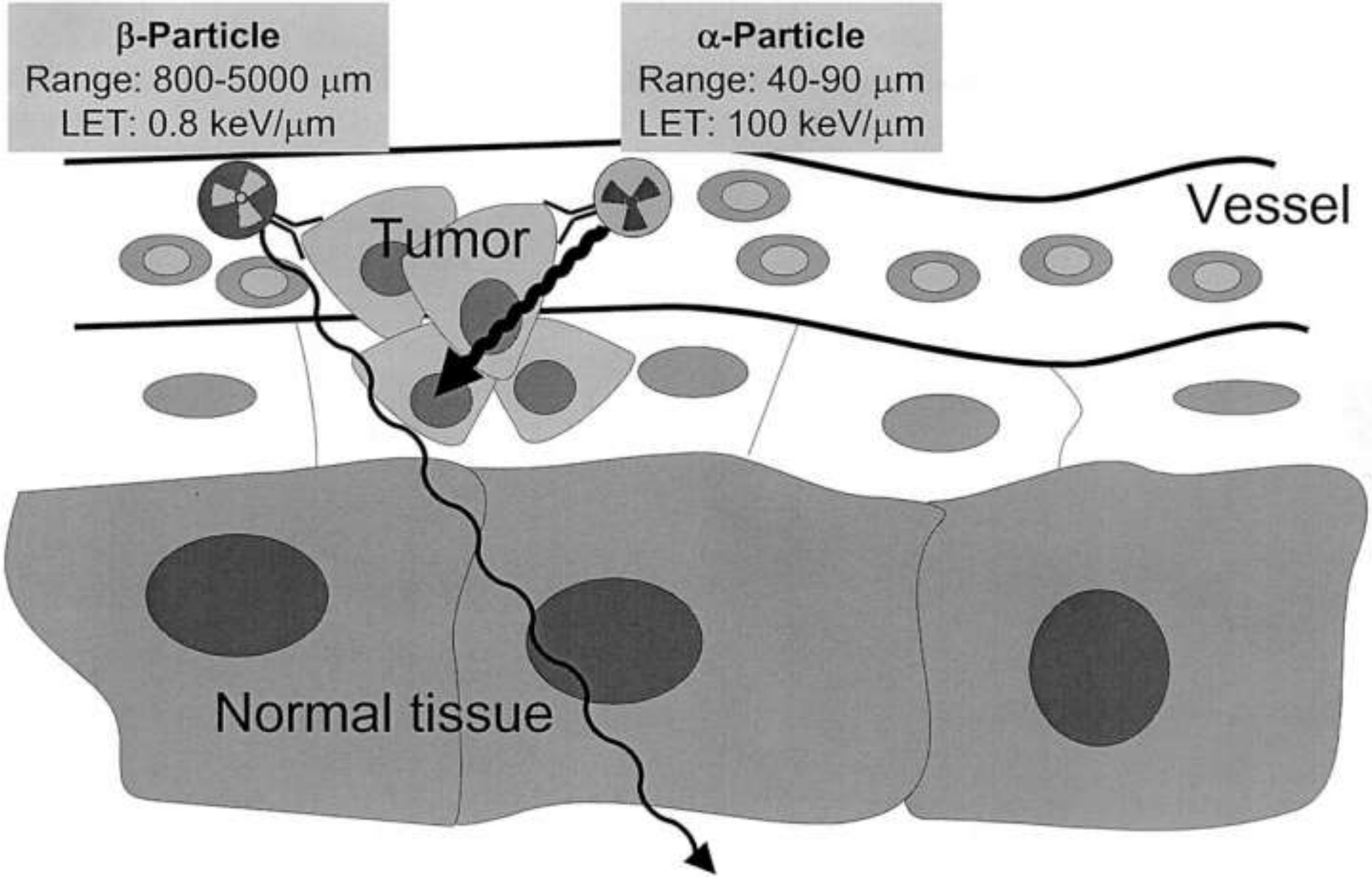
Targeted Alpha Particle Therapy: Imaging, Dosimetry and Radiation Protection

Michael Lassmann

Klinik und Poliklinik für Nuklearmedizin
Direktor: Prof. Dr. A. Buck

Targeted Therapy – Basic Principles



Influence of the particle type

0.01 Gy gamma photons

50 ± 7 electron tracks per cell (on average)

0.01 Gy alpha

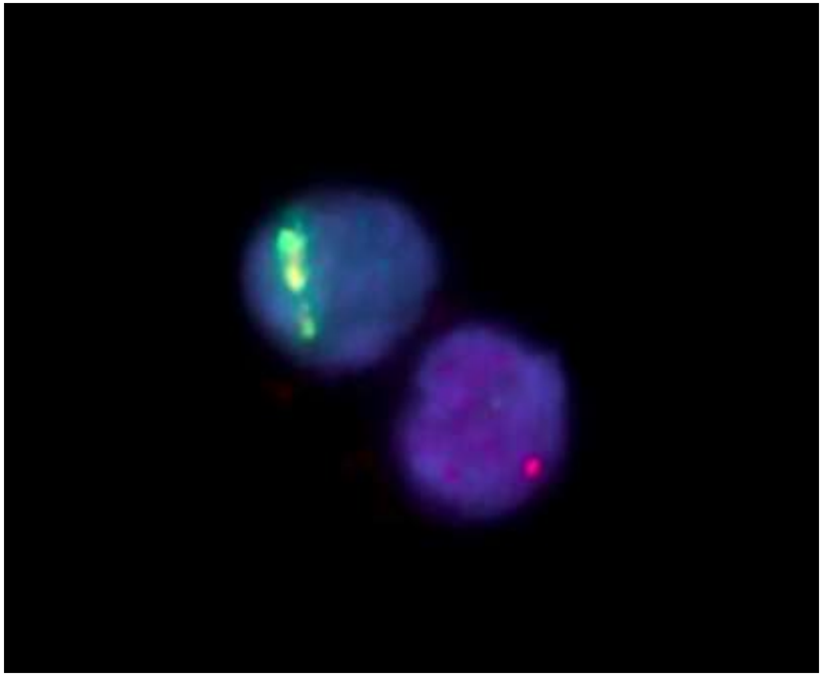
dose spectrum, from 0 to 0.30 Gy

mean hit number: 0.1

90% of cells are spared !

(Goodhead in *Dosimetry of ionizing radiations*, Kaze, Bjarngard and Attix ed., Orlando1987)

DNA Damage by Alpha Particles



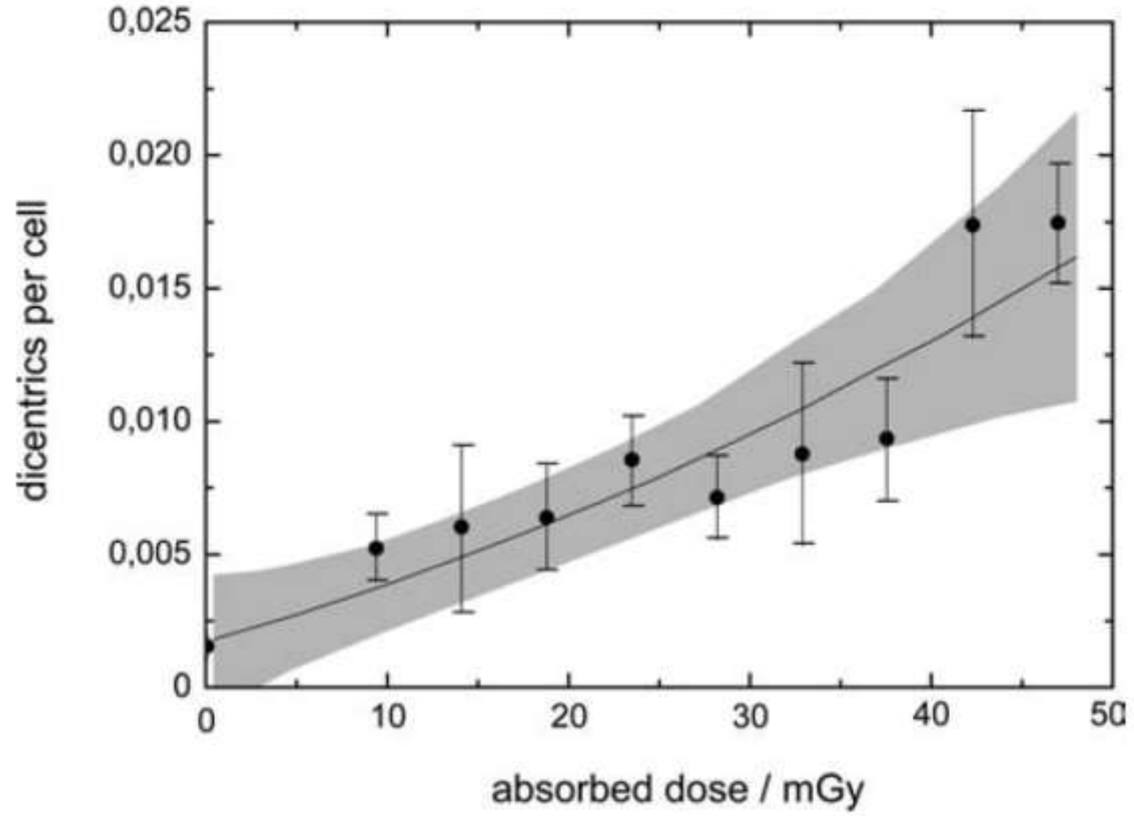
DNA damage caused by the track of an alpha particle through a human lymphocyte visualized by the γ-H2AX assay

