Dosimetry and patient treatment planning for TAT

Stig Palm

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Targeted Alpha Therapy group at the University of Gothenburg

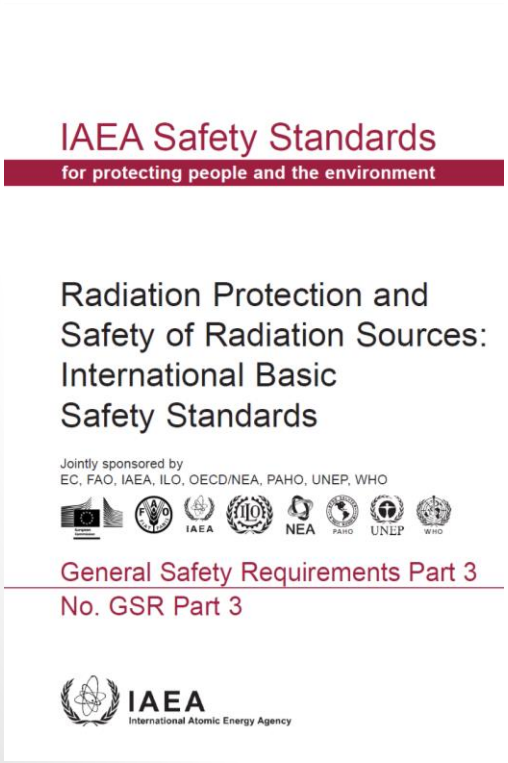
Why dosimetry?

- “probably does not correlate with biological effect; and definitely not with clinical outcome”
- “it’s too expensive”
- “field is immature”
- “no qualified staff”
- “low/no accuracy”
- “hinders developments of the field”

Boring answer:

- It's the law!

(but not necessarily enforced)

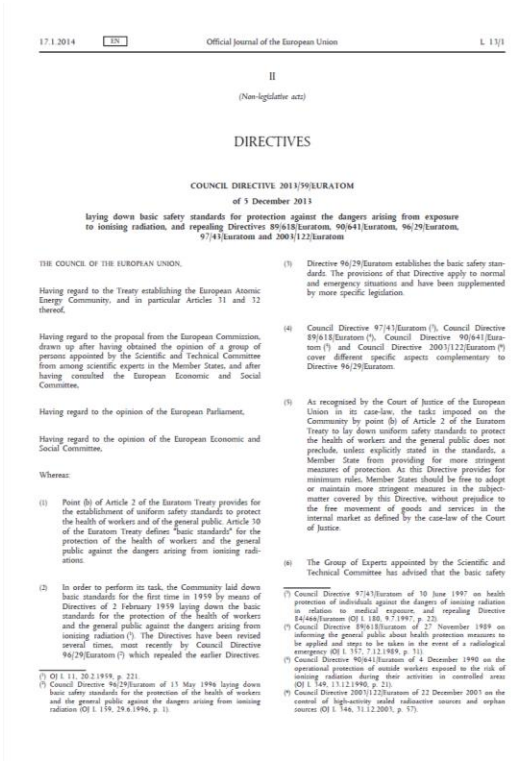

IAEA Safety Standards
for protecting people and the environment

Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards

Jointly sponsored by
EC, FAO, IAEA, ILO, OECD/NEA, PAHO, UNEP, WHO

General Safety Requirements Part 3
No. GSR Part 3

IAEA
International Atomic Energy Agency


17.1.2014 EN Official Journal of the European Union L 13/1

II

(Non-legislative acts)

DIRECTIVES

COUNCIL DIRECTIVE 2013/59/EURATOM

of 5 December 2013

laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Atomic Energy Community, and in particular Articles 31 and 32 thereof,

Having regard to the proposal from the European Commission, drawn up after having obtained the opinion of a group of persons appointed by the Scientific and Technical Committee from among scientific experts in the Member States, and after having consulted the European Economic and Social Committee,

Having regard to the opinion of the European Parliament,

Having regard to the opinion of the European Economic and Social Committee,

Whereas:

(1) Point (b) of Article 2 of the Euratom Treaty provides for the establishment of uniform safety standards to protect the health of workers and of the general public. Article 30 of the Euratom Treaty defines "basic standards" for the protection of the health of workers and the general public against the dangers arising from ionising radiations.

(2) In order to perform its task, the Community laid down basic standards for the first time in 1959 by means of Directives of 2 February 1959 laying down the basic standards for the protection of the health of workers and the general public against the dangers arising from ionising radiation (1). The Directives have been revised several times, most recently by Council Directive 96/29/Euratom (2) which repealed the earlier Directives.

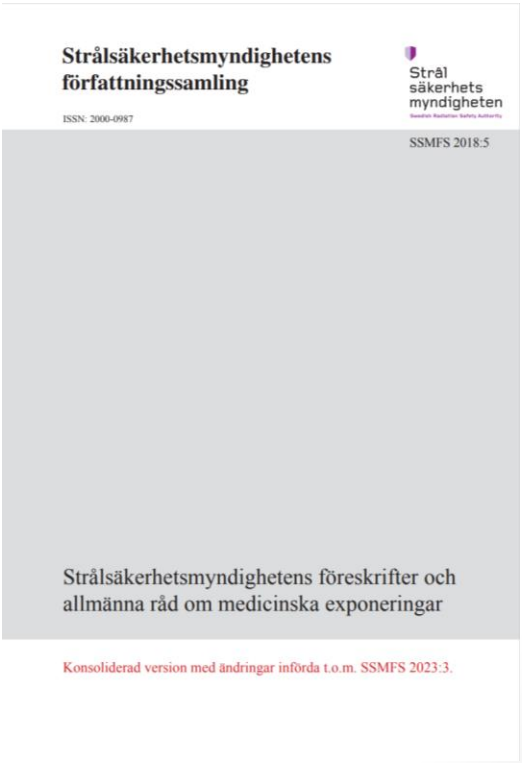
(3) Directive 96/29/Euratom establishes the basic safety standards. The provisions of that Directive apply to normal and emergency situations and have been supplemented by more specific legislation.

(4) Council Directive 97/43/Euratom (3), Council Directive 89/618/Euratom (4), Council Directive 90/641/Euratom (5) and Council Directive 2003/122/Euratom (6) cover different specific aspects complementary to Directive 96/29/Euratom.

(5) As recognised by the Court of Justice of the European Union in its case-law, the tasks imposed on the Community by point (b) of Article 2 of the Euratom Treaty to lay down uniform safety standards to protect the health of workers and the general public does not preclude, unless explicitly stated in the standards, a Member State from providing for more stringent measures of protection. As this Directive provides for minimum rules, Member States should be free to adopt or maintain more stringent measures in the subject-matter covered by this Directive, without prejudice to the free movement of goods and services in the internal market as defined by the case-law of the Court of Justice.

(6) The Group of Experts appointed by the Scientific and Technical Committee has advised that the basic safety

(1) OJ L 11, 20.2.1959, p. 221.
(2) Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionising radiation (OJ L 159, 29.6.1996, p. 1).
(3) Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionising radiation in relation to medical exposure, and repealing Directive 84/466/Euratom (OJ L 180, 9.7.1997, p. 22).
(4) Council Directive 89/618/Euratom of 27 November 1989 on informing the general public about health protection measures to be applied and steps to be taken in the event of a radiological emergency (OJ L 357, 7.12.1989, p. 31).
(5) Council Directive 90/641/Euratom of 4 December 1990 on the operational protection of outside workers exposed to the risk of ionising radiation during their activities in controlled areas (OJ L 349, 13.12.1990, p. 21).
(6) Council Directive 2003/122/Euratom of 22 December 2003 on the control of high-activity sealed radioactive sources and orphan sources (OJ L 346, 31.12.2003, p. 57).


Strålsäkerhetsmyndighetens författningssamling

ISSN: 2000-0987

Strål säkerhets myndigheten

SSMFS 2018:5

Strålsäkerhetsmyndighetens föreskrifter och allmänna råd om medicinska exponeringar

Konsoliderad version med ändringar införda t.o.m. SSMFS 2023:3.

Legal words:

Article 18

Education, information and training in the field of medical exposure

1. Member States shall ensure that practitioners and the individuals involved in the practical aspects of medical radiological procedures have adequate education, information and theoretical and practical training for the purpose of medical radiological practices, as well as relevant competence in radiation protection.

For this purpose Member States shall ensure that appropriate curricula are established and shall recognise the corresponding diplomas, certificates or formal qualifications.

Physician specialized in radiation oncology

Medical Physicist specialized in nuclear medicine

Legal words:

Article 56

Optimisation

1. Member States shall ensure that all doses due to medical exposure for radiodiagnostic, interventional radiology, planning, guiding and verification purposes are kept as low as reasonably achievable consistent with obtaining the required medical information, taking into account economic and societal factors.

For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

Each radionuclide treatment must be preceded by an individual adaptation of the radiation dose to the target volume, taking into account other exposed tissues.

Legal words:

Article 68
Tasks for the undertaking
Member States shall require the undertaking to carry out the following tasks:
(a) achieve and maintain an optimal level of protection of members of the public;
(b) accept into service adequate equipment and procedures for measuring and assessing exposure of members of the public and radioactive contamination of the environment;
(c) check the effectiveness and maintenance of equipment as referred to in point (b) and ensure the regular calibration of measuring instruments;

Article 56
Optimisation
4. Member States shall ensure that the optimisation includes the selection of equipment, the consistent production of adequate diagnostic information or therapeutic outcomes, the practical aspects of medical radiological procedures, quality assurance, and the assessment and evaluation of patient doses or the verification of administered activities, taking into account economic and societal factors.

