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MIRD formalism: theory and examples

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Radiation dose

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- **Radiation dose D** = the quantity of radiation energy deposited in an absorber per kg of absorber material.
- SI unit: **Gy**
1 Gy = 1 J energy deposited per kg absorber
- Old unit: rad
1 rad = 1 cGy



Equivalent dose

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Equivalent dose H = absorbed dose D x Q

Q is the radiation weighting factor for a specified type and energy of radiation accounts for the effectiveness of the radiation in causing biological damage.

Unit: **Sievert (Sv)**

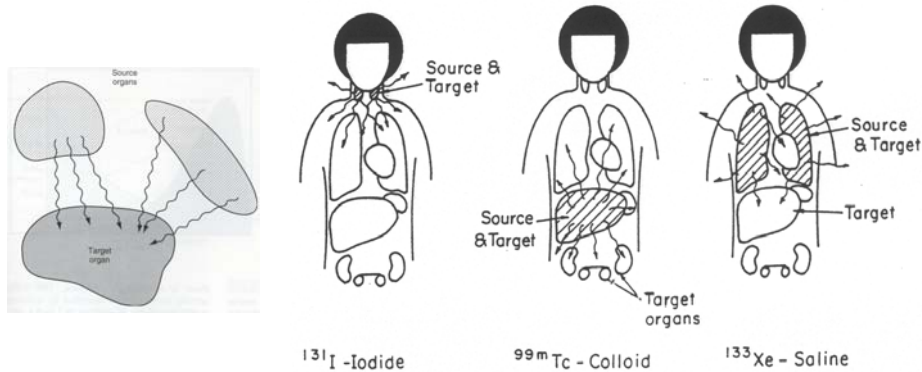
Old unit:
1 rem = 10 mSv

Type of radiation	Weighting factor Q
Photons, all energies	1
Electrons and muons, all energies	1
Neutrons, energy	
<10 keV	5
10 - 100 keV	10
100keV - 2 MeV	20
2 - 20 MeV	10
>20MeV	5
Protons, energy > 2 MeV	5
Alpha particles	20

Source and target organs

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- Source organs (i.e. organs with significant uptake of isotope)
- Target organs (i.e. organs that are receiving radiation)



MIRD (Medical Internal Radiation Dose)

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1. The amount of activity and time in source and target organs
2. Total amount of radiation energy emitted by the radioactivity
3. Fraction of energy emitted by the source organ that is observed by the target organ



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MIRD method

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The amount of activity and time in source and target organs

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- Activity in an organ is continuously changing due to various factors:
 - uptake of the radiopharmaceutical
 - excretion from the organ
 - physical decay
- Time activity curves (TAC)
physical and biological properties
- $A(t)$ activity in organ at time t .

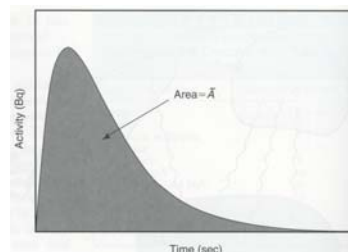


The amount of activity and time in source and target organs

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- **Cumulated activity \tilde{A}**
- SI unit: **Bq.s**
 - Activity administered to the patient at $t=0$
 - Measurement until complete disappearance from the organ ($t \rightarrow \infty$).
- **Residence time τ**

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



$$\tau = \tilde{A} / A_{\text{injected}}$$



Calculation of \tilde{A}

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- Situation 1: uptake by the organ is instantaneous (= very rapid with respect to the half-life of the radionuclide) and there is no biological excretion

$$A(t) = A(0) \cdot \exp(-\ln(2) \cdot t/t_{1/2})$$

$$\tilde{A} = t_{1/2} \cdot A(0)/\ln(2)$$

- Example: cumulated activity in the liver for an injection of 100 MBq of a ^{99m}Tc -labeled sulfur colloid assuming that 60% of the injected colloid is trapped by the liver (and retained there)

$$\tilde{A} = 6.02 \text{ hr} \times (0.6 \times 100 \text{ MBq})/\ln(2) = 521 \text{ MBq} \cdot \text{hr} = 1.88 \times 10^{12} \text{ Bq} \cdot \text{s}$$

$$\tau = 5.21 \text{ hr}$$



Calculation of \tilde{A}

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- Situation 2: Uptake is instantaneous and clearance is by both physical decay and biological excretion. Biological half-life = T_b .

