RADIATION PROTECTION ISSUES IN RADIONUCLIDE THERAPY – WORKERS (MEDICAL STAFF), THIRD PERSONS, WASTE MANAGEMENT

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- Introduction to challenges of the radiation protection in radionuclide therapy
- Examples of challenges in justification
- Radiation protection in connection to traditional treatments with I-131, P-32, Sm-153, Y-90, Sr-89
- Radiation protection in connection to new treatments with, Lu-177, Rh-188, Ac-225, Th-227, Ho-166
- Waste management
- Deceasing and cremation
- Guidelines

INTRODUCTION TO CHALLENGES IN RADIATION PROTECTION IN RADIONUCLIDE THERAPY

- Comprihensive European guidelines exist only for I-131 therapy
 - Lack of information on new treatments for radiation protection
- Training of the workers (especially new groups of workers and on dosimetry) concerning new radionuclide therapies
- Waste management of radionuclide treatments

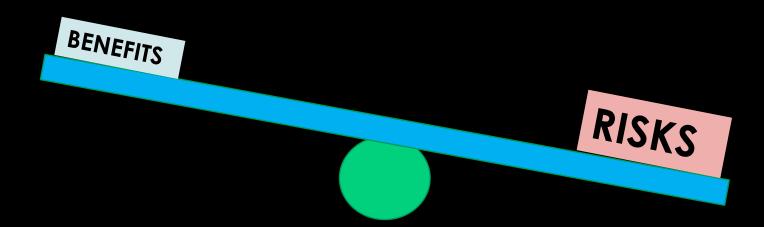
 glass vials, injection needles, plastic parts and tissue papers
 - Special issue: patient's excreta
- A patient as a source
 - Protection of carers and comforters
 - Release criteria and a released patient after radionuclide therapy
 - Patient at another ward department
 - Cremation

INTRODUCTION: WHAT TO AUTHORIZE?

- What should by authorized by a radiation protection authority?
 - Nuclear medicine as a practice
 - Radionuclides
 - A radionuclide and a pharmaceutical
 - Marketing authorization by EMA
 - A radionuclide and a medical device
 - CE marking: By affixing the CE marking to a product, a manufacturer declares that the product meets all the legal requirements for CE marking and can be sold throughout the EEA.

JUSTIFICATION OF RADIONUCLIDE THERAPIES

- Role of EMA (European Medicine Agency)
- Justification when the radiation risks are too high for workers or members of the public?



JUSTIFICATION OF RA-223: EXAMPLE OF INTERNAL EXPOSURE

Ra-223 (alpha emitter)

- Intake by ingestion
 - 20 mSv from **200 kBq** and 1 mSv from **10 kBq**
 - 14 MBq/6 ml \rightarrow 200 kBq/85 μ l and 10 kBq/4 μ l
- Intake by inhalation (workers)
 - 20 mSv from 3 kBq and 1 mSv from 150 Bq
 - 14 MBq/ 6 ml \rightarrow 3 kBq/1 μ l and 150 Bq/0,06 μ l

Ac-227 as an impurity, $T_{1/2}$ is 21,8 y

- Intake by ingestion
 - 20 mSv from **18 kBq** and 1 mSv from 900 Bq
 - 560 kBq/6 ml \rightarrow 18 kBq/192 μ l and 900 Bq/10 μ l
- Intake by inhalation (workers)
 - 20 mSv from 32 Bq and 1 mSv from 2 Bq
 - 560 kBq/6 ml \rightarrow 32 Bq/0,3 μ l and 2 Bq/0,2 μ l

Also waste management may be an issue if there is more than one vial! Exemption level for Ac-227 is 1000 Bq.

QUALITY ASSURANCE OF RADIOPHARMACEUTICALS

- A general requirement on quality assurance applies on radionuclide therapies
- Role of Medical Agencies highlighted
 - EMA: Monographs of the Pharmacopeia
 - Not always available when treatments start For example:

A monograph to liquid Lu-177 exist, but not yet for Lu-177-PSMA

Can radiation protection authority authorize a practice without comprihensive QC of a radiopharmaceutical?