(Image courtesy of H. Scherthan, Bundeswehr Institute of Radiobiology, Munich, Germany)

Chromosome Aberrations after ^{224}Ra Therapy

Treatment for Ankylosing Spondilytis

Total administered actvity: 10 MBq



Stephan et al. Radiat Environ Biophys (2005) 44: 23–28

Alpha emitting isotopes for therapeutic applications in nuclear medicine

Radionuclide	Half-Life	Max. Particle Energy
At-211	7.2 hrs	6.0 MeV
Bi-213	46 min	6.0 MeV
Ra-223	11.4 days	5.8 MeV
Ac-225	10.0 days	5.9 MeV

Therapy Modalities (Generic Use)

Metabolic active radiopharmaceuticals

- Radioiodine Therapy of Thyroid Diseases (benign/malignant) (^{211}At in-vitro studies)
- Bone Pain Palliative Treatment of Bone Metastases (^{223}Ra)

Specifically binding radiopharmaceuticals

- Radiopeptide therapy (addressing specific antigens or receptors) (^{213}Bi, ^{225}Ac)
- Treatment of lymphoma using antibodies (^{212}Pb)

Locoregional therapies

- Selective Internal radiotherapy (Alpha Emitter: possible option?)

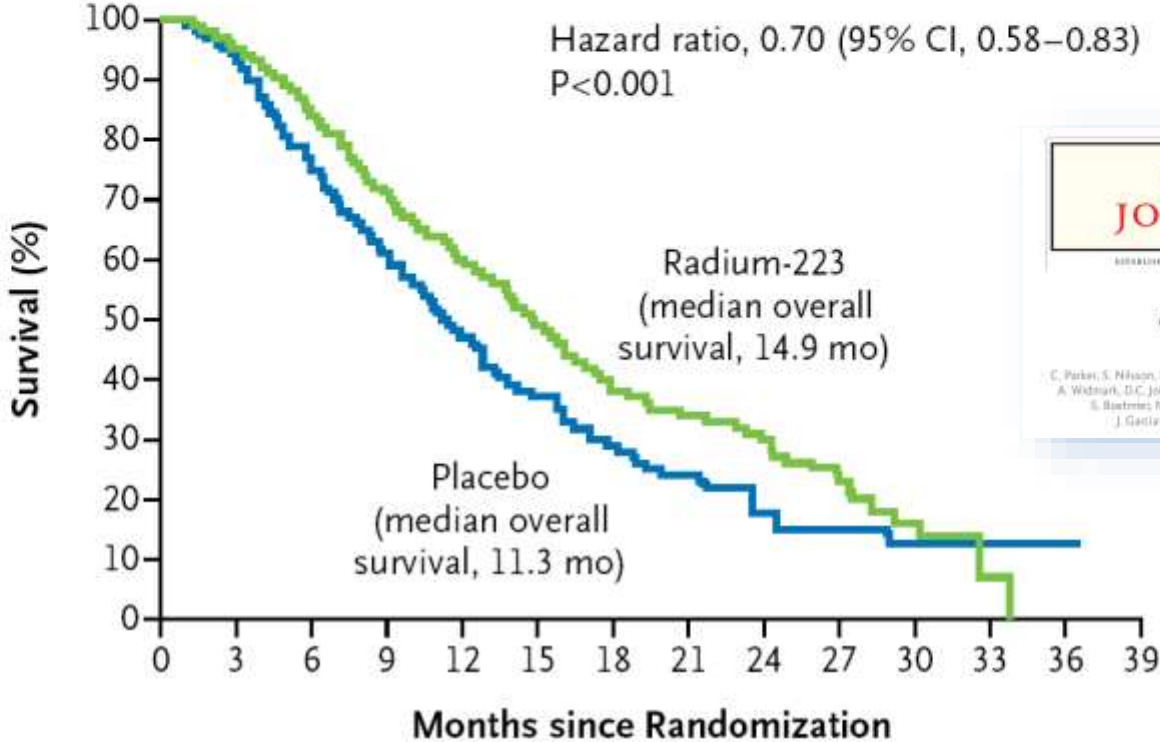
Radium

http://www.rsc.org/chemistryworld/Issues/2011/January/ElementsOfInspiration.asp

^{223}Ra - Phase III Randomised Trial (ALSYMPCA)

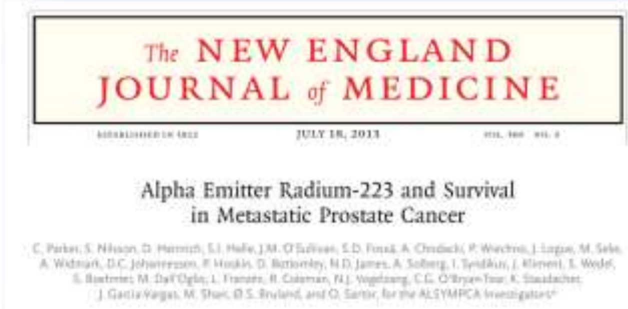
N= 921
0.05 MBq/kg

A Overall Survival



No. at Risk

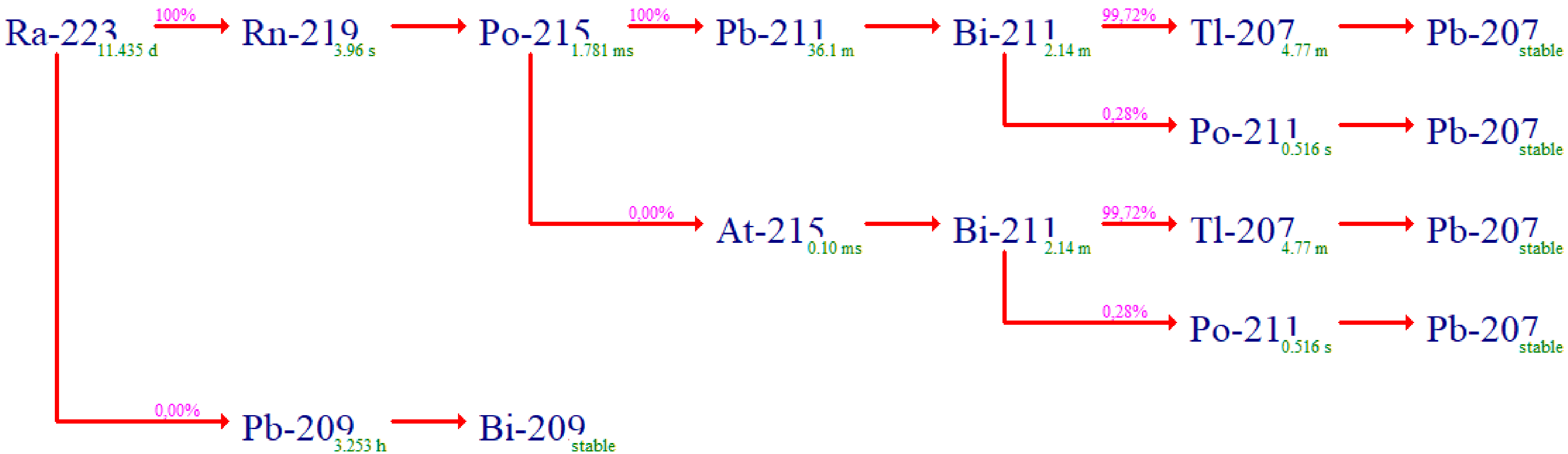
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0