Total clearance is described by

$$\frac{1}{T_e} = \frac{1}{T_b} + \frac{1}{T_{1/2}}$$

$$T_e = \frac{T_b T_{1/2}}{T_b + T_{1/2}}$$

$$\tilde{A} = T_e \cdot A(0)/\ln(2)$$

- If there is more than one component to the biological excretion curve, then each component i (with fraction f_i) has a biological half-life of T_{b_i} and an effective half-life T_{e_i}

$$\tilde{A} = [f_1 \cdot T_{e_1} + f_2 \cdot T_{e_2} + \dots] \cdot A(0)/\ln(2)$$



Calculation of \tilde{A}

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- Example: 100 MBq of ^{99m}Tc -labeled microspheres are injected into a patient, with essentially instantaneous uptake of activity in the lungs. Suppose that because of a metabolic defect 60% of the activity is excreted from the lungs with a half-life of 2 hours and 40% with a half-life of 3 hours. The cumulated activity in the lungs is given by:

$$\tilde{A} = [0.6 T_{e1} + 0.4 T_{e2}] 100 \text{MBq} / \ln(2)$$

$$\text{with } T_{e1} = 6.02 \times 2 / (2 + 6.02) \text{ hr} = 1.5 \text{ hr}$$

$$T_{e2} = 6.02 \times 3 / (3 + 6.02) \text{ hr} = 2.0 \text{ hr}$$

$$\tilde{A} = 245.3 \text{ MBq}\cdot\text{hr} = 88.31 \times 10^{10} \text{ Bq}\cdot\text{s}$$

$$\tau = 2.45 \text{ hr}$$



Calculation of \tilde{A}

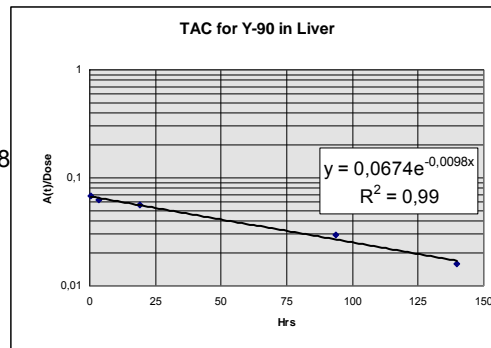
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- Example: uptake of ^{90}Y in the liver based on 5 measurements.
- Fit monoexponential and from this determine $A(0)$ and T_e .

$$A(t)/A_{\text{injected}} = 0.0674 \exp(-0.0098t)$$

$$A(0)/A_{\text{injected}} = 0.0674; T_e = \ln(2)/0.0098$$

$$\tau = T_e \cdot A(0)/A_{\text{injected}} = 6.9 \text{ hr}$$





Calculation of \tilde{A}

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- Situation 3: uptake by the organ is not instantaneous (radionuclides that have a slow pattern of uptake in comparison to their physical half-life).

Uptake is described by $A(0) \cdot [1 - \exp(-\ln(2) \cdot t/t_u)]$

Excretion by a half-life of T_b

Physical half-life: $t_{1/2}$

$A(t) = A(0) \cdot [1 - \exp(-\ln(2) \cdot t/t_u)] \cdot \exp(-\ln(2) \cdot t/t_{1/2}) \cdot \exp(-\ln(2) \cdot t/T_b)$

$$\tilde{A} = T_e \cdot (T_{ue}/T_u) \cdot A(0)/\ln(2) \text{ with } T_{ue} = T_u \cdot T_e / (T_u + T_e)$$



Calculation of \tilde{A}

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- Example: 250 MBq of a radioactive gas having a half-life of 20s is injected in an intravenous solution. It appears in the lungs with an uptake half-time of 30s and is excreted with a biological half-life of 10s. Uptake is described by $\sim 1 - \exp(-\ln(2) \cdot t/t_u)$