Contamination measurements and monitoring of discharges are part of qualtiy assurance.

RADIATION PROTECTION ASPECTS CONCERNING TRADITIONAL TREATMENTS - EXAMPLES

Table 2 Effective dose rates at 1 metre distance, estimated corresponding (residual) activities and period for instructions to be followed.

Effective dose rate at 1 metre distance from the patient	Corresponding to an estimated	Recommended periods fo following
[μSv.h ⁻¹ at 1 metre]	(residual) activity of *	instructions
< 40	< 800 MBq	3 weeks
< 20	< 400 MBq	2 weeks
< 10	< 200 MBq	1 week
< 5	< 100 MBq	4 days
< 3	< 60 MBq	24 hours after administration

These values are based on the physical data mentioned in Annex III

EU RP 97: Radiation Protection following Iodine-131 therapy (exposures due to out-patients or dischargend in-patients) https://ec.europa.eu/energy/sites/ener/files/documents/097_en.pdf

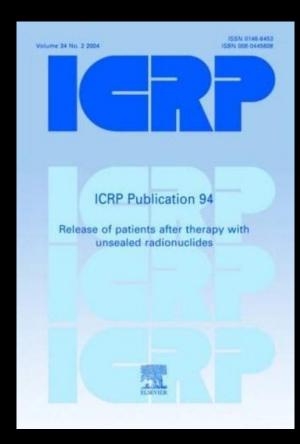


TABLE 9. SOME NATIONAL MAXIMUM ACTIVITIES FOR PATIENT RELEASE

	Retained activity (MBq)							
Radionuclide	USA		C1	F-11		A 1'-		
	NRC [47], NUREG-1556[68]	Germany [64]	Sweden [65]	Finland [71]	Japan [67]	Australia [45]		
Phosphorus-32	a		1200			1200		
Strontium-89	a				200	300		
Yttrium-90	a		1200		1200	4000		
Iodine-131	1200 ^b	75	600	800	500	600		
Samarium-153	26 000					4000		

a Value not given because of minimal exposure of the public.

TABLE 10. EXAMPLES OF OTHER IODINE-131 RELEASE CRITERIA

Country or organization	Release limit for I-131 (MBq		
BSS*	1100 (guidance level)		
European Thyroid Association	800		
Japan	500 or <30 μSv/h at 1 m		
Germany	250 (based on 3.5 μSv/h at 1 m)		
Other EU Member States	95–800, mostly 400–600		

^{*} The revised BSS are not expected to contain numerical values.

b Historic value prior to change in approach to that based on 5 mSv. See Annex II.

IAEA Safety Report Series No. 63: Release of Patients After Radionuclide Therapy

NEW TREATMENTS IDENTIFIED BY HERCA WP ON NUCLEAR MEDICINE 1/2

- 166Ho-microspheres (QuiremSpheres®) for intra-arterial treatment in the liver
- 166Ho-RE (other than QuiremSpeheres®) for intra-arterial treatment in the liver
- 166Ho-microspheres (HoMS) for recurrences of head and neck squamous cell carcinoma
- 166Ho-chitosan for hepatocellular carcinoma (HCC)
- [166Ho]Ho-DOTMP for bone metastases
- ¹⁷⁷Lu-antibodies (e.g. Betalutin®) for non-Hodgin lymphoma
- 177Lu-peptides other than somatostatin analogues and PSMA

NEW TREATMENTS cont. 2/2

- 188Re (Rhenium-SCT®) for non-melanoma skin cancer
- 188Re-HEDP for painful bone metastases
- ²²⁵Ac-PSMA for metastatic castration resistant prostate cancer
- ²²⁵Ac-Lintuzumab for acute myeloid leukemia (AML)
- ²²⁷Th-conjugate CD22 positive non-Hodgin lymphoma
- ²²⁷Th-antibody for ovarian cancer and mesothelioma
- ²²⁷Th-PSMA antibody

EXAMPLES OF NEW COMING TREATMENTS 1/2

- Radiolabeled antibodies, such as
 - ¹³¹I-omburtamab directed against the B7-H3 protein on the surface of neuroblastoma cells;
 - HuMab-5B1, a ⁸⁹Zr/¹⁷⁷Lu-labeled antibody for the treatment of CA19-9-expressing malignancies; and
 - ¹⁷⁷Lu-lilotomab, a CD37 antibody for the treatment of B-cell lymphomas.