The NEW ENGLAND JOURNAL of MEDICINE

JULY 18, 2013

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

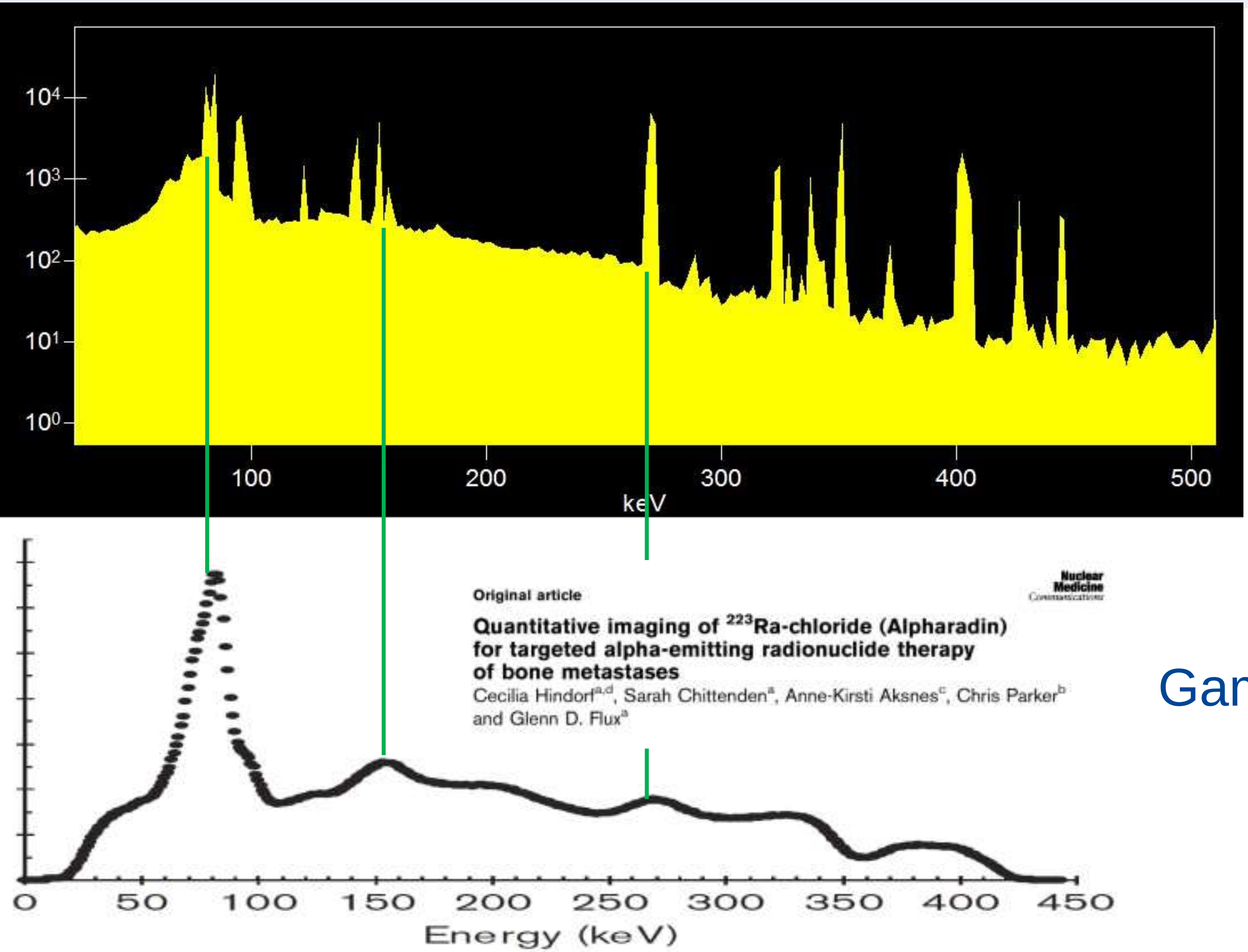
Decay of Ra-223



Decay of Ra-223

Decay Chain	Branching Ratio	Half-life	Alpha and Recoil Nuclei (MeV)	Beta and Auger Electrons (MeV)	Gamma and X-Rays (MeV)
Ra-223		11.43 days	5.77	0.078	0.141
Rn-219	100%	3.96 s	6.88	0.007	0.059
Po-215	100%	1.78 ms	7.49	0.000	0.000
Pb-211	100%	36.10 min	-	0.454	0.064
Bi-211	100%	2.14 min	6.66	0.010	0.047
Tl-207	99.7%	4.77 min	-	0.494	0.002
Po-211	0.3%	0.52 s	7.61	0.000	0.008