Instruments and other equipment used for measurements that determines radiation dose to an individual patient must be calibrated with metrological traceability.

Calibrations, function checks and uncertainty analyzes must be carried out to the extent and with the periodicity needed to maintain metrological traceability.

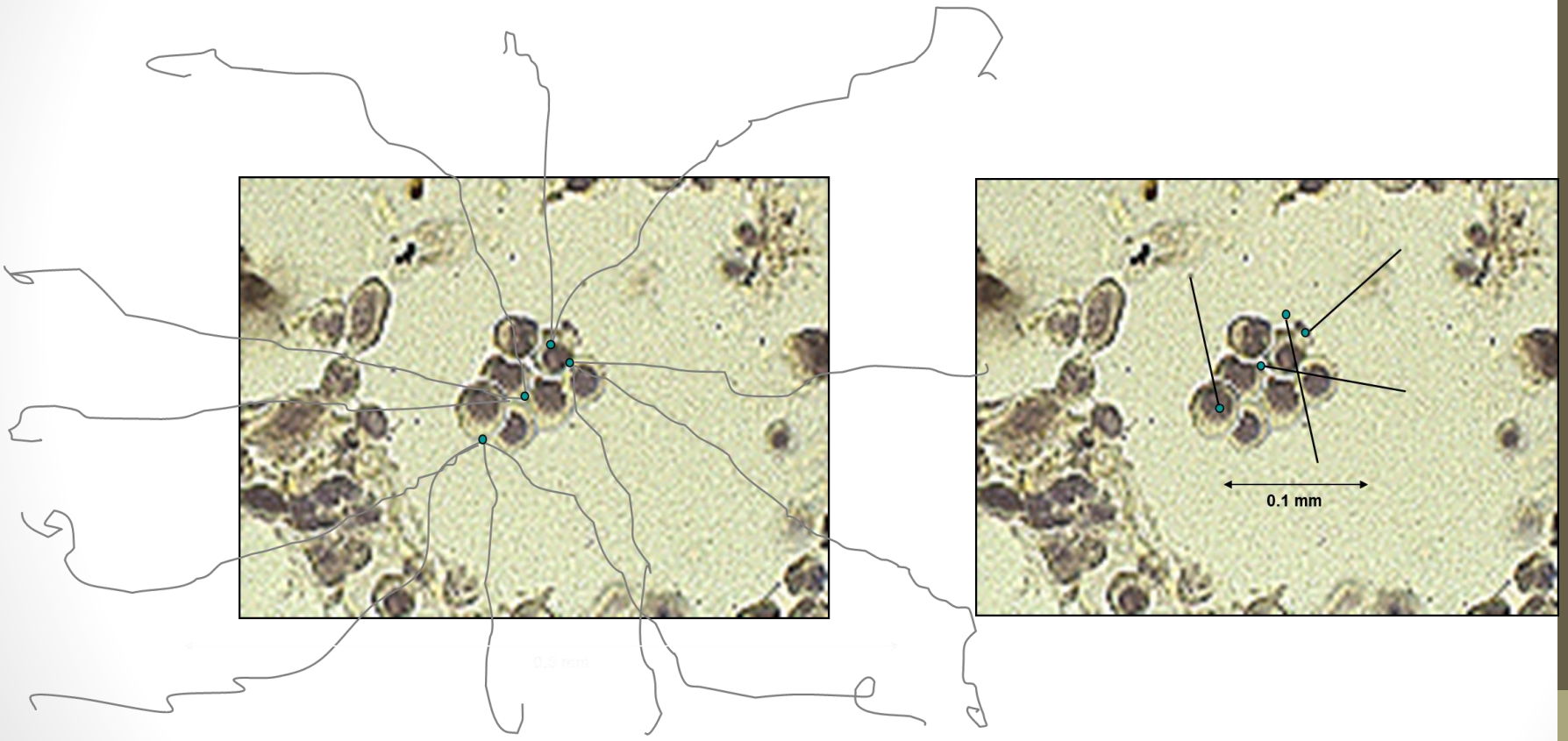
More interesting answer:

- It will benefit the patients!

(just ask your local radiation oncologist….)

Importance of range

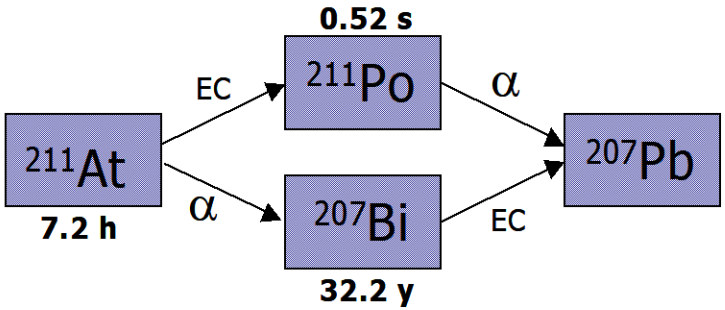
beta-emitters vs alpha-emitters

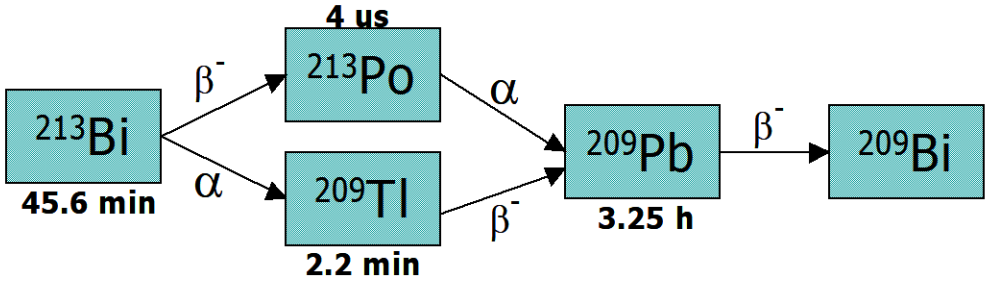


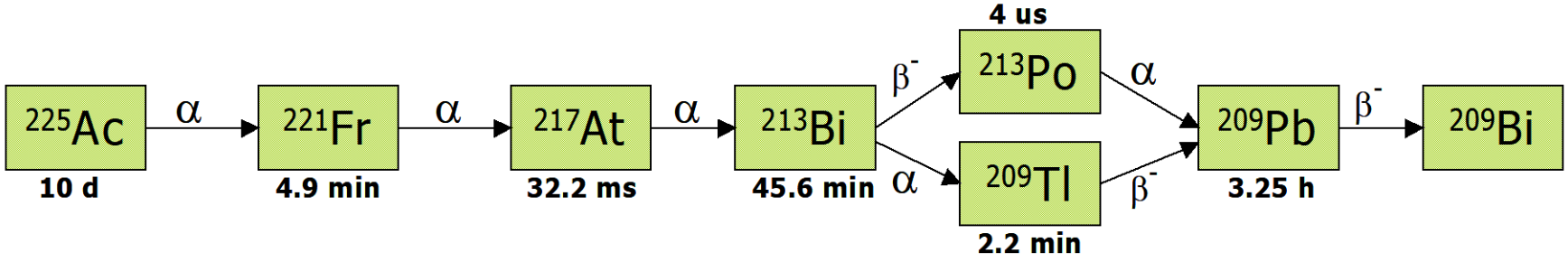
Alpha-particles

- Energy 4 - 8 MeV
- LET ~0.1 MeV/ µm
- Range ~70 µm
- z to cell nucleus per passage: ~0.2 Gy
  - cf electron: ~0.4 mGy
- RBE: 3-10

Some α-emitters







No dosimetry for ^{225}Ac-PSMA-617

Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study

Mike M Sathekge, Ismaheel O Lawal, Chandrasekhar Bal, Frank Bruchertseifer, Sajana Ballal, Giuseppe Cardaci, Cindy Davis, Mathias Eiber, Türkay Hekimsoy, Otto Knoesen, Clemens Kratochwil, Nat P Lenzo, Johncy Mahapane, Letjie C Maserumule, Amanda H Mdlophane, Kgomotso M G Mokoala, Honest Ndlovu, Vineet Pant, Hendrik Rathke, Janet Reed, Ishita B Sen, Aviral Singh, Ashwani Sood, Robert Tauber, Parul Thakral, Madhav Prasad Yadav, Alfred Morgenstern

Between Jan 1, 2016, and May 31, 2023, 488 men with mCRPC received 1174 cycles of ^{225}Ac-PSMA RLT

Study of patients with histologically diagnosed adenocarcinoma of the prostate gland who were treated with ^{225}Ac-PSMA RLT for mCRPC at seven centres in Australia, India, Germany, and South Africa.