EXAMPLES OF NEW COMING TREATMENTS 2/2

- The neurotensin receptor ligand ¹¹¹In/¹⁷⁷Lu-3B-227 has demonstrated high potential in imaging and therapy for several malignancies (e.g., pancreatic adenocarcinomas).
- Targeting of the fibroblast activation protein is currently being explored for different tumor entities using PET imaging with the fibroblast activation protein inhibitor (FAPI) ⁶⁸Ga-FAPI-04, and the first therapeutic applications of ⁹⁰Y-FAPI-04 have been applied.

DATA FOR RADIATION PROTECTION, LU-177

Radiation

- Betas: 490 keV
- Gamma: 113 keV (3 %), 210 keV (11 %)

Gamma Constant

- 7,636E-6 mSv/hr per MBq @ 1 meter
- Unshielded activity of 7400 MBq produces 56,5 µSv/hr @ 1 m (typical activity in Lu-177 DOTATE treatment)

Half-Life [T_{1/2}]

- Physical T_{1/2} 6,7 days
- Biological T_{1/2} GI ~1 days; Lungs ~30 days;
- Effective T_{1/2} GI ~0,9 days; Lungs ~6 days;

Radiotoxicity

- 6,43E-9 Sv/Bq (6,43 mSv/MBq) of
 177Lu ingested
- 3,33E-9 Sv/Bq (3,33 mSv/MBq) of
 177Lu inhaled

Critical organ:

- Lower Large Intestine (ingestion);
- Lung (inhaled)

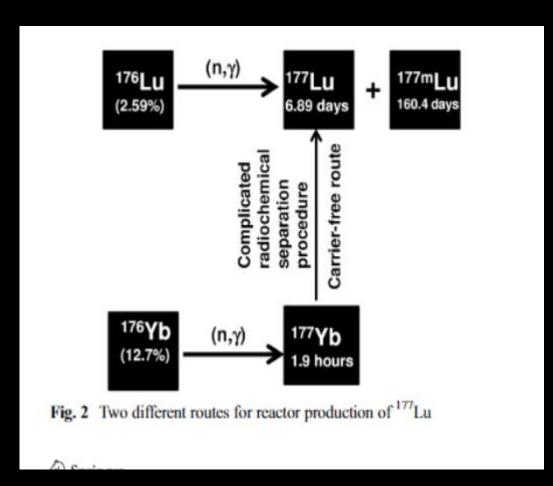
Shielding

- Photons (Lead shielding)
 - HVL 0,6 mm
 - TVL 2,1 mm
- Betas (Plexiglass)
 - HVL 1,35 mm

Source: Health Physics Society:

http://www.hpschapters.org/northcarolina/NSDS/177LuPDF.pdf

LU-177 PRODUCTION



Source: Dash et al.: Production of ¹⁷⁷Lu for Targeted Radionuclide Therapy: Available Options. Nucl Med Mol Imaging (2015) 49:85-107.

- 1. The direct production route
 - Lu-177m impurity
 - $T_{1/2}$ 160 d
 - Beta and gamma emmitter
 - The photon energies in the 177Lu decay are also present in the 177mLu decay
 - Waste management needed
- 2. Indirect production route
 - Complicated radiochemical separation procedure

LU-177 PSMA RADIATION SAFETY ASPECTS 1/2

- In Lu-177-PSMA therapy patients are typically treated with activity of 7400 MBq.
- Dose rate from the patient after the injection is quite high (48 µSv/hr)
- After 5 h the dose rate decreases below 30 µSv h-1 at 1 m distance and exposure of the caregivers remains below 5 mSv
 - Demir, Mustafa, et al. "Evaluation of radiation safety in 177Lu-PSMA therapy and development of outpatient treatment protocol." Journal of Radiological Protection 36.2 (2016): 269.
 https://www.researchgate.net/publication/301363403 Evaluation of radiation safety in 177 Lu-PSMA therapy and development of outpatient treatment protocol