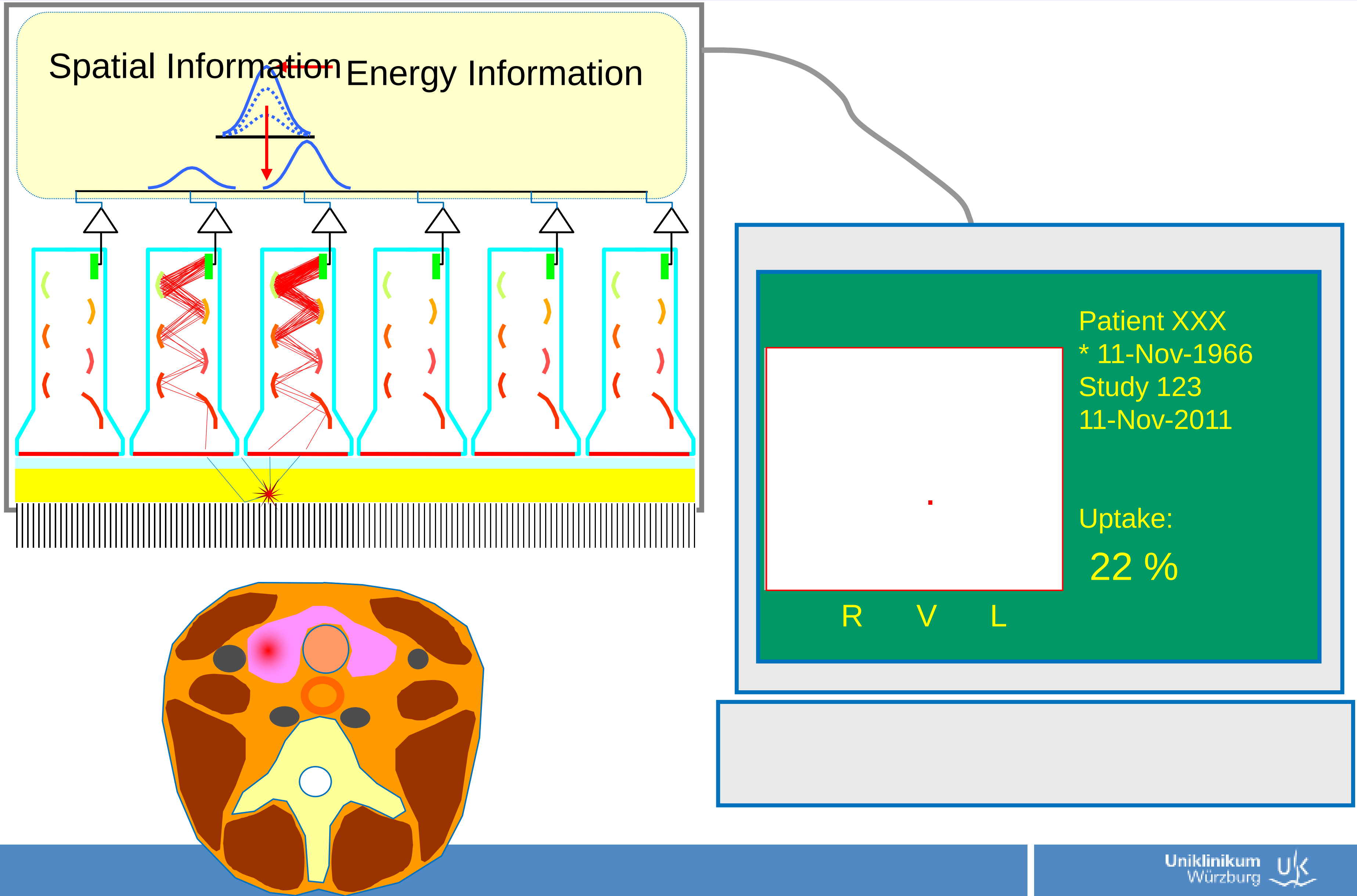
Imaging: gamma spectroscopy of Ra-223



HPGe

NaI
Gamma Camera

Gamma Camera




SIEMENS
Symbia Intevo

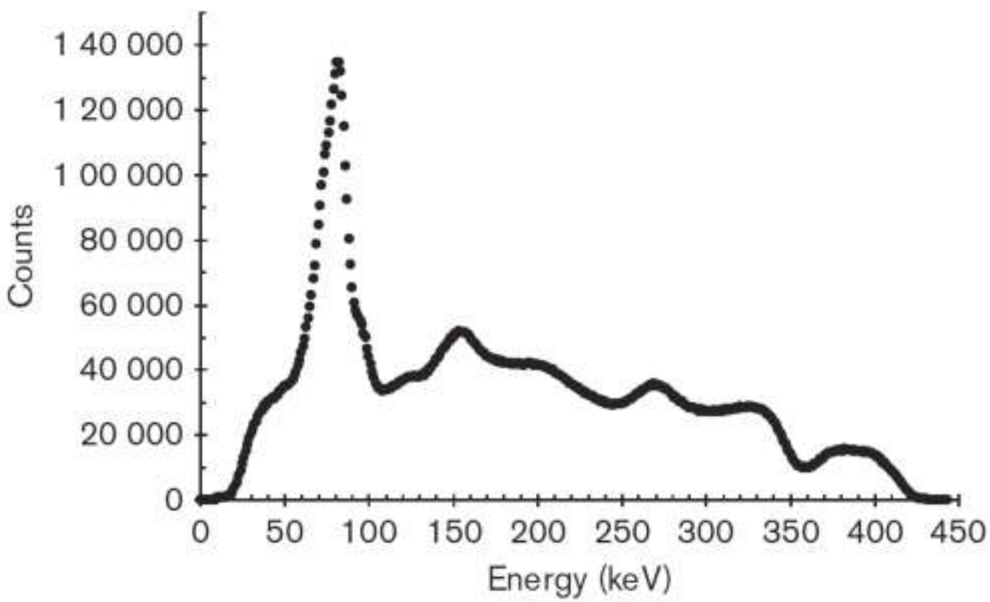
Biodistribution of Ra-223

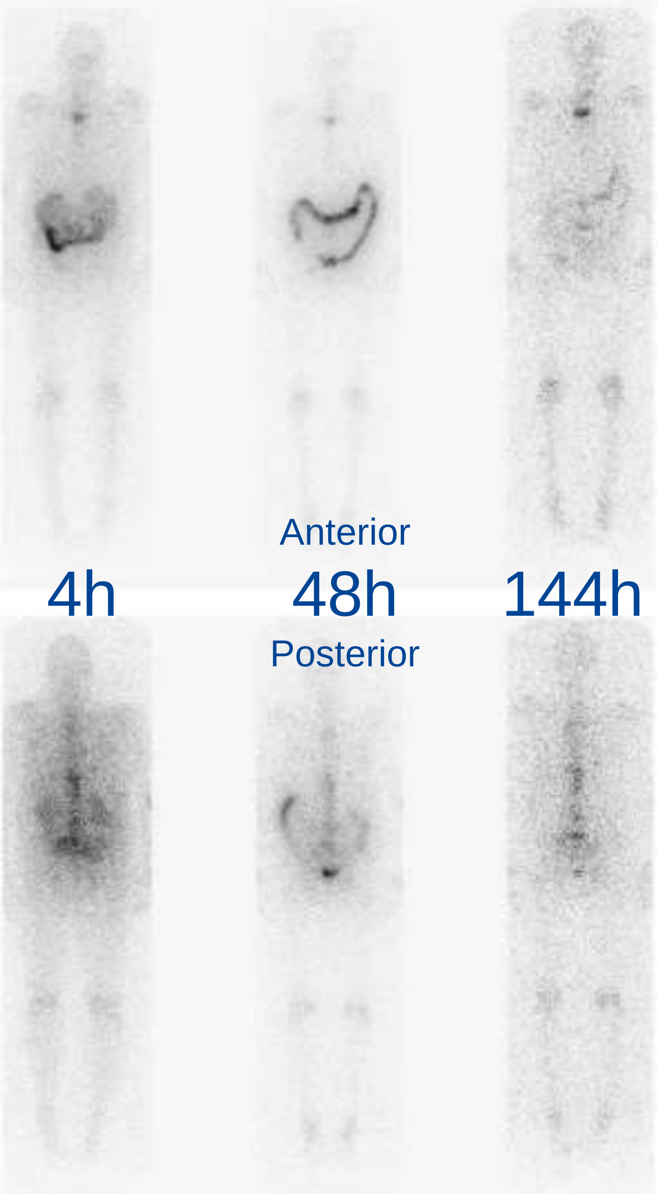
Original article

Nuclear Medicine Communications

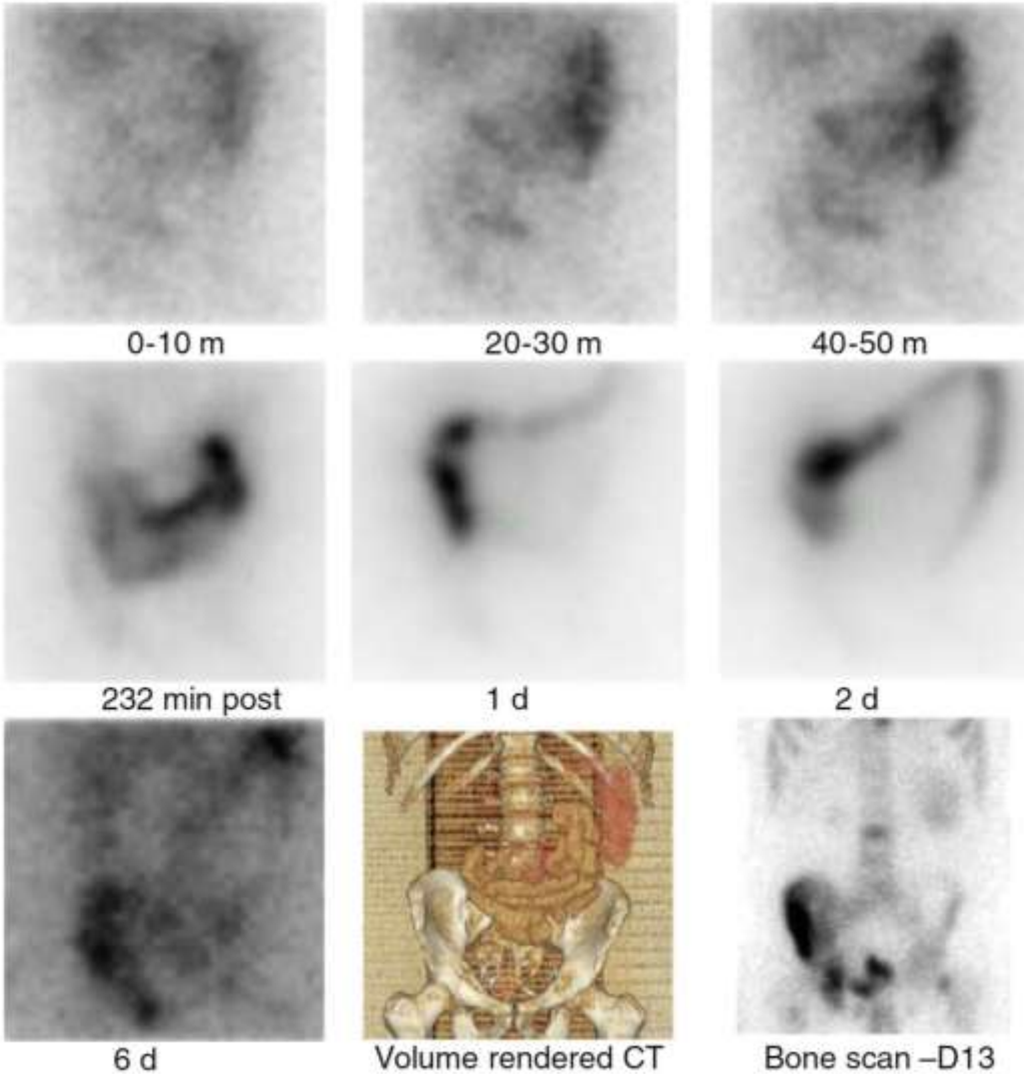
Quantitative imaging of ^{223}Ra-chloride (Alpharadin) for targeted alpha-emitting radionuclide therapy of bone metastases