- The cumulated activity in the lungs is given by:

$$\tilde{A} = T_e \cdot (T_{ue}/T_u) \cdot 250 \text{ MBq} / \ln(2)$$

$$\text{with } T_e = 10 \times 20 / (10 + 20) \text{ s} = 6.7 \text{ s}$$

$$T_{ue} = T_u \cdot T_e / (T_u + T_e) = 30 \times 6.7 / (6.7 + 30) \text{ s} = 5.5 \text{ s}$$

$$\tilde{A} = 6.7 \times (5.5/30) \times 250 / \ln(2) \text{ MBq} \cdot \text{s}$$

$$= 4.4 \times 10^8 \text{ Bq} \cdot \text{s}$$



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MIRD method

1. The amount of activity and time in source and target organs
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Total amount of radiation energy emitted by the radioactivity

- Energy of the radionuclide emissions
- Number of desintegrations
- Physical properties

- Energy emitted per unit of cumulated activity is given by the **equilibrium absorbed dose constant Δ** .



Total amount of radiation energy emitted by the radioactivity

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- The factor Δ must be calculated for each type of emission for the radionuclide.

$$\Delta_i = 1.602 \times 10^{-13} \cdot N_i \cdot E_i \cdot k \text{ [Gy.kg/Bq.s]}$$

E_i is the average energy (in MeV) of the i^{th} emission

N_i is the relative frequency of that emission (number emitted by disintegration).

k = proportionality constant (Gy.kg/Bq.s.MeV)

- The product of cumulated activity \tilde{A} and equilibrium absorbed dose constant Δ_i is the radiation energy emitted by the i^{th} emission (in Gy.kg) during the time that the radioactivity is present in a source organ.



Example

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- A certain radionuclide decays by emitting β particles in 100% of its disintegrations with $\bar{E}_\beta = 0.3\text{MeV}$.

This is followed in 80% of its disintegrations by emission of a 0.2MeV γ -ray and in 20% by emission of a 0.195MeV conversion electron and a 0.005MeV characteristic X-ray.

- Calculation of $\Delta_\beta, \Delta_\gamma, \Delta_e, \Delta_X$
- E.g. $\Delta_\gamma = 1.602 \times 10^{-13} \cdot N_\gamma \cdot E_\gamma \cdot k \text{ [Gy.kg/Bq.s]}$
 $= 1.602 \times 10^{-13} \times 0.8 \times 0.2 \text{ Gy.kg/Bq.s}$
 $= 2.56 \times 10^{-14} \text{ Gy.kg/Bq.s}$



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Absorbed fraction ϕ

- The fraction of the energy emitted by the source organ that is absorbed by the target organ is given by the **absorbed fraction $\phi_i(\text{target} \leftarrow \text{source})$** and it depends on
 - The amount of radiation energy reaching the target organ (tissue and distance attenuation)
 - Volume and composition of the target organ.
 - Type and energy of the i^{th} emission
 - Anatomic relationship of the source-target pair.
- The total energy emitted by the source organ and absorbed in a target organ is given by

$$D(\text{target} \leftarrow \text{source}) = \bar{A}(\text{source}) \cdot \sum_i \phi_i(\text{target} \leftarrow \text{source}) \cdot \Delta_i$$



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Average absorbed dose to the target organ

$$\bar{D} = \frac{1}{m_t} \sum_{source} \tilde{A}(source) \sum_i \phi_i(\text{target} \leftarrow \text{source}) \Delta_i$$

- **S-values**: the mean dose per unit cumulated activity

$$S(\text{target} \leftarrow \text{source}) = \frac{1}{m_t} \sum_i \phi_i(\text{target} \leftarrow \text{source}) \Delta_i$$

- Dose to the target organ

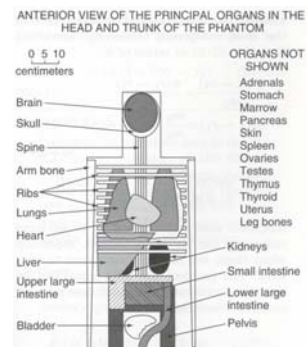
$$\bar{D} = \sum_{source} \tilde{A}(source) S(\text{target} \leftarrow \text{source})$$



