# Lymphoma Radio-Immuno-Therapy Zevalin Dosimetry

## as application & refinement of planar dosimetry

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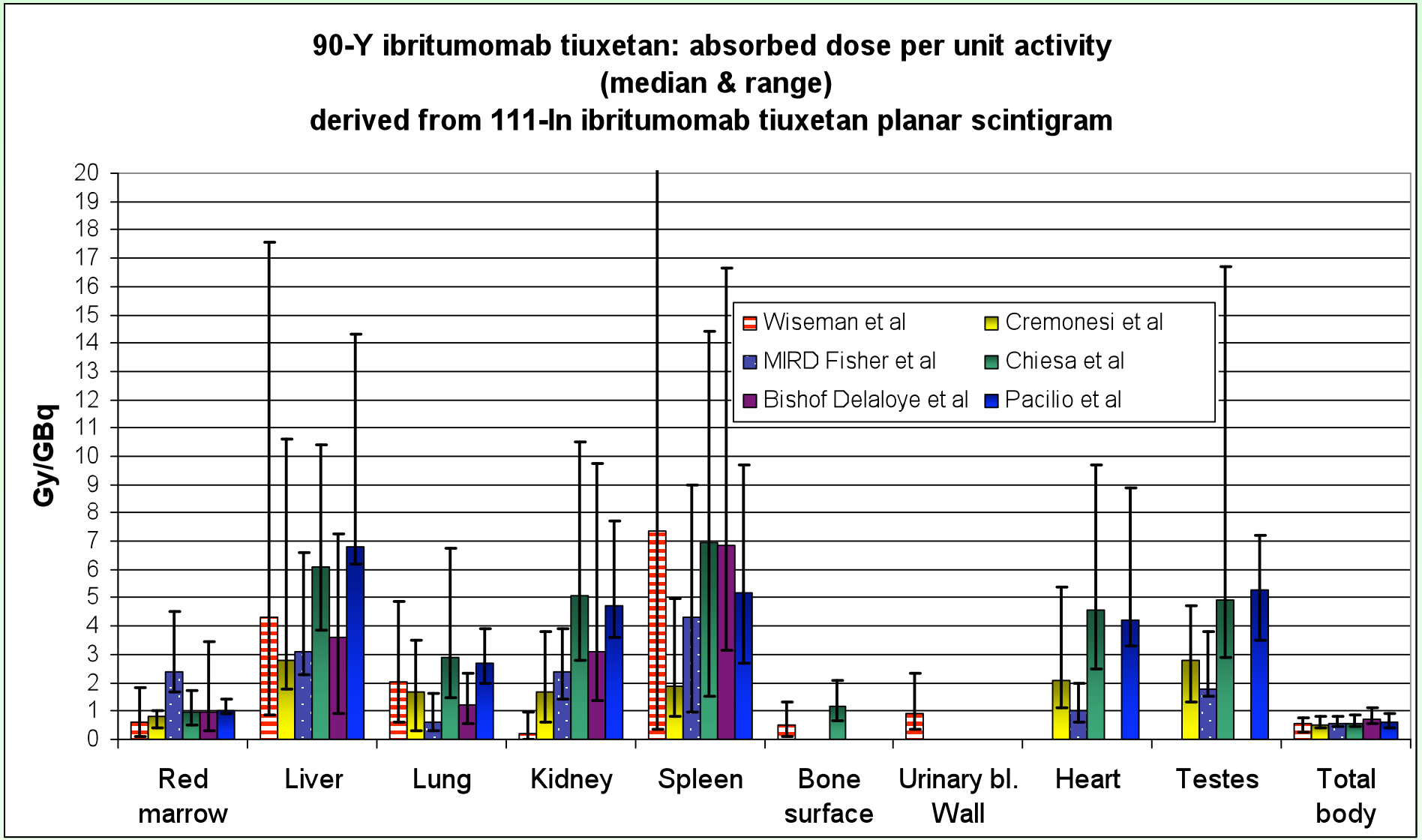
# Available data & methods

| First author | country | Focussed on | # pt |
|---|---|---|---|
| | | **Many organs** | |
| Wiseman | US | Zevalin registration 4 centres trial | 179 |
| Cremonesi | IEO Italy | High activity myeloablative study - Dosimetry for tailored treatment | 22 |
| Fisher | US | MIRD dose estimate report 20 | 10 |
| Chiesa | INT Italy | High activity myeloablative study - Absorbed dose & BED | 27 |
| Bishof Delaloye | Swiss - Germany - The Nederlands | Standard activity phase III multicentre study | 57 |
| Pacilio | Rome Italy | Standard activity study – Absorbed dose & BED | 8 |
| | | **One specific organ** | |
| Baechler | US & Swiss | Kidney absorbed dose | 17 |
| Winter | US | Liver absorbed dose escalation study + chemotherapy | 6 of 44 |
| Assié | France | Comparison between conjugate view and **SPET** | 6 |
| | | **Red marrow** | |
| Meredith | US | Red marrow dosimetry by lumbar vertebrae imaging method | 8 |
| Ferrari | IEO Italy | Red marrow dosimetry by lumbar vertebrae red marrow aspirate | 8 |
| | | **Abnormal biodistribution** | |
| Aricò | IEO Italy | Abnormal biodistribution | 2 |
| Conti | US | Abnormal biodistribution | |

**All studies conducted by planar imaging except Assiè et al**

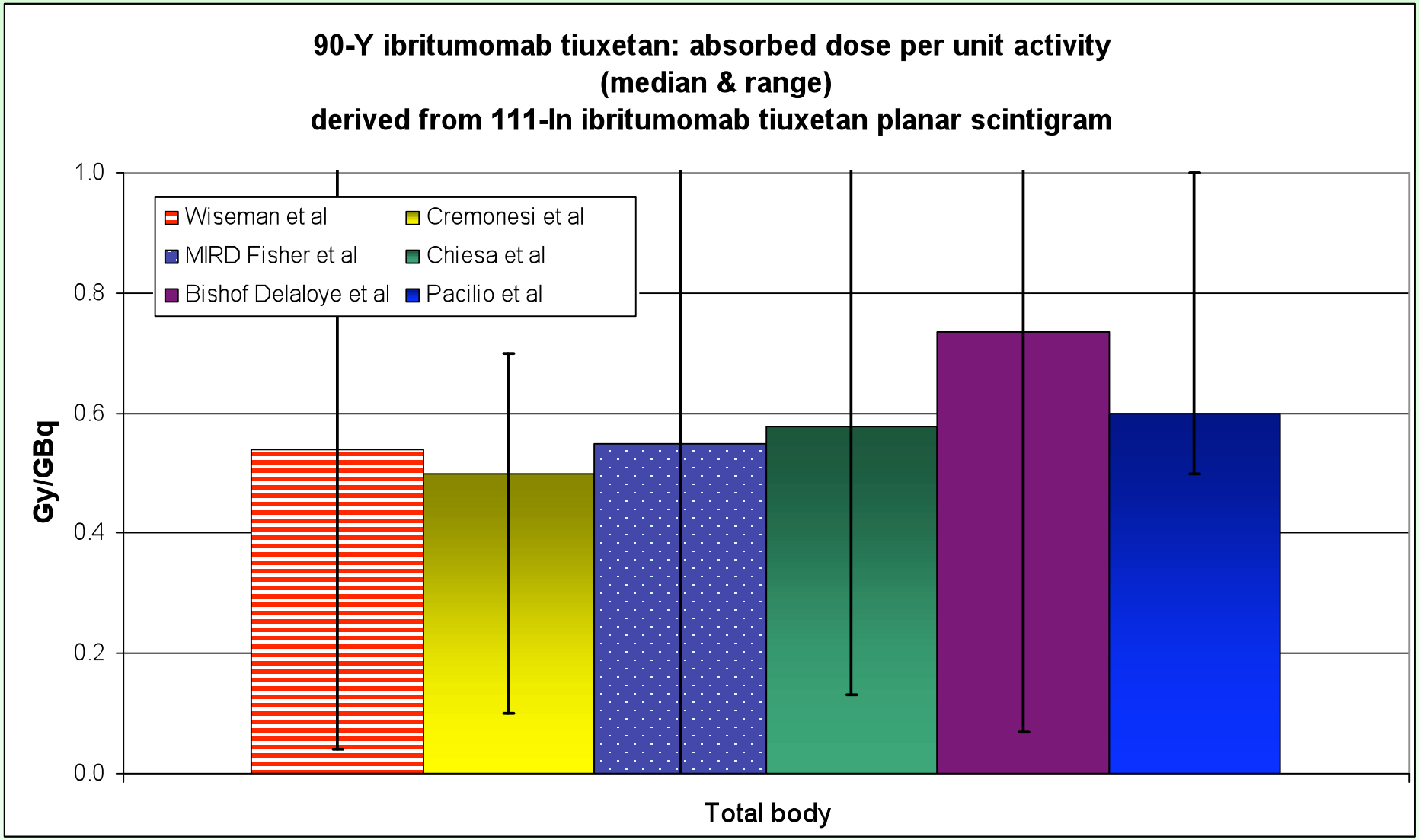
# Dosimetric studies on many organs

Different results from different methods, and different patient samples



# Total body dose:

## the simplest calibration gives excellent agreement between centres



# Large inter-patient variability:
## general agreement
## (importance of dosimetry)

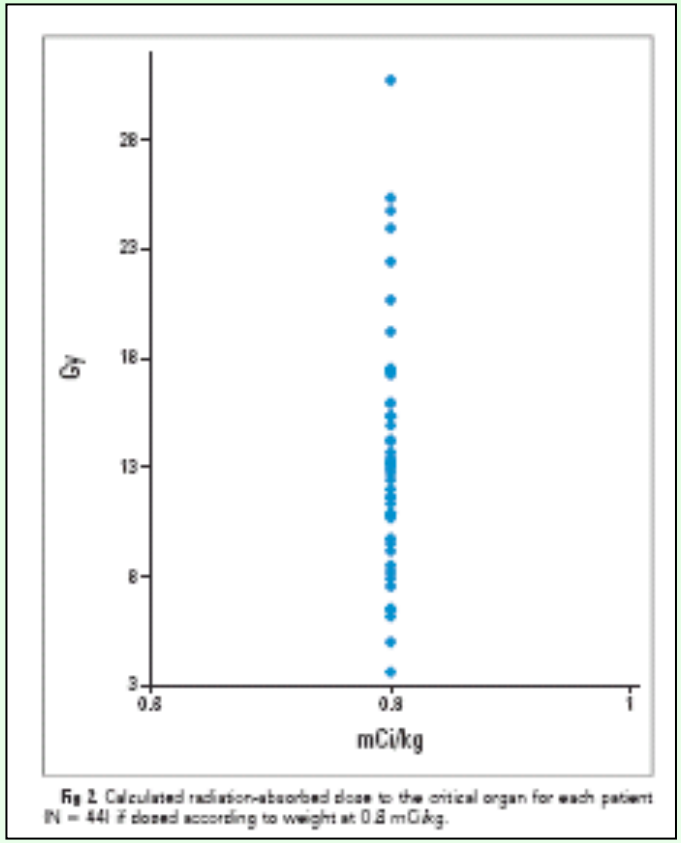
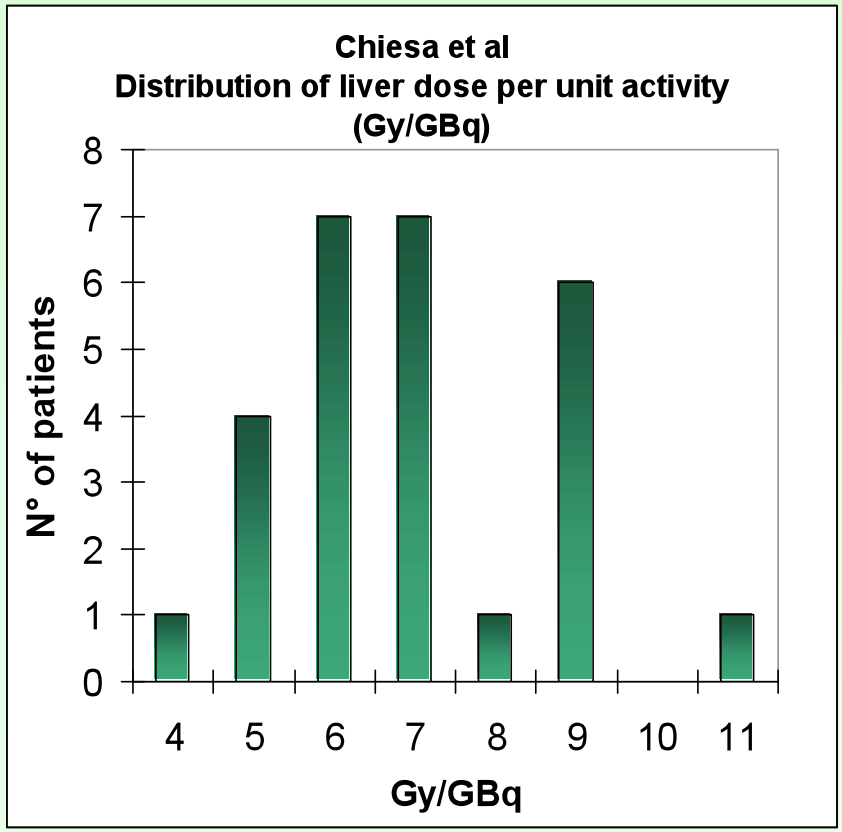



