Dosimetry in management of thyroid carcinoma with I-124 PET/CT

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Contents

What is Nuclear Medicine Therapy Dosimetry

What is Dosimetry?

Medical dosimetry is the calculation of absorbed dose and optimization of dose delivery in radiation therapy. It is often performed by a professional health physicist with specialized training in that field.

- ❑ **External beam**
- ❑ **Radionuclide therapy**

Nuclear Medicine Therapy Dosimetry

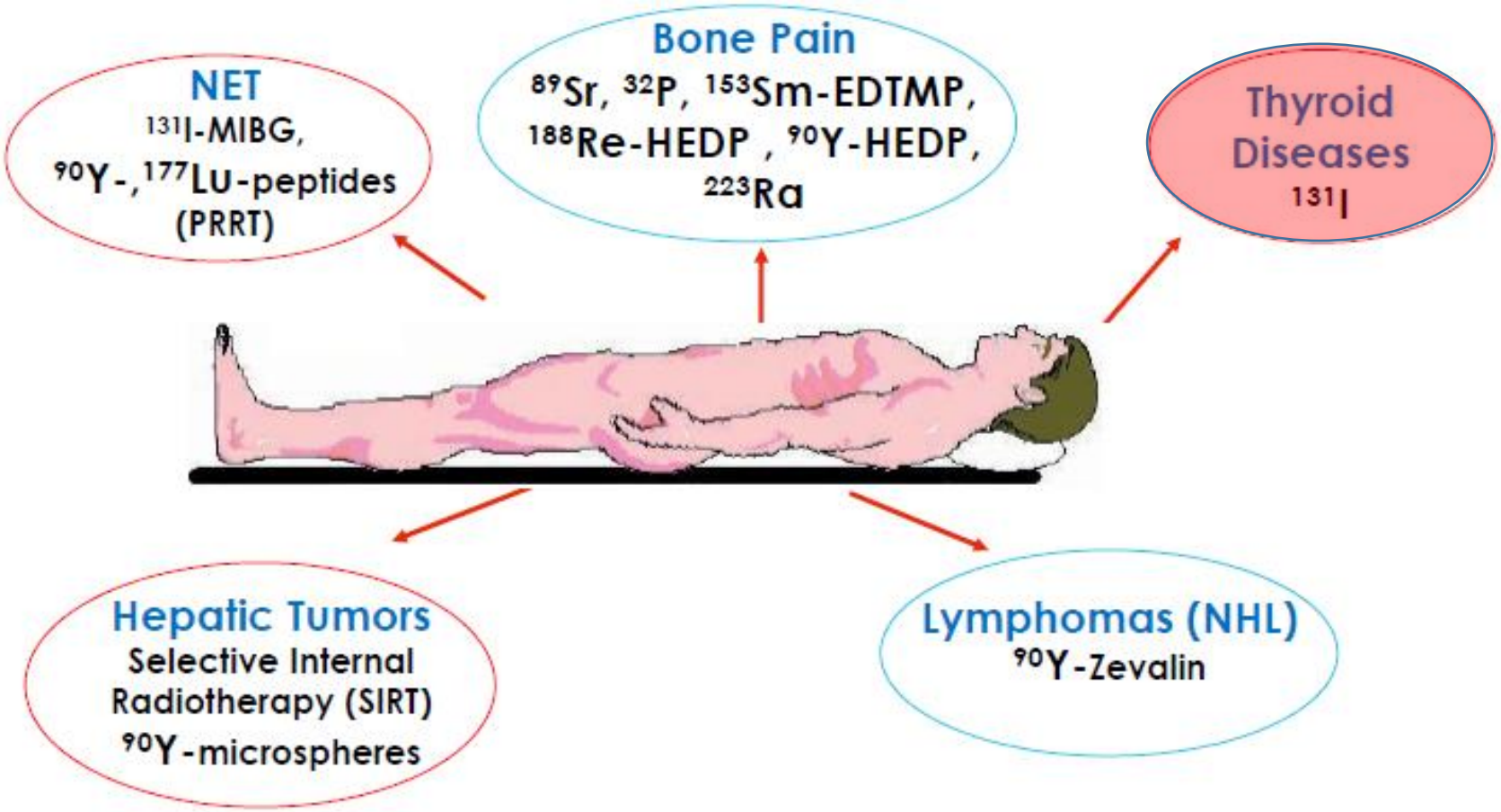
The ability to collect pharmacokinetic data by imaging and use this to perform dosimetry calculations for treatment planning.

- ❑ **Radionuclide Resident time to the target organ.**
- ❑ **The Blood Dosimetry technique Maximum Tolerate Activity (MTA) provides an effective means of treatment in patients who failed to respond adequately to conventional fixed activity therapy.**
- ❑ **As High As Safety Attainable (AHASA) introduced by European Association of Nuclear Medicine in its procedural guidelines.**
- ❑ **To avoid Deterministic Effect.**

Internal dosimetry : different purposes → different levels of accuracy:

- Dosimetry for **diagnostic** procedures utilized in nuclear medicine;
  - Large population
  - Stochastic Effect
- Dosimetry for **therapeutic** procedures (radionuclide therapy);
  - Individual
  - Deterministic Effect
- Dosimetry in conjunction with **accidental intake** of radionuclides.
  - Individual
  - Deterministic Effect

Dosimetry Role in Radionuclide Therapy



Milestones I131 Therapy Dosimetry

- The radiation dose estimates from internal sources of radioactivity for thyroid organ was introduce by Marinelli and Quimby (1948)
- The introduction of maximum safe limit dose (less 2 Gy) into Bone Marrow from I-131 therapy proposed by Benua et al., (1962)
- Benua et al., (1986) a whole-body retention threshold of 2.96 GBq (80 mCi) at 48 h has been used to limit the radioactivity of 131I administered to thyroid cancer patients with diffuse pulmonary metastases.