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S-values

- Values of S have been calculated for mathematical humanoid models incorporating organs and anatomic structures of average size and shape.
- **Phantoms**: adult male and female, newborn, 1-year, 5-year, 10-year, 15-year old child, pregnant woman



Organ masses for the Cristy and Eckerman adult male phantom

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Organ	Mass (g)	Organ	Mass (g)
Adrenals	16.3	Ovaries	8.71
Brain	1420	Pancreas	94.3
Breasts (excluding skin)	351	Skeleton	
Gallbladder contents	55.7	Active marrow	1120
Gallbladder wall	10.5	Cortical bone	4000
Gastrointestinal tract		Trabecular bone	1000
Lower large intestine contents	143	Skin	3010
Lower large intestine wall	167	Spleen	183
Small intestine contents and wall	1100	Testes	39.1
Stomach contents	260	Thymus	20.9
Stomach wall	158	Thyroid	20.7
Upper large intestine contents	232	Urinary bladder contents	211
Upper large intestine wall	220	Urinary bladder wall	47.6
Heart contents	454	Uterus	79.0
Heart wall	316		
Kidneys	299	Remaining tissue	51,800
Liver	1910		
Lungs	1000		

Tabulated S-values

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S, MEAN DOSE PER UNIT CUMULATED ACTIVITY, (RAD/ μ CI-H) IODINE-131 — HALF-LIFE 193.0 HR

Target organs	Source organs									
	Skeleton									
	Ovaries	Pancreas	Red marrow	Cort. bone	Tra. bone	Skin	Spleen	Testes	Thyroid	Total body
Adrenals	1.4E-06	2.3E-05	6.1E-06	4.3E-06	4.3E-06	2.1E-06	1.8E-05	1.7E-07	5.2E-07	1.2E-05
Bladder wall	1.9E-05	5.0E-07	2.1E-06	1.6E-06	1.6E-06	1.7E-06	4.5E-07	1.4E-05	2.1E-08	1.1E-05
Bone (total)	2.9E-06	2.8E-06	2.5E-05	9.2E-05	6.5E-05	2.4E-06	2.3E-06	2.0E-06	2.2E-06	1.0E-05
G.I. (stomach wall)	2.3E-06	5.0E-05	2.9E-06	1.6E-06	1.6E-06	1.7E-06	2.7E-05	2.5E-07	2.6E-07	1.1E-05
G.I. (SI)	3.3E-05	5.1E-06	7.4E-06	2.2E-06	2.2E-06	1.5E-06	3.9E-06	1.4E-06	3.4E-08	1.1E-05
G.I. (ULI wall)	3.1E-05	6.1E-06	5.8E-06	2.0E-06	2.0E-06	1.5E-06	3.7E-06	9.7E-07	3.5E-08	1.1E-05
G.I. (LLI wall)	4.0E-05	1.5E-06	8.4E-06	2.8E-06	2.8E-06	1.6E-06	1.9E-06	7.8E-06	3.4E-08	1.1E-05
Kidneys	3.0E-06	1.8E-05	6.5E-06	2.6E-06	2.6E-06	2.0E-06	2.4E-05	2.4E-07	1.4E-07	1.1E-05
Liver	1.7E-06	1.2E-05	2.8E-06	1.9E-06	1.9E-06	1.8E-06	3.0E-06	1.4E-07	4.0E-07	1.1E-05
Lungs	2.7E-07	6.8E-06	3.4E-06	2.8E-06	2.8E-06	1.9E-06	6.2E-06	4.0E-08	2.9E-06	1.0E-05
Marrow (red)	9.8E-06	5.4E-06	2.3E-04	1.0E-05	1.0E-04	2.3E-06	3.5E-06	1.6E-06	2.4E-06	1.1E-05
Other tissues (muscle)	5.6E-06	5.0E-06	3.6E-06	3.0E-06	3.0E-06	2.4E-06	4.1E-06	3.4E-06	3.8E-06	9.8E-06
Ovaries	3.9E-02	1.1E-06	8.4E-06	2.6E-06	2.6E-06	1.1E-06	2.4E-06	0.0	4.1E-08	1.1E-05
Pancreas	1.5E-06	4.7E-03	4.6E-06	2.8E-06	2.8E-06	1.6E-06	5.4E-05	1.6E-07	2.4E-07	1.1E-05
Skin	1.4E-06	1.4E-06	2.0E-06	2.3E-06	2.3E-06	1.6E-04	1.6E-06	4.3E-06	2.4E-06	8.3E-06
Spleen	1.8E-06	5.4E-05	2.4E-06	2.2E-06	2.2E-06	1.8E-06	2.6E-03	2.3E-07	3.6E-07	1.1E-05
Testes	0.0	2.0E-07	1.1E-06	1.7E-06	1.7E-06	2.6E-06	2.4E-07	1.3E-02	7.2E-09	1.0E-05
Thyroid	4.1E-08	4.7E-07	2.3E-06	2.8E-06	2.8E-06	2.3E-06	3.8E-07	7.2E-09	2.2E-02	9.7E-06
Uterus (nongravid)	5.4E-05	1.8E-06	5.8E-06	1.7E-06	1.7E-06	1.4E-06	1.2E-06	0.0	3.8E-08	1.1E-05
Total body	1.2E-05	1.1E-05	1.0E-05	9.9E-06	9.9E-06	8.3E-06	1.1E-05	9.8E-06	9.5E-06	9.9E-06