Cecilia Hindorf[a,d], Sarah Chittenden[a], Anne-Kirsti Aksnes[c], Chris Parker[b] and Glenn D. Flux[a]





Biodistribution of Ra-223



Eur J Nucl Med Mol Imaging (2013) 40:1384–1393
DOI 10.1007/s00259-013-2427-6

ORIGINAL ARTICLE

Phase I pharmacokinetic and biodistribution study with escalating doses of ^{223}Ra-dichloride in men with castration-resistant metastatic prostate cancer

Jorge A. Carrasquillo · Joseph A. O'Donoghue · Neeta Pandit-Taskar · John L. Humm · Dana E. Rathkopf · Susan F. Slovin · Matthew J. Williamson · Kristine Lacuna · Anne-Kirsti Aksnes · Steven M. Larson · Howard I. Scher · Michael J. Morris

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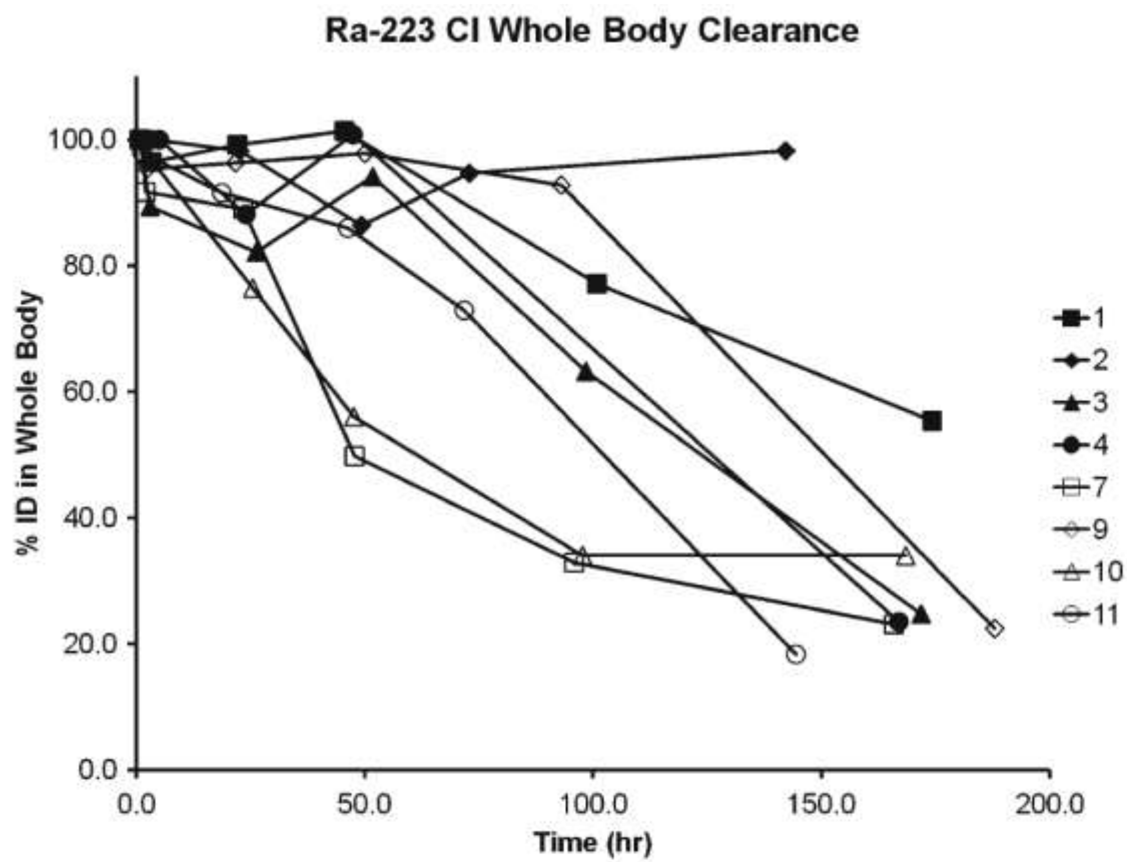


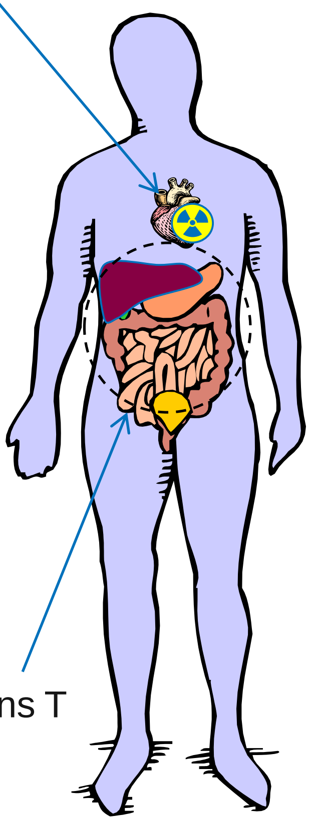
Fig. 1 Decay-corrected percentage of ^{223}Ra retained in the whole body (initial pre-void counts taken as 100 %) in patients (n=8) over a period of approximately 1 week post-administration

Nuclear Medicine Dosimetry

Diagnostics	Therapy
Low activities ~<1GBq, short-lived nuclides, γ/β^+ emitters	High activities ~>1GBq for beta emitters, > 10MBq for alpha emitters long-lived nuclides, α/β^- emitters
Stochastic risk	Deterministic damage and stochastic risk
Model-based dosimetry in a representative group of volunteers or patients	Patient-specific dosimetry
Optimize image quality	Maximize tumor absorbed doses
Minimizing radiation-associated risk	Minimize the absorbed doses to the organs-at-risk

Internal Dosimetry in Nuclear Medicine Therapy

- Aspects that alter the absorbed dose
  - *Administered activity*
  - *Physical and chemical properties of the radiopharmaceutical*
  - *Source organs irradiate target organ/s*
  - *Biokinetics and biodistribution*
    - Biological uptake and excretion



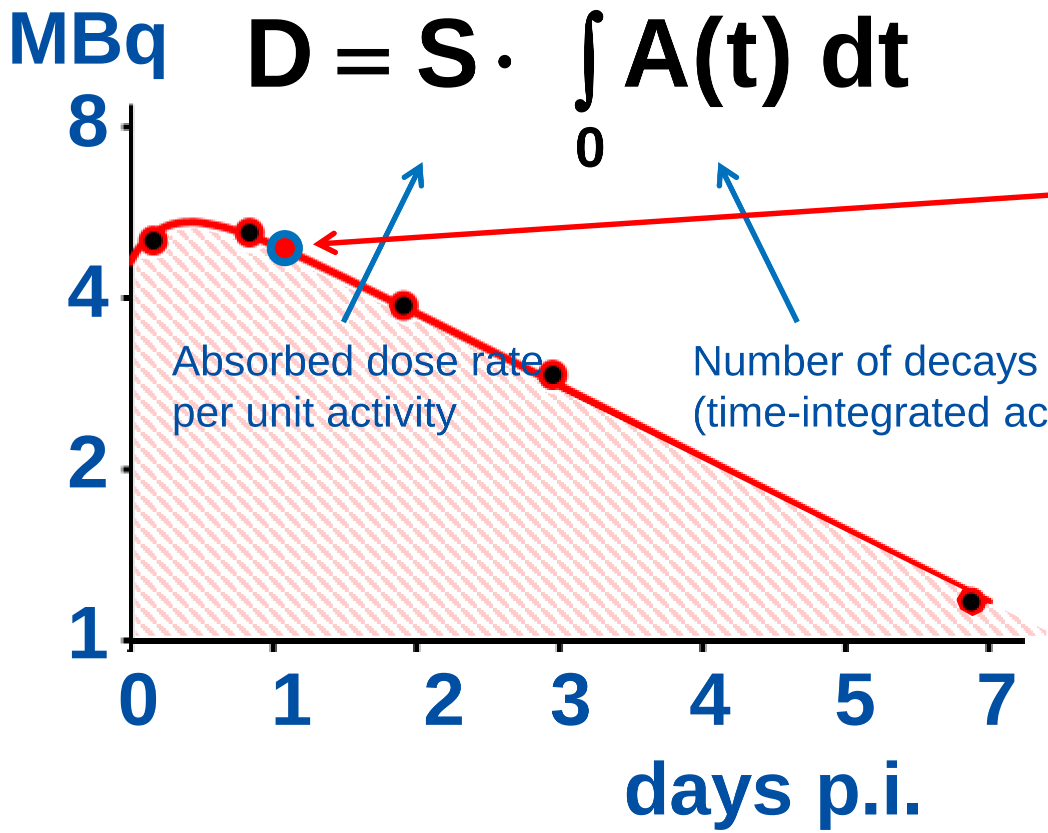
- Absorbed dose calculation:
  - *MIRD*-Scheme (1976)*
  - *Summing over all organ contributions*
  - $\boldsymbol{D_T} = A_0 \cdot \sum_{\boldsymbol{s}} \int_{\boldsymbol{0}}^{\infty} \boldsymbol{A_S(t')\,dt'} \cdot \boldsymbol{S_{T\leftarrow S}} = A_0 \cdot \sum_{\boldsymbol{s}} \tau_S \cdot \boldsymbol{S_{T\leftarrow S}}$