Clinical Impact

The "Holy Gray"…

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-014-2824-5

REVIEW ARTICLE

2014

The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy

Lidia Strigari · Mark Konijnenberg · Carlo Chiesa · Manuel Bardies · Yong Du · Katarina Sjögreen Gleisner · Michael Lassmann · Glenn Flux

"…the **evidence strongly implies** a correlation between the absorbed doses delivered and the response and toxicity, indicating that dosimetry-based personalized treatments would improve outcome and increase survival…"

Dosimetry that works (1)

Eur J Nucl Med Mol Imaging (2011) 38:673–680
DOI 10.1007/s00259-010-1689-5

ORIGINAL ARTICLE

The absorbed dose to the blood is a better predictor of ablation success than the administered ^{131}I activity in thyroid cancer patients

Frederik A. Verburg · Michael Lassmann · Uwe Mäder · Markus Luster · Christoph Reiners · Heribert Hänscheid

Blood absorbed doses > 350 mGy
n=144, successful ablation: 63.9%

Blood absorbed doses < 350 mGy
n=305, successful ablation: 3.1%

- p=0.03

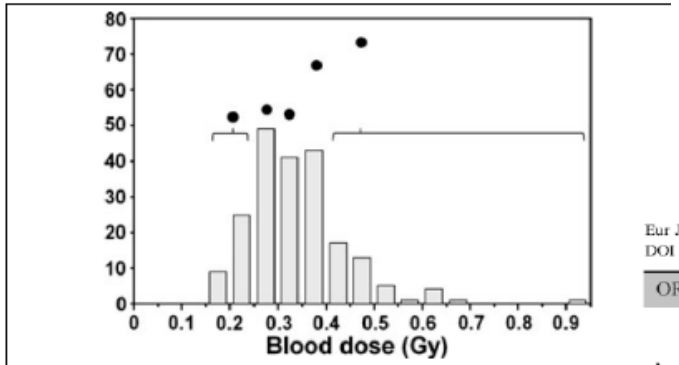


Fig. 2 Distribution of blood doses in 209 patients receiving therapeu activities of 3.5 GBq ± 5%. The ordinate shows both numbers of patie and percentage of successful ablation (*filled dots*) in five blood d intervals

Dosimetry that works (2)

Eur J Nucl Med Mol Imaging (2010) 37:270–275
DOI 10.1007/s00259-009-1261-3

ORIGINAL ARTICLE

A dose-effect correlation for radioiodine ablation in differentiated thyroid cancer

Glenn D. Flux · Masud Haq · Sarah J. Chittenden · Susan Buckley · Cecilia Hindorf · Kate Newbold · Clive L. Harmer

- Maximum voxel absorbed dose to thyroid remnants for complete ablation: 99±128 Gy.
- Patients with persistent uptake: absorbed doses of 25±17 Gy

t-test: p=0.030

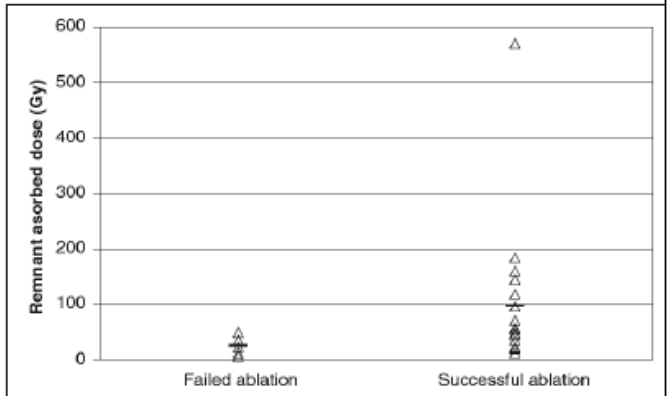


Fig. 3 Patient response as a function of maximum absorbed dose to the thyroid remnant. The *horizontal bars* indicate the mean values (25 Gy for failed ablation and 99 Gy for successful ablation)

THE MEDICAL INTERNAL RADIATION DOSE FORMALISM

Basic concepts

The absorbed dose D to a target region from activity in a source region is calculated as the product between the time-integrated activity $\tilde{A}$ and the S value

$$D = \tilde{A} \times S$$

gray (Gy)
(1 J/kg = 1 Gy)

absorbed dose
OAR

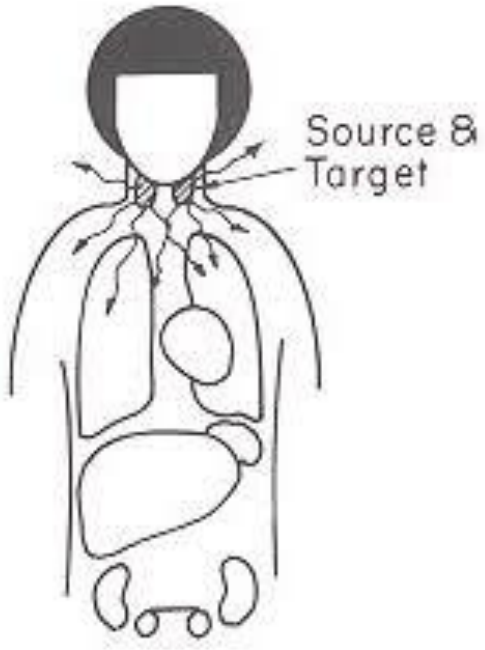
becquerel · s

cumulated activity: decays that take place in a certain source region **SERIAL IMAGE**

$Gy \cdot (Bq \cdot s)^{-1}$
often $mGy \cdot (MBq \cdot s)^{-1}$

absorbed dose rate per unit activity, or absorbed dose per cumulated activity (or absorbed dose per decay) **OLINDA**

MIRD Concept



^{131}I -Iodide

The source region is denoted r_S and the target region r_T:

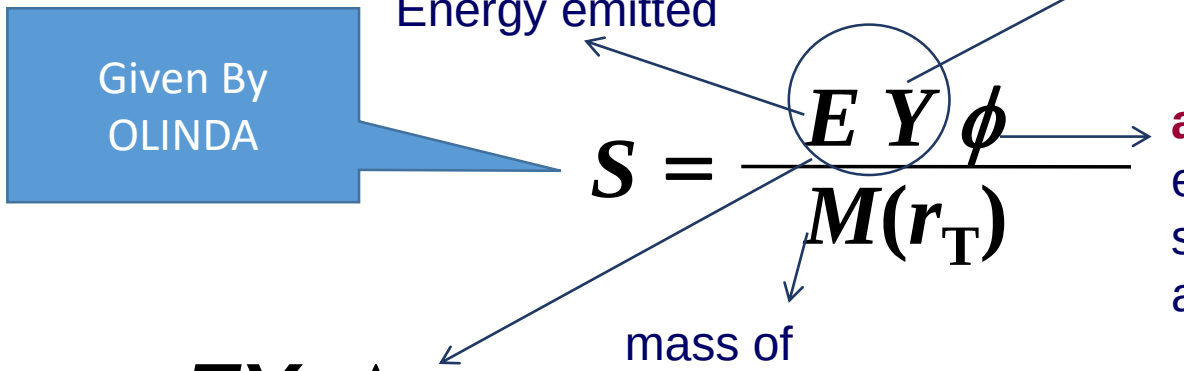
$$D(r_T) = \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S)$$

or, in case of several source regions:

$$D(r_T) = \sum_S \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S)$$

THE MEDICAL INTERNAL RADIATION DOSE FORMALISM

Basic concepts



depends on the **shape, size and mass** of the source and target regions, the **distance** and **type** of material between the source and the target regions, the **type of radiation** emitted from the source and the **energy** of the radiation

Internal Dosimetry in Therapy

Possible if

- ❑a relationship between lesion response and absorbed dose exist,
- ❑toxicity of the organs at risk can be predicted,
- ❑a solid “macro” dosimetry methodology exist,
- ❑pre-therapy and intra-therapy kinetics are similar,
- ❑time and effort are acceptable
- ❑a therapeutic benefit is expected

IKN Experiences

- I-124 Internal Dosimetry (MTA, LdpA) since July 2015
  - 68 procedures
    - 26 pts x1
    - 16 pts 2x
    - 2 pts 3x
    - 1 pts x4
- I-131 Internal Dosimetry (MTA) since Feb 2017
  - 8 procedures
- Wide inter-patient and intra-patient variability in the LDpA, therefore dosimetry must be done before each treatment.
- There is intra-patient variation in MTA, reducing MTA.
- Bone marrow suppression up to 8 week post I-131 therapy.

Any Different between I124/I131?

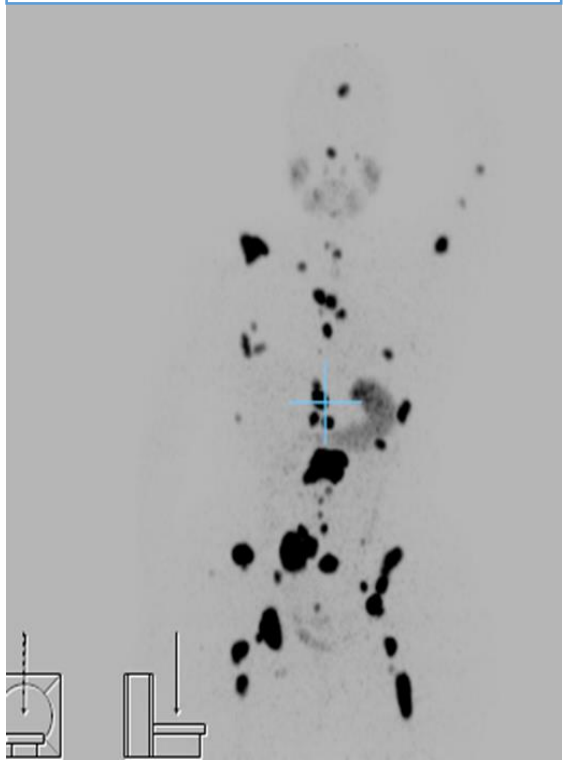
Nucl Med Commun. 2018 May;39(5):457-464. doi: 10.1097/MNM.0000000000000817.

Pretherapeutic 124I dosimetry reliably predicts intratherapeutic blood kinetics of 131I in patients with differentiated thyroid carcinoma receiving high therapeutic activities.

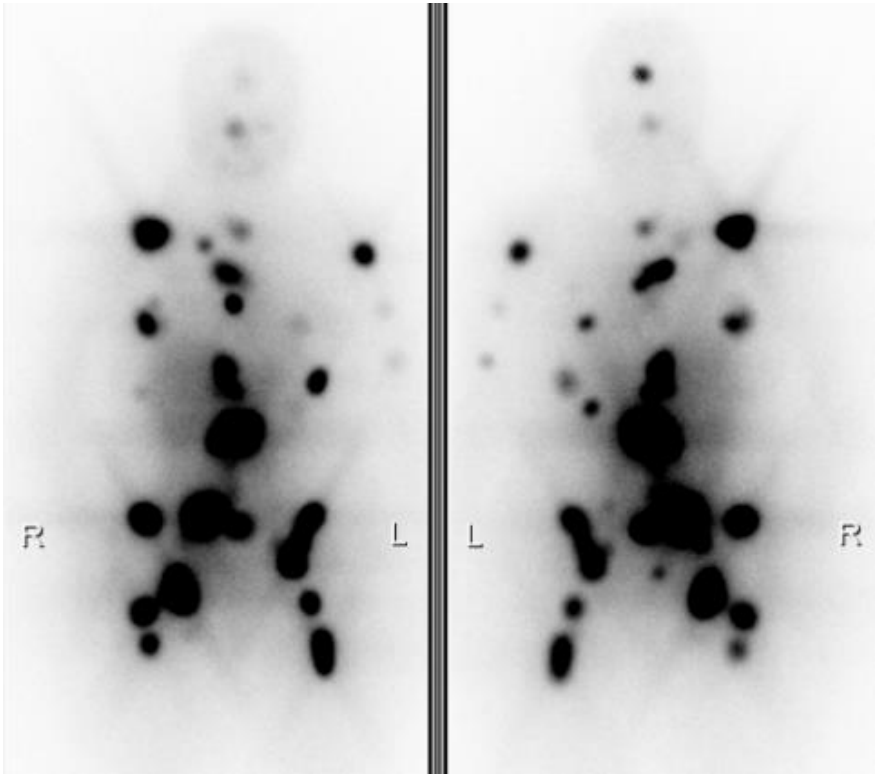
Ruhlmann M[1,2], Sonnenschein W[1], Nagarajah J[1,3], Binse I[1], Herrmann K[1], Jentzen W[1].