Fig 2. Calculated radiation-absorbed dose to the critical organ for each patient (N = 44) if dosed according to weight at 0.8 mCi/kg.

Winter et al JCO 27 (2009)



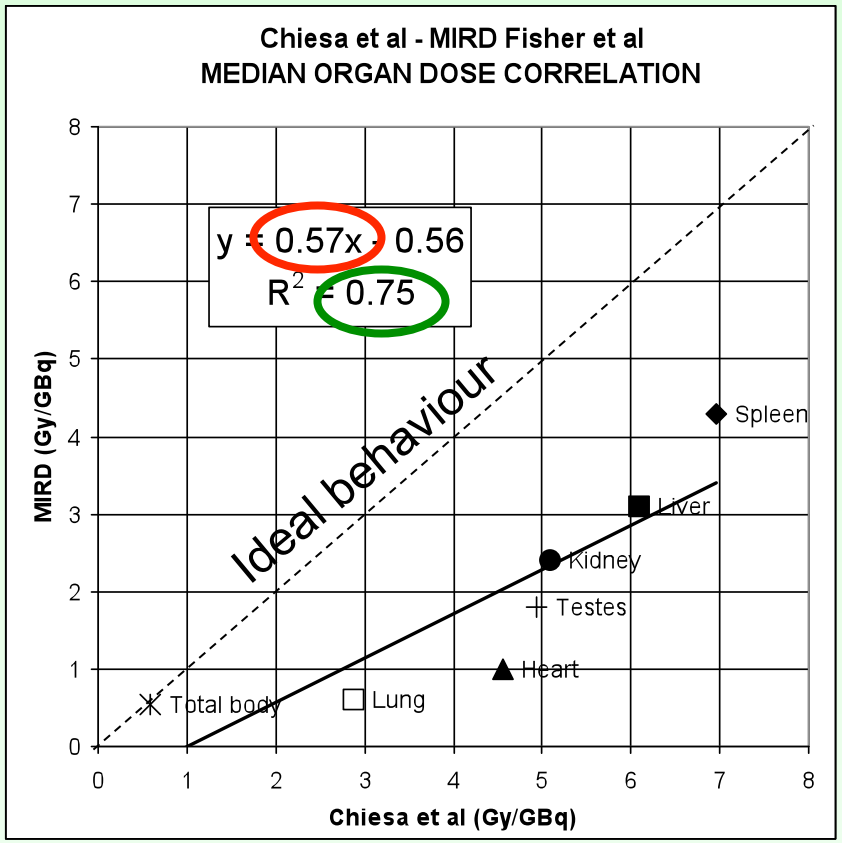

Chiesa et al Eur J Nucl Med Mol Im (2009) 36 1745-1757

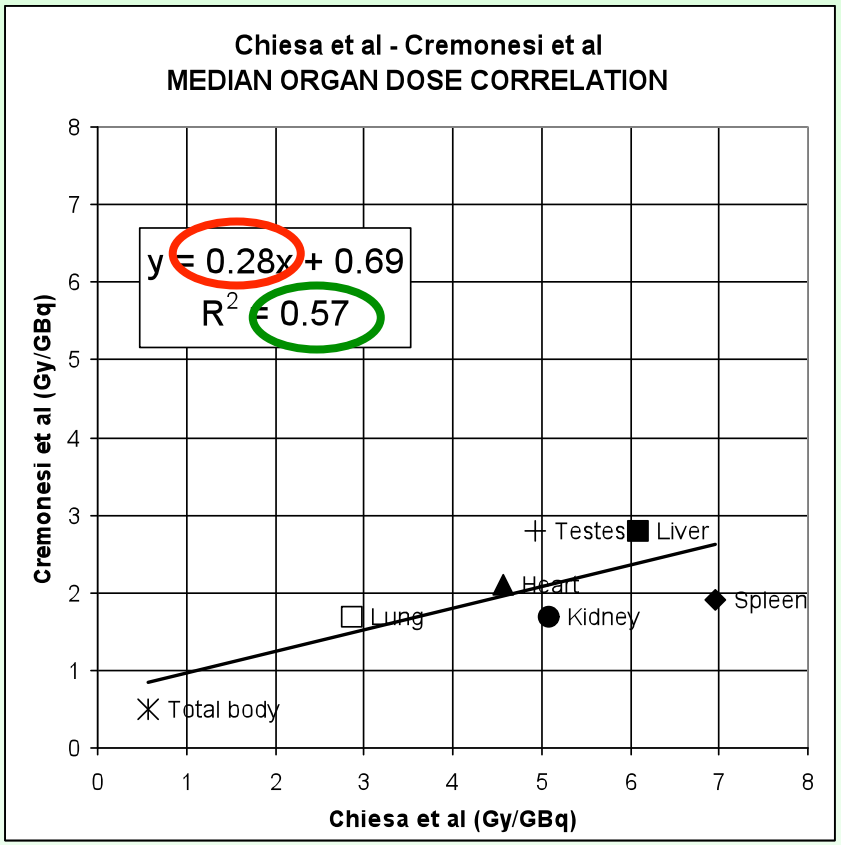
# Large inter-centre variability

The large error bars and different patient samples make difficult to obtain statistically significant differences organ by organ.

However, considering two the set organs doses derived by two centres as two set of paired data, some interesting information could be deduced.

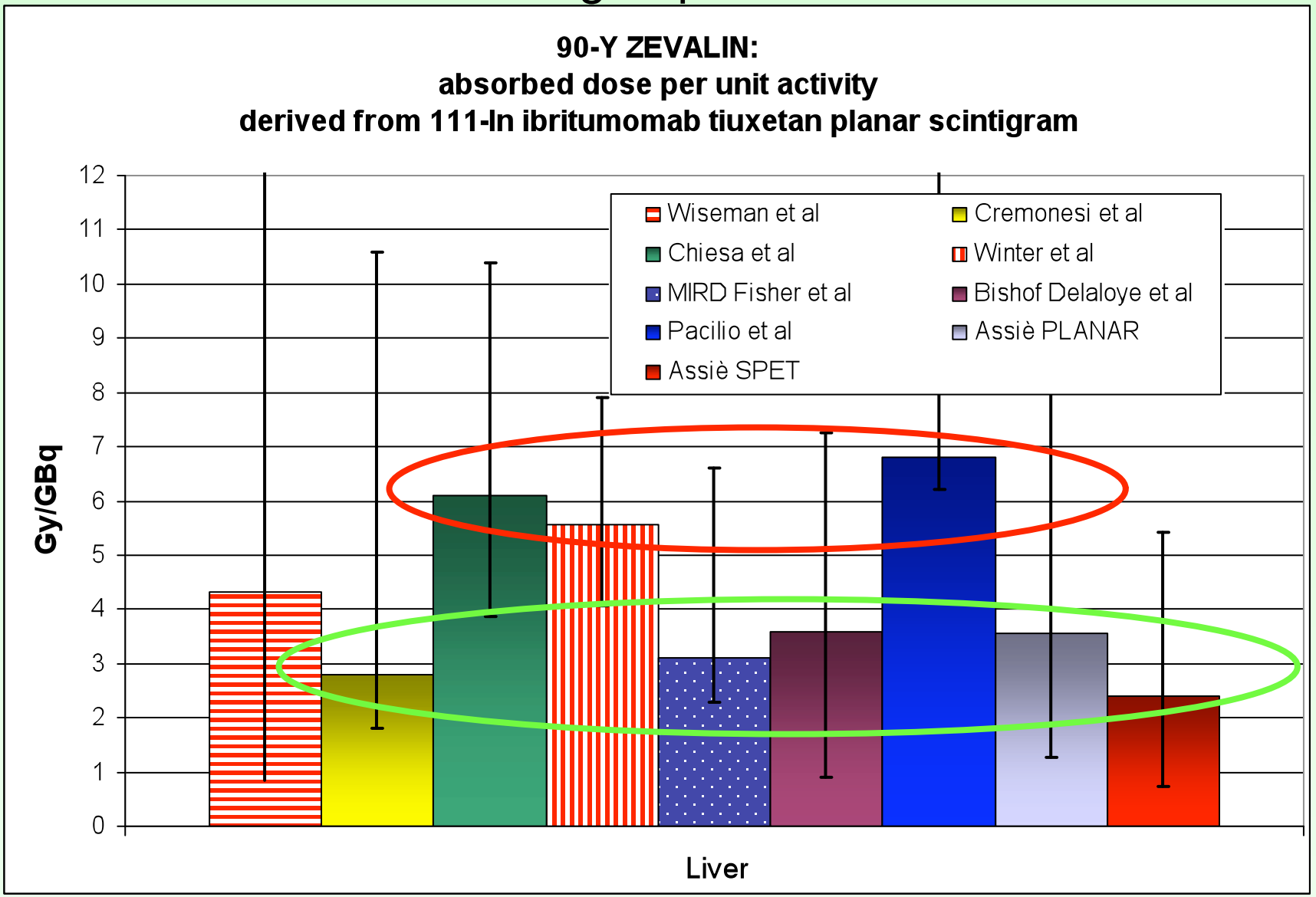
For instance, Chiesa's values are "correlated" but definitely higher than those by Cremonesi & Fisher