Table 1. Dose rate	Table 1. Dose rate values (μ Sv h ⁻¹) at different distances and time marks.							
Time after infusion (hours)	0 m (μSv h ⁻¹)	0.25 m (μSv h ⁻¹)	0.50 m (μSv h ⁻¹)	$1.00 \text{ m} \ (\mu \text{Sv h}^{-1})$	2.00 m (μSv h ⁻¹)			
0	536 ± 89	297 ± 68	137 ± 28	48 ± 13	24 ± 7			
1	468 ± 71	245 ± 54	118 ± 18	38 ± 7	21 ± 6			
2	299 ± 62	198 ± 32	94 ± 15	33 ± 9	17 ± 6			
4	180 ± 41	123 ± 27	62 ± 14	23 ± 6	11 ± 4			
6	162 ± 36	91 ± 18	44 ± 11	15 ± 4	8 ± 3			
18	118 ± 32	69 ± 16	33 ± 8	11 ± 3	5 ± 1			
24	105 ± 27	31 ± 6	21 ± 6	7 ± 2	3 ± 1			
48	63 ± 16	21 ± 5	11 ± 3	5 ± 1	1 ± 0.3			
120	11 ± 3	4 ± 1	3 ± 0.8	1 ± 0.2	0.3 ± 0.1			

No hospitalization needed after 5 hours.

Instructions for the patient needed to avoid other persons; analog to I-131 treatments.

LU-177 PSMA RADIATION SAFETY ASPECTS 2/2

• To keep dose to care givers and to the public in acceptable levels might require hospitalization (isolation) of the patient (in Germany).

Kurth, J., et al. "External radiation exposure, excretion, and effective half-life in 177 Lu-PSMA-targeted therapies." EJNMMI research 8.1 (2018): 32.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5897276/pdf/13550_201

8 Article 386.pdf

Table 4 Calculated doses to the public for each cycle of ¹⁷⁷Lu-PSMA-617 therapy for different time points of discharge of the patient from the hospital using different assumptions for the effective half-life

Estimated dose to the public [µSv] after 1 cycle of ¹⁷⁷Lu-PSMA-617 therapy Time point of discharge 24 h p. i.a 48 h p. i. 72 h p. i.b Type of half-life $T_{1/2\text{phys}}$ $T_{1/2\text{phys}}$ $T_{1/2ind}$ $T_{1/2\text{max}}$ $T_{1/2ind}$ $T_{1/2\text{max}}$ $T_{1/2\text{ind}}$ $T_{1/2\text{phys}}$ $T_{1/2\text{max}}$ Mean 396 208 71 263 139 200 105 Std. Dev. 131 100 76 Min 25 13 93 560 204 443 233

^aFor the effective individual half-life, the value from the 48-h measurement point was used (see the "Results" section)

^bThese data are only available for 25 patients (cohort of Department 2)

LU-177 SOMATOSTATIN ANALOGS: RADIATION SAFETY ASPECTS 1/2

- In Lu-177 somatostatin analog therapy typically with activity of 7400 MBq.
- Hospitalization needed for 1 day, dose constraint for public 0,3 mSv.
- Children aged 2-5 years remains 13 days.

Levart D. et al. "Radiation precautions for inpatient and outpatient177Lu DOTATATE peptide receptor radionuclide therapy of neuroendocrine tumours." EJNMMI Physics (2019) 6:7.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6484059/pdf/40658_2019_Article_243.pdf

Table 3 Mean (SD) [range] measured and estimated dose rates and dose rate per MBq administered activity at 0.1 and 1 m from the mid-abdomen