Author information

I-124 Dosimetry



131 I WBS



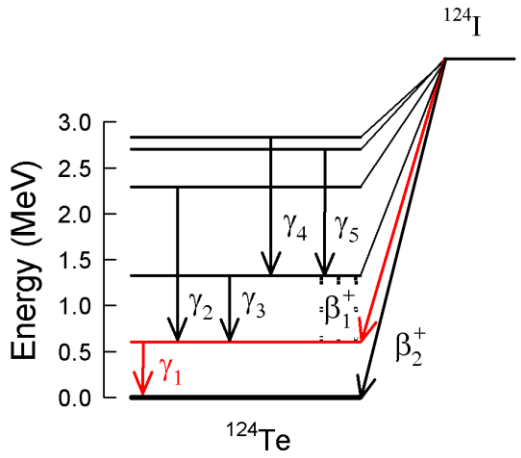
Iodine-124 is an ideal tracer for pre-therapy dosimetry

Radioiodine isotopes (half-life)	^{123}I (0.55 d)	^{124}I (4.18 d)	^{131}I (8.04 d)
Radiation	γ, ε	β^+, ε	γ, β^-
Imaging device	SPECT/CT	PET/CT	SPECT
Low „stunning“ effect*	+++	+++	+
Availability	No	++	+++
Effective dose (mSv/MBq)**	+++ (0.01)	+ (0.1)	+ (0.07)
Effective dose (mSv/exam)	2 – 5	2 – 3	7 – 30
Costs (RM)	N/A	+ (4,000)	+++ (100)
Imaging quality	++	+++	+
Sensitivity (cps/Bq)	++	+++	+
Quantification (μ, $\gamma \rightarrow \gamma'$)	+	+++	+
Spatial resolution (mm)****	++ (10)	+++ (7-8)	+ (14)
Late imaging $\geq$96 h	No!	+++	+++

*McDougall et al. *Sem Nucl Med.* 2012;41:105; **Effective dose for zero thyroid uptake; ****Rault et al. *Cancer Biother Radiopharm*. 2007;22:423

Tracer Dosimetry in RIT Using Iodine-124

Decay scheme of ^{124}I



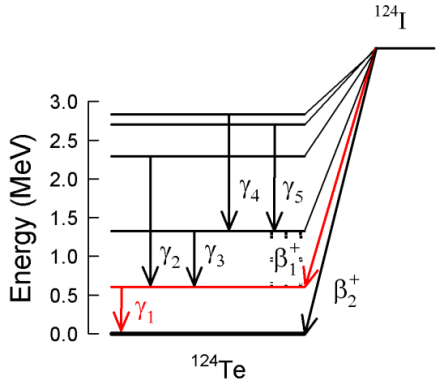
β+ and γ radiation			X-ray radiation		
	Energy (keV)	Frequency (%)		Energy (keV)	Frequency (%)
β^+_1	1535	11.7	Te-$L_{\alpha1}$	4	2.3
β^+_2	2138	10.8	Te-$L_{\beta1}$	4	1.4
			Te-$L_{\alpha2}$	27	16.7
γ_1	603	63.0	Te-$L_{\alpha1}$	27	31.0
γ_2	1691	10.9	Te-$L_{\beta3}$	31	2.8
γ_3	723	10.4	Te-$L_{\beta1}$	31	5.4
γ_4	1510	3.1	Te-$L_{\beta2}$	32	1.6
γ_5	1376	1.7			

- **Non-pure positron-emitting nuclide (γ, X-rays)**
- **X-rays (58%) ≈ 20-40 keV**
- **Cascading γ's causing prompt gamma coincidences (PGC)**
- **High positron energy**
- **Branching ratio only 23%**

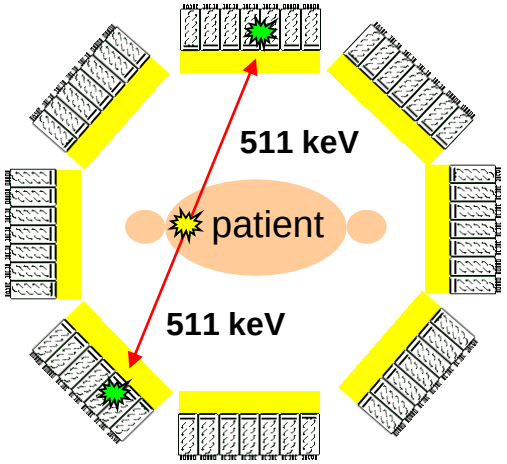
=> Activity measurement (vial materials and volume) and PET quantification (spurious coincidences) may be impaired

Pre Dosimetry Using Iodine-124

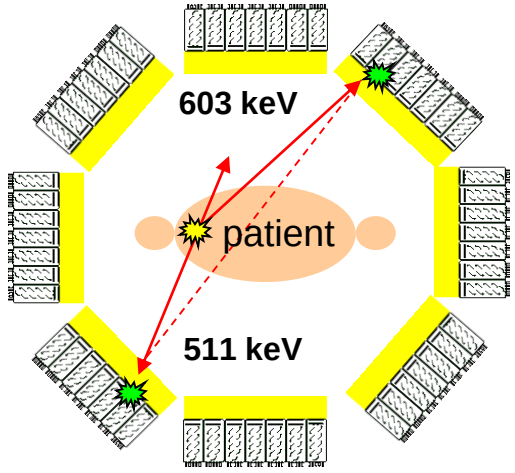
Prompt gamma coincidence (PGC) in the ^{124}I decay



β+ and one γ radiation		
	Energy (keV)	Frequency (%)
β^+_1	1535	11.7
β^+_2	2138	10.8
γ_1	603	63.0



"True coincidence"



"Prompt gamma-annhilation coincidence (PGC)"

PET energy window (350–650 keV or 435–650 keV)

