldest formality for therapy in nuclear medicine.

Retained activity could be applied only for photon emitting radionuclides and for the measurements a basic radiation detector is needed. The following points should be considered:

1. Define a fixed distance from a standing patient which is distinguish marked for dose rate measurement such as 1 m.
2. Immediately after the administration and before any excretion, measurement of dose rate from the patient at this fixed distance should be done.

3. More future measurements post administration could be obtained at this distance and the retained activity at any time of measurement is estimated from:

$$A_R = \frac{A_0 D}{D_0}$$

where,

A_R is the retained activity at the time of measurement

A_0 is the administered activity

D_0 is the dose rate immediately after administration and

D is the dose rate at the time of measurement.

In general, for practical purposes, it is convenient to relate the activity remaining in the patient at the time of discharge to exposure of the public and family.

Table 5.2: Activities (MBq) for release of patients depending on the external doses to other people (mSv effective dose) has been provided by US **NRC, 1997** [12] and such data is especially useful indeed.

Table 5.2 Activities (MBq) for release of patients depending on the external doses to other people (mSv effective dose)

Radionuclide	Half life	MBq for 5 mSv	MBq for 1 mSv
Cr-51	28 days	4800	960
Cu-64	13 h	8400	1700
Cu-67	61 h	14,000	2900
Ga-67	78 h	8700	1700
I-123	13 h	6000	1200
I-125	60 days	250	50
I-131	8 days	1200	240
In-111	67 h	2400	470
P-32	14.29 days	[a]	[a]
Re-186	90 h	28,000	5700
Re-188	17 h	29,000	5800
Sm-153	47 h	26,000	5200
Sn-117m	13.61 days	1100	210
Sr-89	50.5 days	[a]	[a]
Tc-99m	6 h	28,000	5600
Tl-201	74 h	16,000	3100
Y-90	64 h	[a]	[a]

[a]No value given because of minimal exposures of the public

Table 5.3 Activities and dose rates below which patient release is authorized

Radionuclide	Activity (GBq)	Dose rate at 1 m (mSv/h)
Ga-67	8.7	0.18
I-123	6.0	0.26
I-131	1.2	0.07
In-111	2.4	0.2
P-32	[a]	[a]
Re-186	28	0.15
Re-188	29	0.20
Sm-153	5–26	0.06–0.3
Sr-89	[a]	
Tc-99m	28	0.58
Tl-201	16	0.19
Y-90	[a]	

[a]No value given because of minimal exposures of the public

From the same document, Table 5.3 tabulates activities and dose rates below which patient release is authorized.

5.4.2.2 Specific Instructions at Releasing the Radioactive Patient

At discharge, an official detailed report is given to the patient's referring clinician reporting all the relevant information regarding the administrating dose of the isotope, the date of delivery, and contact restrictions for the meta-infusion days.

Additional recommendations and instructions for the patient or legal guardian shall be written, provided with a view to the restriction of doses to persons in contact with the patient as far as reasonably achievable, and information on the risks of ionizing radiation. The IAEA gives example information/leaflet in Safety Reports Series No. 63 [9].

Some of the specific instructions are concerning the spread of contamination, minimization of exposure to family members, cessation of breast-feeding, and conception after therapy. The amount of time that each precaution should be implemented should be determined according to the retained activity in patients prior to discharge and on the estimation of the dose that is mighty to be received by carers and comforters or members of the public. For example, patients travelling

after radionuclide therapy with a private automobile rarely present a hazard if the patient is keeping the 1 m distance from the other passengers and the travel time is short but, for longer times and traveling by public transport, special instructions are necessary.

In conclusion specific radiation protection consultations for the patient and the family members should be well organized, taking care of all the possibilities and situations by the medical physicist or by the radiation protection officer to avoid any hazard and risk.