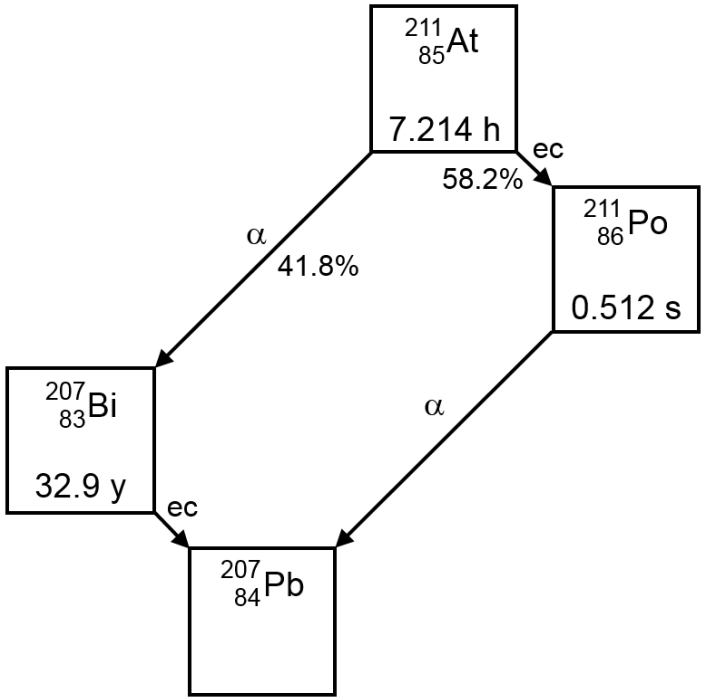
Patients included received 8 MBq of ^{225}Ac-PSMA RLT administered intravenously every 8 weeks until disease remission, disease progression, death, or patient withdrawal from treatment.

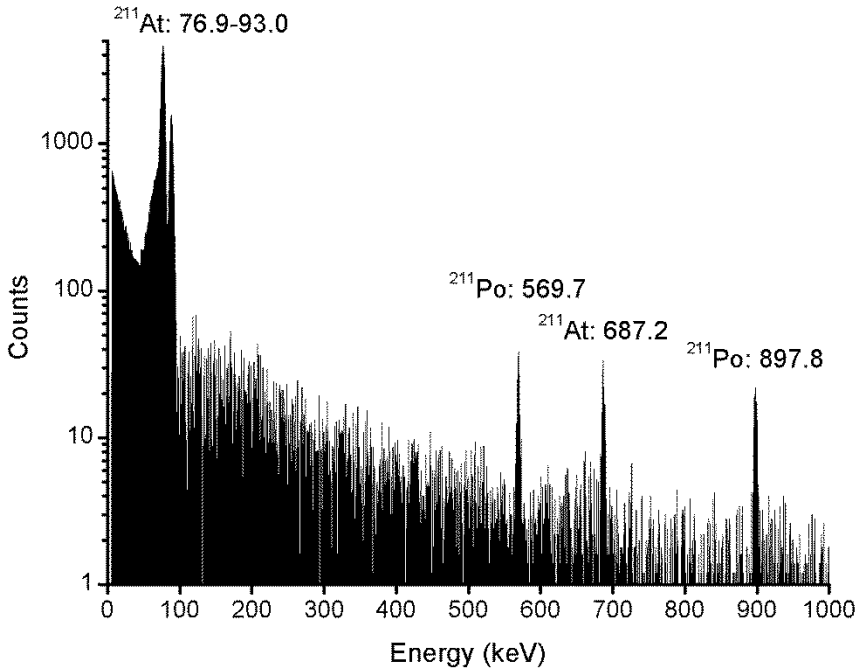
^{225}Ac-PSMA RLT is not an approved treatment for mCRPC and was administered on a compassionate use basis in patients with advanced progressive mCRPC based on local and national laws of the respective contributing centres.

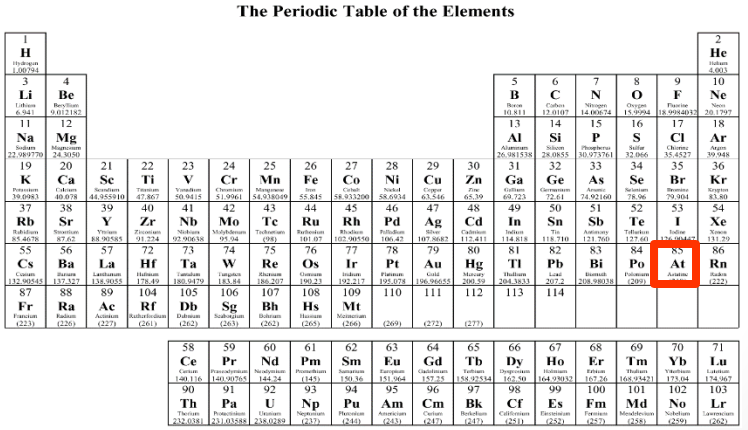
www.thelancet.com/oncology **Published online January 10, 2024 https://doi.org/10.1016/S1470-2045(23)00638-1**

^{211}At ($t_{1/2}$ = 7.21 h)

Particle	α_1	α_2 (from ^{211}Po)
E_α [MeV]	5.869	7.450
I [%]	41.8	58.2
LET [keV/µm]	106	122
R [µm]	48	70







www.nucleide.org

- Laboratoire National Henri Becquerel (LNHB, France)
- Physikalisch-Technische Bundesanstalt (PTB, Germany)
- Idaho National Engineering & Environmental Laboratory (INEEL, USA)
- Lawrence Berkeley National Laboratory (LBNL, USA)
- Khlopin Radium Institute (KRI, Russia)

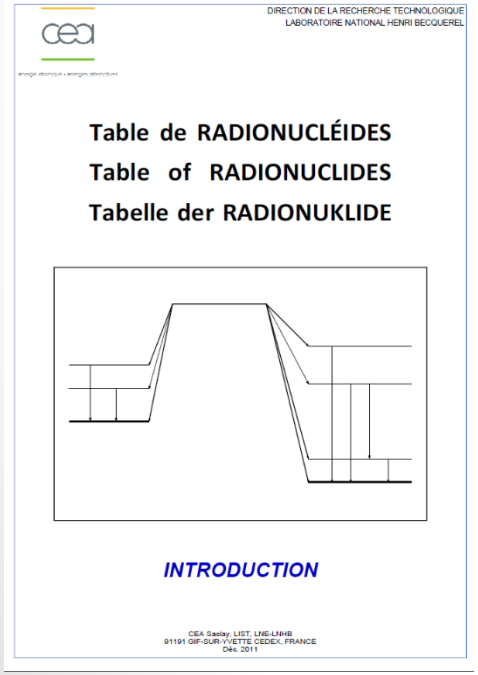

DIRECTION DE LA RECHERCHE TECHNOLOGIQUE
LABORATOIRE NATIONAL HENRI BECQUEREL

Table de RADIONUCLÉIDES
Table of RADIONUCLIDES
Tabelle der RADIONUKLIDE

INTRODUCTION

CEA Saclay, LIST, LNE-LNHB
91191 GIF-SUR-YVETTE CEDEX, FRANCE
Déc. 2011

Chapter 6

RULES FOR EVALUATION AND COMPILATIONS

Two main groups of data sources are used to obtain the recommended data:

- specific values evaluated from all available original publications,
- compiled data already evaluated by specialists (for example: Q-values), if a new experimental value exists, it may be taken into account. In this case, the corresponding reference is mentioned in the reference list of this radionuclide.

6.1 Rules for evaluation

All intermediate stages in the compilation and evaluation of a decay parameter are not presented in detail in order to avoid unnecessary complexity. The main stages comprise the following:

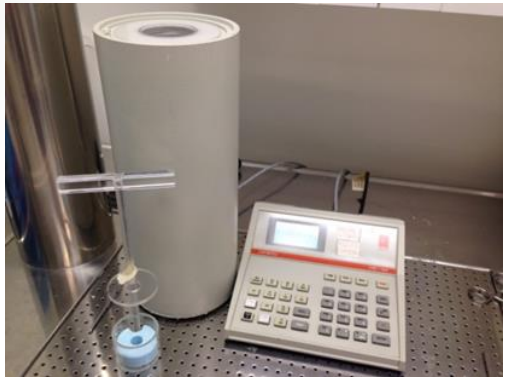
- critical analysis of published results and, if necessary, correction of these results to account for more recent values hitherto unavailable to the original experimentalists; as a rule, results without associated uncertainties are discarded, and the rejection of values is documented;
- data obtained through private communications are only used when there is no published article available;
- adjustments may be made to the reported uncertainties;
- only one result, generally the latest one, is taken into account per laboratory (or author);
- recommended values are derived from an analysis of all available measurements (or theoretical considerations), along with the standard deviations corresponding to the 1 σ confidence level.

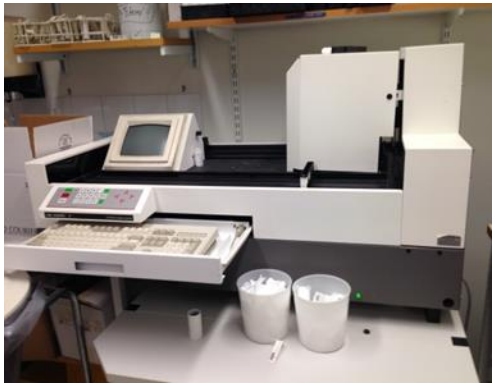
LNE-LNHB/CEA

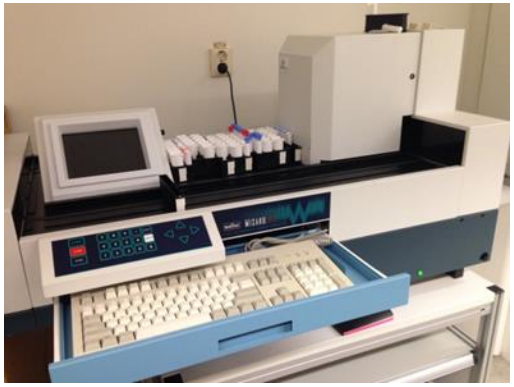
6.2 Gamma Emissions

	Energy keV	Photons per 100 disint.
$\gamma_{3,2}$(Bi)	149,72 (10)	~ 0,00005
$\gamma_{3,1}$(Bi)	222,69 (10)	~ 0,00004
$\gamma_{1,0}$(Bi)	669,77 (7)	0,0038 (3)
$\gamma_{1,0}$(Po)	687,2 (7)	0,245 (12)
$\gamma_{2,0}$(Bi)	742,74 (7)	0,00125 (19)
$\gamma_{3,0}$(Bi)	892,46 (7)	~ 0,00014

Cross-calibrations







Energy (keV)	Photons per 100 disint.
76.864	12.66 ± 0.09
79.293	21.08 ± 0.12
89.256 89.807 90.363	7.26 ± 0.12
92.263 92.618 92.983	2.26 ± 0.05

TABLE 1 Completed clinical studies using ^{211}At. (*NTC number*) is the ClinicalTrials.gov identifier.

