Universität Rostock

Traditio et Innovatio

Universitätsmedizin Rostock

Radiation Protection in therapies with other radionuclides (beyond Iodine-131)

J. Kurth

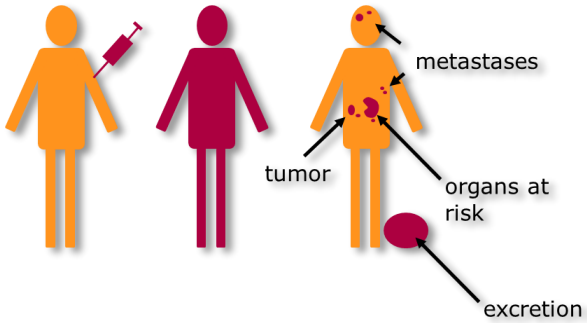
Department of Nuclear Medicine, Rostock University Medical Center, Rostock, Germany

ICTP The Abdus Salam International Centre for Theoretical Physics

IAEA International Atomic Energy Agency

Joint ICTP-IAEA Workshop on Radiation Protection in Diagnostic and Therapeutic Nuclear Medicine | (smr 4112)

Principle of Radionuclide Therapy – Radiation Protection



- Accumulation in target tissue
- Short range irradiation
  → Ionization (β^-, α, Auger-Emitter)

Steps to be considered in Radiation Protection

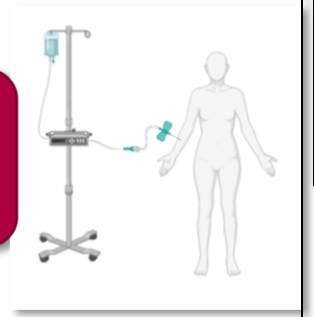
- save preparation and application
- handling of waste
- patient care
- stay in the hospital (inpatient vs. outpatient) - How long?
- protection of relatives, caregivers and the general public

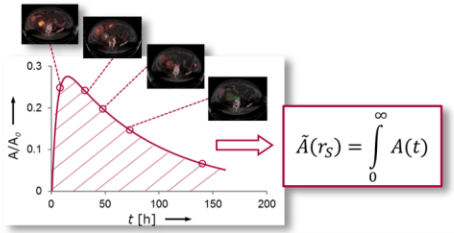
Radiation Protection – Whom do we have to protect?

Radiation Protection of the Patient – General Aspects

Quality Control of the Radiopharmaceuticals
- Activity
- Identity

proper application
- Extravasation
- Shielding
- Speed of application





$$\tilde{A}(r_S) = \int_0^\infty A(t)$$

Dosimetry if possible
(ALARA)

Agenda

- Focus on Lutetium-177-based therapies ([^{177}Lu]Lu-DOTAT-TATE, [^{177}Lu]Lu-PSMA-617), and SIRT (^{90}Y)
  - Save preparation and application
  - in-patient vs out-patient treatment
  - handling of waste (solid and fluid)
  - radiation protection of relatives and caregivers
  - radiation protection of staff
- Alpha Emitters

RADIATION PROTECTION IN THERANOSTICS – GENERAL ASPECTS

Radiation Protection – Regulatory Framework

International

UNSCEAR

United Nations Scientific Committee on the Effects of Atomic Radiation

Collection of data (scientific level)

ICRP
INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

Recommendations & Standards

International Basic Safety Standards (iBSS)

IAEA
International Atomic Energy Agency

Recommendations

Europe

EURATOM

Establishment of guidelines and regulations

Guideline 2013/59/EURATOM

Euratom BSS Directive

Radiation Protection – Regulatory Framework
What do we need ?

- Radioactive Material (RAM) - License
- Appropriate infrastructure
  - Rooms for diagnostics and therapy, radiopharmacy, waste and wastewater treatment, …
- Adequately trained staff (in sufficient number)
  - Physicians, Technologists, Chemisicts, Medical Physicists, Radiation Protection Officer, …
- Clinical services (diagnosis (e.g. PET/CT, SPECT/CT) and therapy)
- Equipment (Diagnostics, Treatment, Shielding, Radiation Meters, Quality Control, …)
  - Regularly checked for reliability and performance
- Hospital radiopharmacy and laboratories
- System of quality control and assessment
- System of error awareness

Challenges in Radiation Protection In Non-Iodine-131 Radionuclide Therapies

- Comprehensive guidelines exist only for I-131 therapy
- Training of the staff concerning new radionuclide therapies
- Waste management of radionuclide treatments– glass vials, injection needles, plastic parts and tissue papers, patient's excreta
- patient as a source
  - Protection of caregivers and comforters
  - Release criteria and a released patient after radionuclide therapy

- In General
  - Same rules for safe handling of radionuclides are applicable and must be followed

Challenges in Radiation Protection In Non-Iodine-131 Radionuclide Therapies

- Comprehensive guidelines exist only for I-131 therapy
- Training of the staff concerning new radionuclide therapies
- Waste management of radionuclide treatments– glass vials, injection needles, plastic parts and tissue papers, patient's excreta
- patient as a source
  - Protection of caregivers and comforters
  - Release criteria and a released patient after radionuclide therapy

- In General
  - Same rules for safe handling of radionuclides are applicable and must be followed

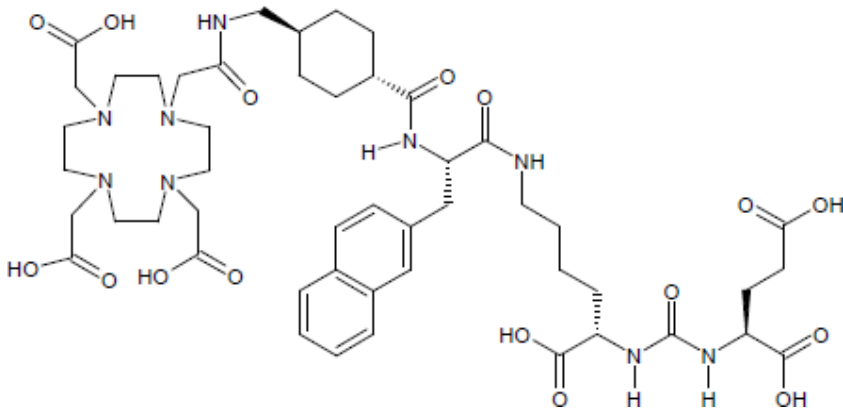
LU-177-BASED RADIOTHERAPIES (DOTA-TATE AND PSMA)

Delivery of the Radiopharmaecutiacls

- Lu-177-DOTA-TATE (Lutathera®)is deliverd as a single dose per cycle
  - 7.4 GBq per vial
  - typically 4 cycles (every 8…10 weeks) will be applied