	Time	Dose rate (μSv/h)		Dose rate per	Dose rate per MBq (nSv/h/MBq)		
	(hours)	0.1 m	1 m	0.1 m	1 m		
¹⁷⁷ Lu-DOTATATE Mallinckrodt	0	407 (83)	20 (2)	58 (12)	3 (0.3)		
Inpatient measured		[250–750]	[15–25]	[35–99]	[2.1–3.6]		
¹⁷⁷ Lu-DOTATATE Mallinckrodt	18.1	148 (77)	7 (3)	21 (11)	1 (0.5)		
Inpatient estimated		[49–334]	[4–15]	[5–46]	[0.4–2]		
¹⁷⁷ Lu-DOTATATE Mallinckrodt	5.2	258 (75)	13 (3)	37 (10)	2 (0.4)		
Outpatient estimated		[100–435]	[6–20]	[14–60]	[0.8–3]		
Lutathera® AAA Outpatient measured	5.7	-	15 (5) [5–25]	_	2 (0.6) [0.6–3]		

Table 5 Mean (upper 95th percentile) [range] restriction durations for inpatient and outpatient ¹⁷⁷Lu-DOTATATE administrations to limit dose for close relatives to 1 mSv per cycle and 0.3 mSv per year for members of the public

Restriction	Inpatient therapy period (days)	Outpatient therapy period (days)
Restrict day contact < 1 m and sleep apart from partner	8 (15) [3–15]	9 (16) [4–16]
Restrict contact < 1 m with < 2 year old child	9 (16) [4–16]	9 (17) [5–17]
Restrict contact < 1 m with child aged 2–5 years	5 (13) [1–13]	6 (13) [1–13]
Restrict contact < 1 m with child aged 5–11 years	3 (9) [0-9]	3 (10) [1–10]
Remain off work	1 (5) [0–5]	1 (6) [0–6]

LU-177 SOMATOSTATIN ANALOGS: RADIATION SAFETY ASPECTS 1/2

• When a patient is released immediately after administration of the labeled somatostatin analogue (7400 MBq), the cumulative dose to which the general public is exposed is estimated to range from 1.00 to 8.81 [mSv/course of treatment]. In such an event, the cumulative dose might exceed 1 mSv per year.

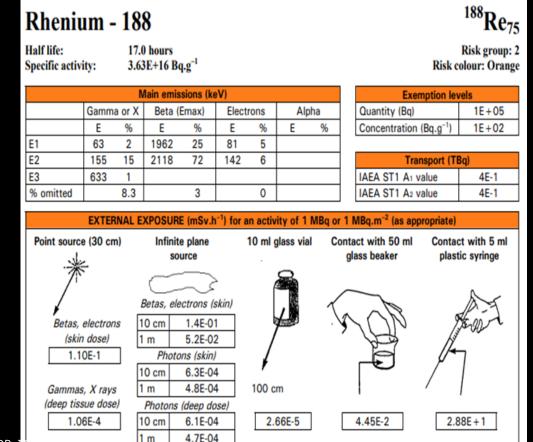
Hosono M. et al. "Manual on the proper use of lutetium-177-labeled somatostatin analogue (Lu-177-DOTA-TATE) injectable in radionuclide therapy (2nd ed.)Annals of Nuclear Medicine (2018) 32:217–235. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5852188/pdf/12149 2018 Article 1230.pdf

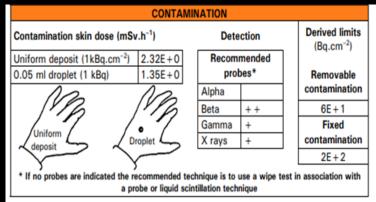
Table 7 Calculation of the cumulative dose to which a third party is exposed immediately after and at a certain point after a patient is administered the labeled somatostatin analogue at a dose of 7400 MBq

	Immediately after admin. (mSv/course of treatment)	24 h after admin. (mSv/ course of treat- ment)	48 h after admin. (mSv/course of treatment)
Caregiver	2.00	1.40	1.04
General public	1.00	0.70	0.52

DATA FOR RADIATION PROTECTION, RE-188

Radionuclide and Radiation Protection Data Handbook, Nuclear Technology Publishing





SHIELDING (mm)					
Betas and electrons					
(Tota	l absorpti	on)			
Glass	4.	4			
Plastic	8.	3			
(half a	na and X nd tenth v hickness)				
(half a	nd tenth v				
(half a	nd tenth v hickness)	alue			