Institution, Reference	Clinical situation	Nb. Pts.	Study Objective	TAT-agent	Target	Adminis-tration	Act-ivity	Toxicity/ effect
Duke University Medical Center, Durham, USA (9) (*NCT00003461*)	Recurrent surgically resected glioblastoma	18	Feasibility and safety	^{211}At-ch81C6	tenascin	Surgically created resection cavity	71–347 MBq	MTD, Not reached
Sahlgrenska University Hospital, Gothenburg, Sweden (8, 10–12) (*NCT04461457*)	Relapsed ovarian cancer	12	Safety, Toxicity Pharmacokinetics	^{211}At-MX35 F(ab')2	NaPi2b	Intra peritoneal	34–355 MBq	MTD, Not reached
Carl Gustav Carus University Hospital, Dresden, East Germany (7)	Recurrent carcinoma of the tongue	1	Palliation	^{211}At-labeled human serum albumin microspheres (15–25μm)	Tumor vasculature	Intra arterially (left lingual artery)	200 MBq	Tumor necrosis/ tongue necrosis
University of California Berkeley and San Francisco, USA (2)	Thyroid gland disorders	8	Tracer study	^{211}At	Na^+/I^- symporter (NIS)	Per oral in 25ml water	1.85 MBq	Thyroid uptake was established

TABLE 2 Ongoing and planned clinical trials with ^{211}At. (NTC number) is the ClinicalTrials.gov identifier.

Institution, reference	Clinical situation	Planned size (nb Pts.)	Study objective(s)	TAT-agent/ Carrier	Target	Primary outcome
Fred Hutchinson Cancer Center, Seattle, USA (*NCT04466475*)	Multiple Myeloma	24	Feasibility and safety	^{211}At-OKT10-B10	CD38	MTD
Fred Hutchinson Cancer Center, Seattle, USA (*NCT04579523*)	Multiple Myeloma	30	Dose escalation	^{211}At-OKT10-B10	CD38	MTD
Fred Hutchinson Cancer Center, Seattle, USA (*NCT04083183*)	HCT for non-malignant disease	40	Dose escalation	^{211}At- BC8-B10	CD45	Graft rejection
Fred Hutchinson Cancer Center, Seattle, USA (*NCT03670966*)	High-risk acute leukemia or MDS	30	Dose-escalation	^{211}At- BC8-B10	CD45	Toxicity
Fred Hutchinson Cancer Center, Seattle, USA (*NCT03128034*)	High-risk AML, ALL, MDS or Mixed-phenotype acute leukemia	50	Dose-escalation	^{211}At- BC8-B10	CD45	Toxicity, MTD
Osaka University Hospital, Suita, Japan (*NCT05275946*)	Thyroid cancer	11	To establish recommended dose for Phase II trial	[^{211}At] NaAt	NIS	Treatment-related adverse events
Fukushima Medical University, Japan	Malignant pheochromocytoma	Up to 18	Dose escalation	^{211}At-MABG	Norepinephrine transporter	Toxicity, MTD

HCT, Hematopoietic cell transplantation.

rontiers | Frontiers in Medicine

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SPONDENCE

Astatine-211 based radionuclide therapy: Current clinical trial landscape

Per Albertsson[1,2]*, Tom Bäck[3], Karin Bergmark[1,2], Andreas Hallqvist[1,2], Mia Johansson[1,2], Emma Aneheim[1,3], Sture Lindegren[3], Chiara Timperanza[3], Knut Smerud[4] and Stig Palm[3]

Logistics of the therapy

- **Preparations**
  - Laparoscopy
  - Peritoneal catheter insertion
  - Peritoneal scintigraphy with ^{99m}Tc
  - Pretreatment with $KClO_4$ or KI (Patient 6-12)

Infusion

- 1-2 L Extraneal solution
- 33-170 MBq ^{211}At-MX35F(ab')$_2$
- 0.2 MBq ^{125}I-albumin

- **Sampling**
  - Blood (1-48h)
  - I.p.fluid (1-24h)
  - Urine (1-48h)
  - Gamma camera (1-48 h)

Follow up

- Hematology
- TSH
- Creatinine
- HAMA

^{211}At administered to patients

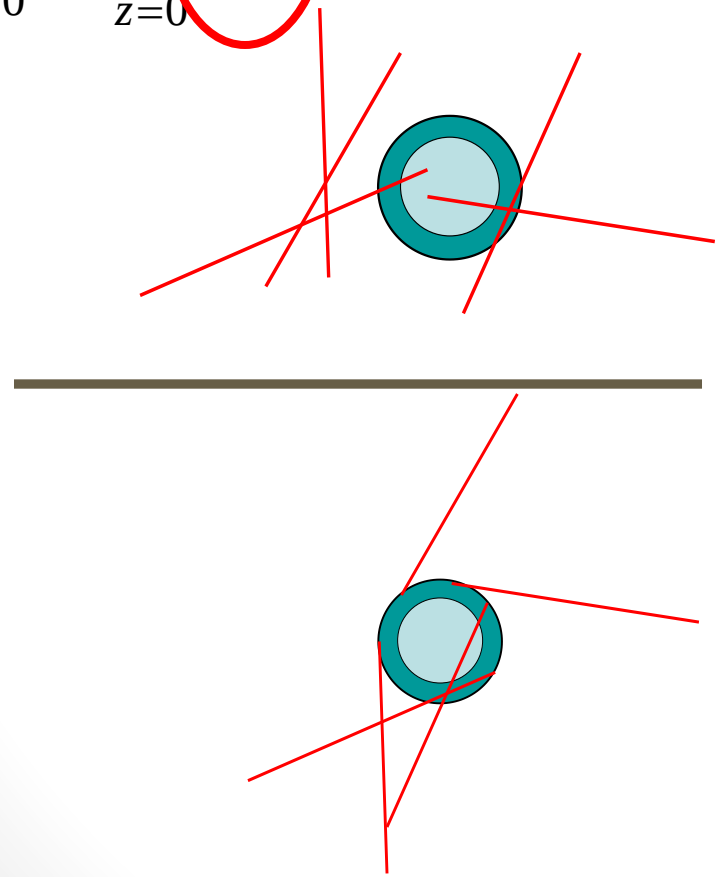
Pat. No.	Administered activity ^{211}At (MBq)	Infusate volume (L)	Initial ^{211}At-concentration (MBq L^{-1})	Specific activity (MBq mg^{-1})
1	34	1.5	22	61
2	48	2.0	24	105
3	40	2.0	20	81
4	42	2.0	21	212
5	92	2.0	46	69
6	103	2.2	47	83
7	119	1.2	101	-
8	83	1.1	73	64
9	65	1.2	53	50
10	297	1.7	180	293
11	333	1.6	203	624
12	355	1.7	215	743

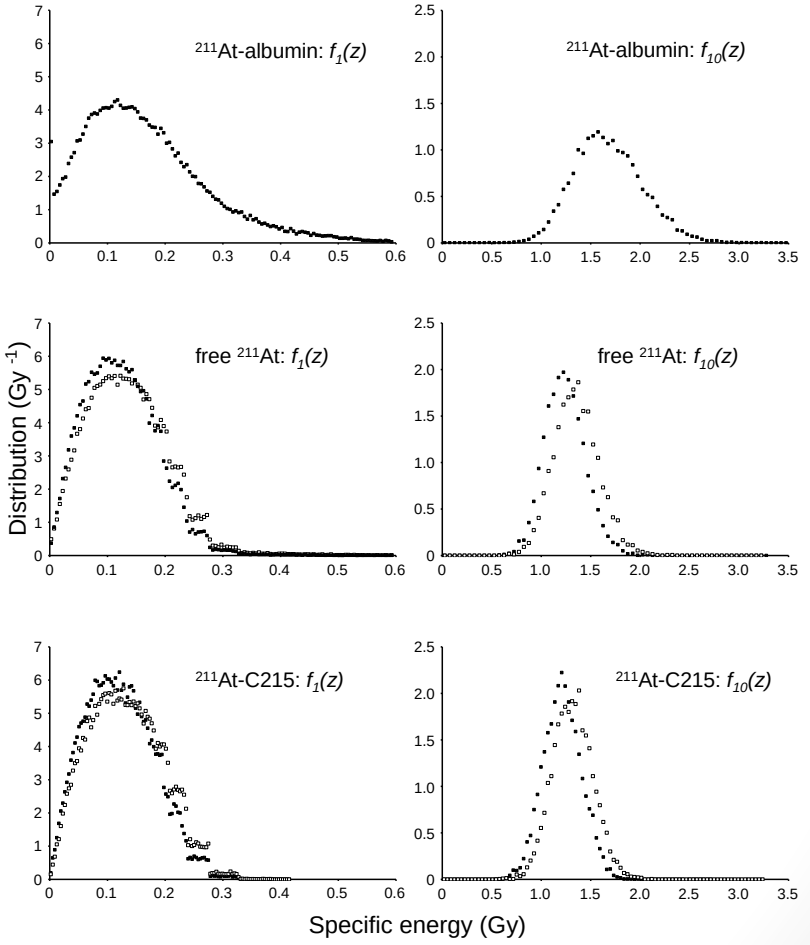
Decipher the information

- Immunohistochemistry
  - From +/+++ to # ag/cell
- Amount of radioactivity
  - # atoms
- ”Dose” of mAbs (mg)
  - # of mAbs
- Specific activity
  - How many mAbs carry a radionuclide
- Affinity constant (k_D)
  - On-rate and off-rate