Annihilation

Line of spurious coincidence

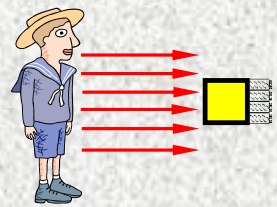
Pre Dosimetry Using Iodine-124

The ^{124}I Dosimetry Concept – „the two main pillars“

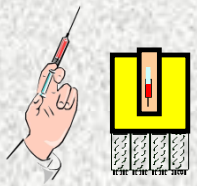
Application of approx. MBq 37 ^{124}I

Organ-at-risk dosimetry

Prediction of the toxicity using the maximum tolerable ^{131}I activity (MTA)



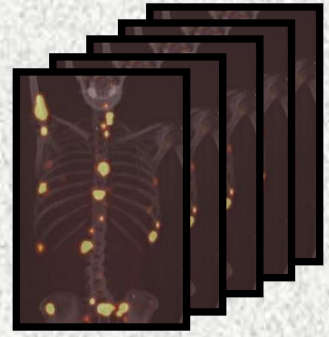
Whole body counting



Blood sampling

Lesion dosimetry

Prediction of the absorbed dose per unit ^{131}I activity (LDpA)



Serial PET/CT imaging

Determination of the individualized therapy activity to deliver a high absorbed dose to lesion without exceeding the MTA

Pre Dosimetry Using Iodine-124

Organs at Risk and their Toxicities

Maximum tolerated activity (MTA) is the therapy activity without producing toxic effects

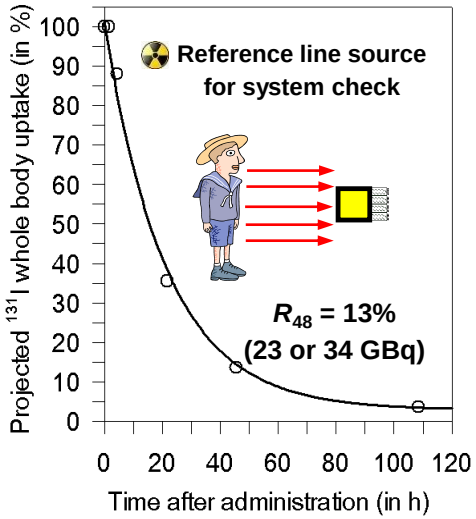
Organ at risk	Toxicity parameter (surrogates)	Threshold *
Bone marrow	Dose to blood as surrogate (=>bone marrow depression)	2.0 Gy
Lung	48-h whole body retention activity with or without diffuse pulmonary mets. (=> pneumonitis)	3.0 GBq 4.4 GBq

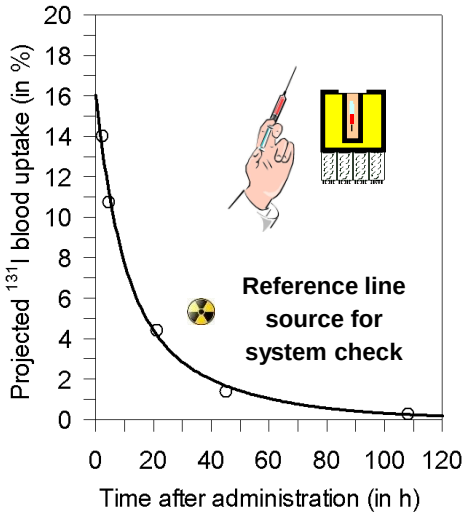
* Benua et al. *Am J Roentgenol Radium Ther Nucl Med*. 1962;87:171; Leeper et al. *Medical Clinics of North America*. 1985:69:1079

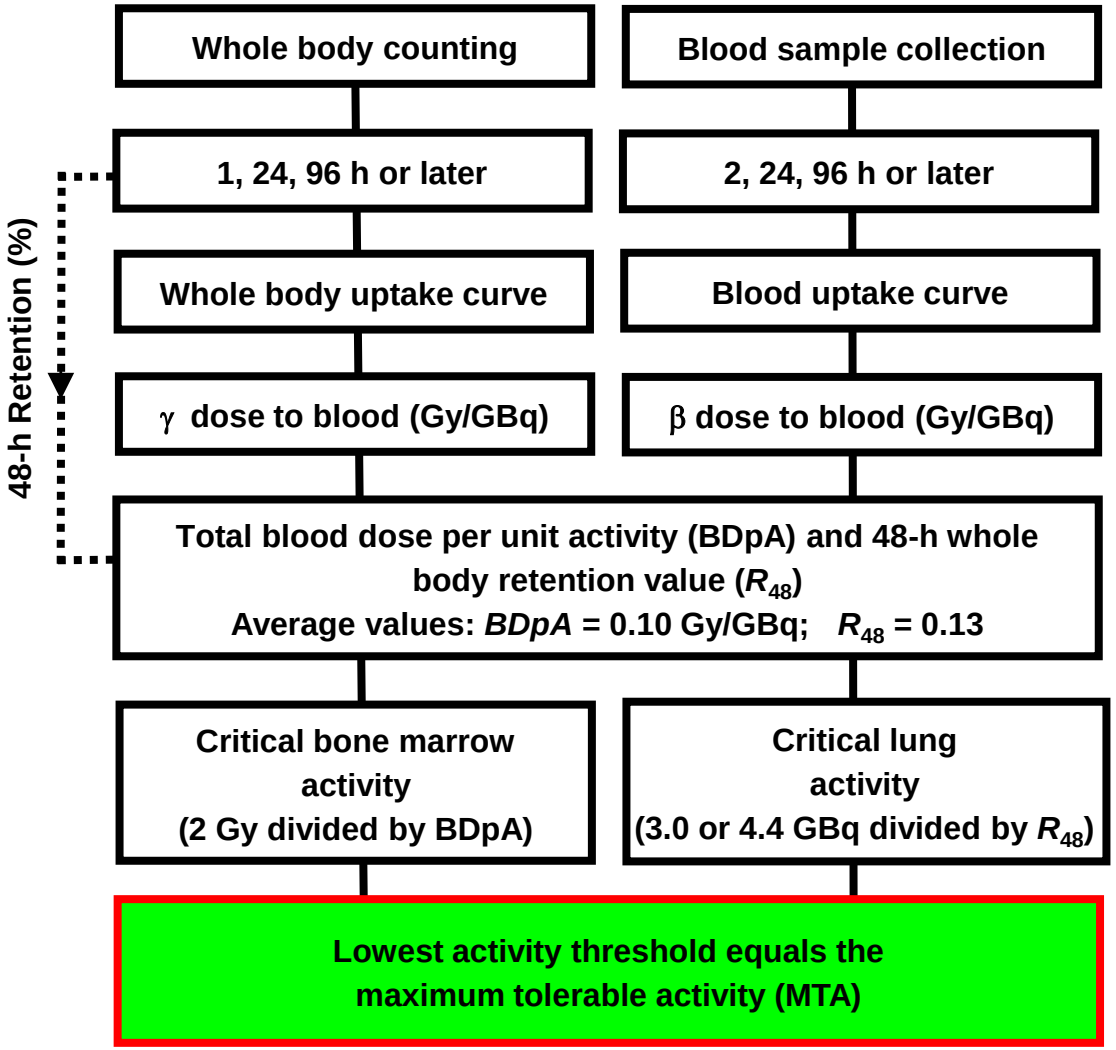
=> Calculation of the blood dose per unit activity (BDpA) and measurements of 48-h retention value (R_{48}) of the whole body