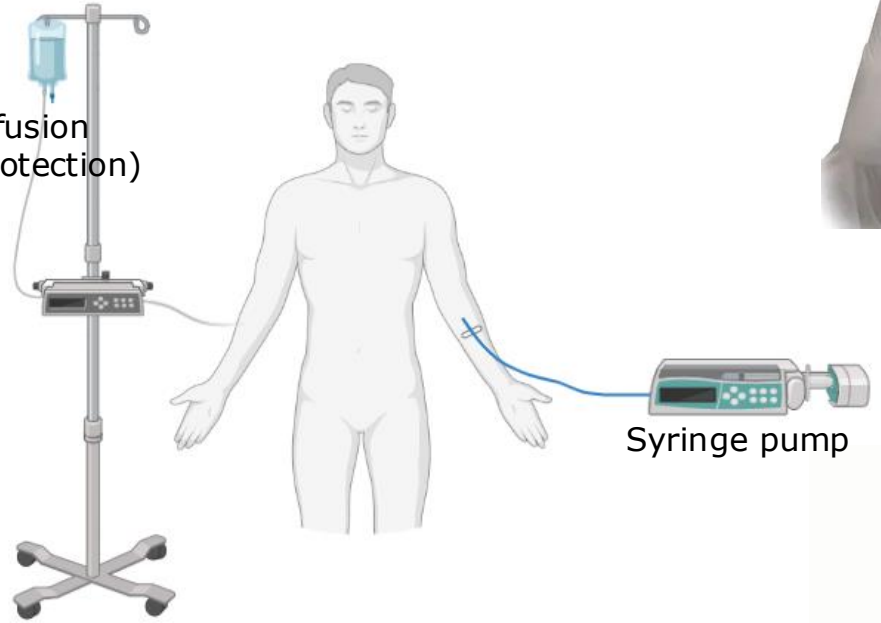
- Lu-177-PSMA-617 (Pluvicto®)→ approved by EMA and FDA
  - 7.4 GBq per vial
  - typically 6 cycles (every 6…8 weeks) will be administerd

  → Incidence of prostate cancer is approximately 40 times higher than NET
  → Increased use of PSMA-targeted therapies.



PSMA-617

Application of Radiotherapeutics /I - Administering via syringe



- therapy is administered by direct i. v. injection by the physician
- slow bolus: 10 … 20 sec
- sometimes used for PSMA-therapies

- Syringe is administered by i. v. injection using a perfusion pump
- 20 … 30 min
- DOTATATE-therapies, PSMA-targeted therapies

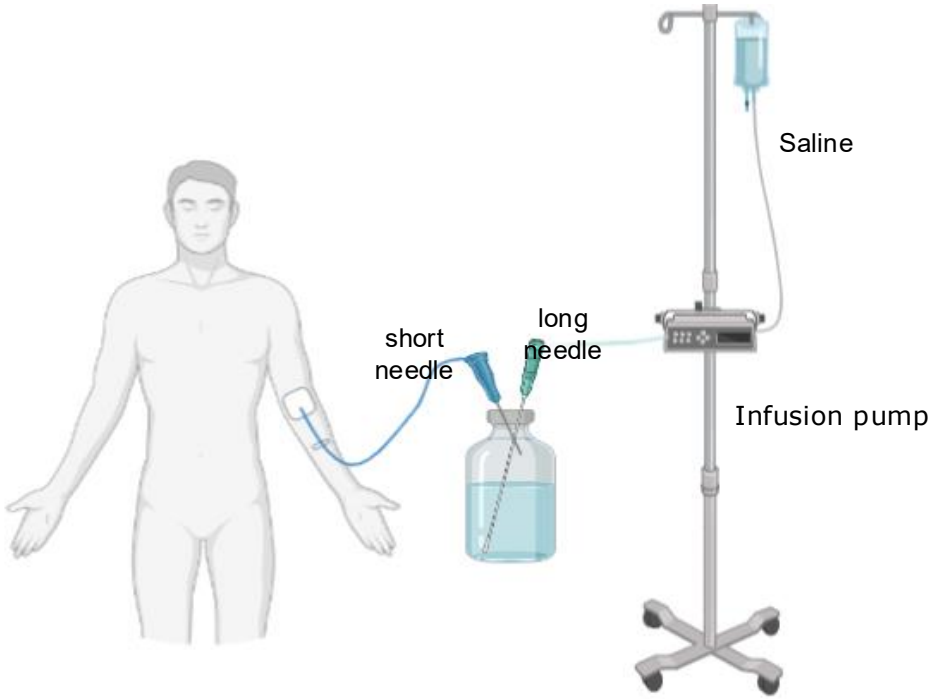
Application of Radiotherapeutics /I - Administering via syringe

- If therapy is administered directly from the syringe → hybrid/layerd syringe shield is recommended
  - ~ 5 mm Perspex surrounded by 2 to 3 mm lead or tungsten

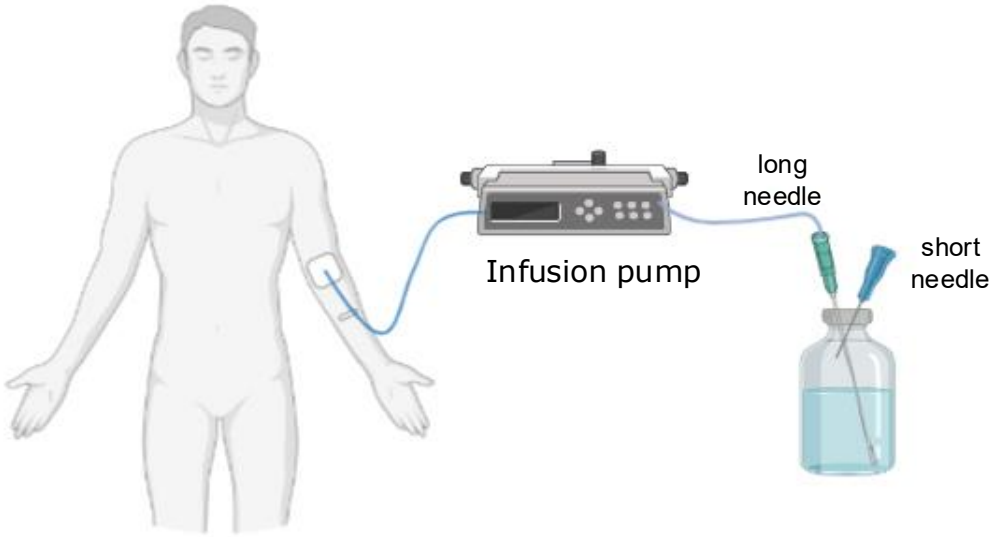
- If therapy is administered using syringe pump → pump may be placed inside of a shielded box

Shielded box on wheels (1 cm perspex, surrounded by 1 cm of lead)

Application of Radiotherapeutics /II - Infusion



- direct infusion of saline into the vial → overpressure → infusion into the patient
- 20 … 30 min
- recommended by AAA for Lutathera®