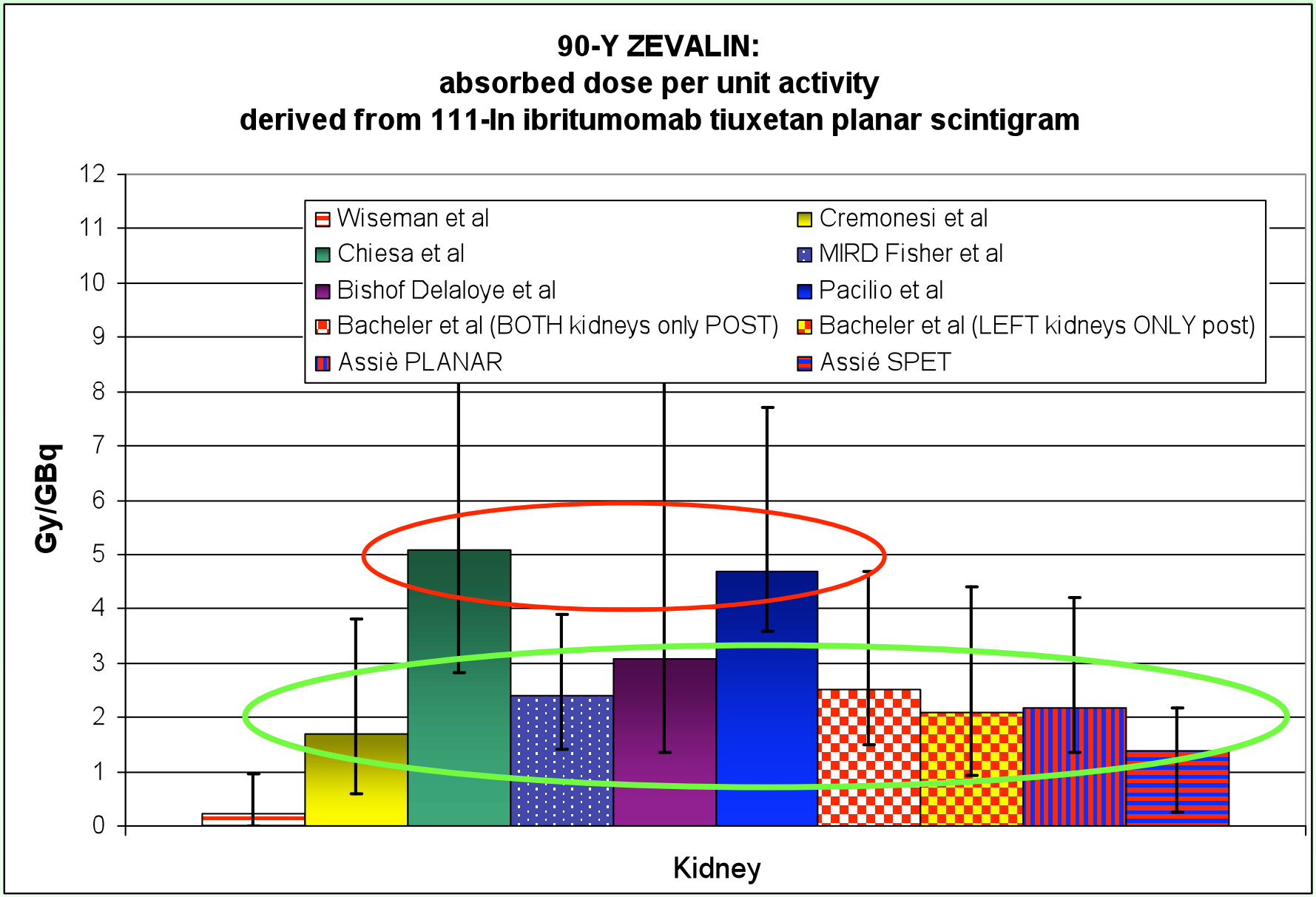
# Liver - additional studies:

## values seems grouped in two classes



# Kidney: additional studies

## values seems grouped in two classes



# Factor affecting quantification in organ dosimetry

MIRD 16: Siegel et al J Nucl Med 1999; 40:37S-61S

**Calibration of gammacamera**

$$A = \sqrt{\frac{I_A \, I_P}{\exp(-\mu(^{111}I) * T)}} * \frac{f}{C}$$

- Photon attenuation in patient body
- Background of overlapping structures
- Scatter
- Self absorption of source object
- Partial volume effect for small objects
- Dead time count losses (only after therapeutic activity)

$$ACF(^{111}In) = \sqrt{\frac{1}{\exp(-\mu(^{111}I) * T)}}$$

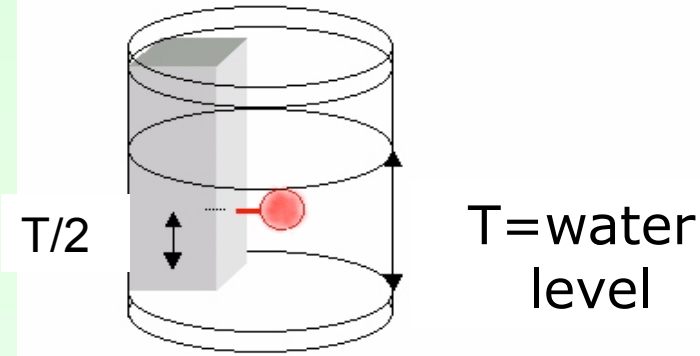
# Absolute gamma camera calibration Chiesa's Factor C: counts → activity

MIRD 16 pseudoextrapolation numbers

Conjugate view formula reversed during calibration

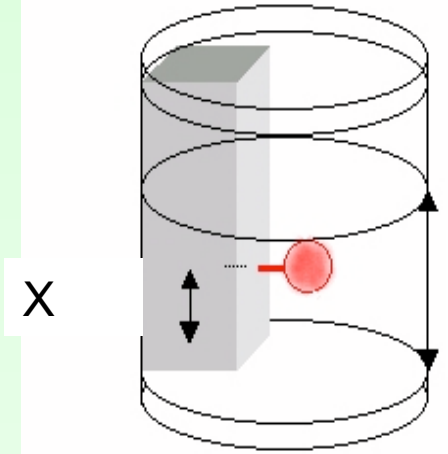
$$C\exp(-\mu(^{111}I)/2*T_n) = \sqrt{\frac{I_A(T_n)\,I_P(T_n)}{}} * 1/A$$

- Different methods are proposed by MIRD 16
- Chiesa et al: 20 mL spere of known activity in water (closer to the clinical condition)
- Scan for $T_n$ = 0, 4, 8 ….cm
- Spere always at $T_n/2$
- Method indicated by O. Sharkey (priv. Comm 2001)



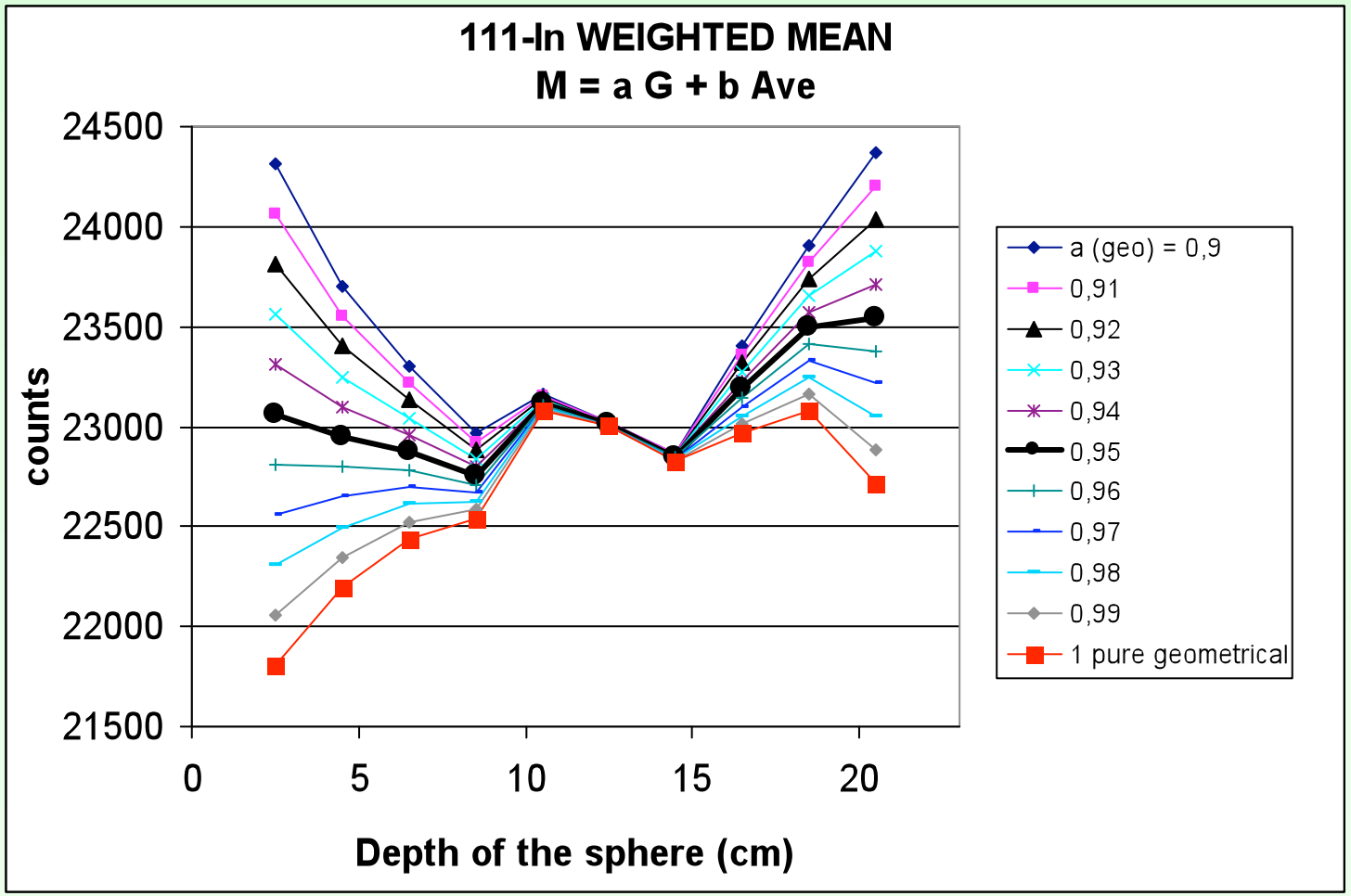
# Experimental dependence of geometic mean on depth

- Keeping fixed the water level (T=20 cm), acquire at diffent depth X
- Consider the geometrical mean G and the arithmetical mean Ave of counts $I_A$ and $I_P$
- Make a linear combination M of them, with a + b = 1
- M = a G + b Ave
- Plot M vs X for different choices of (a,b)



Geometric mean is not independent from depth (5% variation)
Weighted mean M is less dependent on depth of the source
(Sharkey O. , private comm)

Expanded scale




GE INFINIA

1" CRYST

$^{111}$In

a=0.95

b= 0.05

$^{131}$I

a=1.00

b= 0.00

# Absolute gammacamera calibration
## Fisher's factor C & $\mu(^{111}In)$

- Calibration with source in air: 10 mL source lying on the patient bed (Dose overestimation ?)
- Calibration sources of different size were adopted for different organs
  - 150 mL kidney
  - 50 mL vertebra
- $\mu$(111In) obtained by phantom resembling each single patient
- Kidney were studied on posterior image only. When right kidney was encapsulated > 25% in liver, only left kidney was considered.

- Different C, $\mu(^{111}In)$ for each organs and each patient
- **Basic idea: make a phantom copy of the patient and derive data from there**
- Highly individualized dosimetry - Practicability ?