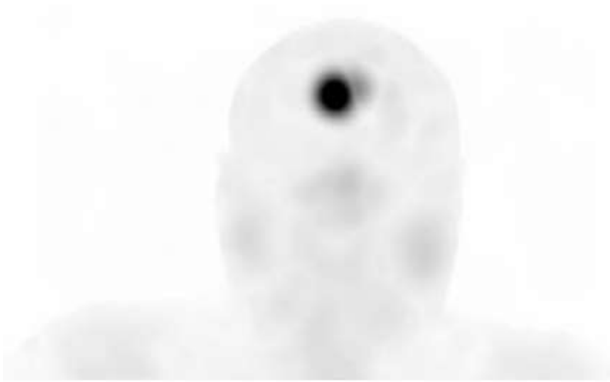
Dosimetry in Nuclear Medicine

$$D = S \cdot \int_0^{\infty} A(t)\, dt$$

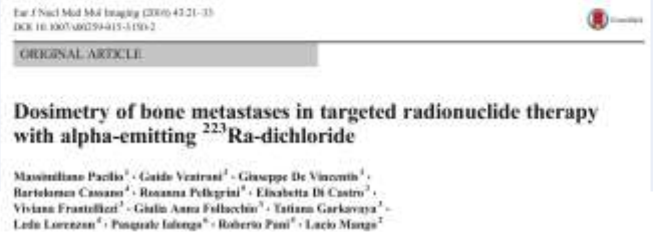
Absorbed dose rate per unit activity

Number of decays
(time-integrated activity coefficient)





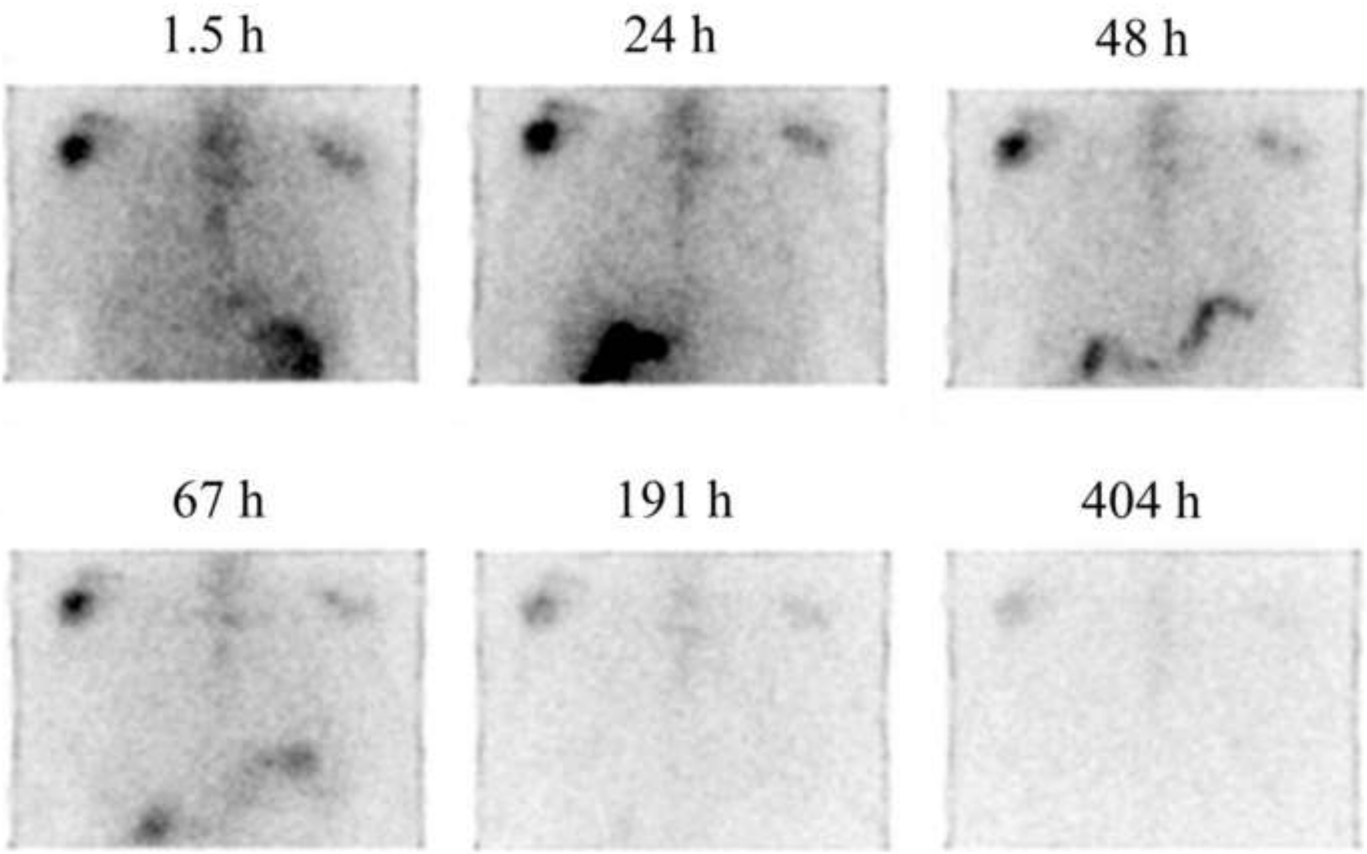
Dosimetry of Metastases


Eur J Nucl Med Mol Imaging (2016) 43:21–33
DOI 10.1007/s00259-015-3150-2

ORIGINAL ARTICLE

Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting ^{223}Ra-dichloride

Massimiliano Pacilio · Guido Ventroni · Giuseppe De Vincentis · Bartolomeo Cassano · Rosanna Pellegrini · Elisabetta Di Castro · Viviana Frantellizzi · Giulia Anna Follacchio · Tatiana Garkavaya · Ledo Lorenzon · Pasquale Ialongo · Roberto Pani · Lucio Mango