From macro- to microdosimetry

$$S = \sum_{n=0}^{\infty} F_n \int_{z=0}^{\infty} f_n(z) e^{-z/z_{37}} dz$$





Monte Carlo simulations

random selection from weighted cell radii distribution

random placement of ^{211}At atom on cell surface

0.583 prob. of ^{211}Po branch

0.417 prob. of ^{207}Bi branch

select life-time *t* for ^{211}Po atom

generate distance *x* from eq. 5 for *t*

position ^{211}Po atom distance *x* from cell surface

random direction of α particle

if α particle enters cell nucleus, calculate for specific energy

Med Phys. 2004 Feb;31(2):218-25. doi: 10.1118/1.1640951.

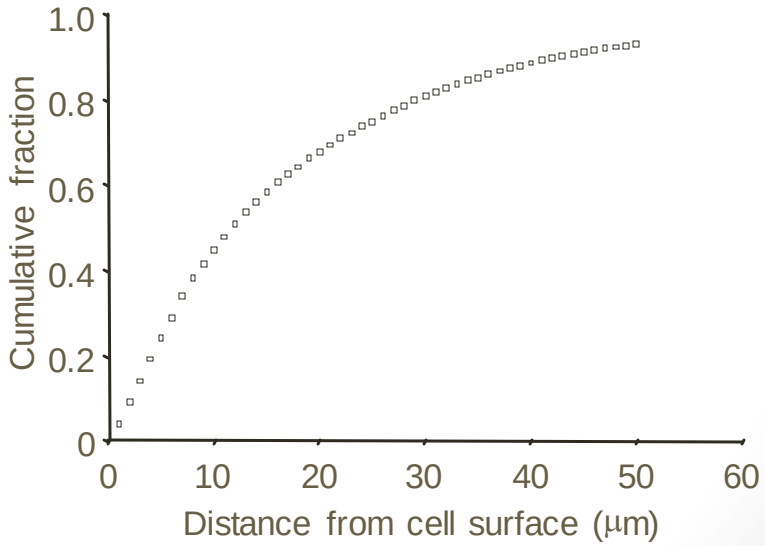
Microdosimetry of astatine-211 single-cell irradiation: role of daughter polonium-211 diffusion

Stig Palm [1], John L Humm, Robert Rundqvist, Lars Jacobsson

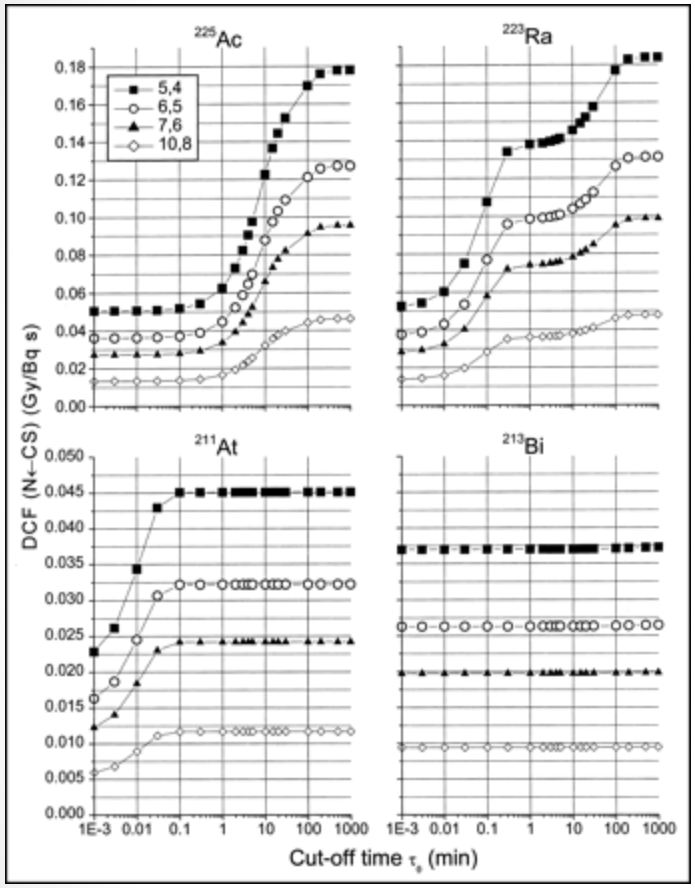
Affiliations + expand

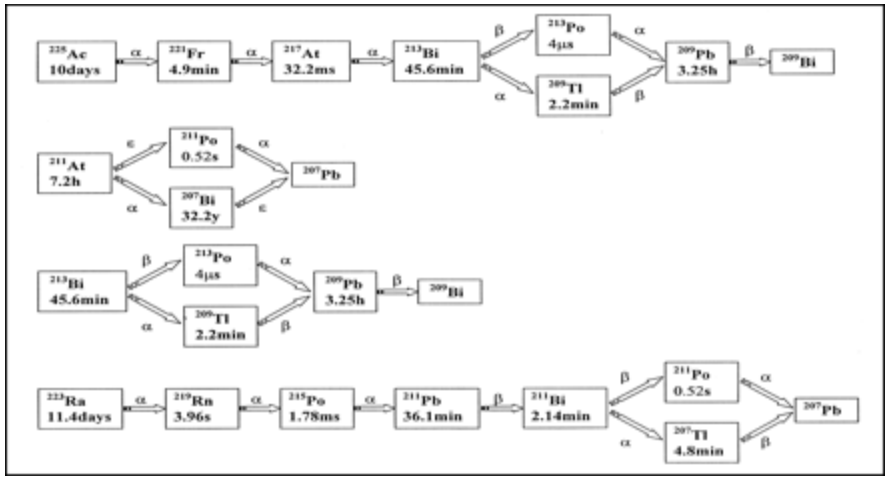
PMID: 15000607 DOI: 10.1118/1.1640951

$$\frac{d<x^2>}{dt} = 2kBT$$



Cellular dose conversion factors



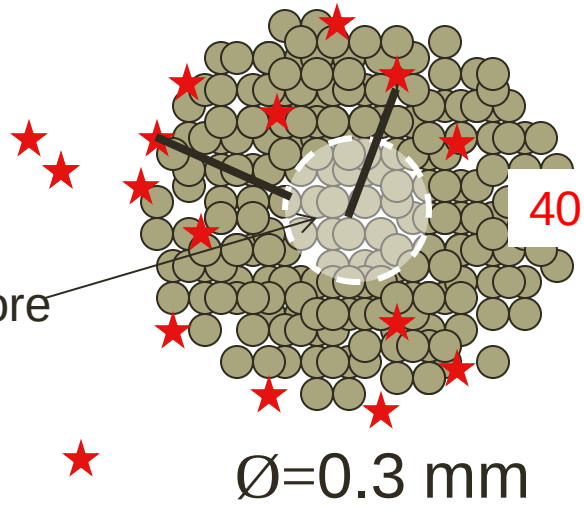


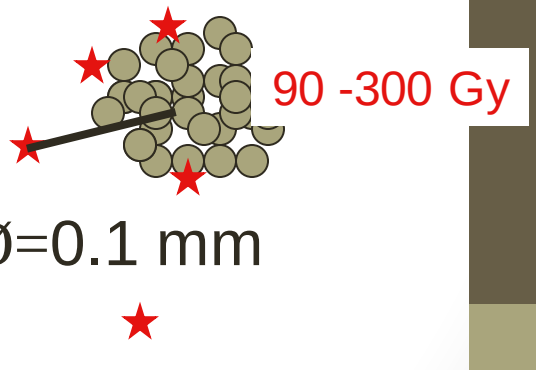
Hamacher et al, J Nucl Med 42 (8) 1216-21

Goddu et al, MIRD Cellular S Values Reston, VA: Society of Nuclear Medicine; 1997.