# Absolute gammacamera calibration
# Dependence on object size
## MIRD 16 pseudoextrapolation number
Chiesa et al unpublished data – GE Infinia II VC 1" Crystal

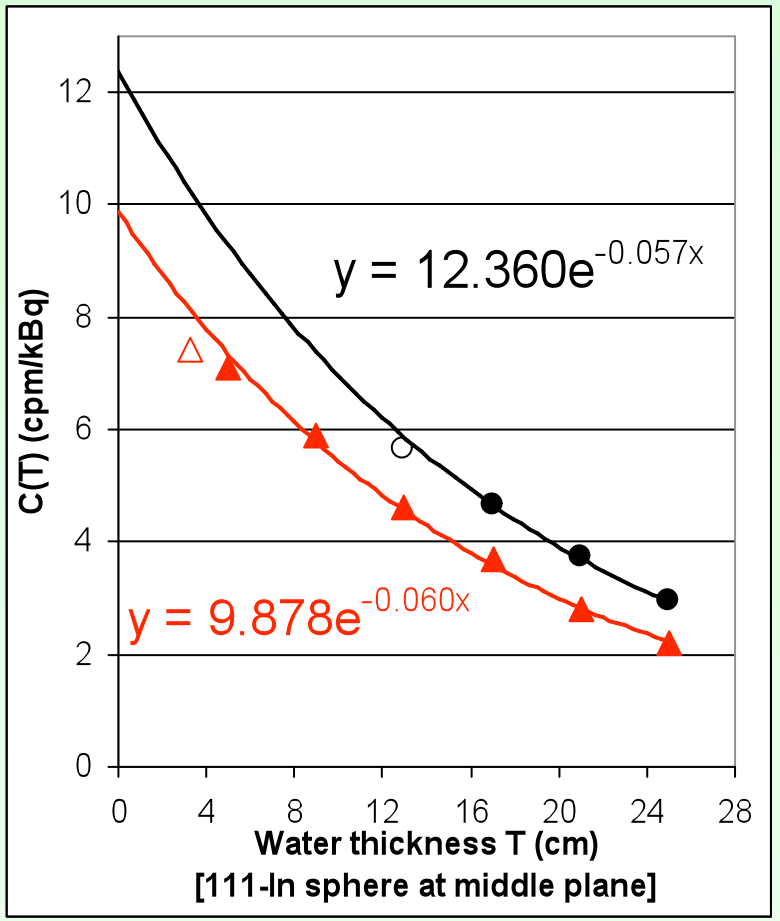
- 20 mL SPHERE IN WATER
- $C_{extrapol}$ = **9.9** cpm/kbq
- $C_{air}$ = 7.4 cpm/kbq
- $C_{air}$ → 33 % of activity overestimate
- Experimental $\mu(^{111}In)$ also obtained $\mu(^{111}In)$ = 2 x 0.060 / cm = 0.12 / cm

Advantage:

- scatter correction somehow included

Possible drawback:

- Will these $C_{extrapol}$ & $\mu(^{111}In)$ be the same for large organs (liver) ?
- 2000 mL BOTTLE IN WATER
- $C_{extrapol}$ = **12.4** cpm/kbq (**25% dose reduction !**)
- $\mu(^{111}In)$ = 2 x 0.057 / cm = 0.119 / cm (identical)




**Chiesa's doses must be reduced by 25%**

# Patient relative gammacamera calibration

- Some author obtain the calibration factor C as ratio between total cpm in the first scan (without micturition) and the known injected activity
- Total body attenuation should be included

TWO PROBLEMS

- Total body attenuation is strongly non uniform (arms & legs vs trunk) and affected by low accuracy
- Relative calibration factor depends on the biodistribution, through the attenuation
- Slow organ uptake (antibodies) vs fast organ uptake (radiopeptides)

# Example of patient relative gammacamera calibration

- 111In ibritumomab tiuxetan: first scintigram without voiding; 85 kg adult male
- $C_{pt} = \sqrt{(I_{ant}\ I_{post})} / A_0 =$ 5.6 cpm/kbq
- Neglecting attenuation correction gives too low C
- We include the AVERAGE TB attenuation. This is affected by limited accuracy of a TB ROI contour on trasmission scan (empty spaces betweeb arms and trunk, and between legs).
- Thickness from transm scan is 9.7 cm
- $C_{pt} = \sqrt{(I_{ant}\ I_{post})} / A_0 \times \exp(\mu \bullet 9.7 / 2) =$ 9.9 cpm/kbq
- Tickness from patient weight /area is 12.7 cm
- $C_{pt} = \sqrt{(I_{ant}\ I_{post})} / A_0 \times \exp(\mu \bullet 12.7 / 2) =$ 11.9 cpm/kbq
- Including self absorption f=0.91
- $C_{pt} = \sqrt{(I_{ant}\ I_{post})} / A_0 \times \exp(\mu \bullet 12.7 / 2) \bullet f =$ 10.8 cpm/kbq

ABSOLUTE CALIBRATION

- $C_{air}$ sphere = 7.4 cpm/kbq
- $C_{extrapol}$ sphere = 9.9 cpm/kbq
- $C_{extrapol}$ BOTTLE = 12.4 cpm/kbq IT SHOULD GIVE THE LOWEST DOSES

# Test of relative calibration: attention must be payed with fast kinetics

- 111In pentetreotide 185 MBq; Two patients

Injection

WB without micturition: 100 %

2 h waiting without micturition

WB without micturition : 92%

Injection

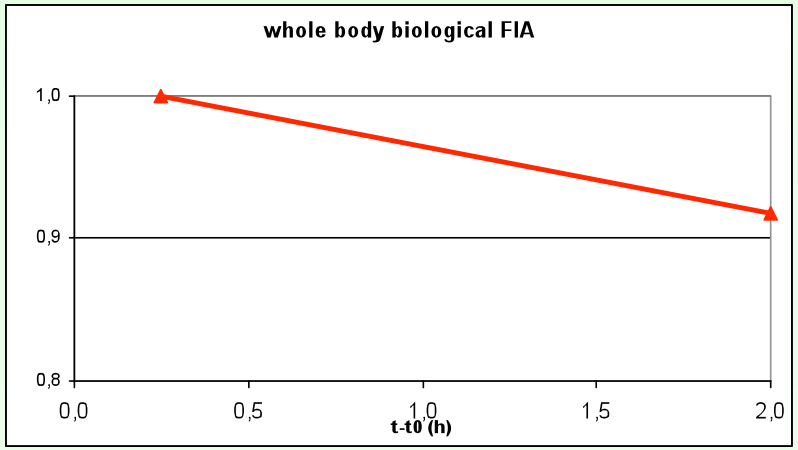
WB without micturition: 100 %

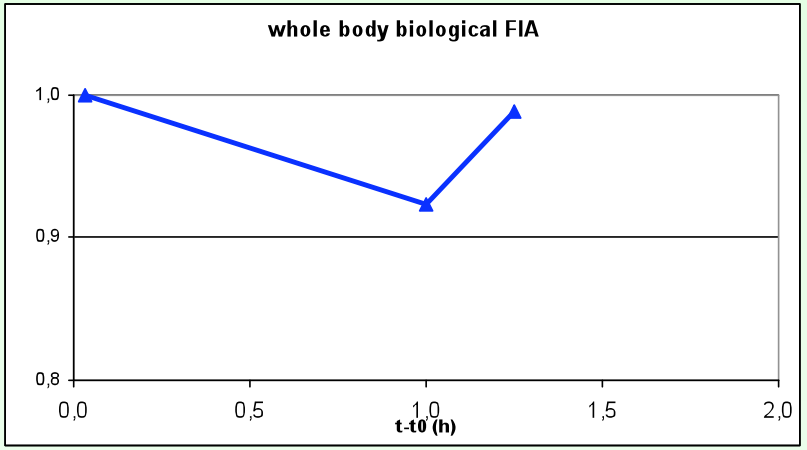
1 h waiting without micturition

WB without micturition : 92%

Micturition in bottle

WB with urine bottle: 99%




**TOTAL BODY COUNTS COUNTS ARE NOT SIMPLY RELATED TO ACTIVITY !**

# Attenuation correction coefficient: Fisher et al MIRD dose estimate report 20

The importance of attenuation correction in quantitative imaging has long been recognized (*20,21*). We obtained attenuation-correction factors using $^{57}$Co transmission images, with and without the patient on the imaging table, according to methods previously described (*22*). For example, the attenuation correction factor for the liver was determined by:

$$ACF_{(^{111}In)} = \left[\sqrt{\frac{N_{nopt}}{N_{pt}}}\right]^{\frac{\mu(^{111}In,Liver)}{\mu(^{57}Co,Liver)}}, \qquad \text{Eq. 1}$$

where $N_{pt}$ and $N_{nopt}$ represent the liver ROI counts in the $^{57}$Co transmission images with and without the patient, respectively.

**MIRD Fisher**

**$\mu$(111In)/$\mu$(57Co) = not reported !**

**Mean liver ACF (111In)= 2.5**

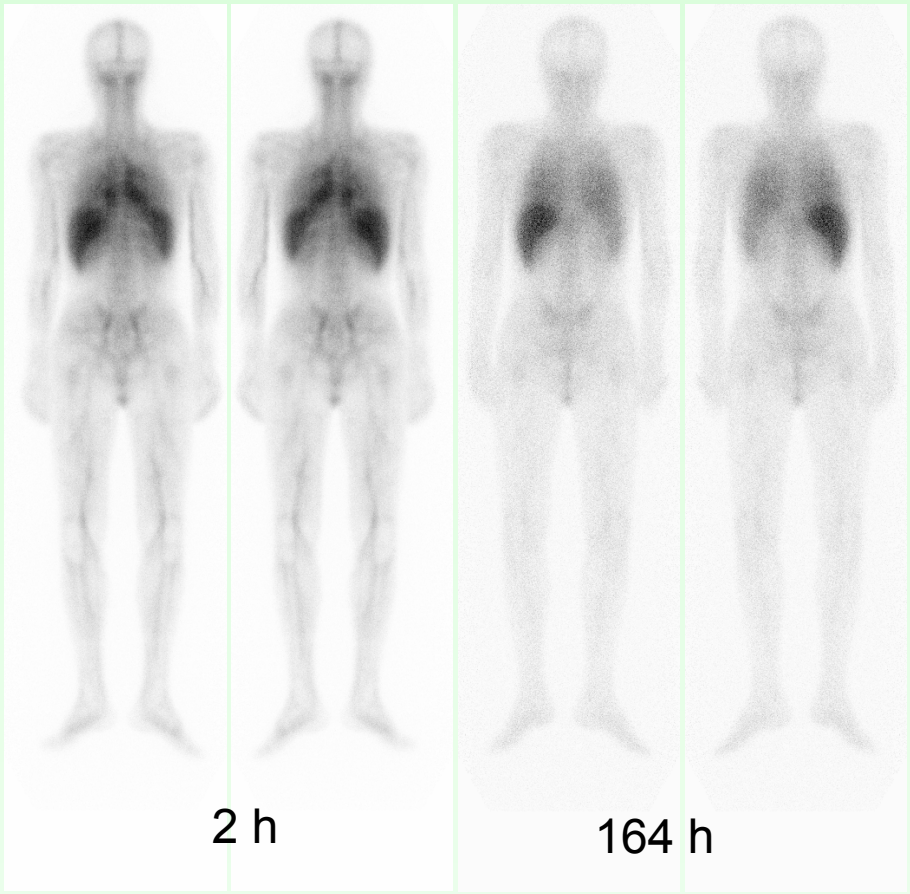
**Chiesa et al**

**$\mu$(111In)/$\mu$(57Co) = 1.025**

**Mean liver ACF (111In) = 4.1**

# Background correction
## (Overlapping activity problem)

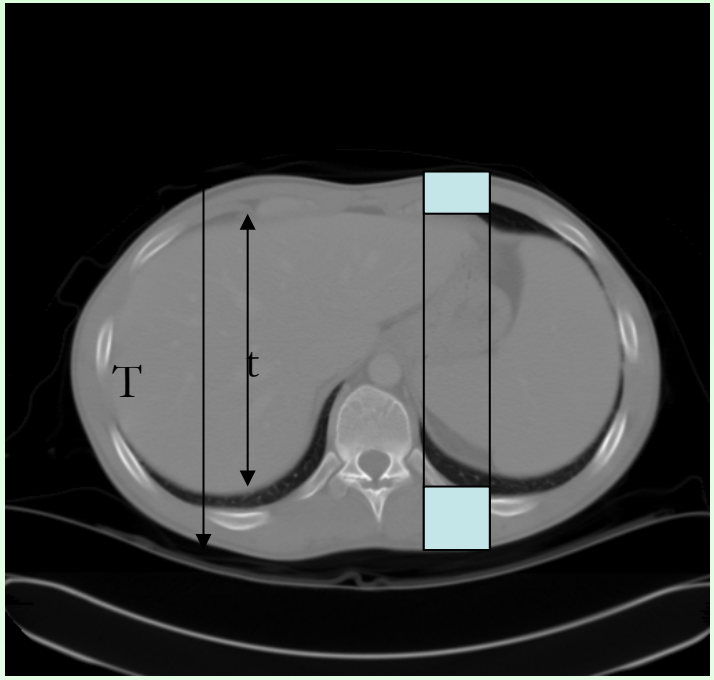
$^{111}$In-hLL2 pz. n° 2




- The main and potentially most serious drawback of quantification in planar imaging (Jonnson et al)
- The amount of background activity is strongly dependent upon the uptake and kinetics of the radiopharmaceutical
- Worst case: antibodies (slowest blood clearance)