Pre Dosimetry Using Iodine-124

Comprehensive protocol of the organ-at-risk ^{124}I dosimetry



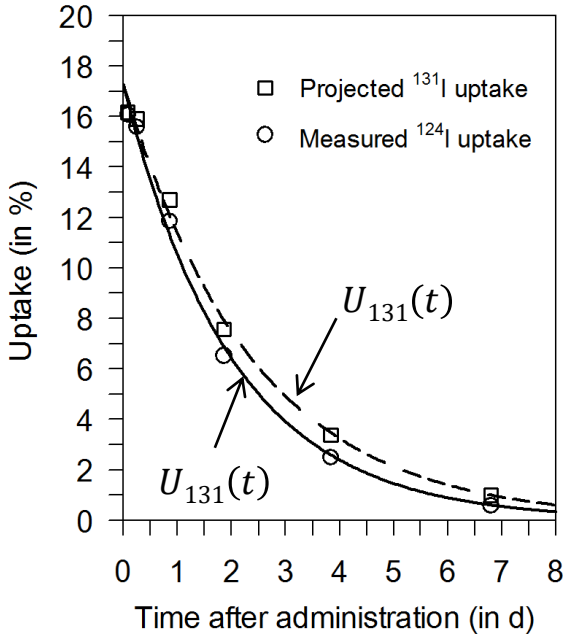




Lassmann et al. *Eur J Nucl Med Mol Imaging*. 2008;35:1405; Jentzen et al. *J Nucl Med.* 2015;56:832

Tracer Dosimetry Using Iodine-124

Matched pair approach – key assumption!



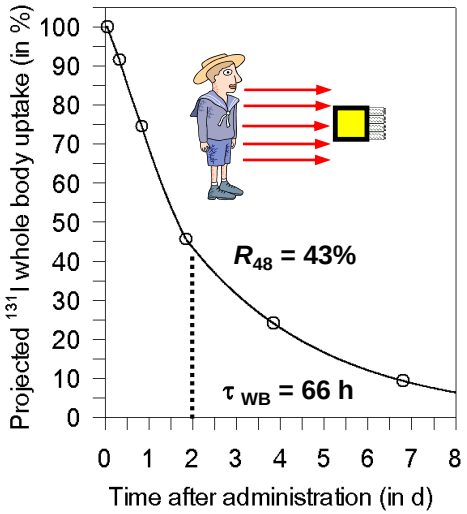
Physical half-life correction

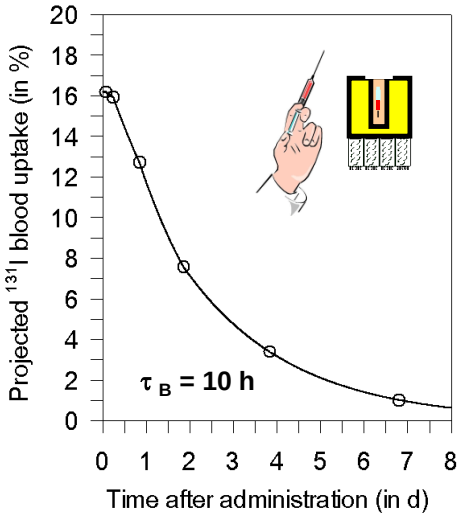
$$U_{131}(t) = U_{124}(t) \cdot \exp\left(0.69 \cdot {}^{t}/_{T_{\mathrm{p124}}}\right) \cdot \exp\left(-0.69 \cdot {}^{t}/_{T_{\mathrm{p131}}}\right)$$

Projected ^{131}I uptake value

It is assumed that the radiopharmacokinetics of ^{124}I (tracer radionuclide) is similar to that of ^{131}I (therapeutic radionuclid)

Pre Dosimetry Using Iodine-124





Example for organ-at-risk ^{124}I dosimetry

Blood residence time

Whole body residence time

$$\frac{BDpA}{\mathrm{Gy/GBq}} = 108 \cdot \frac{(\tau_B/\mathrm{h})}{(V_B/\mathrm{mL})} + 0.0188 \cdot \frac{(\tau_{WB}/\mathrm{h})}{(m_p/\mathrm{kg})^{2/3}}$$

Total blood volume, V_B (m_p, height, sex, age)

Patient's weight

Total blood dose per unit activity (BDpA): 0.33 Gy/GBq
Whole body retention value (R_{48}): 43%

Critical bone marrow activity: 6.1 GBq

Critical lung activity (no diffuse lung mets.): 10.2 GBq

Maximum tolerable activity (MTA): 6.1 GBq

Lassmann et al. *Eur J Nucl Med Mol Imaging*. 2008;35:1405; Pearson et al. *Br J Haematol*. 1995;89:748

Tracer Dosimetry Using Iodine-124

Blood volume (V_B) calculation using Pearson's approach

Male

Mean normal RCM [ml] = (1486 × S) – 825

Mean normal PV [ml] = 1578 × S

Female

Mean normal RCM [ml] = (1.06 × years of age) + (822 × S)

Mean normal PV [ml] = 1395 × S

S is the body surface area expressed in m^2.

$$S = W^{0.425} \times h^{0.725} \times 0.007184,$$

where W is the real body weight [kg] and h is the body height [cm].