Microscopic tumors

- Outside (in the fluid)
- Binding only to surface cells
- Limited penetration
- Free diffusion (homogenous uptake)

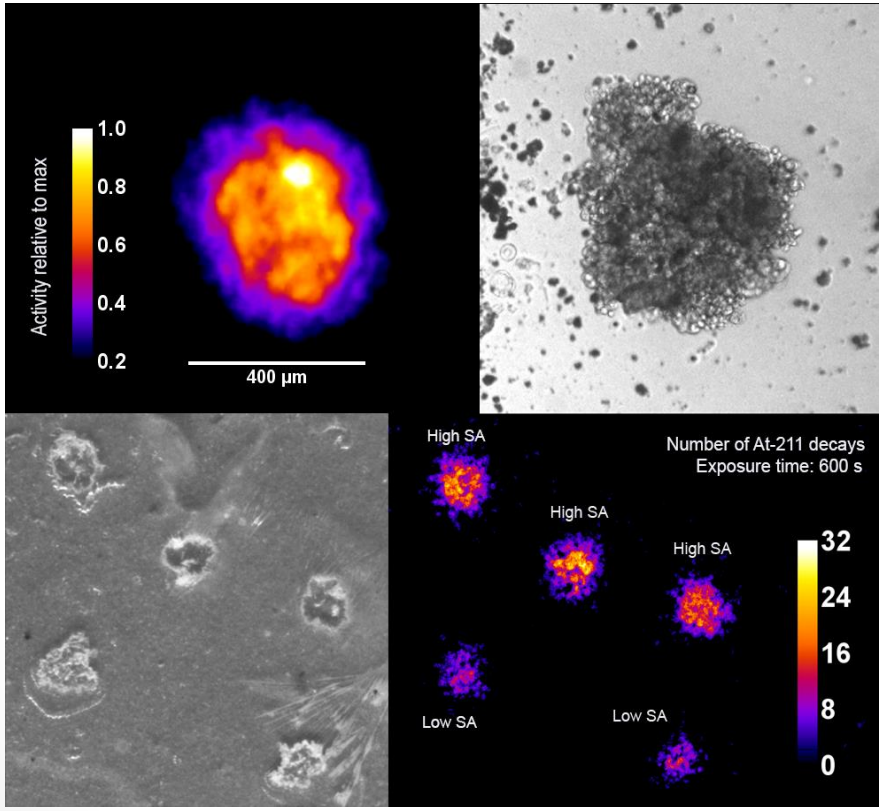


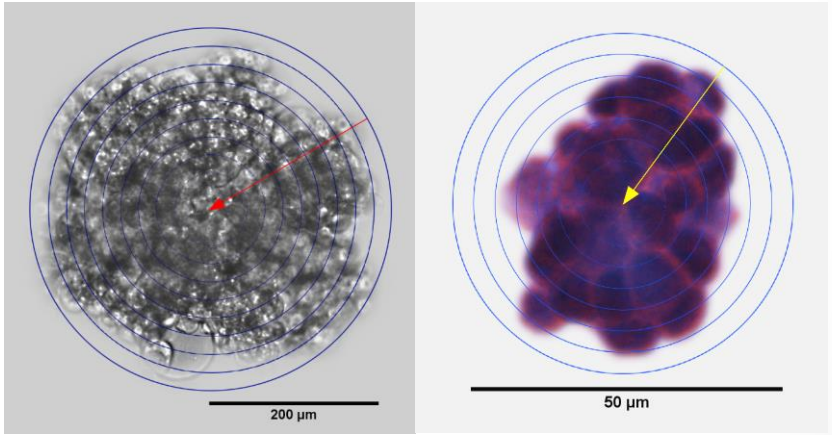


High mean absorbed doses
But tumor core (inside 70 µm) may not be irradiated

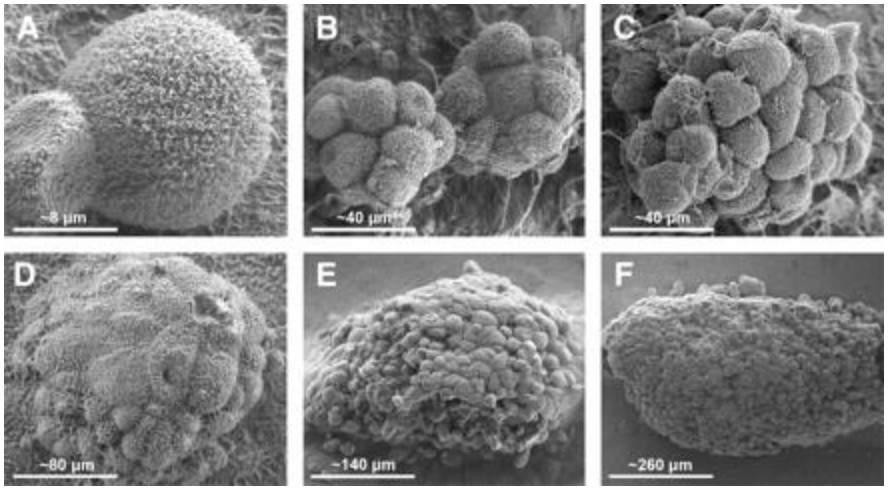
Peritoneum

Alpha imaging: ^{211}At-MX35-IgG on tumor spheroids





Tumor cell data



Elgqvist et al, J Nucl Med. 2006;47:1342-50

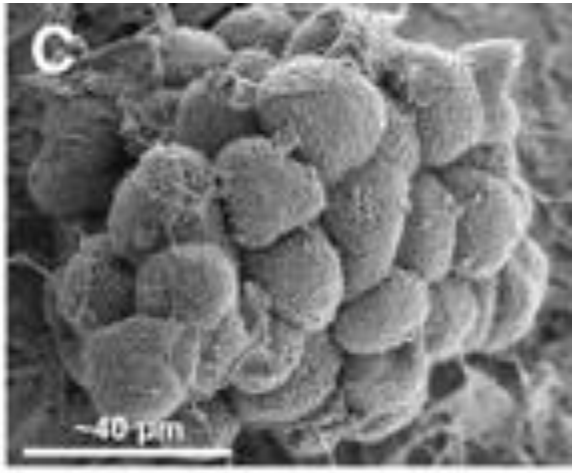
- Cell diameter = 18 µm
- Cell nucleus diameter = 14.4 µm
- Apparent equilibrium association constant, K_a = 44 000 $s^{-1}M^{-1}$
- B_{max} = 700 000 antigenic sites / cell

Tumor dose

- 300 MBq At-211
- 1.5 L Extraneal
- 1/800 ^{211}At-labelled mAb

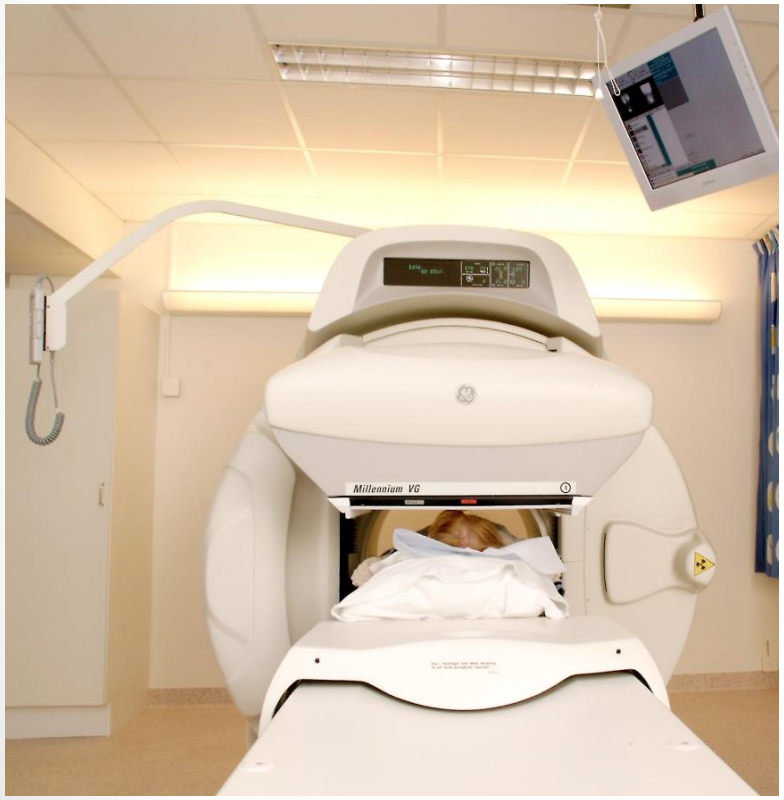
Ø = 90 mm

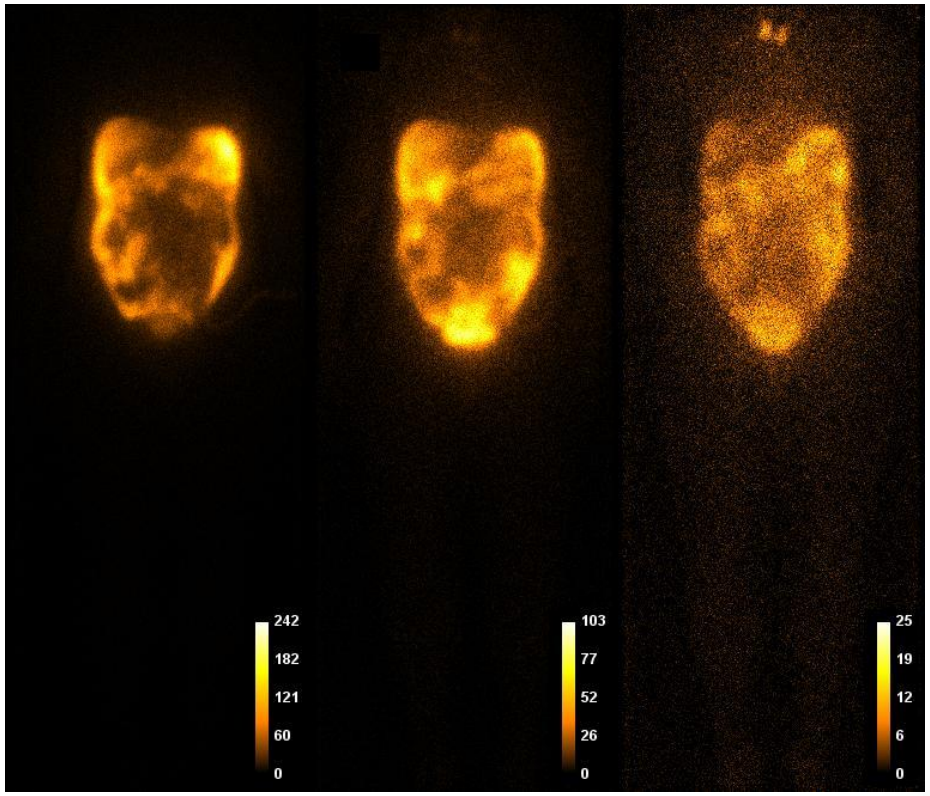
$D_{(r=0)}$ = 34 (+4) Gy
$D_{(r=9.45)}$ = 40 (+4) Gy
$D_{(r=18.9)}$ = 44 (+4) Gy
$D_{(r=28.4)}$ = 52 (+5) Gy
$D_{(r=37.8)}$ = 68 (+6) Gy