# Partial background subtraction for large organs

## Buijs et al J Nucl Med 39 (1998) 2167-2172




$I'_{ANT} = I_{ANT} - I_{BKG}/A_{BKG} * A_{OBJECT} * F$

$F = 1 - t/T$

F is the thickness which really contributes to background

- Average object thickness t = volume/$Area_{object}$
- Volume from CT
- $Area_{object}$ from ROI area (usually overestimated for spatial resolution enlargment)
- T is derived from attenuation measurement

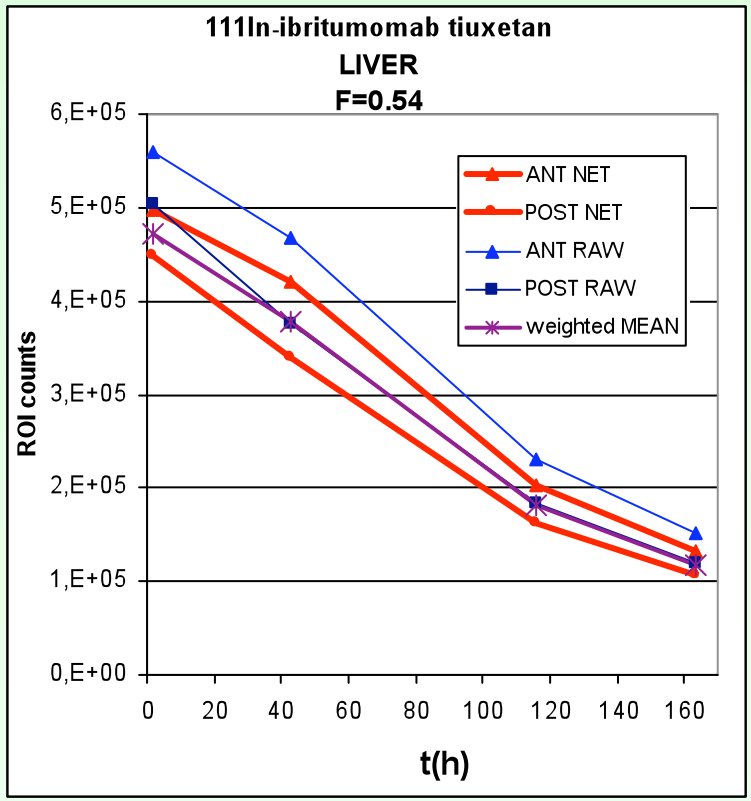
# Impact of liver partial BKG correction

## Sensitive but minor influence

Chiesa et al

Partial BKG F= 0.54

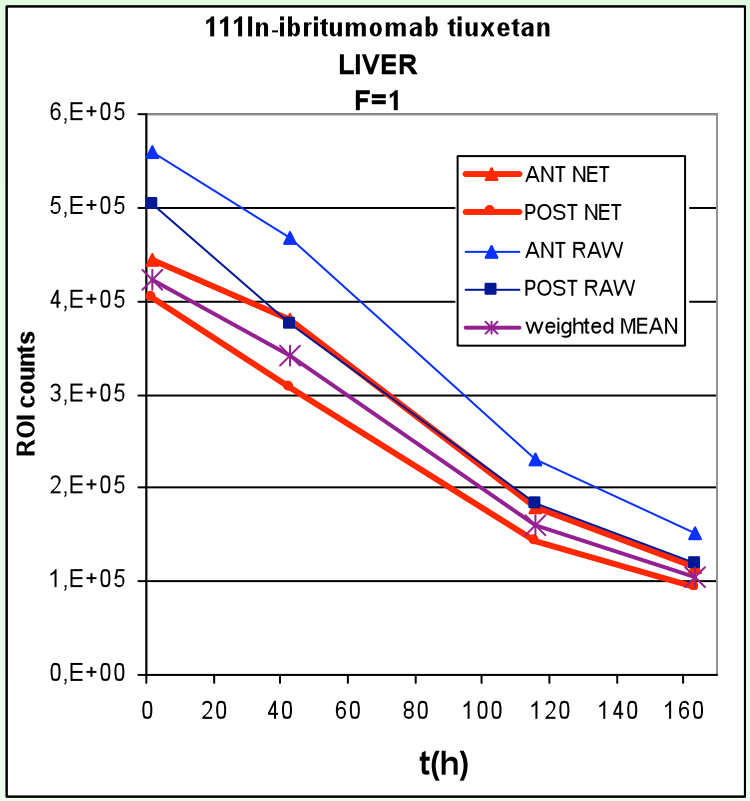
NDs / $A_0$ = 14.8 h




Cremonesi et al

Integral BKG F = 1

NDs / A0 = 13.2 h (-12%)



# Many organ planar dosimetry: different results derives from many difference in methodology

| | Wiseman et al | Cremonesi et al | Fisher et al MIRD | Chiesa et al |
|---|---|---|---|---|
| **Acquisition days** | **0.25, 1, 3, 4-5, 6** | **0, 0.7, 1, 2, 4, 6** | **0, 1, 3, 6** | **0, 1, 2, 4-5, 5-6** |
| **Counts to activity conversion** | Patient relative | Patient relative | Absolute - MIRD16 source in air | Absolute - MIRD16 source in water |
| **Red marrow dosimetry** | blood & sacrum | Blood | Lumbar vertebrae without aorta subtraction | Blood |
| **ROI drawing method** | n/a | Different ant/post ROIs | Identical ant/post ROIs | Identical ant/post ROIs |
| **Attenuation correction** | One value for all organs | Blank/trasm for each organ | Blank/trasm for each organ | Blank/trasm for each organ |
| **Scatter correction** | NO | DW on 171 keV peak | NO | Pseudo extrapolation numbers |
| **Background correction** | n/a | Integral bkg subtraction | Partial bkg subtraction | Partial bkg subtraction |
| **Kidney evaluated** | n/a | Always both | Sometime only the left | Always both |
| **Heart residence time** | n/a | 100% Heart content | Careful ROI drawn | 90% Heart content; 10% Heart wall |
| **AUC calculation** | Multi-exponential fit | Multi-exponential fit | Multi-exponential fit | Sum of trapezoid + monoexponential extrapolation |
| **Individual organ masses** | No for kidneys | Measured on CT | Measured on CT | Measured on CT |
| **S values source** | MIRDOSE 3.1 | OLINDA/EXM | OLINDA/EXM | OLINDA/EXM |

Bishof Delaloye et al: no description of methodology

# RED MARROW

# DOSIMETRY

# RED MARROW DOSIMETRY

$$D_{RM} = \tilde{A}_{RM} S_{RM \leftarrow RM} + \sum_h \tilde{A}_h S_{RM \leftarrow h}$$

SELF (beta) contribution

CROSS (gamma) contribution + beta from bone

TWO MODELS AVAILABLE for MEAN red marrow dose

1. NO MEDULLAR NOR BONE UPTAKE NOR RBC UPTAKE:
   Sgouros G. *Bone marrow dosimetry for radioimmunotherapy: theoretical considerations*. J Nucl Med 1993; 34:689-694 (SELF only from blood)

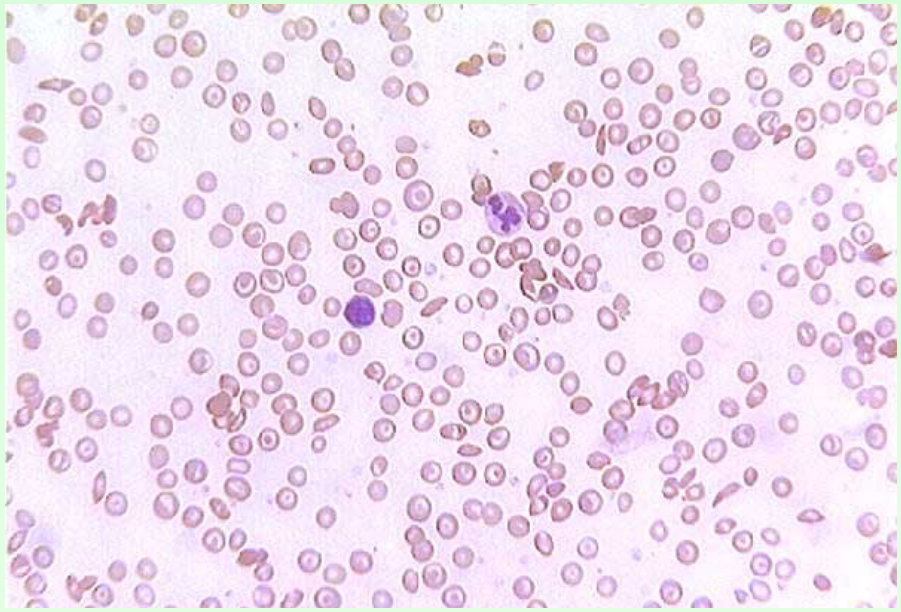
2. Uniform bone or red marrow uptake (ROI on bones): imaging is required

- Non uniform medullar or bone uptake: NO MODEL AVAILABLE

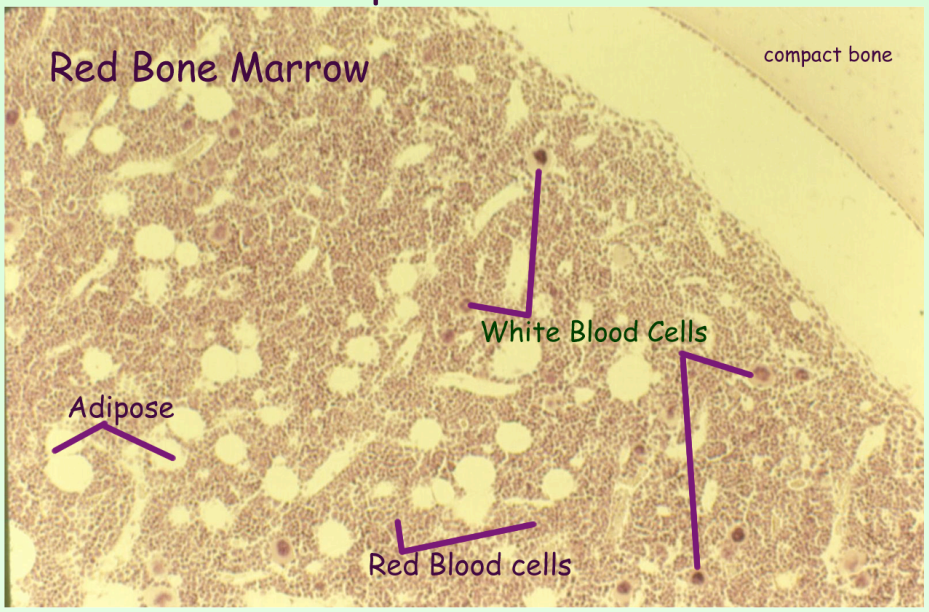
# Sgouros' model

# RADIOACTIVITY IS CONFINED TO PLASMA

Blood



Hematopoeitic Tissue




$[A_{BL}] = [A_{PL}] (1\text{-HCT})$

plasma

$[A_{RM}] = [A_{PL}]$ RMECFF

**Red Marrow To Blood Concentration Ratio RMBLR = RMECFF / (1-HCT)**

**The volume ratio available to plasma.**

## Sgouros' model

## RADIOACTIVITY IS CONFINED TO PLASMA

- Only 1 published paper (Michelsen Acta Physiol Scand 1969)
- Rabbit thigh bone RMECFF = 0.19

$$\mathbf{RMBLR = 0.19/(1\text{-}HCT)}$$

$$\mathbf{A_{RM} = RMBLR\ [A_{BL}]\ m_{RM}}$$

BUT .....