- Pharmaceutical is sucked out of the vial by infusion pump
- 20 … 30 min
- flushing with saline via short needle → re-infusion

if septum of the vial is damaged →risk of contamination

no air should be infused

Application of Radiotherapeutics /II - Infusion

Placement of the shielded via behind a shield of lead glas

Kings College, London

In-patient vs out-patient treatment – Rules to follow

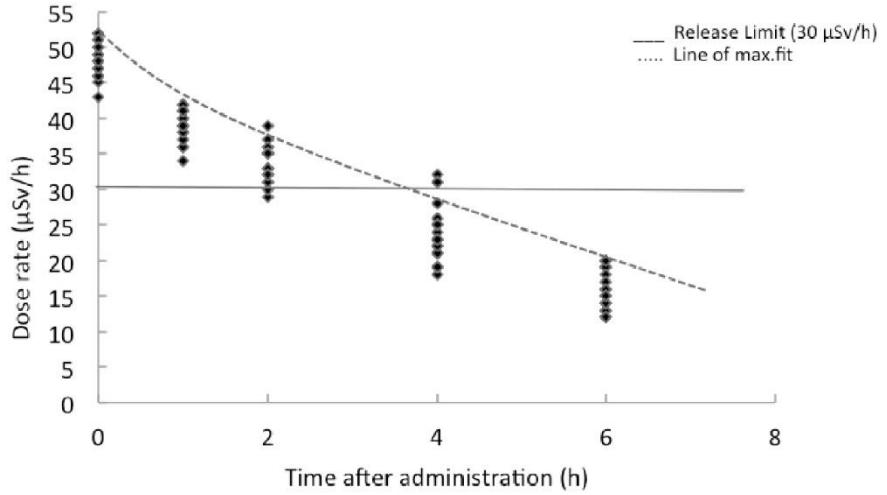
- recommendations from the International Commission on Radiological Protection (ICRP)
- IAEA - International Basic Safety Standards
- European Commission Basic Safety Standards (BSS) (Ionising Radiations Regulations 2017 (IRR17)
  - specifies that the effective dose limit to a member of public should not exceed 1 mSv per year
  - legislation has the provision that the dose limit may be averaged over 5 years (5 mSv in 5 years) to allow for doses greater than 1 mSv in any single year to friends and family members who may be in close proximity to the patient but cannot be treated as a comforter and carer

In-patient vs out-patient treatment – PSMA-Therapy / I

- 23 patients
- typically treated with activity of 7.4 GBq
- dose rate measured at several time points and distances
- Relatives carried OSL –dosimetry devices at home after discharge for up to 4–5 d
- Urine excretion was measured

Results

- Dose rate from the patient after the injection is quite high (48µSv/hr@1m) → but drops relatively fast
- After 5h the dose rate decreases below 30 µSv/h@ 1 m distance and exposure of the caregivers remains below 5mSv
- mean total dose to caregivers was 202.3 ± 42.7 *µ*Sv (4-5 d)
- patients excreted ~45% of the administered activity during the first 6 h after the infusion



outpatient treatment is possible

Written instructions for the patient are needed; analog to I-131 treatments.

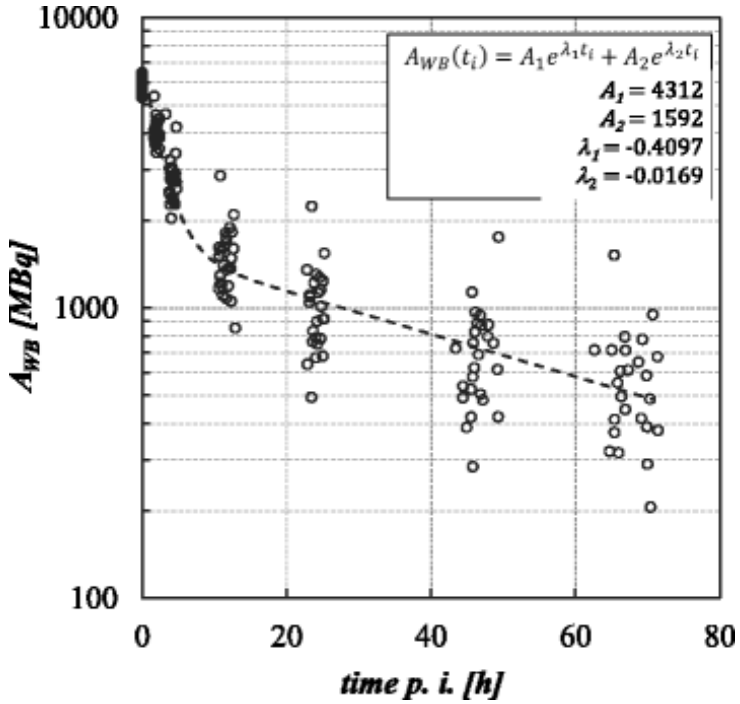
Demir M et al. "Evaluation of radiation safety in 177Lu-PSMA therapy and development of outpatient treatment protocol." Journal of Radiological Protection 36.2 (2016): 269.

In-patient vs out-patient treatment – PSMA-Therapy / II

- 50 patients, treated with ~ 6.3 GBq
- dose rate and activity measured at several time points at a distance of 2m
- Urine excretion was measured

Results

- Unbound ^{177}Lu-PSMA-617 is rapidly cleared from the body
- after 4 h, ~ 50% and, after 12 h, ~ 70% of the activity are excreted → mainly via urine
- maximum dose to members of the public is ~ 250 µSv when the patient is discharged after 48 h
- however, up to 6 cycles are applied per patient and year → needs to be considered



inpatient treatment is necessary (based on national rules)

Written instructions for the patient are needed

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

In-patient vs out-patient treatment – Dotatate-Therapy / I

- Data of 34 patients, applied activity of 7.400 MBq
- Dose rate were estimated for several time-points and distances
- Sophisticated model on social contact times
- equivalent dose to individuals of the public were estimated

Results

- Restriction in social contacts should be followed
- Both in-patient and out-patient treatment should be an option → depending personal life circumstances

	Partner	Child < 2 years	Child 2–5 years	Child 5–11 years	Work colleague	8 h private transport	2 h public transport
Inpatients	6.2 (4.6) [2.0–17.9]	7.0 (5.2) [2.3–20.4]	3.5 (2.5) [1.2–9.8]	1.7 (1.3) [0.6–4.9]	0.3 (0.2) [0.1–0.8]	0.05 (0.03) [0.02–0.1]	0.3 (0.2) [0.1–0.7]
Outpatients	7.1 (5.1) [2.4–20.0]	8.2 (5.7) [2.6–22.8]	4.0 (2.7) [1.4–11.0]	2.1 (1.4) [0.7–5.5]	0.3 (0.2) [0.2–0.8]	0.07 (0.03) [0.03–0.1]	0.4 (0.2) [0.1–0.8]