INTERNAL EXPOSURE FOR WORKERS							
COMMITTED EFFECTIVE DOSE PER UNIT INTAKE (Sv.Bq ⁻¹)							
Ingestion	f1		Inhalation		1 μm	5 μm	
All compounds	0.800	1.4E-09	All unspec. compounds	F	4.7E-10	6.6E-10	
			Oxid., hydrox., halid. & nitrat.	M	5.5E-10	7.4E-10	
				S			
Highest dose organ Lungs							

MAXIMUM RECOMMENDED ACTIVITIES IN LOW LEVEL OR INTERMEDIATE LEVEL LABORATORIES (Bq)								
	Subject to external exposure requirements which may be more restrictive							
PHYSICOCHEMICAL STATE	Volatility Supervised area			Controlled area				
	factor (k)	Bench	Fume hood	Bench	Fume hood	Glove box		
All compounds	0.01	6E+05	6E+06	2E+06 2E+07 2E+0				

The values above do not include Bremsstrahlung radiation.

RHENIUM-188 LABELED RADIOPHARMACEUTICALS

- The high beta emission has an average energy of 784 keV and a maximum energy of 2.12 MeV, sufficient to penetrate and destroy targeted abnormal tissues. In addition, the low-abundant gamma emission of 155 keV (15%) is efficient for imaging and for dosimetric calculations. Moreover, the highly reproducible on-demand availability of 188Re from the 188W/188Re generator system permits installation in hospital-based or central radiopharmacies for availability of no-carrier-added (NCA) 188Re.
- Rhenium-188 and technetium-99m exhibit similar chemical properties and represent a "theranostic pair."
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6587137/

RE-188-SCT (SKIN CANCER THERAPY)

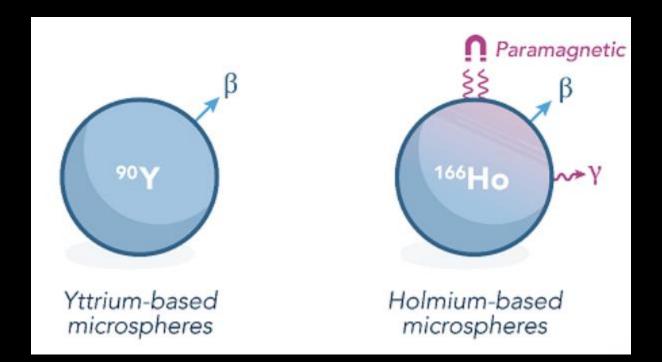
- Beta and gamma emitter
- https://www.oncobeta.com/rhenium-sct/
- A medical device with a radionuclide



Images: Oncobeta

A RADIONUCLIDE AND A MEDICAL DEVICE

- RE-188-Oncobeta
- Selective Internal Radiation Therapy (SIRT)
 - radioactive microspheres
 - CE-marked



- Diameter 20-60 micrometers
- Glass or resin

HO-166

- Beta and gamma emitter, 81 keV gamma suitable for SPECT imaging
- $T_{1/2}$ is 26,8 h
- Produced via neutron activation either directly from Ho-165 (high purity) or from Dy-164 with two neutrons (Dy-166/Ho-166 generator) impurities negligble from radiation protection point of view.
- Magnetic susceptibility dosimetry possible using MRI
- Density suitable for CT imaging
- Radiation protection: guidelines for I-131 can be applied taking into account faster decaying

AC-255

- 225 Ac ($T_{1/2}$ = 9.9 d)(alpha emitter) and its short-lived daughter nuclide 213 Bi ($T_{1/2}$ = 46 min) (alpha and beta emitter)
- Production based on radiochemical extraction from ²²⁹Th sources as well as accelerator driven processes.
 - An important advantage of the proton irradiation of 226 Ra targets in a cyclotron is that no other long-lived actinium isotopes such as 227 Ac ($T_{1/2} = 21.8$ y) are co-produced, and chemical purification of the irradiated targets yields 225 Ac of high isotopic purity.
- Generators of ²²⁵Ac/²¹³Bi.
- Waste management of ²²⁷Ac has to be taken into consideration.