# Sgouros' model
# RADIOACTIVITY IS CONFINED TO PLASMA

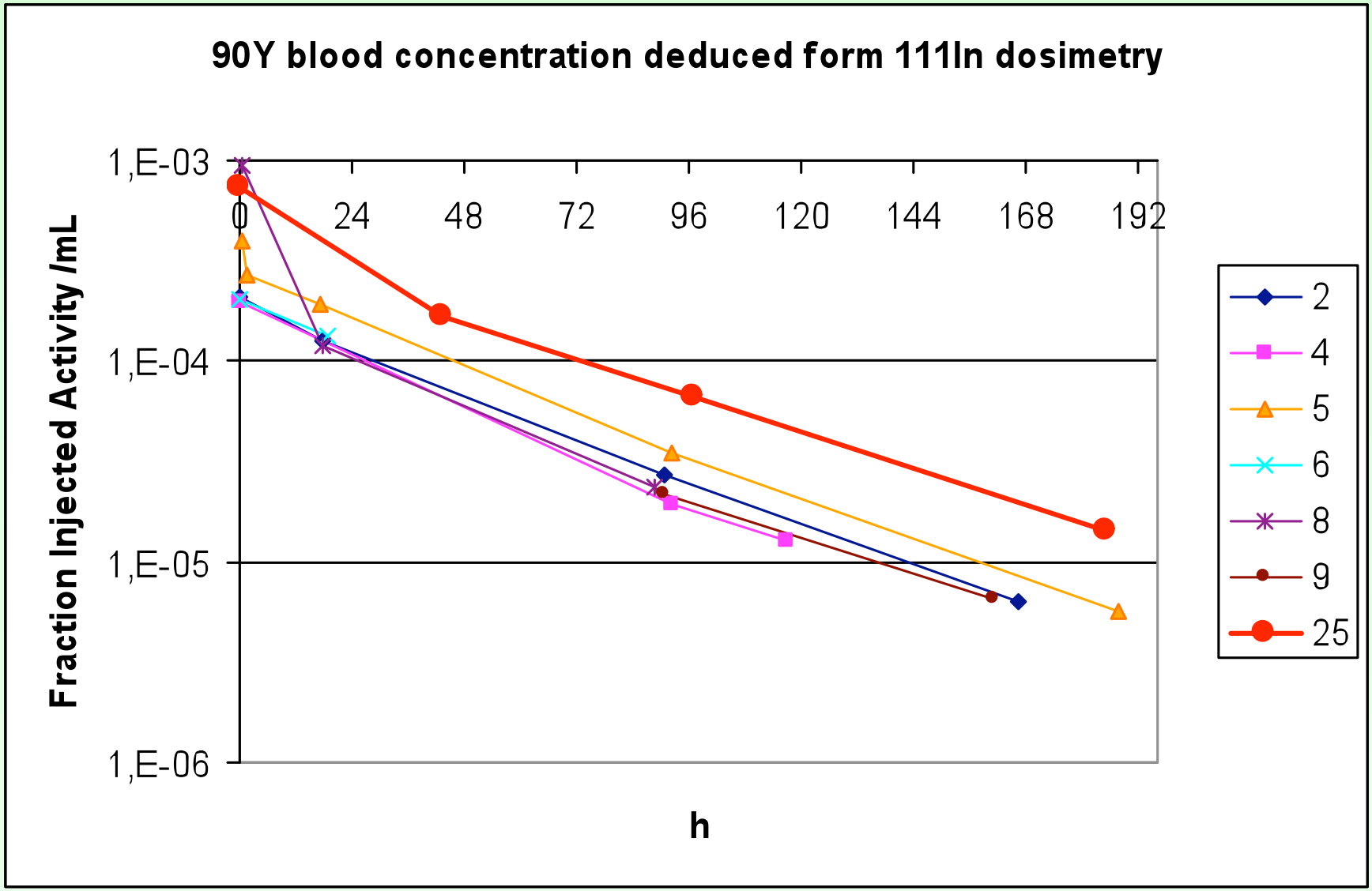
- Evidence of values close to 1, for Fabs (Behr et al Cancer Bioth & Radiopharm 17(4) 2002 445-464)
- The validity of RMBLR equation can be roughly checked from the initial distribution volume

$$V_d = 1/[A_{BL}]$$

- MoAbs $V_d$ = 2.5 – 4 L , $^{131}I$ $V_d$ 17 - 25 L (Sgouros JNM 2005) , mIBG $V_d$ > 100 L , radiopeptides Vd ~ 20 L
- **In cases of $V_d$ larger than blood volume, use conservatively RMBLR = 1**

# Activity concentration in blood

## Devices with periodical volume calibration check


90Y blood concentration deduced form 111In dosimetry
Fraction Injected Activity /mL
1,E-03
1,E-04
1,E-05
1,E-06
0
24
48
72
96
120
144
168
192
h
2
4
5
6
8
9
25

T ½ = 37 ± 5 h

# Red marrow dosimetry - red marrow uptake

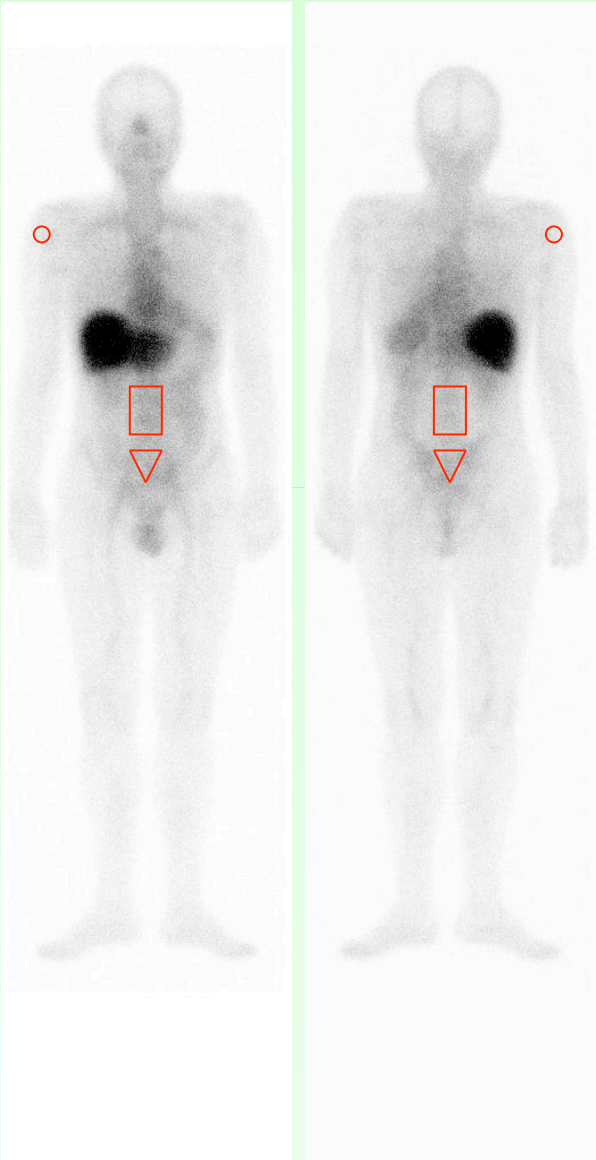
Sgouros, Stabin, Erdi, Akabani (Med Phys 2000)

- A standard fraction of total red marrow is assumed in different bone district
  - L2 L3 L4 = 6.6 %
  - Sacrum = 9.9 %
  - Humerus head = 2.1 %
- A ROI quantification gives the amount of activity in that district
- The total RM activity is obtained dividing by that fraction
- The underlying assumption is that RM uptake is uniform in all districts

PROBLEM

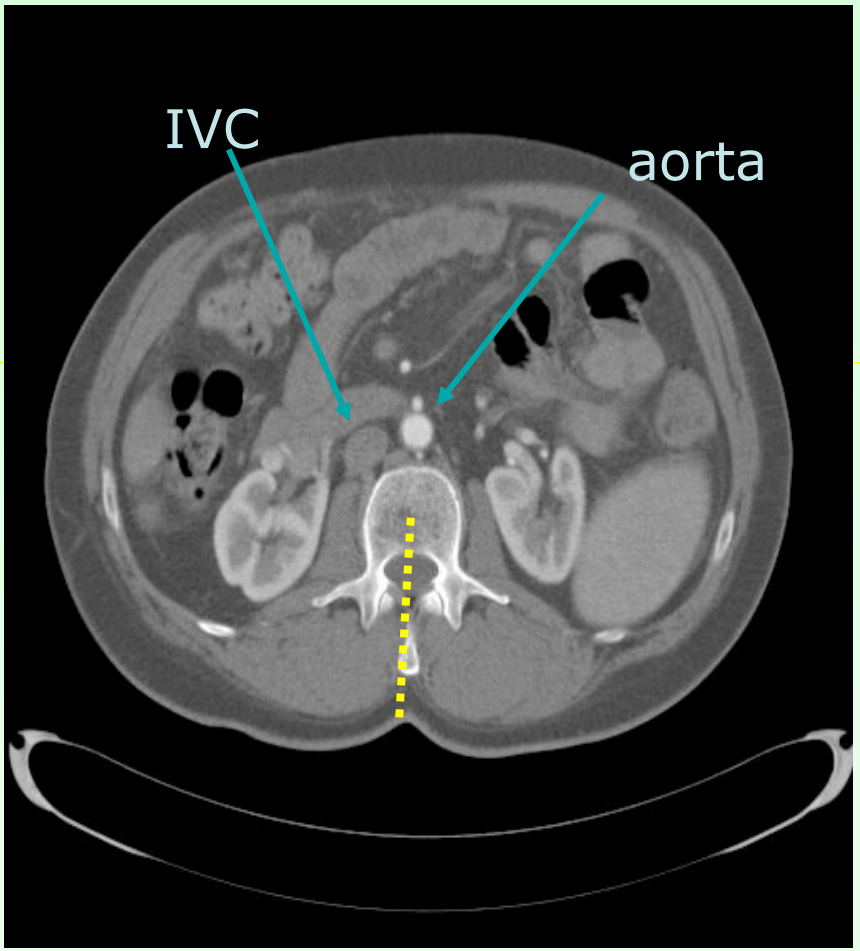
1. 111In ibritumomab tiuxetan uptake is visible in the spine, NOT IN OTER DISTRICT
2. A comparison of red marrow doses deduced from different district gave strong disagreement

- THE RED MARROW UPTAKE IS NOT UNIFORM
- The validity of any mean dose calculation should be carefully interpreted.