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

In-patient vs out-patient treatment – Dotatate-Therapy / I

- Inpatient precautions
  - Refrain from close contact (< 1 m) with young children and pregnant women for 7 days
  - Refrain from very close contact (< 30 cm) with young children and pregnant women for 14 days
  - Refrain from very close contact (< 30 cm) with other adults for 7 days
  - Avoid sharing a bed with another person for 14 days
  - Always flush toilet twice after use for 7 days, ask male patients to urinate sitting down
- Outpatient precautions
  - the same rules: + 1 day

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

Waste Management

- Needs to be collected, segregated and disposed of according to local rules
- Faeces, urine and other liquids should be disposed of via the toilet.
- Contaminated clothing, linen, food items etc stored in a separate plastic bag labeled “RADIOACTIVE”
- Disposable cutlery and dishes should be used

Exemption limit for ^{177m}Lu: 10 Bq/g
Exemption limit for ^{177m}Lu in municipal sewage: 50 kBq/mL

Production of Lutetium-177

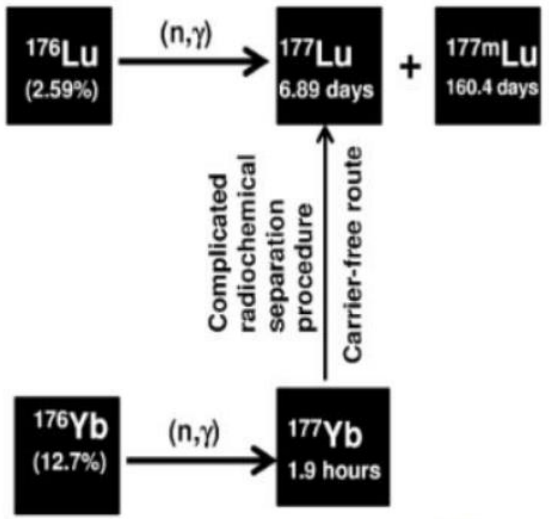


Fig. 2 Two different routes for reactor production of ^{177}Lu

Indirect production route

decay product of the neutron irradiation of ytterbium-176 (^{176}Yb(n,γ) reaction)

\+ No long-lived contamination

\- more complex → expensive

Direct production route

direct neutron irradiation of a lutetium-176 target (^{176}Lu (n,γ) reaction)

\+ significantly easier → cheaper

\- Long-lived isotope → ^{177}mLu

- Lu-177m contaminant (0.02 … 0.05 %), might cause a problem
- means a contents of 1.5 – 3.7 MBq of ^{177m}Lu in a vial with 7.400 MBq of ^{117}Lu

Exemption limit for 177mLu: 10 Bq/g
Exemption limit for 177mLu in municipal sewage: 50 kBq/mL

Dash, A et al. Nucl Med Mol Imaging, 2015. 49(2): p. 85-107.

Lu-177-therapies - Radiation Hazards for the Staff

- Spillage or contamination during dispensing, administration or transportation to administration room
- External radiation dose from isotope/patient
- Contamination via bodily fluids

Staff position	Mean (SD) exposure (µSv) from each ^{177}Lu therapy day	Mean annual exposure (µSv) 32 GBq ^{177}Lu (23 therapy days per annum)	Mean total exposure of staff (µSv) per year, averaged over 5 years	Percentage of mean annual exposure attributable to ^{177}Lu (%)
Nurse	33.2 (13.9)	759	1480	51
Physician	7.6 (1.5)	184	738	25
Physicist	9.1 (3.9)	207	380	54
Radiopharmacist	17.4 (8.4)	391	2137	18
Nucl. Med. Tech.	6.8 (2.2)	156	1570	10

Calais et al. Radiation safety of outpatient 177Lu-octreotate radiopeptide therapy of neuroendocrine tumors. Annals of Nuclear Medicine, 28, p 531–539 (2014).

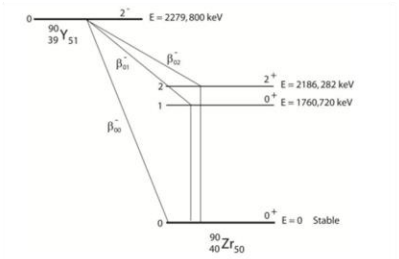
Conclusions on Lutetium-177

- ^{177}Lu-labeled pharmaceuticals will see an increased use in future
- ^{177}Lu-therapies are a safe treatment option
- preparation, administration have to be performed carefully using apropriate shielding → high activities
- In case of contamination with long-lived ^{177m}Lu → separate waste management might b enecessary
- ^{177}Lu retention at discharge depends on
  - patient; excretion and tumour burden
  - Length of stay in department
- External dose rates make an inpatient- or outpatient therapy service possible

SIRT-THERAPY - RADIATION PROTECTION

^{90}Y Microspheres

Yttrium-90 Physical Half-Life: 2.7 d



PHYSICAL DATA
Positron
0.015 % abundance → 511 keV

Beta
2284 keV (99% abundance / maximum)

Maximum Beta Range in Water: 10,7 mm
Maximum Beta Range in Air: ~ 870 cm

SHIELDING

Betas and electrons
9 mm of plastic

Gamma and X-rays
none

considerable Bremsstrahlung
(4E-03 µGy/h per 1 MBq @ 100 cm)

INTERNAL EXPOSURE FOR STAFF

Critical Organ: Lungs

Effective Doses per Unit intake (Sv/Bq)
Ingestion: 2.7E-9
$ALI_{ingestion}$ ~ 7.4 MBq

Inhalation: 1.6E-9
$ALIi_{nhalation}$ ~ 12 MBq

Delacroix et al. RADIONUCLIDE AND RADIATION PROTECTION DATA HANDBOOK 2002

- Pure beta emitter
- Range in tissue: 2.5 mm (average)
  ~11 mm (max) → can be shielded by ~1 cm perspex

- Mean energy: 0.94 MeV
- half-life: 64h (2.7 d)
- ~ 94% of the emitted radiation within 11 d