Blood normal volume (V_B) = Mean normal RCM + Mean normal PV

Pearson et al. *Br J Haematol*. 1995;89:748

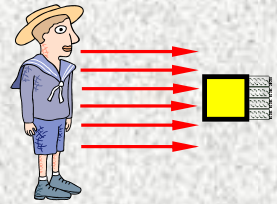
Tracer Dosimetry in RIT Using Iodine-124

The ^{124}I Dosimetry Concept – „the two main pillars“

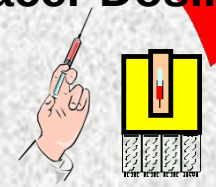
Application of approx. 25 MBq ^{124}I

Organ-at-risk dosimetry

Prediction of the toxicity using the maximum tolerable ^{131}I activity (MTA)



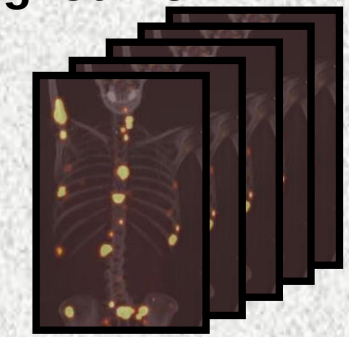
Whole body counting



Blood sampling

Lesion dosimetry

Prediction of the absorbed dose per unit ^{131}I activity (LDpA)



Serial PET/CT imaging

Tracer Dosimetry Using Iodine-124

Determination of the individualized therapy activity to deliver a high absorbed dose to lesion without exceeding the MTA

Tracer Dosimetry Using Iodine-124

Accepted target dose derived from scintigraphy (1983)

Lesion (mets. and thyroid remnants)	Target dose (in Gy)	Response rate *
Lymph node metastases	≥ 85	80–90%
Pulmonary metastases	unknown	unknown
Bone metastases	unknown	unknown
Thyroid remnant tissues	≥ 300	80–90%

* Maxon et al. *N Engl J Med.* 1983;309: 937; Maxon et al. *Endocrinol Metab Clin North Am*. 1990;19:685

=> ^{124}I PET-base response rates

Tracer Dosimetry Using Iodine-124

Response rates derived from ^{124}I PET (2014/2015)

PET-based data verified Maxon's data, but poor response rate for bone metastases (updated)

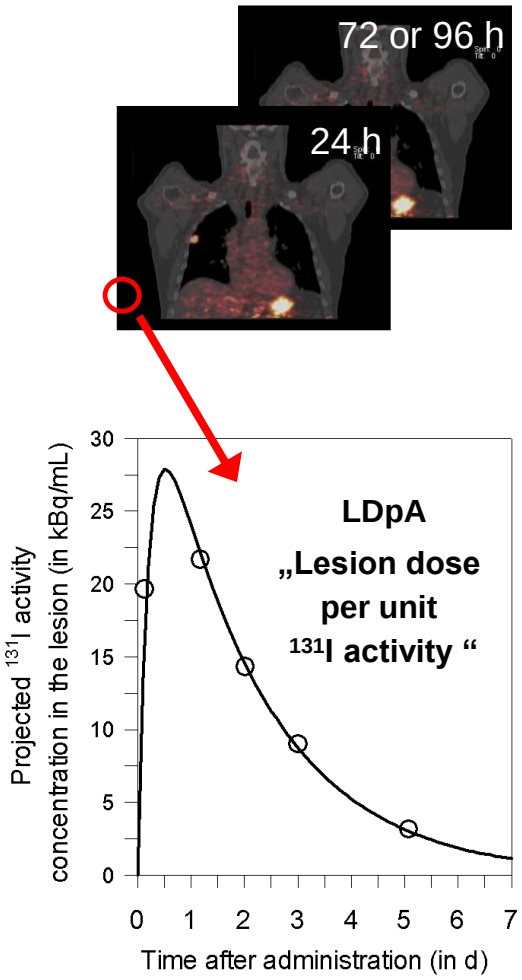
Lesion (mets and thyroid remnants)	Target dose (in Gy)	Response rate
Lymph node metastases (*n*=57)	≥ 85	75% *,+
Pulmonary metastases (*n*=26)	≥ 85	96% **
Bone metastases (*n*=55)	≥ 85 (500-700)	45% (70-80%) **
Thyroid remnant tissues (*n*=54)	≥ 300 *	91% *