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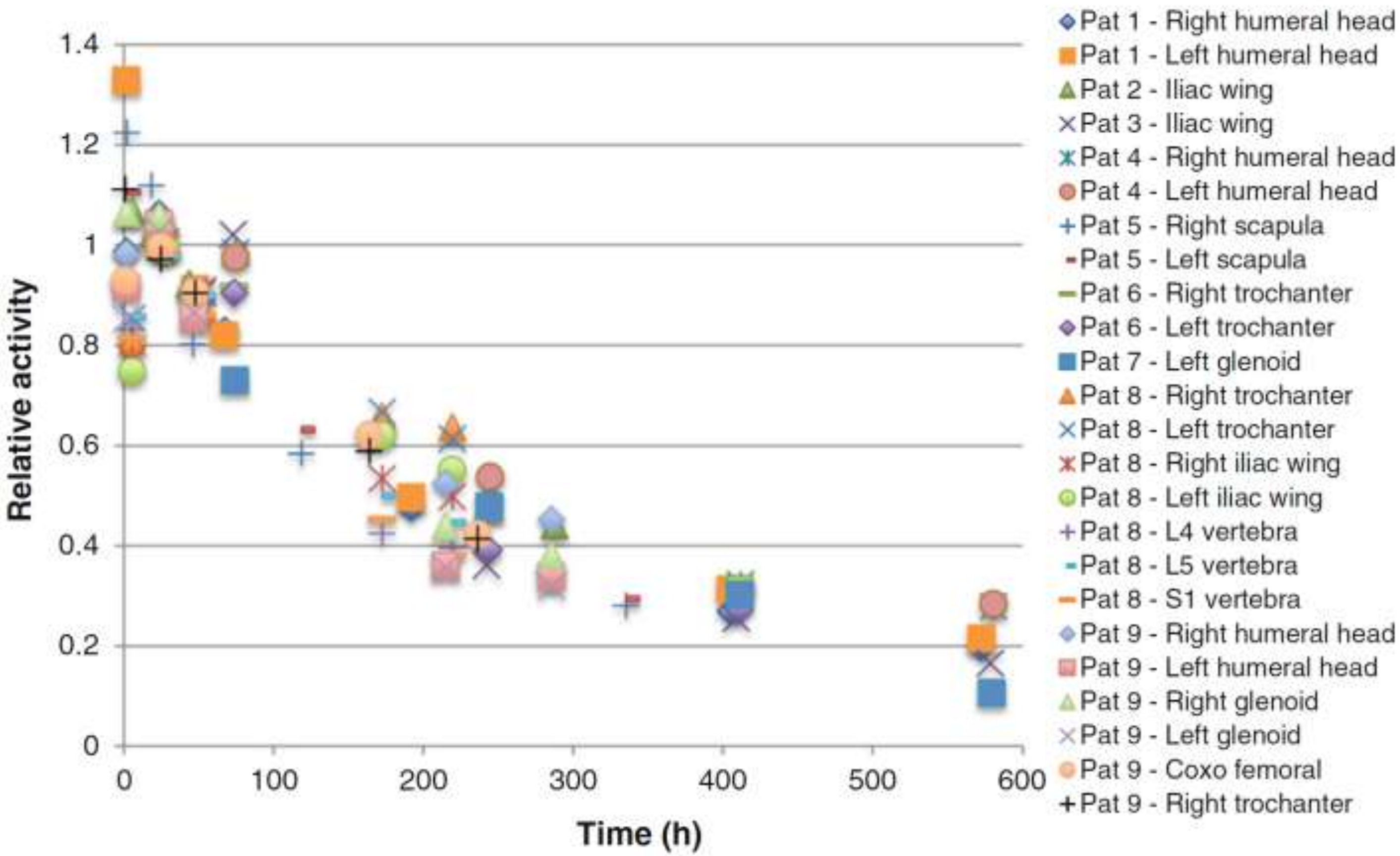
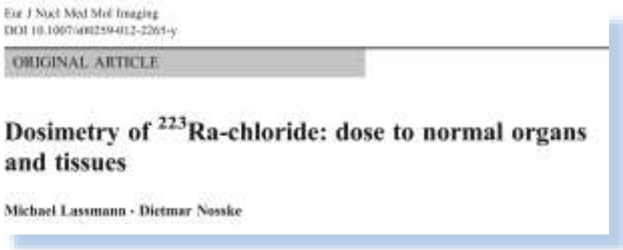


Mean absorbed dose after 1st injection: 0.7 (0.2-1.9) Gy

Total RBE weighted dose (D_{RBE5}): 18.9 Gy

Biokinetic Modelling for Radium – ICRP 67

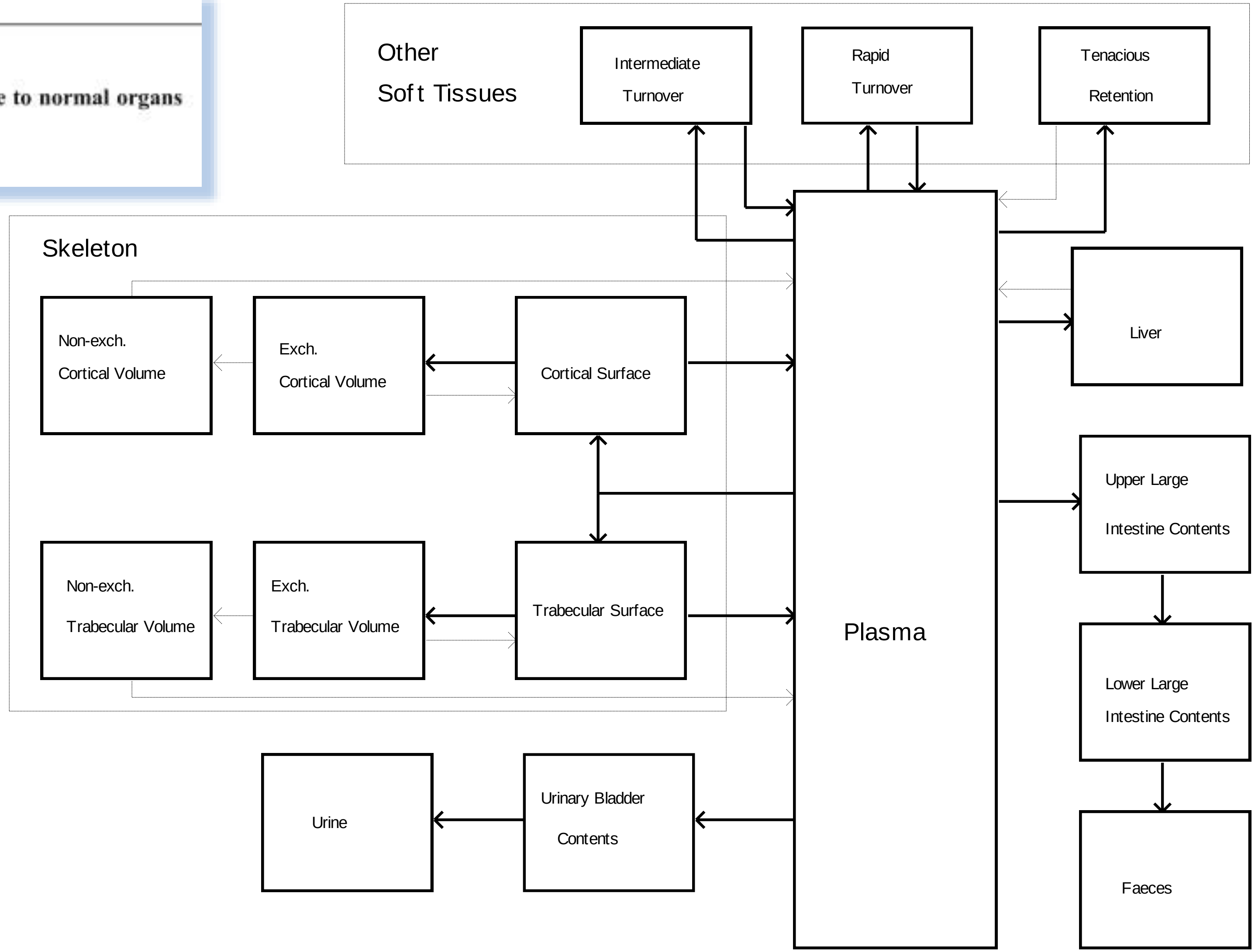


Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-012-2265-y

ORIGINAL ARTICLE

Dosimetry of ^{223}Ra-chloride: dose to normal organs and tissues

Michael Lassmann · Dietmar Nosske



Doimetry of Ra-223

Table 1 Organ dose estimates after intravenous administration of ^{223}Ra-chloride