# Red marrow dosimetry - red marrow uptake from lumbar vertebra Meredith et al J Nucl Med 2008 49:279-284

- MANDATORY CORRECTION with slow kynetics MoAb: subtraction of the blood content in the tract L2 L3 L4
- Aorta & Inferior vein cava volume are measured on CT (section & length)
- Blood concentration are known from blood samples
- Attenuation correction from known $\mu$ and depth of vertebra
- Only posterior view is used
- Reduction in red marrow dose mean 17% range [9% -24%]

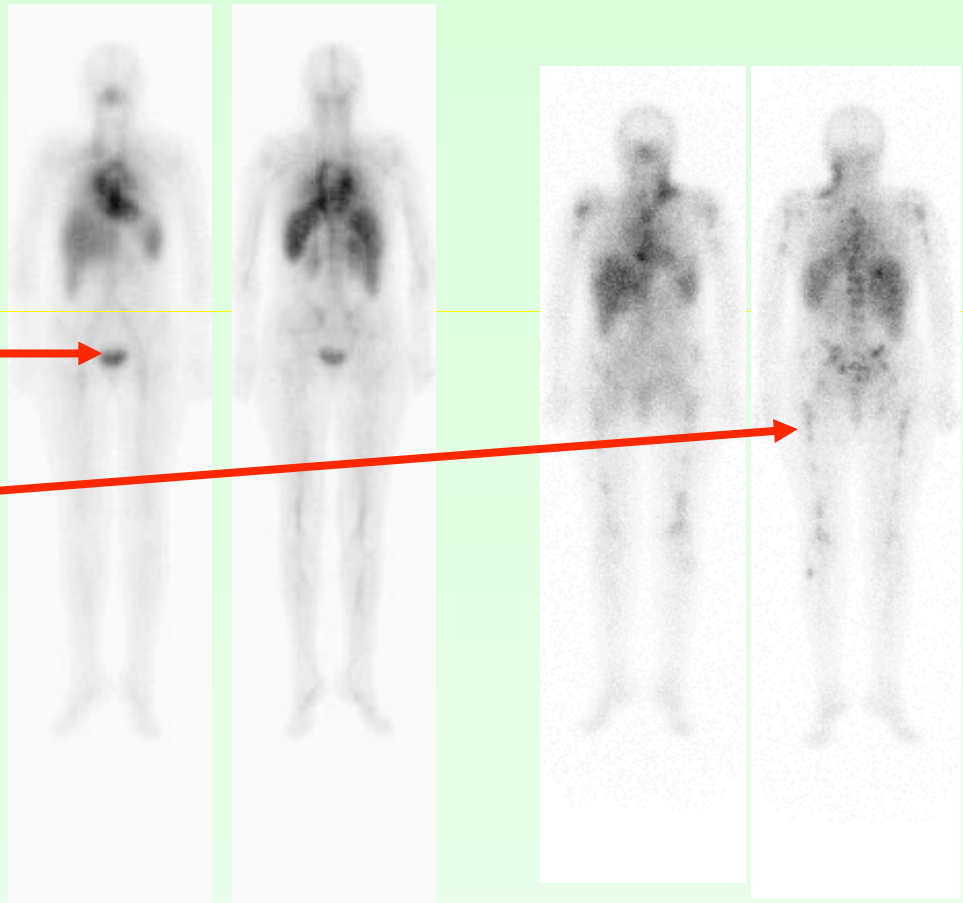


# Red marrow dosimetry
## problems of uniform red marrow uptake

LIMITS

- Background from overlapping vessels

- Non uniform red marrow uptake



$^{111}$In-hLL2 ANTI CD22 24 & 96 h

# Red Marrow dosimetry
# Other organs contribution is COMPLETELY NEGLIGIBLE

$$D_{RM} = \tilde{A}_{RM} S_{RM \leftarrow RM} + \tilde{A}_{RB} S_{RM \leftarrow RB}$$

$$S_{RM \leftarrow RB} = S_{RM \leftarrow TB} \frac{m_{TB}}{m_{RB}} - S_{RM \leftarrow RM} \frac{m_{RM}}{m_{RB}}$$

OLINDA APPROXIMATION

$$S_{RM \leftarrow RB} \approx S_{RM \leftarrow TB}$$

Self irradiation counted twice

# RED MARROW DOSIMETRY
# Guideline in press

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-010-1422-4

GUIDELINES

## EANM Dosimetry Committee guidelines for bone-marrow and whole-body dosimetry

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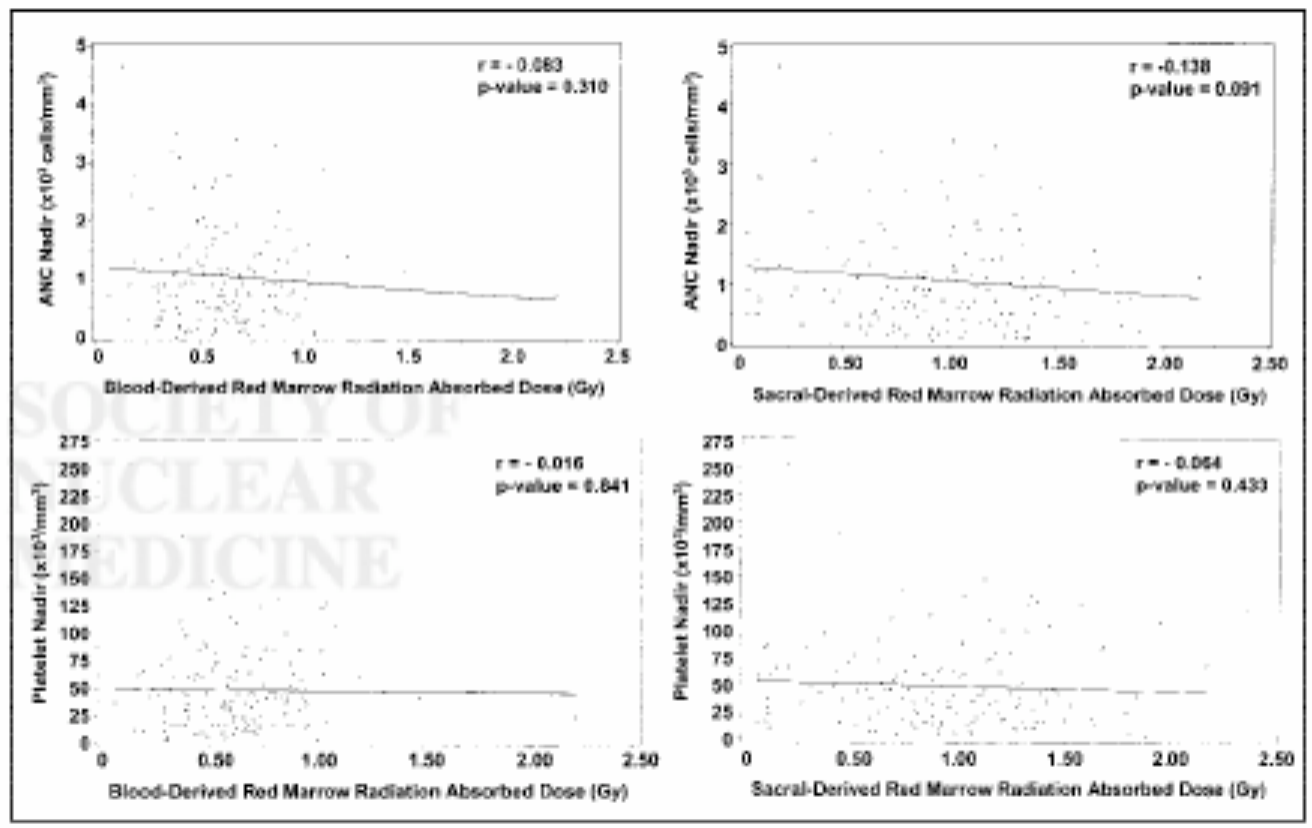
# Red marrow dose toxicity correlation

## Wiseman et al: no correlation → no dosimetry

Blood method | Sacrum ROI

ANC

PLT

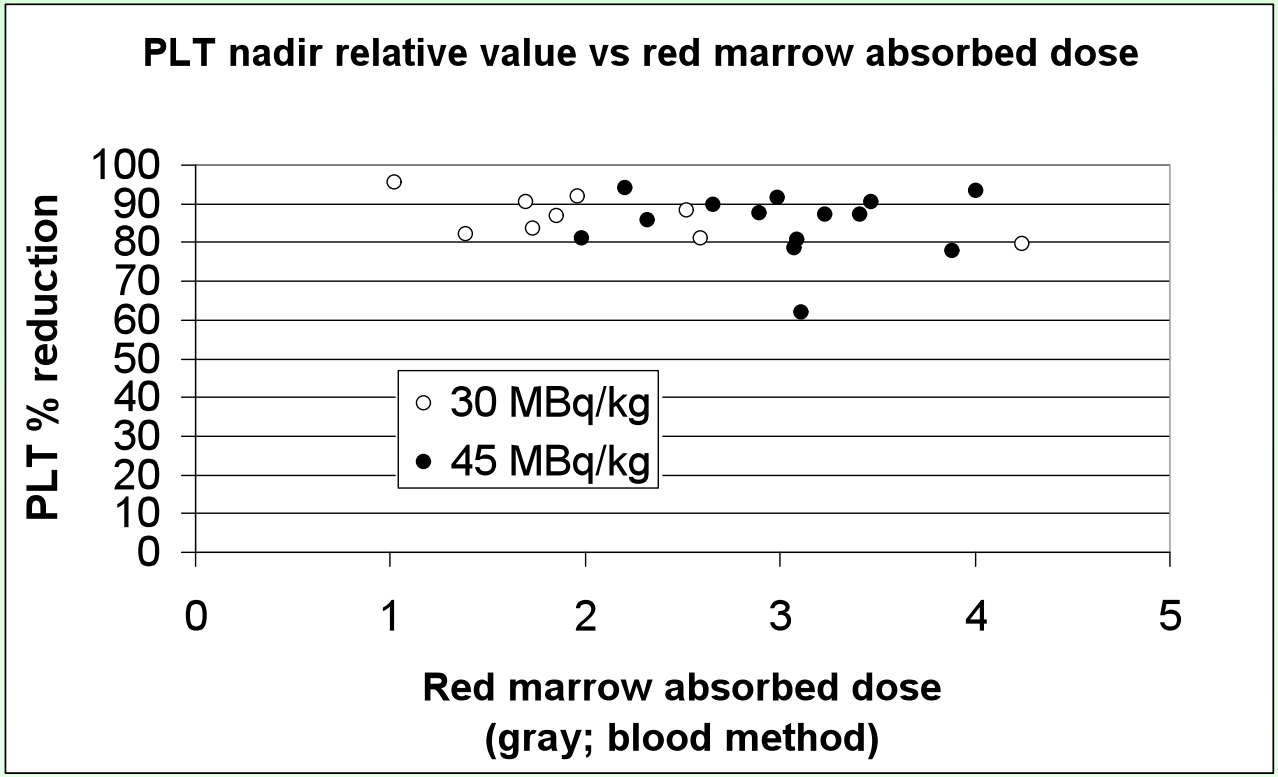



Two possible explanation

a) Wrong calculation method; b) heavily pre treated marrow

# Chiesa et al (myeloablative treatment):

almost complete myelosuppression in all patients, no matter the dose




- Better dose-effect representation with relative reduction
- A sigmoid curve would indicate that we are in the plateau region
- Dose toxicity correlation analysis is meaningless under these circumstances