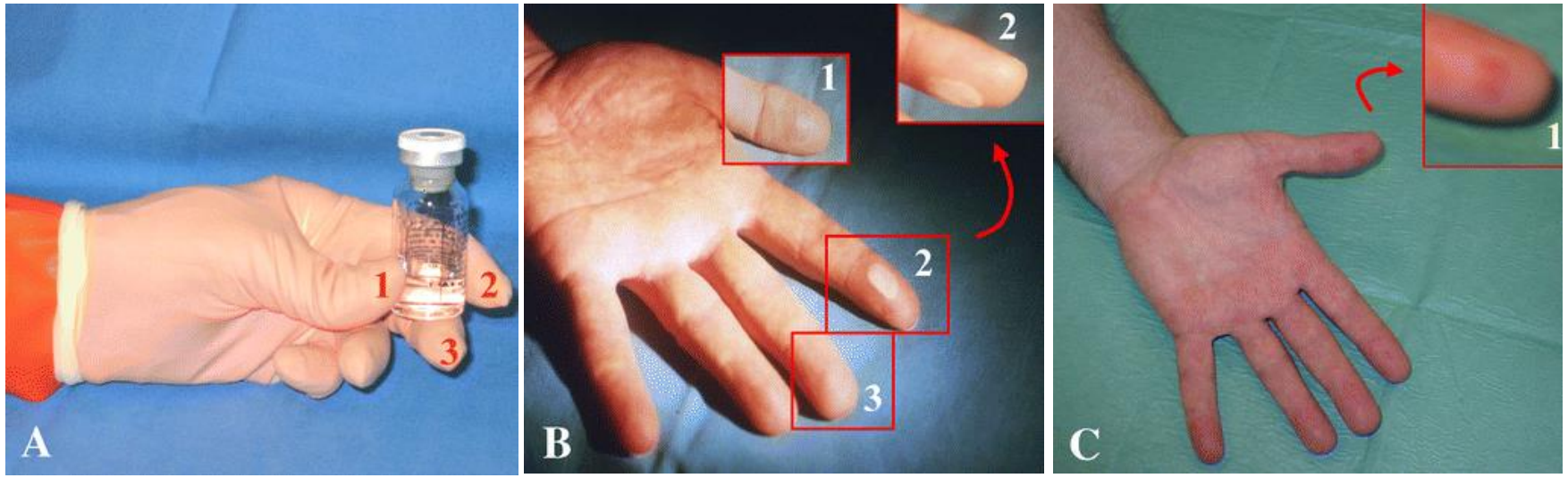
^{90}Y – Take care – High Dose Rates

1 kBq Y-90 in 50 µl, distributed at 1 cm² skin:

- Y-90: 1.350 µSv/h
- Tc-99m: < 9 µSv/h → Faktor 150

Radiodermatitis of three fingertips of an operator due to an inappropriate labelling procedure

a) The inappropriate procedure responsible for the damage: manipulation of the vial without the use of tongs
b) The radiodermatitis of the fingertips of the thumb (1), the index finger (2) and the middle finger (3) as it appeared 2 weeks after the exposure.
c) The lesions progressively recovered, with a sequela of telangiectasis



Y-90 : 16,7 GBq
Handling time: **~10 s**
skin dose: **12 Gy**
TLD: 70 mGy

M.Cremonesi et al. EJNM 33,1321,2006

SIRT preparation – General Rules

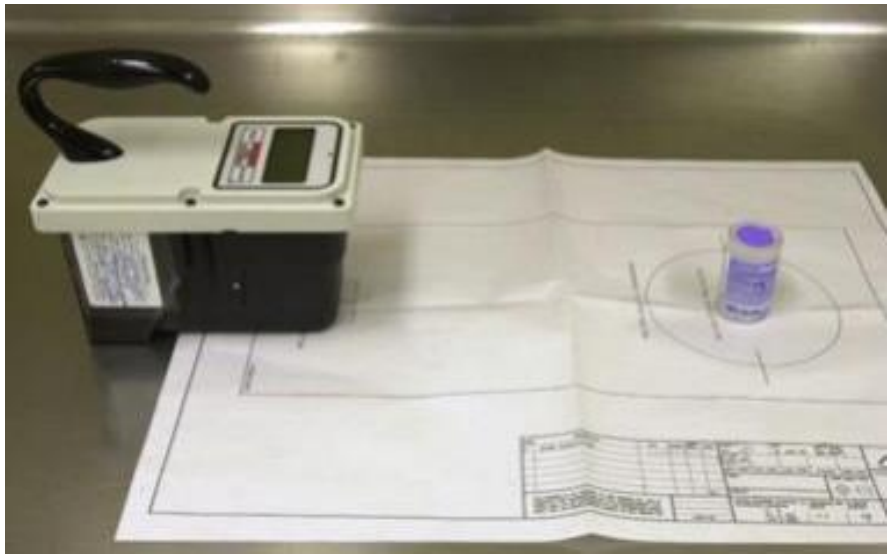
- successfully completed training in the operation of the delivery system, safety procedures, and clinical use for the type of Y-90 microsphere
- Radiation Safety Officer (RSO) must have training in radiation safety, regulatory issues, and emergency procedures for Y-90 microsphere to be used
- for every procedure a written directive is necessary, which must be dated and signed before the administration
  - patient name
  - The treatment site
  - radionuclide (including the physical form [Y-90 microspheres])
  - The model of spheres (e.g. TheraSphere® or SIR-spheres®) or manufacturer
  - prescribed dose or activity

SIRT preparation – General Rules

- follow normal ALARA practices of time, distance, and shielding
  - for preparation, application and waste management
  - care to the patient post-treatment
- record delivery, label and secure the activity until application
- preparation activity
  - TheraSpheres (Boston Scientific)
    - Single, patient-specic activity
    - assays the dose and records results
  - SIRSpheres (SirTeX)
    - bulk dose
    - Patient-specific activity needs to be drawn
- measure activity in calibrated dose calibrator
  - since mainly bremsstrahlung is used for measurement, the calibration must be geometry-specific