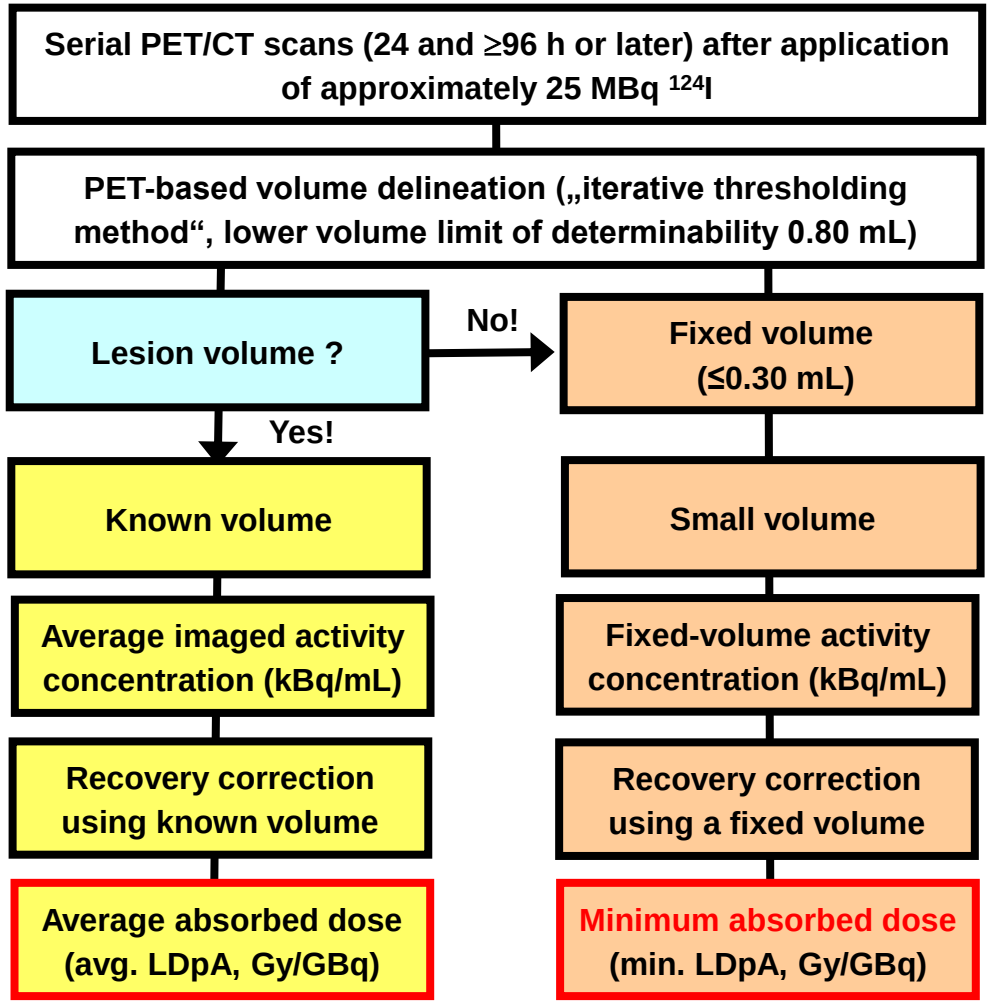
* Jentzen et al. *J Nucl Med.* 2014;55:1759; **Jentzen et al. *J Nucl Med.* 2015, in preparation; + Lymph node metastases included with follow-up times less than 4 months

=> Calculation of the lesion dose per unit activity (LDpA) to predict therapy efficacy

Tracer Dosimetry in RIT Using Iodine-124

Comprehensive protocol of ^{124}I PET/CT lesion dosimetry





Jentzen et al. *J Nucl Med.* 2007;48:108; Jentzen *Phys Med Biol*. 2010;55:2365; Jentzen et al. *J Nucl Med.* 2014;55:1759

Sample PET I-124 Dosimetry Report

Critical organ
a) Marrow
b) Lung

Planning target dose to the lesion

Date and time of absolute activity measurement (MBq)	6.9.18 14:30	52.65
Date and time of administration (MBq)	6.9.18 14:30	52.65
Scanner *I* scaling factor for RC match	GE Discovery ST	0.90
PET spatial resolution (mm)/ lower volume limit (mL)	8.20	0.29
OSEM reconstruction (Iter., Subs; x,y,z voxel length, filter)	4i, 15s;2.2x2.2x3.3; 4-mm Gauss	

Result of the Organ-at-risk Dosimetry

Blood residence time (h)	2.71		
Whole bode residene time (h)	29.20	48-h retention value (%)	23.84

	BDpA (Gy/GBq)	CBA (GBq)	
Bone moarrow toxcicity	0.12	17.4	
Lung toxcicity	48-h WB uptake (%)	CLA (GBq)	
		12.4	Presence of diffued lung mets. (Yes)
		18.6	Presence of diffused lung mets. (No)
MTA (GBq)		17	

Result of the Lesion Dosimetry

Foci ID #	LDpA (Gy/GBq)	τ (min)	24-h RIU (%)	V (mL)	ρ (g/mL)	Remarks
1	7	4.01	0.0596	0.79	1.30	Left Occipital (SUV28.7)
2	6	34.21	0.7096	8.81	1.30	Proximal Shaft of Left Humerus (SUV54.1)
3	39	0.91	0.0079	0.03	1.30	Greater Wing of Left Sphenoid (SUV7.7)
4	7	11.77	0.1742	2.52	1.30	T4&T5 (SUV52.6)
5	8	163.07	3.3216	32.57	1.30	T10 to L2 (SUV121.2)
6	8	161.30	3.0370	31.83	1.30	L5, Body Sacrum & rt Sacrala (SUV109.6)
7	11	105.29	2.1404	13.85	1.30	Right Acetabulum (SUV113.6)
8	7	27.46	0.4921	5.81	1.30	Bileteral Trochanteric region of femur (SUV140.74)
9	9	62.15	1.2713	10.32	1.30	Proximal Shaft of Bilateral Femur (leftSUV99.0)
10	5	0.84	0.0144	0.23	1.30	Right 8th rib (SUV

Prerequisites for ^{124}I Dosimetry in DTC

- Calibration of the dose calibrator and standardized activity measurement are mandatory
- Recovery coefficients for the PET system used to correct for prompt gamma and primarily for partial volume effect (heuristic approach)
- Reconstructed PET spatial resolution for volume segmentation
- Calibrated gamma counter required for blood sample measurements (blood uptake curve)
- Probe system for whole-body measurements (whole-body uptake curve)

Major Challenges

Cost to buy radiopharmaceutical/develop.
- RM 4000 per patients

Facility and Equipment.
- I-131 Ward and PET-CT camera (TOF) in same compound is a good setup.

Software
- Image Kinetics Analysis + Software Dosimetry Software an advantage

Expertise
- Confidence team

Time Consuming
- Near 2 week to complete the procedure

Clinical Impact
- No clinical trial due to insufficient fund and technical issues.

Conclusion

I-124 PET/CT is a superior imaging agent as compared to diagnostic I-131 planar whole body scintigraphy with lesion detectability similar to post-treatment I-131 scans.

However, due to the physical properties of I-124 and its complex decay schema, there remains a need for improved correction methods to ensure the accuracy of diagnostic images and quantitative analysis.

Also, there is a need for larger prospective trials to address the number and timing of scans needed for optimal dosimetry protocols.

Despite its benefits in lesion detection and measurement of metabolic tumor volumes, for I-124 to be used mainstream, it needs to be more commercially available and at a lower cost.