$$1 \text{ rad}/(\text{mCi}\cdot\text{hr}) = 7.51 \times 10^{-11} \text{ Gy}/(\text{Bq}\cdot\text{s})$$

Whole-body dose, effective dose equivalent (H_E) and effective dose (E)

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To compare the dose of different nuclear medicine procedures: need for a single number.

Whole-body (or total body TB) dose $\bar{D}(TB) = \tilde{A}(TB) \cdot S(TB \leftarrow TB)$

Effective dose (E) and effective dose equivalent (H_E) represent the whole-body dose that would result in the same overall risk as a nonuniform dose distribution actually delivered. Differ only in the weighting factors W for the doses of different organs

Organ	$W(H_E)$	$W(E)$
Gonads	0.25	0.20
Red marrow	0.12	0.12
Colon	—	0.12
Lungs	0.12	0.12
Stomach	—	0.12
Bladder	—	0.05
Breasts	0.15	0.05
Liver	—	0.05
Esophagus	—	0.05
Thyroid	0.03	0.05
Skin	—	0.01
Bone surfaces	0.03	0.01
Remainder	0.30 split equally between five organs with highest dose	0.05 split equally between adrenals, brain, upper large intestine, small intestine, kidneys, muscle, pancreas, spleen, thymus, and uterus

Limitations of the MIRD formalism

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- Standard models (not patient specific)
- Assumed that the activity is distributed uniformly within each organ and that the energy is uniformly deposited throughout the organ
- Local radionuclide concentrations can be much higher than organ average calculations might suggest.



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Application 1: Radiation dose estimates for tracers used in nuclear medicine



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Example: radiation dose estimates for ^{18}F -FDG in an adult

Organ Dose	(mGy/MBq Administered)	Organ Dose	(mGy/MBq Administered)
Adrenals	1.3×10^{-2}	Muscle	1.1×10^{-2}
Brain	1.9×10^{-2}	Ovaries	1.7×10^{-2}
Breasts	9.2×10^{-3}	Pancreas	2.6×10^{-2}
Gallbladder wall	1.4×10^{-2}	Red marrow	1.3×10^{-2}
Lower large intestine wall	1.7×10^{-2}	Bone surfaces	1.2×10^{-2}
Small intestine	1.4×10^{-2}	Skin	8.4×10^{-3}
Stomach	1.3×10^{-2}	Spleen	3.7×10^{-2}
Upper large intestine wall	1.3×10^{-2}	Testes	1.3×10^{-2}
Heart wall	6.0×10^{-2}	Thymus	1.2×10^{-2}
Kidneys	2.0×10^{-2}	Thyroid	1.0×10^{-2}
Liver	1.6×10^{-2}	Urinary bladder wall	1.9×10^{-1}
Lungs	1.7×10^{-2}	Uterus	2.3×10^{-2}

Determined on normal subjects

Tables for many tracers used in nuclear medicine



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Application 2: Patient specific dosimetry in radio-immuno therapy (RIT)