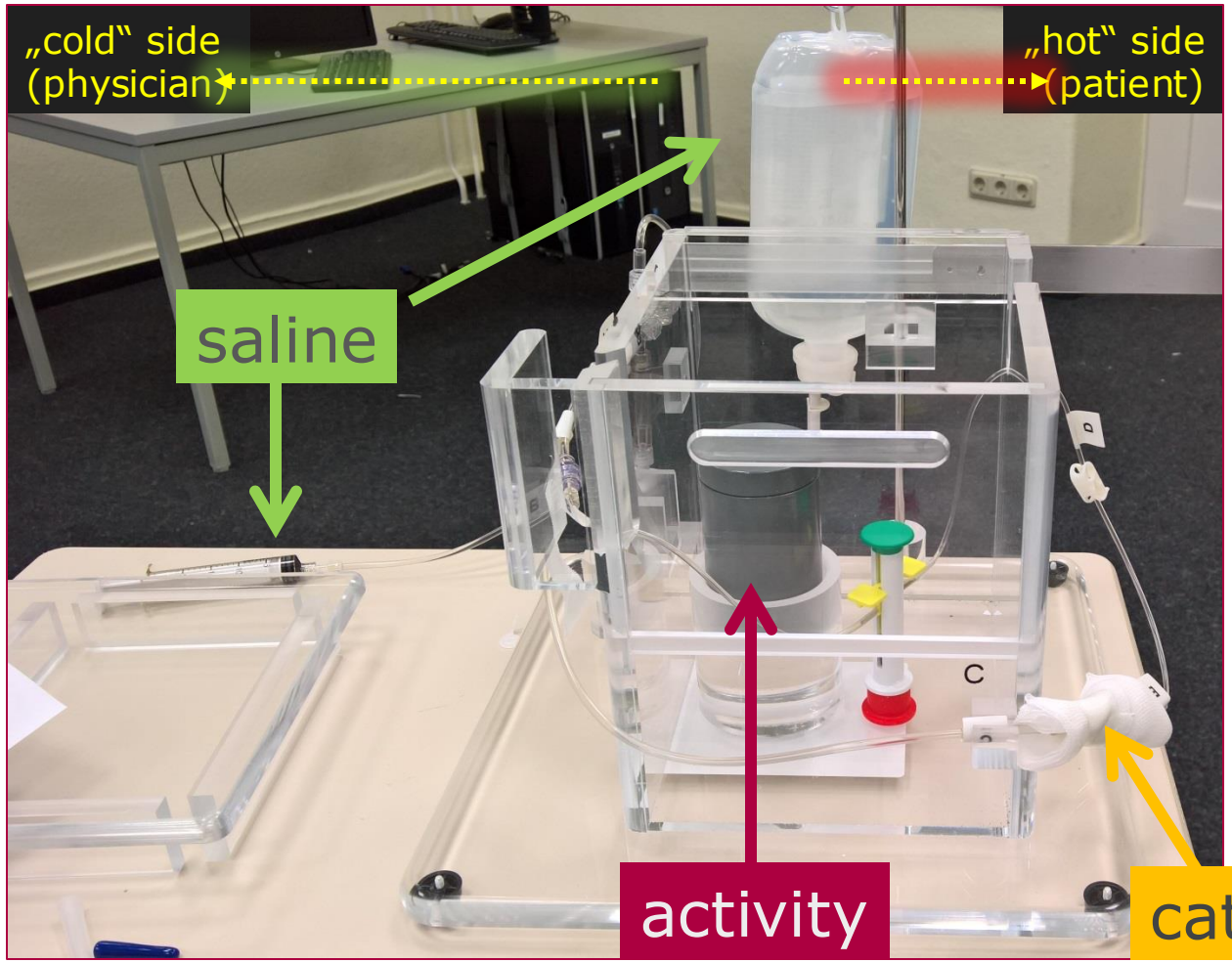
SIRT – Calculation of Activity Applied

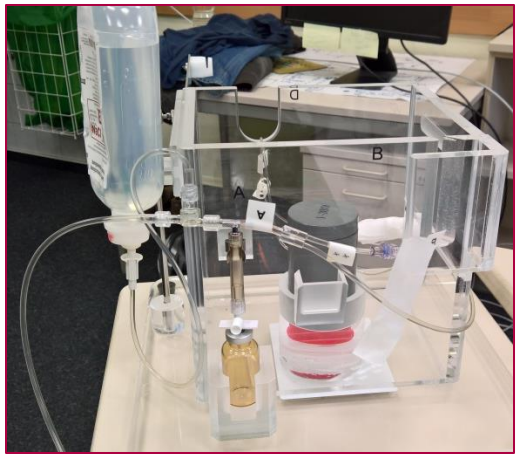
The percentage of activity delivered is calculated by comparing the measurements of the vial before administration and the waste container after administration.

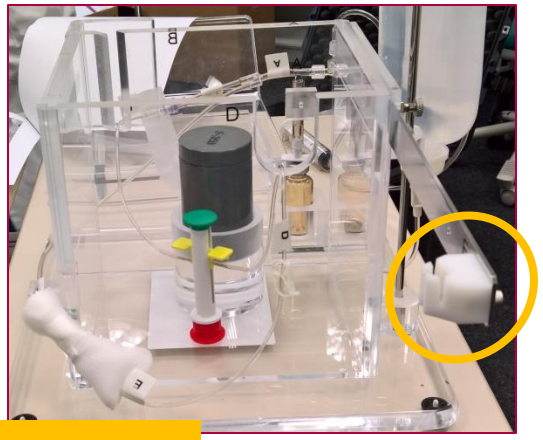


Measurement of the dose rate at specific distance from the surface of the vial prior to application

SIRT – practical application







SIRT-procedure

sterile
(radiologist)

non-sterile
(nuclear medicie physician)

- interventional room should be labeled as controlled area
- Work area should be generously covered with cloths
- Everyone in interventional room has to wear lead vest and thyroid shield
- physician should wear x-ray googles, others may also
- If not enough space to keep distance – use extra rolling perspex shields
- maximize distance
- no pregnant staff in room

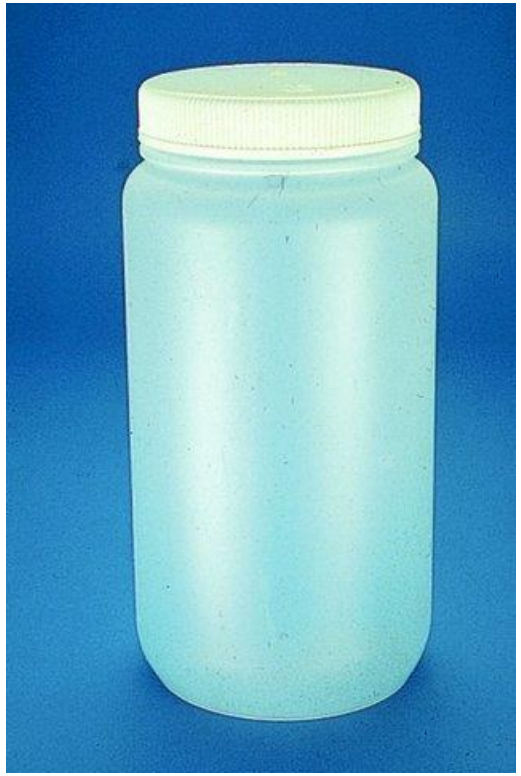
SIRT – practical application

SIRT – practical application

bad example
no additional gown
no X-ray googles

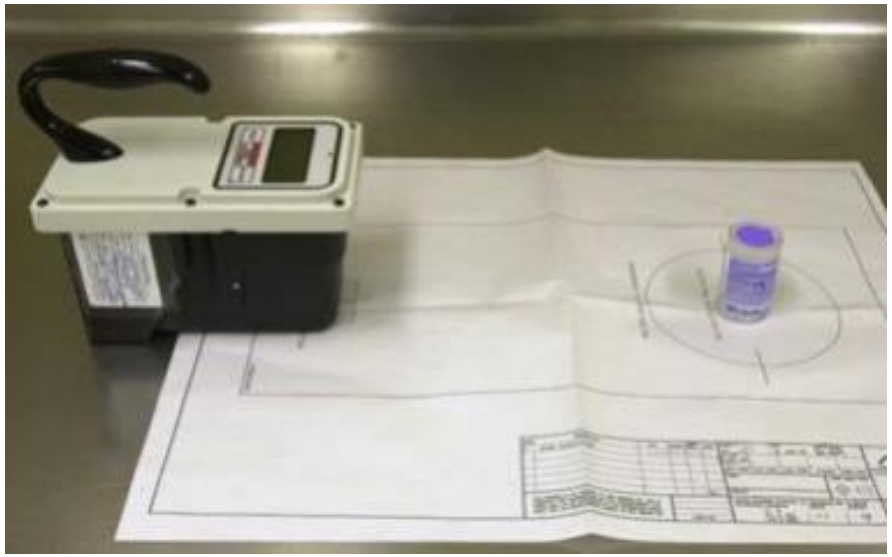
Following SIRT procdeure – Waste

- Physician puts catheters, dose vial, gloves, towels used to wrap end of catheter, and other waste into the 2L Nalgene waste container
- Label container (nuclide, date, estimated activity --> see next slide) and log into long lived radioactive waste storage