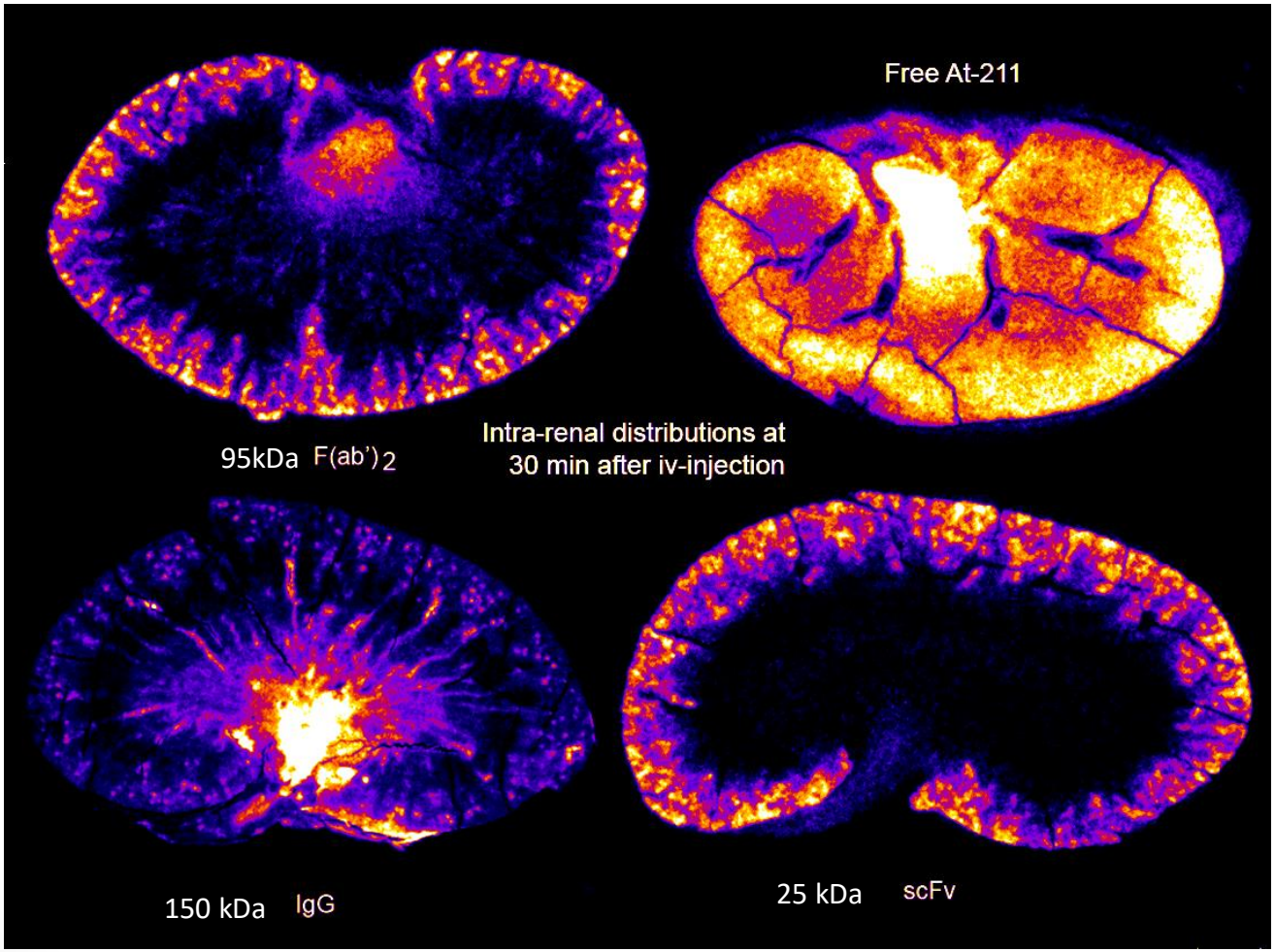
Elgqvist et al, J Nucl Med. 2006;47:1342-50

Gamma-camera imaging



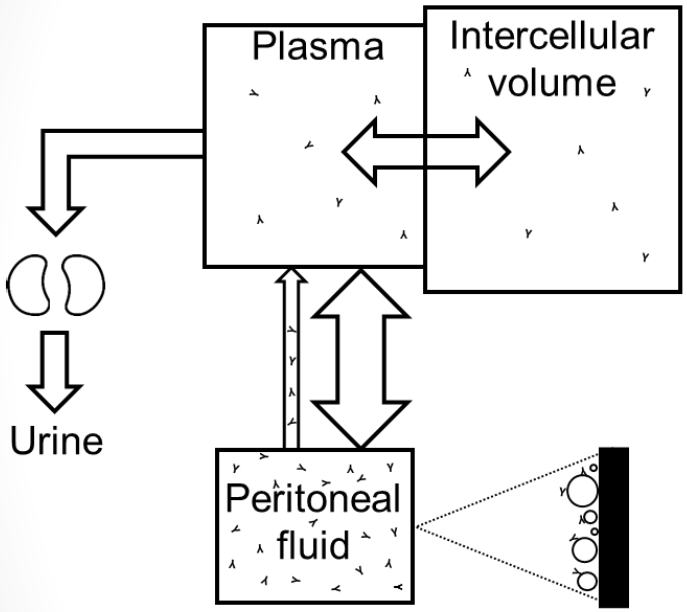


Alpha imaging: Activity distribution in mouse kidneys
Influence of molecular size of ^{211}At-labeled vectors



Measuring samples

Biokinetic model



Enlargement: mAbs on microtumors on the peritoneum

Fluid volumes	[L]	Comments	Reference
Plasma	2.3	36 mL/kg body weight	(*15*)
Distribution volume in tissue	5.9	91 mL/kg body weight	(*16*)
Administered i.p. fluid	1.7		
Residual i.p. fluid	0.2		

I.p. fluid transport	[mL/min]		
Lymphatic drainage			
I.p. fluid ⇒ plasma	0.3	Mean delay 5 h (±6 h; SD)	Model fit
Water reabsorption			
I.p. fluid ⇒ plasma	0.7	When >200 mL peritoneal fluid	Model fit
Water inflow at equilibrium			
I.p. fluid ⇐ plasma	0.3	When 200 mL peritoneal fluid	Model fit
Water inflow osmotic effect		Proportional to i.p. icodextran	Model fit
I.p. fluid ⇐ plasma		concentration 0–24 h	
	3.1–1.5		

MAb conjugate transfer coefficients	[h^{-1}]		
TER (plasma ⇔ intercellular volume)	0.065		(*17*)
Degradation/excretion (plasma ⇒ urine)	0.0096–0.03	Radiolabel dependent	Model fit

MAb binding parameters			
Association k_{on} [M^{-1} s^{-1}]			(*6*)
Ip fluid ⇒ tumor cell	44 000		
Dissociation k_{off} [s^{-1}]			(*6*)
Tumor cell ⇒ ip fluid	0		
Number of sites/cell	700 000		(*6*)