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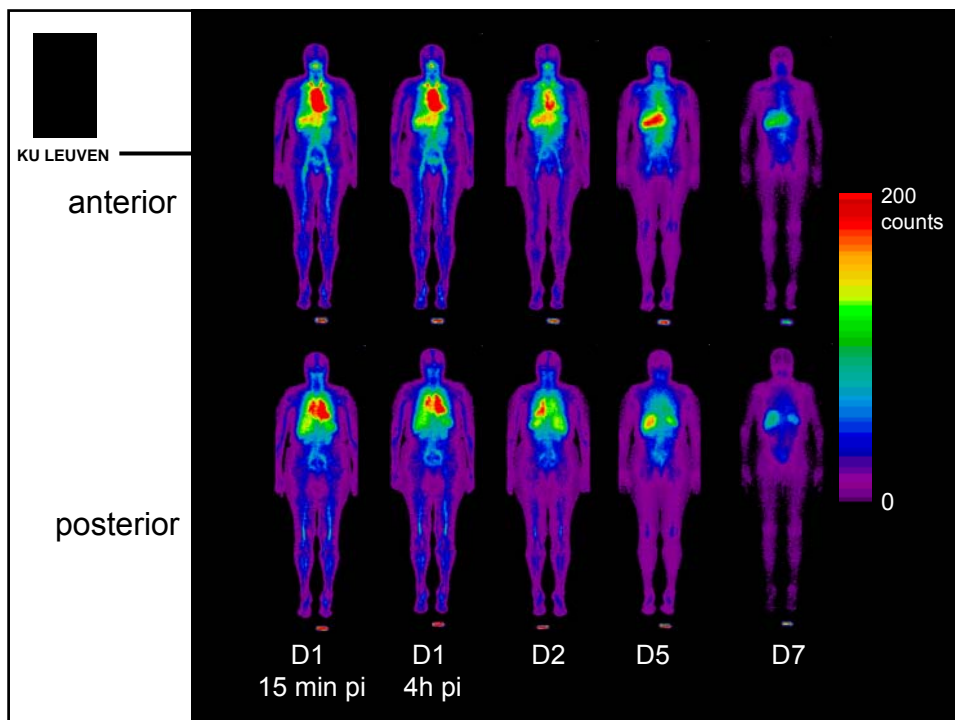
Introduction

- Ibritumomab tiuxetan (Zevalin) is a promising radio immunotherapy for lymphoma patients.
- Therapy: ^{90}Y -zevalin
 - ^{90}Y : decay (β -emission) to ^{90}Zr
 - $t_{1/2} = 64.0$ hr
 - Average β -energy = 935 keV
- Dosimetry: ^{111}In -zevalin
 - ^{111}In : decay (EC) to ^{111}Cd
 - $t_{1/2} = 67.9$ hr
 - $\gamma_1 = 171$ keV, $\gamma_2 = 245$ keV

Acquisition

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- 185 MBq ^{111}In -zevalin
- Dual-head gamma camera with medium-energy collimators
- 5 Planar whole body images
 - Day1: 15 min post injection and 3-6h post-injection
 - Day 2, 5 and 7
- Blood samples were taken immediately after each whole body scan.
- Imaging standard with a dose of 1.8 MBq was positioned just below the left foot.
- Blood samples and a standard of 20 kBq were measured in a well counter.





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MIRD formalism

- Residence times were calculated for lungs, liver, spleen, kidneys, red marrow, whole body and the remainder.
- Radiation dose for the different organs was calculated using the MIRD formalism for a therapeutic dose of 14.8 MBq/kg ^{90}Y -ibritumomab tiuxetan (with a maximum dose of 1.2 GBq).
- Organs doses < 2000 cGy
- Bone marrow dose (the restrictive organ) < 300cGy
- Combination of patient specific data and models