TH-227

- Alpha emitter, Ra-223 is a daughter
- Clinical trials going on in several European countries
- Thorium is considered as nuclear material, but in practice only Th-232 is of interest.
- ²²⁷Th-PSMA-IgG1 T_{1/2} 18,7 d

WASTE MANAGEMENT ASPECTS

- Discharges and waste: Application of exemption and clearance values of the BSSD
- Waste minimized and segregated, packages labeled, storaged for decaying.
- Some countries require short term storage of hospital waste (usually urine only) containing radionuclides from hospitalized therapy patients until the activity has reached a particular level.
- ICRP 94 Release of Patients after Therapy with Unsealed Radionuclides: "Radionuclides released into modern sewage systems are likely to result in doses to sewer workers and the public that are well below public dose limits."

DECEASE OF A PATIENT AFTER RADIONUCLIDE THERAPY

- Example 1: A patient in a car accident: how to find out that the patient has recieved a radionuclide treatment?
 - There should be a document with a patient to notify of the treatment.
 - An example of a card on the HERCA website: https://www.herca.org/docstats/HERCA_Patient_release_Card.pdf

Medical Treatment Card In case of emergency The under named patient has undergone a medical treatment with a radioactive substance. This person left the treatment unit after verification according to International safety standards. Radiation safety can Information about this patient can be therefore be guaranteed, provided the instructions given given by: to the person are observed. Patient ID Radioactive substance : Contact : X Full name: Isotope: Institution Address: Time of administration Phone number : 00000000000000 DD/MM/YYYY Activity administrated: MBq National authority address and logo Card developed by: This card should be carried at all times until dd/mm/yyy This card should be carried at all times until dd/mm/yyyy

AUTOPSY, BURIAL AND CREMATION

TABLE 14. SUGGESTED CORPSE ACTIVITY LIMITS (adapted from information reviewed in ICRP 94 [2] from Australia [79], Sweden [65], the UK [76–78, 80, 81] and the USA [82])

	Activity limit (MBq)					
Radionuclide	Autopsy/embalming	Burial	Cremation			
Phosphorus-32	100 (IPEM) ^a 300 (Aus) ^b 400 (S) ^c	2000 (IPEM)	30 (IPEM) 400 (Aus) 400 (S)			
Strontium-89	50 (IPEM)	2000 (IPEM)	20 (IPEM)			
Yttrium-90	200 (IPEM) 150 (colloidal, Aus) 450 (sealed, Aus) 200 (S)	2000 (IPEM)	70 (IPEM) 1000 (Aus) 1200 (S)			
Iodine-131	10 (IPEM) 450 (Aus) 600 (S)	400 (IPEM) 400 (UK)	400 (IPEM) 1000 (Aus) 1200 (S)			
Gold-198	150 (Aus) colloidal 450 (Aus) scaled		1000 (Aus)			
All			74 (US)			

⁸ IPEM: The Institute of Physics and Engineering in Medicine.

 Example: A patient dies one week after Th-227 treatment and a cremation is planned. When it would be possible from radiation protection point of view?

- Cremation is safe after 4,5 months. (Based on a case study in Finland.)
- More examples needed!

IAEA Safety Report Series No. 63: Release of Patients After Radionuclide Therapy

b Aus: Australia.

c S: Sweden.

EUROPEAN GUIDELINES NEEDED

- What kind of guidelines are needed?
 - Radiation protection should be based on the requirements in the BSSD.
 - The selected dose constraints should be clearly stated and motivated.
 - Fractionation of new treatments should be taken into account.
 - Waste management should be re-evaluated taking into account new challenges (long lived nuclides, patients' household waste such as radioactive diapers)
- Harmonization may not be possible, but it is possible to increase understanding of requirements and recommendations in other European countries
- HERCA is collecting data on exisiting national guidelines concerning
 - Local rules
 - Patient release criteria after new radionuclide therapies
 - Cremation



Radiation protection 97



Radiation Protection following Iodine-131 therapy (exposures due to out-patients or discharged in-patients)







Thank you for your attention!