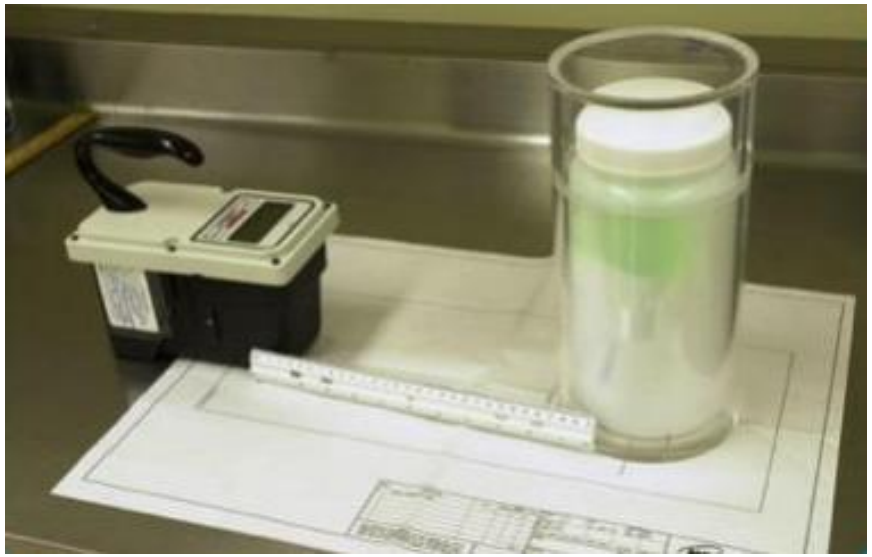


SIRT – Calculation of Activity Applied

The percentage of activity delivered is calculated by comparing the measurements of the vial before administration and the waste container after administration.



Measurement of the dose rate at specific distance from the surface of the vial prior to application



Measurement of the dose rate at specific distance from the surface of waste container → comparable geometry to pre-therapeutic measurement

Following SIRT procedure - Survey of Staff and Room

Check with Geiger-Muller meter after each procedure for potential contamination

- hands and feet of the staff before they leave the interventional room
- Administration kit and cart
- Floor
- Linens
- Fluoro Table and Footswitch
- Trash
- each survey should be documented (date, results of the survey, instrument used, and the name of the individual who performed the survey)

In Case of Contamination

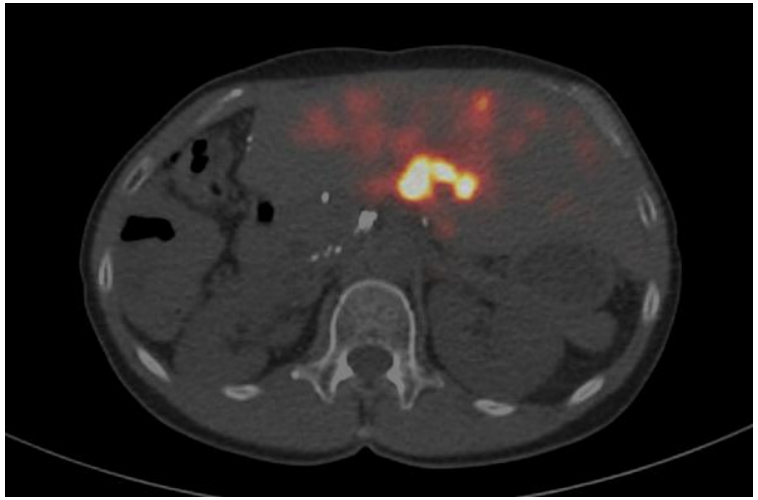
- Spheres are difficult to remove
- Try to detect contamination using a GM meter
- if floor is contaminated → cover with Perspex absorber
- Plaster is well suited to remove the spheres from a surface

Perspex absorber (1cm) to cover contamination on the floor

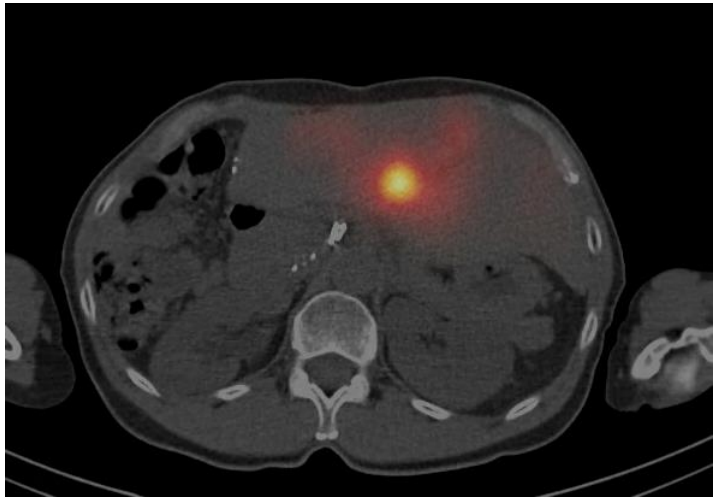
^{90}Y SIRT - Activity Applied

within 24 hours after SIRT, a post-therapy SPECT or PET scan of the upper abdomen may be performed

→ verification of application and dose



^{90}Y-PET/CT, 24h p.i.



^{90}Y-SPECT/CT, 6h p.i.