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ROI's



Draw the same regions on every whole body image
copy the original region
and translate/rotate

input data

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Anterior Scans

Scan Date & Time	Scan Duration (min.)	Counts in Region of Interest							
		Standard	Whole body	Lungs		Liver	Spleen	Kidneys	
				Right	Total			Right	Total
1/08/2002 14:14	20	69042	4615106		276045	428062	73021		137608
1/08/2002 17:09	20	67883	4562162		261573	350020	67328		128201
2/08/2002 8:55	20	57214	3937523		214275	323272	59876		119167
5/08/2002 11:33	40	54359	3576074		148493	351417	58110		83561
7/08/2002 9:43	40	35048	2070676		72921	196064	34662		62548

Posterior Scans

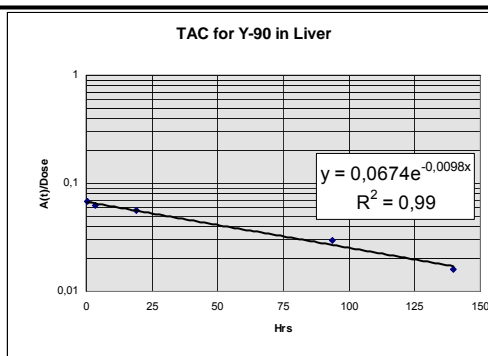
Scan Date & Time	Scan Duration (min.)	Counts in Region of Interest							
		Standard	Whole body	Lungs		Liver	Spleen	Kidneys	
				Right	Total			Right	Total
1/08/2002 14:14	20	65328	4168082		358419	212271	103197		137608
1/08/2002 17:09	20	63640	4104905		306403	217412	114501		128201
2/08/2002 8:55	20	54188	3580350		215964	192762	94347		119167
5/08/2002 11:33	40	51832	3101930		162749	217729	67113		83561
7/08/2002 9:43	40	32117	1784893		77681	122069	43216		62548

Calculation of the geometric mean = $(\text{value1} * \text{value2})^{1/2}$

Calculation of residence times

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Transfer data obtained from ^{111}In to ^{90}Y by taking the difference in half-life into account.



Fitting monoexponential: $A(t)/\text{Dose} = 0.0674 \exp(-0.0098t)$

$A(0)/\text{Dose} = 0.0674$ and $T_e = \ln(2)/0.0098$

Residence time = $\bar{A} / \text{Dose} = T_e \cdot A(0)/\text{Dose} = 6.9 \text{ hr}$

Example: input data (blood data)

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- Blood samples will be 1 ml with water or saline added to bring to 5 ml
- ^{111}In standard will be $0.5 \mu\text{Ci}$ with water or saline added to bring to 5 ml
- Counting window will be 140 to 550 keV
- Minimum counting time for standard and sample should produce $>10^4$ counts
- Background subtraction

Blood Sample Drawn:	Counting Data for Blood Sample		
	Start Time	Duration (min.)	Net CPM
1/08/2002 14:06	9/08/2002 9:31	1	301630
1/08/2002 17:03	9/08/2002 9:31	1	265519
2/08/2002 8:51	9/08/2002 9:31	1	200833
5/08/2002 10:02	9/08/2002 9:31	1	95502
7/08/2002 9:28	9/08/2002 9:31	1	65872

Counting standard activity: **0,398** μCi
 Calibration time: **1/08/2002 18:10**

Counting Data for Standard		
Start Time	Duration (min.)	Net CPM
9/08/2002 9:31	1	68495

Residence time in red marrow (RM)

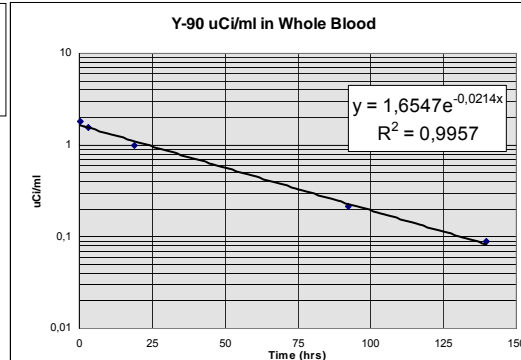
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- RM mass is assumed to be 1120 g for an adult male and 1050 g for a female
- Hematocrit value (as a fraction) should be known

$$T_{rm} = \frac{\tilde{A}_b \times m_{rm} \times \left(\frac{0.19}{1 - \text{hemocrit}} \right)}{uCi_{In-111} \text{ injected}}$$