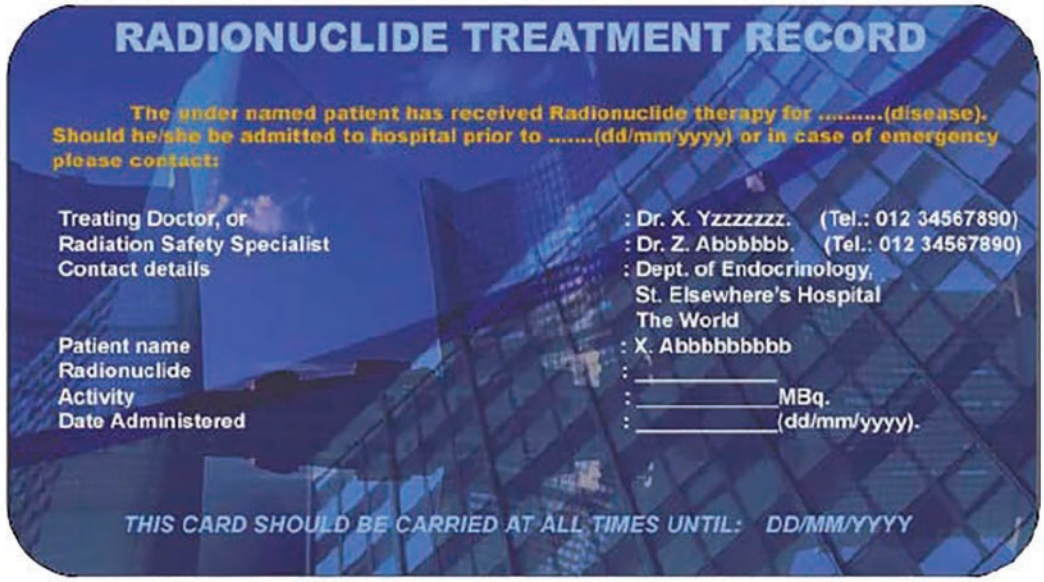
Appendix

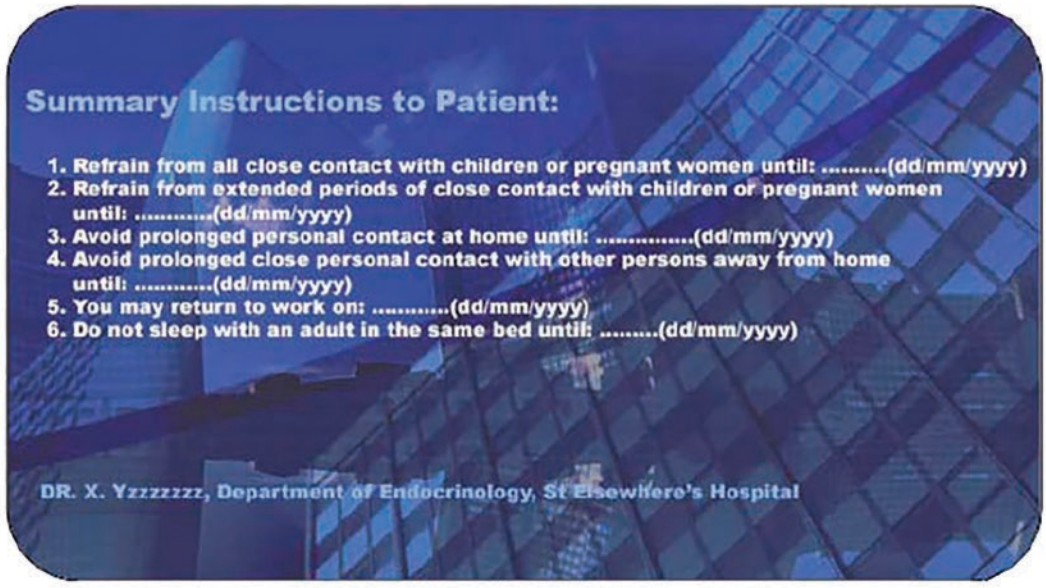
Table 5.4 Multidisciplinary board

Multidisciplinary team approach to reviewing liver cancer patients
Interventional radiologist
Hepatic surgeon
Medical oncologist
Nuclear medicine physician
Pain physician or anesthetist
Gastroenterologist/hepatologist
Radiation physicist
Dedicated clinical (surgical) oncology nursing staff
Desirable
One site consultant medical physicist
Radiologists

Table 5.5 Hospital requirements for initiating radiopeptide therapies

Country	^{111}In-Octreotide License	Specific authority to use radioisotopes within angiography suite
Austria	+	+
Belgium	+	+
Denmark	+	+
Finland	+	–
France	+	+
Germany	+	+
Greece	+	+
Ireland	+	+
Italy	+	+
Poland	+	+
Portugal	+	–
Scotland	+	–
Slovenia	+	+
Spain	+	–
Sweden	+	–
Switzerland	+	–
The Netherlands	+	+
Turkey	+	–
UK	+	+





IAEA: Examples of information/leaflet in Safety Reports Series No. 63

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