Post Administration Patient Care – Release of the patient

- Bremsstrahlung radiation is emitted post-treatment by the patient
- Resin microspheres (SirTeX, SIRSpheres) may have free ^{90}Y on their surface, up to 0.4% of the administered activity.
  - Can be excreted in the urine in the first 24 hours
  - Special precautions may be required for inpatient care
  - Nursing instruction necessary to prevent excessive staff anxiety
- Dose rate typically measured right after administration
  - 20 to 30 µSv/h at surface
  - 2 to 3 µSv/h at 1 m
- Patients can be released as outpatients with no special precautions required
  - However, hospitalization may be required for a period of time due to the intervention or the patient's general condition
  - Written instruction should be given to patient

SIRT – Recommandations to the Patient

- In the first 24 hours, thorough hand washing after using the toilet will help to eliminate any radioactive contamination. Soaking up spilled body fluids such as blood, urine or stool and disposing them of in the toilet is also necessary to avoid accidental exposure
- Avoid sharing a bed with your partner for 3 to 4 days
- Avoid all non-essential close contact with children, infants, and pregnant women for about 10 days
- You should not become pregnant within two months of treatment, as this may cause irreversible damage to the unborn child → effective contraceptive method must always be used during this time
- You must not breastfeed for the first two weeks after treatment and you must not use the milk pumped during this time for bottle feeding your baby

Post-treatment Surgical Considerations

Assuming 10 GBq dose infused (in many cases activity is lower)

Days post calibration	60 days	180 days	270 days
Contact with liver (≤ 1 cm, hands)	6 µSv/h	2.6 µSv/h	0.7 µSv/h
50 cm from center of the treated area	0.07 µSv/h	0.03 µSv/h	0.001 µSv/h

- Standard estimate of daily background dose from natural sources is 5 … 8 µSv/d (depends largely on the particular place in the world)

- estimated 1 hour radiation dose during surgical resection, at 60 days post infusion of TheraSphere®, delivers ~ 1% of normal daily background dose to the body

*TheraSphere® Reference Manual US, 2010
Mehrabi A et al. J Gastr Surg (2019)

Post-Surgical Specimen Handling

- >34 days
  - No precautions required if surgical resection post treatment

- If < 34d post treatment
  - survey specimen with thin window ionization chamber
  - if surface dose rate is >20 µSv/h → label specimen as radioactive, shield it, and wait until 3x background before cleared for routine pathology analysis

surgical specimen of a HCC

Bektas H et al. (2013)

Patient Death

Autopsy

- If <34 days post administration and exposure time>1 hour, surgeon may want to remove liver prior to autopsy

Embalming and Burial

- No special precautions required for glass microspheres

- If <48 hours post administration of resin microspheres, embalming fluid should be saved and stored for radioactive decay

Cremation

- in some countries total activity that can be cremated at any individual crematorium in a year is limited
- depending on regulations, the crematorium may ask for an estimate of radioactivity in the body

ALPHA EMITTERS, RADIUM-223

Ra-223 (Xofigo®)

- Treatment/inhibition of osteoblastic metastases of prostate carcinoma
- Administration by injection i.v.
- total of six doses every four weeks 6 x 3.5 MBq for a standard patient (50kBq/kg)
- T1/2=11.43 d
- Dose coefficient inhalation: 5.7 µSv/Bq
- Excretion is primarily via stool, essentially in the first days after incorporation

Measurement of Activity and Contamination

Applied Radiation and Isotopes 68 (2010) 1367–1370

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Development of secondary standards for ^{223}Ra

Denis E. Bergeron *, Brian E. Zimmerman, Jeffrey T. Cessna

Applied Radiation and Isotopes 68 (2010) 1523–1528

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Standardization of radium-223 by liquid scintillation counting

J.T. Cessna *, B.E. Zimmerman

- Activity measurement possible with common dose calibrators and contamination monitors
- ^{223}Ra-specific calibration factors are needed
  - A standard source should be supplied by the provider
  - Reference values for some relevant model of dose calibrators have been published

Radiation Protection – Extremity Surveillance

Recommended by the German BfS if more than 28 patients per year are handled by a single individual

^{223}Ra - Radiation Protection – Excretion and Contamination

- Ra-223 was found in saliva (median: 22 Bq/g, range: 5.9-124 Bq/g) and excreted with sweat (median: 0.12 Bq/cm2 , range: 0.01 - 0.6 Bq/cm2) in the first 24 hours p.i.
- Contaminations in restrooms and kitchens were low (median: 0.021 Bq/cm2 , range: < DL - 0.35 Bq/cm2)
- The exposure due to inhalation of Rn-219 and its progeny for relatives staying in a room with the patient is expected to be of no concern

Wanke et al, SNMMI Abstract 2015

DOSE TO THE LENS OF THE EYE – A SHORT REMARK

Protection of the lens of the eye – use of protective glasses

ORIGINALARBEIT

Impact of radiation protection means on the dose to the lens of the eye while handling radionuclides in nuclear medicine

Iris Bruchmann[a,*], Bastian Szermerski[a], Rolf Behrens[b], Lilli Geworski[a]

[a] Department for Radiation Protection and Medical Physics, Medical School Hannover, Carl-Neuberg-Str. 1, 30625 Hannover
[b] Physikalisch-Technische Bundesanstalt (PTB), Bundesallee 100, 38116 Braunschweig

Received 29 May 2015; accepted 20 July 2015

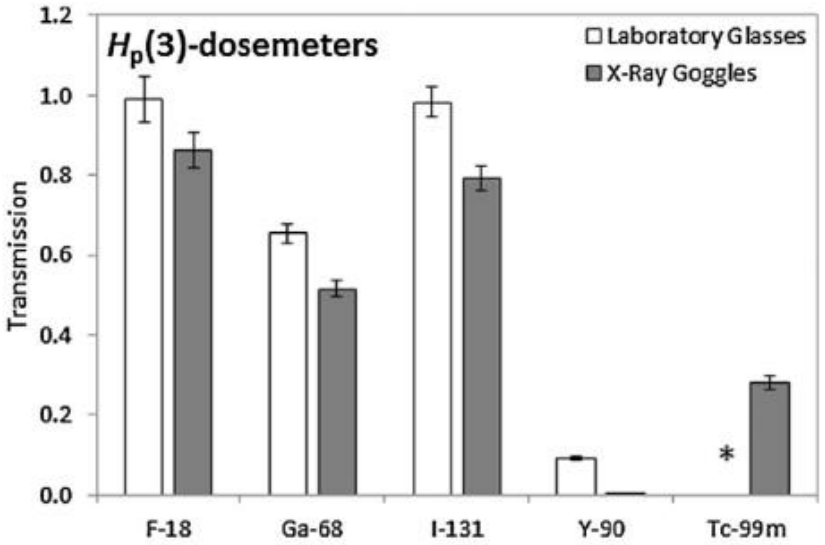


Figure 2. Nuclide-depending mean reciprocal attenuation factors determined for laboratory glasses and X-ray goggles with $H_p(3)$-dosemeters.
*not investigated

Famous words

"Im Strahlenschutz wiegt ein Gramm Hirn mehr als eine Tonne Blei!"

(Felix Wachsmann, München)

„In radiation protection, one gram of brain weighs more than one ton of lead!"

Universität Rostock Traditio et Innovatio

Universitätsmedizin Rostock




Jens Kurth, PhD (EE)

Rostock University Medical Center, Germany
Department of Nuclear Medicine

jens.kurth@med.uni-rostock.de