Organ	Absorbed dose for alpha particles (high LET) Gy/Bq	Absorbed beta/gamma dose (low LET) Gy/Bq	Dose coefficients Gy/Bq[a]	Sv/Bq[b]
Adrenals	3.2E-09	2.4E-10	1.6E-08	6.5E-08
Bladder wall	3.2E-09	4.1E-10	1.7E-08	6.6E-08
Bone endosteum	7.5E-07	1.1E-08	3.8E-06	1.5E-05
Brain	3.2E-09	1.8E-10	1.6E-08	6.5E-08
Breast	3.2E-09	1.6E-10	1.6E-08	6.5E-08
GI tract				
Oesophagus	3.2E-09	1.7E-10	1.6E-08	6.5E-08
St wall	3.2E-09	2.1E-10	1.6E-08	6.5E-08
SI wall	3.2E-09	3.9E-10	1.7E-08	6.5E-08
ULI wall	6.8E-09	1.4E-08	4.8E-08	1.5E-07
LLI wall	1.3E-08	4.0E-08	1.1E-07	3.0E-07
Colon	9.5E-09	2.5E-08	7.3E-08	2.2E-07
Kidneys	3.4E-09	2.4E-10	1.7E-08	6.8E-08
Liver	3.6E-08	1.5E-09	1.8E-07	7.2E-07
Muscle	3.2E-09	2.0E-10	1.6E-08	6.5E-08
Ovaries	3.2E-09	4.3E-10	1.7E-08	6.5E-08
Pancreas	3.2E-09	2.2E-10	1.6E-08	6.5E-08
Red marrow	7.2E-08	5.5E-09	3.7E-07	1.5E-06
Respiratory tract				
ET airways	3.2E-09	1.7E-10	1.6E-08	6.5E-08
Lungs	3.2E-09	1.9E-10	1.6E-08	6.5E-08
Skin	3.2E-09	1.6E-10	1.6E-08	6.5E-08
Spleen	3.2E-09	1.9E-10	1.6E-08	6.5E-08
Testes	3.2E-09	1.8E-10	1.6E-08	6.5E-08
Thymus	3.2E-09	1.7E-10	1.6E-08	6.5E-08
Thyroid	3.2E-09	1.7E-10	1.6E-08	6.5E-08
Uterus	3.2E-09	2.8E-10	1.6E-08	6.5E-08

St stomach, *SI* small intestine, *LLI* lower large intestine, *ULI* upper large intestine, *ET* extrathoracic

[a] Radiation weighting factor of 5 for α radiation, unit Gy as proposed by the ICRP in ICRP Publication 103 as the unit for an RBE-weighted absorbed dose for deterministic biological effects [16]

[b] Radiation weighting factor of 20 for α radiation

6 treatments for a 70 kg person with an administered activity of 0.05 MBq/kg ^{223}Ra-chloride each (overall: 21 MBq ^{223}Ra-chloride):

absorbed alpha dose to the bone endosteum: ~ **16 Gy**

absorbed alpha dose to the red bone marrow: ~ **1.5 Gy**

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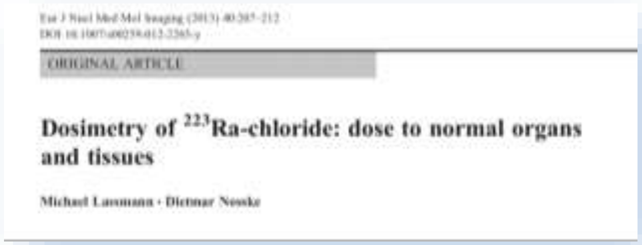
Dosimetry – ^{223}Ra

GI tract	Gy/Bq Alpha	Gy/Bq Beta/Gamma	Relative Beta/Gamma Contribution [%]
Oesophagus	3.2E-09	1.7E-10	5
St wall	3.2E-09	2.1E-10	6
SI wall	3.2E-09	3.9E-10	11
ULI wall	6.8E-09	1.4E-08	67
LLI wall	1.3E-08	4.0E-08	75
Colon	9.5E-09	2.5E-08	72
Kidneys	3.4E-09	2.4E-10	7
Liver	3.6E-08	1.5E-09	4
Muscle	3.2E-09	2.0E-10	6
Ovaries	3.2E-09	4.3E-10	12
Pancreas	3.2E-09	2.2E-10	6
Red marrow	7.2E-08	5.5E-09	7
Respiratory tract			
ET airways	3.2E-09	1.7E-10	5
Lungs	3.2E-09	1.9E-10	6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Radiation Protection

Measured removable contamination detection efficiencies and minimum detectable activities (MDA) of various 1 min integrated survey modalities for ^{223}Ra wipe tests.

			Minimum detectable activity	
Instrument	**Background (cpm)**	**Efficiency (cpm/dpm)**	**(dpm)**	**(Bq)**
Alpha Probe (Zinc Sulfide)[a]	0	0.08	71	1.2
Thin Window Beta/Gamma Probe (GM)[a]	28	0.13	350	5.8
Low Energy Gamma Probe (Sodium Iodide)[a]	94	0.29	1296	21.6
Liquid Scintillation Counter	49	0.97	64	1.1
Gamma Counter	210	0.40	333	5.6

[a]For wipe test evaluations in a fixed geometry at a distance of 0.32 cm.

Health Phys. 2014 April ; 106(4): 494–504. doi:10.1097/HP.0b013e3182a82b37.

RADIATION SAFETY CONSIDERATIONS FOR THE USE OF $^{223}RaCl_2$ DE IN MEN WITH CASTRATION-RESISTANT PROSTATE CANCER

Lawrence T. Dauer[*,†], Matthew J. Williamson[*], John Humm[*,†], Joseph O'Donoghue[*], Rashid Ghani[†], Robert Awadallah[†], Jorge Carrasquillo[†,‡], Neeta Pandit-Taskar[†,‡], Anne-Kirsti Aksnes[§], Colin Biggin[§], Vigdis Reinton[§], Michael Morris[**,††], and Jean St Germain[*]

Radiation Protection – Dose Rate (µSv h^{-1} MBq^{-1})

	50 kBq kg^{-1} Group		
Time post administration (h)	**0.0 m**	**0.3 m**	**1.0 m**
0	0.58 (0.77)	0.12 (0.32)	0.03 (0.18)
24	0.91 (0.95)	0.12 (0.16)	0.03 (0.06)
48	0.19 (0.24)	0.01 (0.06)	0.01 (0.02)
144	0.05 (0.11)	0.01 (0.05)	0.01 (0.03)

Health Phys. 2014 April ; 106(4): 494–504. doi:10.1097/HP.0b013e3182a82b37.

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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/cm^2, range: 0.01 - 0.6 Bq/cm^2) in the first 24 hours p.i.

- Contaminations in restrooms and kitchens were low (median: 0.021 Bq/cm^2, range: < DL - 0.35 Bq/cm^2)

- 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

Radiation Protection – Extremity Surveillance

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

Conclusions I

- Administering alpha emitters opens a promising path to a new treatment option for molecular targeted radiotherapy
- Ra-223-dichloride shows a benefit in survival in CRPC patients; it is administered on a per kg basis
- Measuring the biodistribution in patients is challenging due to the low activities administered and low emission probabilities of suitable photon energies
- For Ra-223 absorbed dose assessments still mostly rely on compartment modelling based on ICRP model

Conclusions II

- The RBE of treating systemically with alpha emitters is yet to be determined

- Normally, no radiation protection measures are needed beyond those needed for high-activity treatment with beta/gamma emitters.
  Further measures are to be considered only if the patient numbers handled by a single person exceed 25 -30

Thank you!

Data Sources for Risk Assessments for Alpha Emitters

Major Number of Treatments:

a) Spiess Cohort, „high dose“ treatment with ^{224}Ra (n=899)
b) Wick Cohort, „low dose“ treatment with ^{224}Ra (n=1588)
c) ALSYMPCA Trial with ^{223}Ra (n=614/921)

Other isotopes used for treatments were applied to few patients and without long-term follow-up

Cancer Induction – Spiess Cohort

RADIATION RESEARCH 174, 377–386 (2010)
0033-7587/10 $15.00

DOI: 10.1667/RR1955.1

Incidence of Malignant Diseases in Humans Injected with Radium-224

Elke Anna Nekolla,[a,1] Linda Walsh[a] and Heinz Spiess[b]

[a] BfS Federal Office for Radiation Protection, 85764 Neuherberg, Germany; and [b] Children's Hospital, University of Munich, 80336 Munich, Germany

- Cohort of 899 patients with several injections of ^{224}Ra between 1945 and 1955
- Patients were treated with high doses (mean bone surface dose: 30 Gy, mean specific activity: 0.66 MBq/kg)
- Almost all of those exposed during childhood or adolescence
- Treatment mainly for either TB (455 patients including 214 children and juveniles), especially bone TB, or AS (393 patients who were mostly male adults)
- The AS patients continued were treated in the late 1950s and in the 1960s with ^{224}Ra.