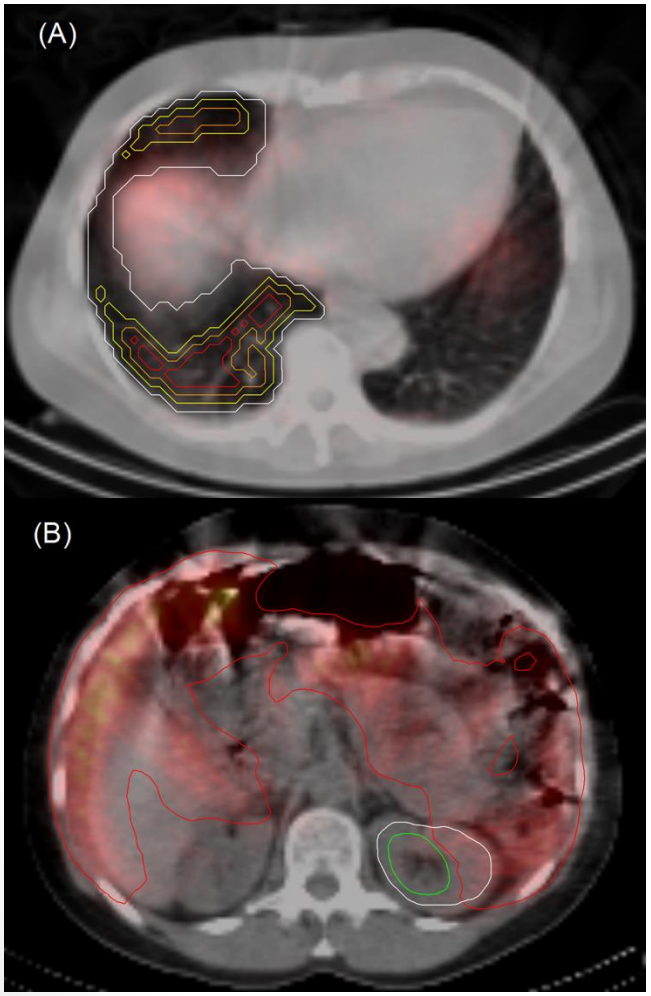
Dosimetric calculations

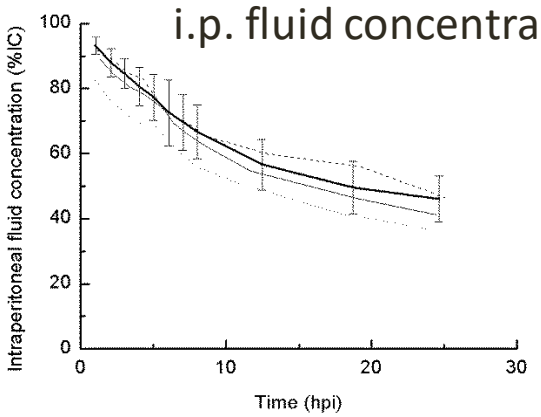
- Thyroid
  - Gamma-camera Uptake 0-24h
  - m = 20 g
- Peritoneum
  - I.p. concentration 0-24h
  - Half equilibrium dose
- Bone marrow
  - Blood concentration 0-48h
  - BM/Blood ratio = 0.32
- Urinary bladder wall
  - Urine data 0-48h
  - Half equilibrium dose
- Tumor (fictitious)
  - Biokinetic model + Monte Carlo
  - Tumor cluster, Ø = 0.1 mm

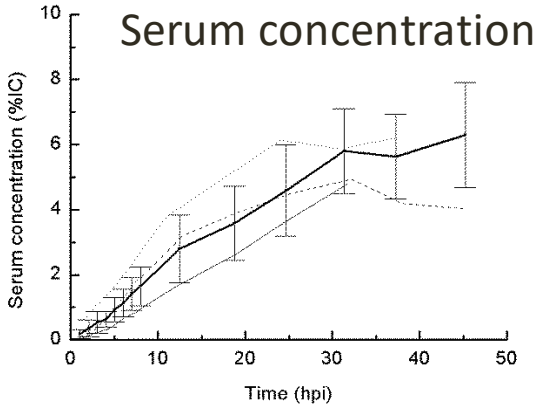
Dosimetry for risk assessment

Lower lungs

Kidneys







Effective dose estimate

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Physics Contribution

Absorbed Doses and Risk Estimates of ^{211}At-MX35 F(ab')$_2$ in Intraperitoneal Therapy of Ovarian Cancer Patients

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Table 4 Contributions to the radiation dose per MBq/L of ^{211}At-MX35 F(ab')$_2$ of icodextrin

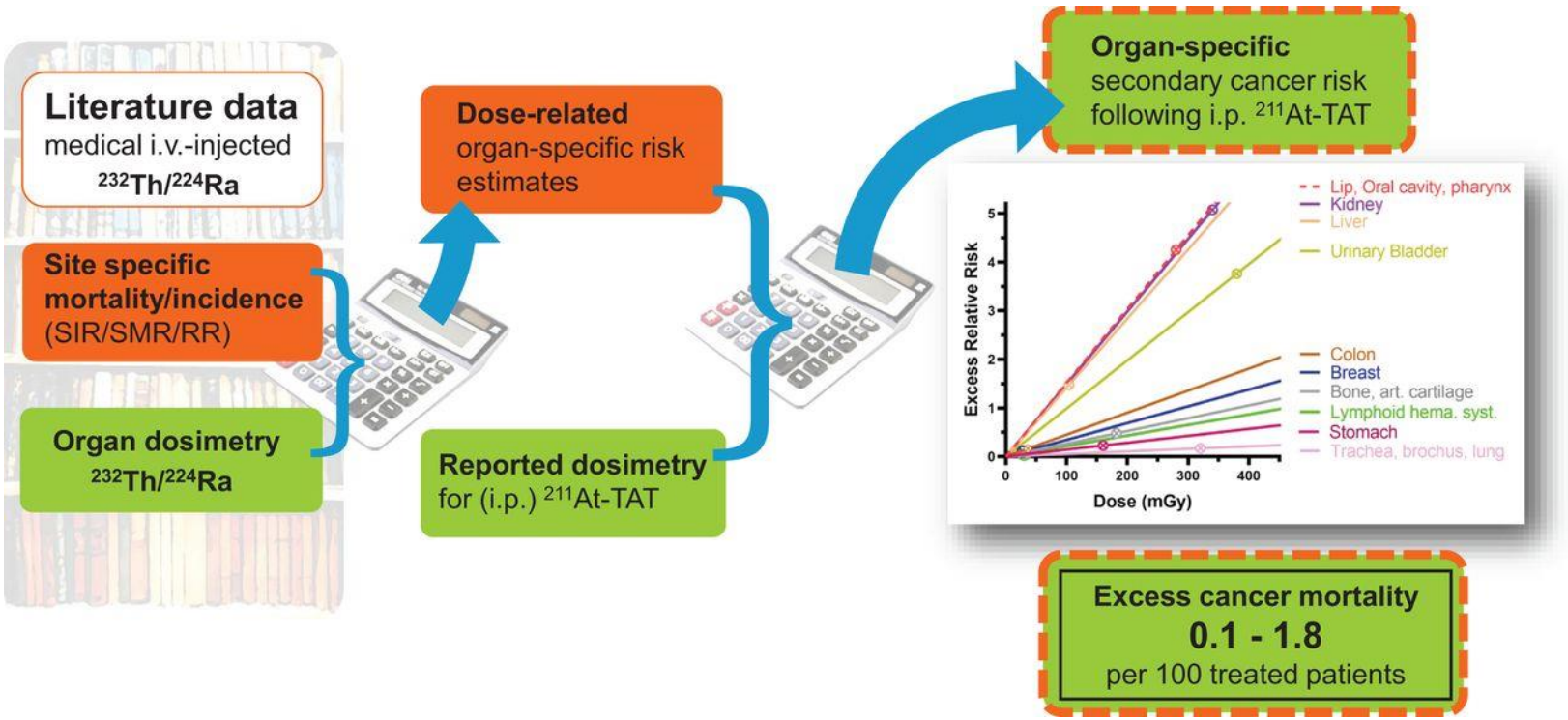
Organ	Absorbed dose from photons (mGy)	Absorbed dose from α particles (mGy)		Equivalent dose (mSv) (RBE = 5)	Tissue-weighting factor	Contribution to effective dose (mSv)
		Clinical data	Mice*			
RBM	<0.005	0.15		0.75	0.12	0.35
Colon	0.01		0.18	0.91	0.12	0.42
Lungs	0.01	1.6		8.0	0.12	3.7
Stomach	0.02		0.80	4.0	0.12	1.9
Breasts	<0.005	0.14		0.70	0.12	0.32
Urinary bladder	0.01	1.9		9.5	0.04	1.5
Esophagus	<0.005†	0.91‡		3.0	0.04	0.73
Liver	0.01	0.52		2.6	0.04	0.42
Thyroid	<0.005	1.8		9.0	0.04	1.4
Bone surfaces	<0.005	0.91‡			0.01	0.18
Brain	<0.005	0.91‡			0.01	0.18
Salivary glands	<0.005†		1.4	7.0	0.01	0.30
Skin	<0.005	0.91‡			0.01	0.18
Remainder tissues						
Adrenals	0.01					
ET region						
Gallbladder						
Heart	0.01	1.2		6.0		
Kidneys	0.01	1.7		8.5		
Lymph nodes						
Muscle	<0.01		0.11	0.55	0.12	1.6
Oral mucosa						
Pancreas	0.03					
Small intestine	0.01		0.25	1.3		
Spleen	<0.01	1.3		6.5		

Abbreviations: RBM = red bone marrow; ET = Extrathoracic.

* Data from reference Bäck T et al (26).

† Assuming that the photon contribution for esophagus and salivary glands is equal to that of the thyroid.

‡ Assuming that the α contribution to esophagus, bone surfaces, brain, and skin is equal to the mean result of evaluated "remainder tissues."



Erik Leidermark et al. J Nucl Med 2023;64:165-172

Conclusions

- Imaging is possible
- Dosimetry is possible
- Model for minimal residual disease

…some final words

The use of α-emitters provides the perfect stimulus to the medical dosimetry community to fully embrace new advances in molecular biology and in vivo microimaging and to redefine and expand its role and function as it seeks improved methods for predicting biologic response…

(W. Bolch: α-Particle Emitters in Radioimmunotherapy: New and Welcome Challenges to Medical Internal Dosimetry, JNM 2001 42:1222-1224)