$$m_{rm} = \text{RM mass}$$

$$\tilde{A}_b / m_b = T_{eb} \cdot A_b(0) / m_b$$





Dosimetry calculations: result

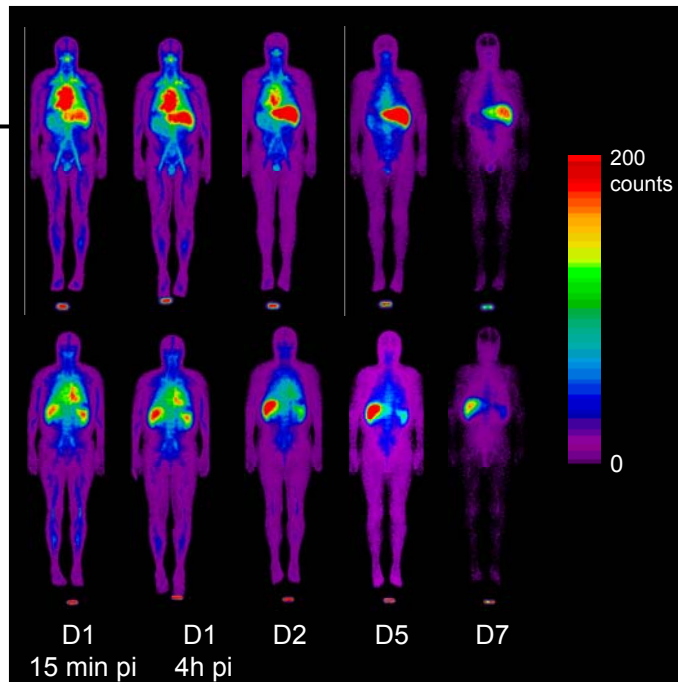
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Organ System	Residence Time (hrs)	Calculated Dose Factor cGy/MBq	Calculated Dose for 974.0 MBq cGy
Organs identified in protocol			
Kidneys	2,63	0,51	501
Liver	6,9	0,26	257
Lungs	4,42	0,30	290
Red Marrow	5,48	0,16	156
Spleen	1,74	0,63	610
Total Body	88,8	0,09	87
Remainder	73,2		
Other target tissues			
Bone surfaces		0,00	
Unspecified organs		0,12	119
		0,07	72



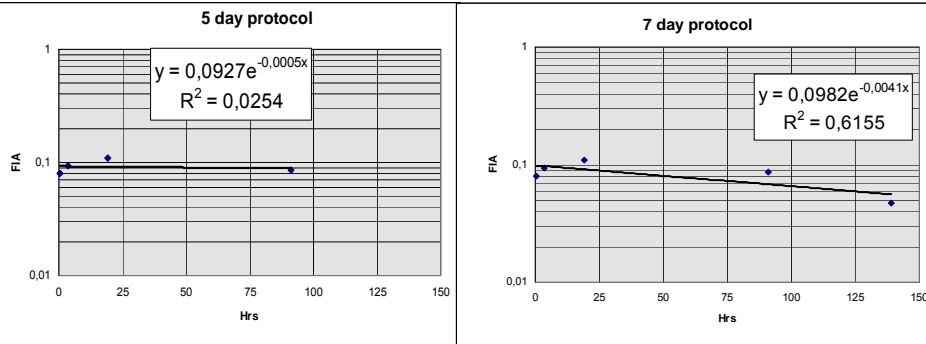
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1 patient was showing a problem in the liver: high residence time



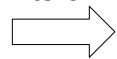
TAC in liver

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Estimated dose for liver: 6170 cGy
Bad fits of monoexponential.

797 cGy



⁹⁰Y-zevalin therapy was NOT given!

References and acknowledgments

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- References:
 - Cherry, Sörenson and Phelps. Physics in nuclear medicine 3rd edition (Saunders, 2003)
 - Loevinger, Budinger and Watson. MIRD primer for absorbed dose calculations (Society for nuclear medicine, 1997)

- Acknowledgements
 - Sigrid Stroobants, Koen Van Laere, Shivani Ghoorun, Kristof Baete, Hubert Vanbilloen, Bruno Raes, Liesbet De Ceuninck