# Cremonesi et al: EANM congress 2007

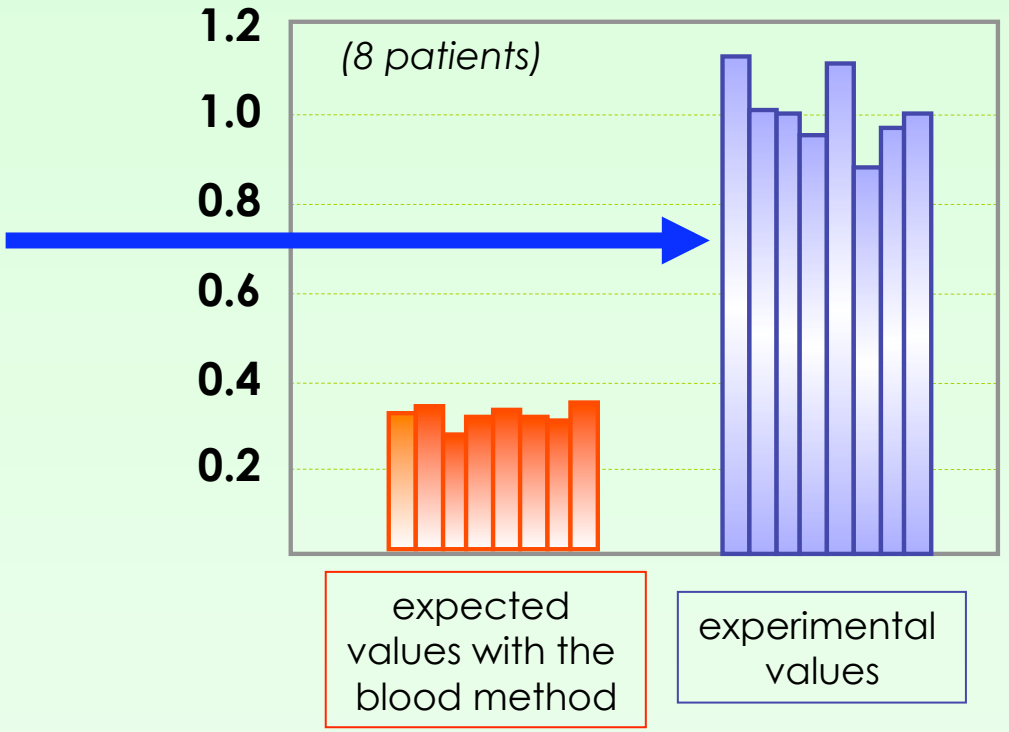
Lumbar red marrow aspirate on 8 patients on day 7 after 111In ibritumomab tiuxetan

Comparison between activity concentration in the aspirate & in the blood

Delicate measurement, but strong indication of red marrow uptake by **lumbar vertebrae**

Experimental values of the "f factor" =

$[A]_{M.aspirate} / [A]_{blood}$

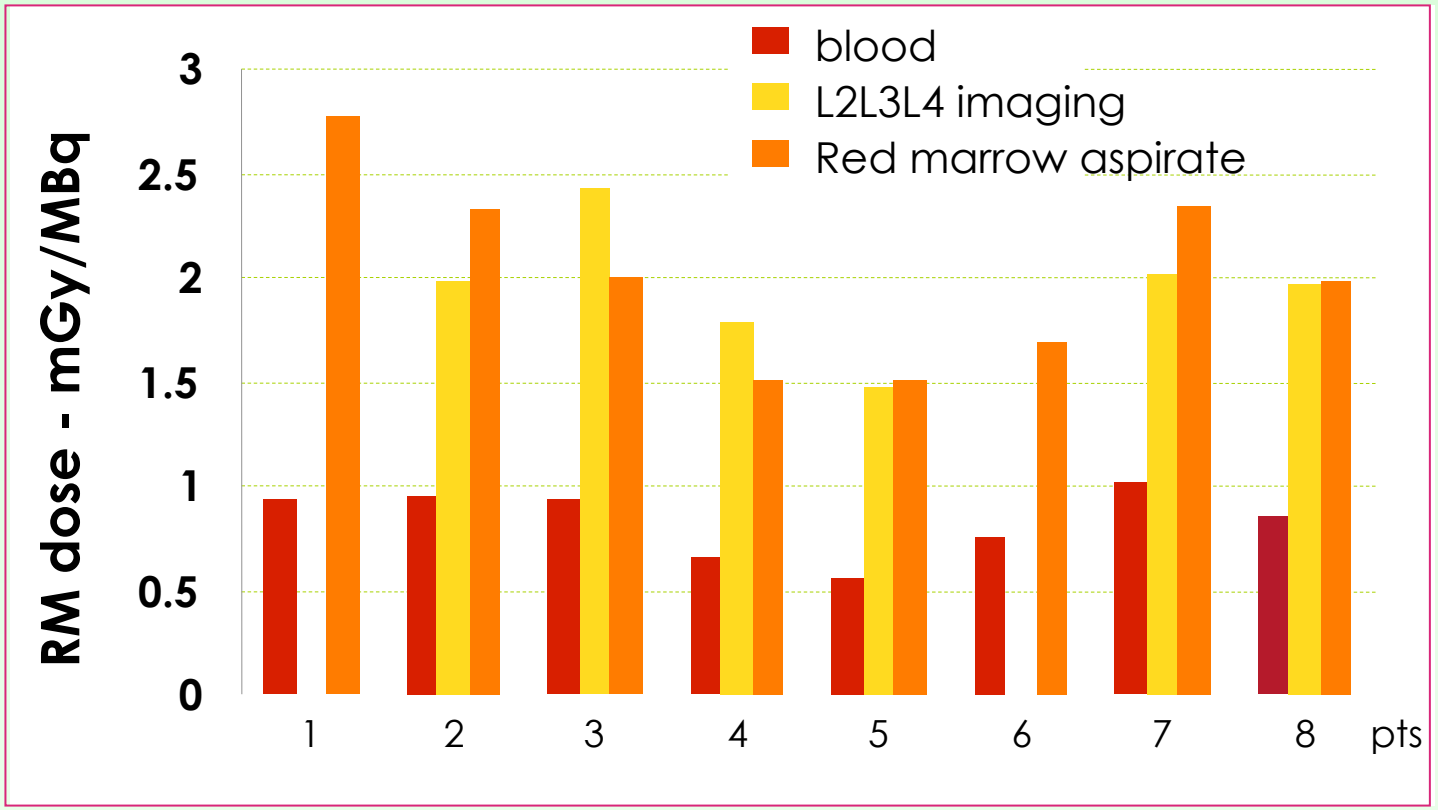



*Courtesy of Marta Cremonesi*

*IEO Milan*

# Cremonesi et al: EANM congress 2007

**Red marrow dose per unit activity (mGy/MBq)**
**evaluated by different methods**




*Courtesy of Marta Cremonesi*

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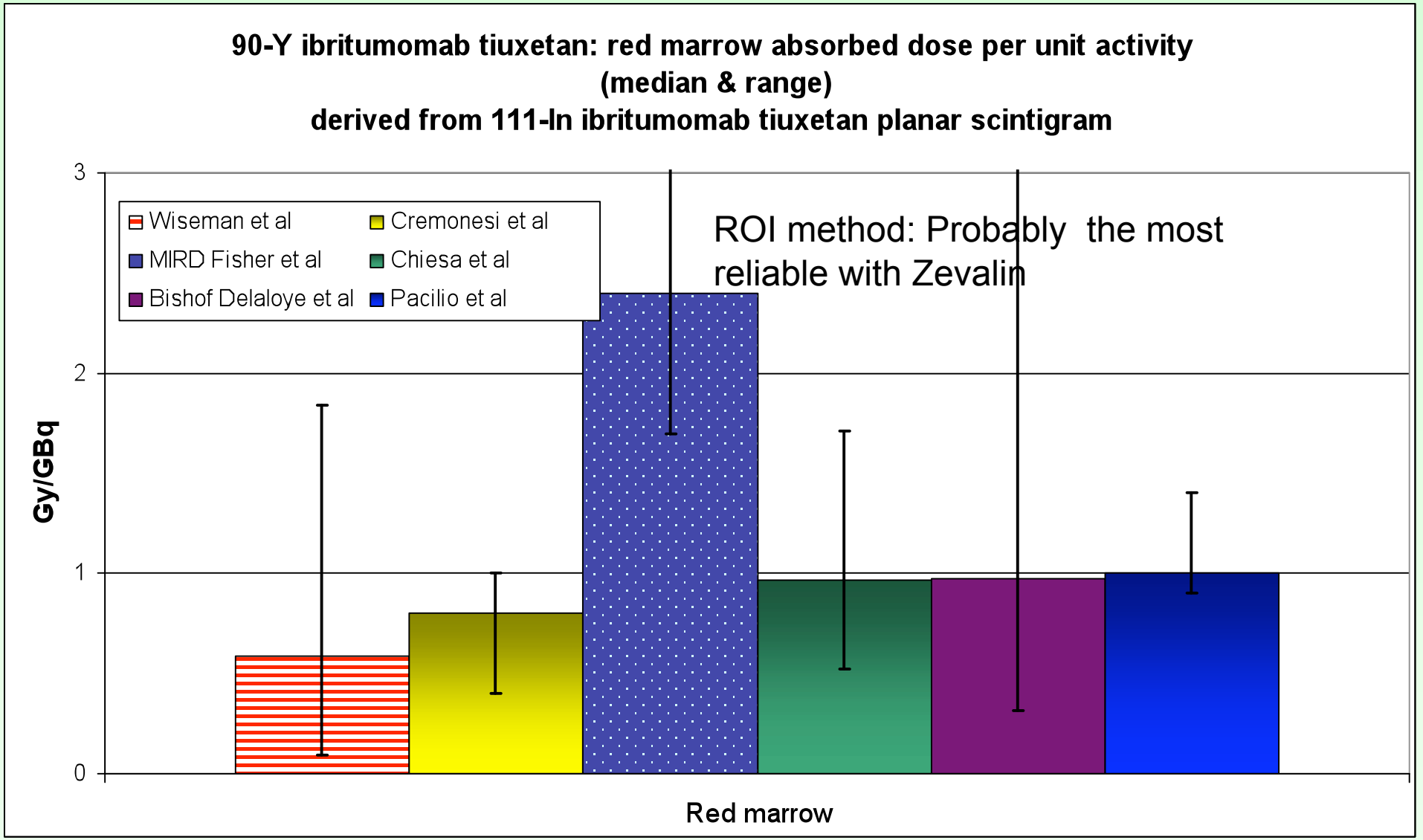
# Red marrow dosimetry: conclusions



# Red Marrow dosimetry: Olinda/EXM approximation

$$D_{RM} = \tilde{A}_{RM} S_{RM \leftarrow RM} + \tilde{A}_{RB} S_{RM \leftarrow RB}$$

$$S_{RM \leftarrow RB} = S_{RM \leftarrow TB} \frac{m_{TB}}{m_{RB}} - S_{RM \leftarrow RM} \frac{m_{RM}}{m_{RB}}$$

In the former MIRDOSE3.1 software, the selection of a zero vs non zero red marrow residence time switched between the use of $S_{RM \leftarrow TB}$ to $S_{RM \leftarrow RB}$

No switch is present in OLINDA ANY MORE, and the following approximation is adopted [M. Stabin private comm]:

$$S_{RM \leftarrow RB} \approx S_{RM \leftarrow TB}$$

Self irradiation then counted twice.

OLINDA $^{90}$Y Zevalin blood based red marrow dosimetry gives a +15% overestimation

# Myeloablative treatment:

## Residual dose to stem cells after re-infusion

ASSUMPTIONS:

- Stem cells dose equal to red marrow dose
- Red marrow dose given only by direct blood irradiation (no remainder of the body contribution – 15% under-estimation)
- Monoexponential blood clearance (well verified apart from initial unbound tracer faster clearance)

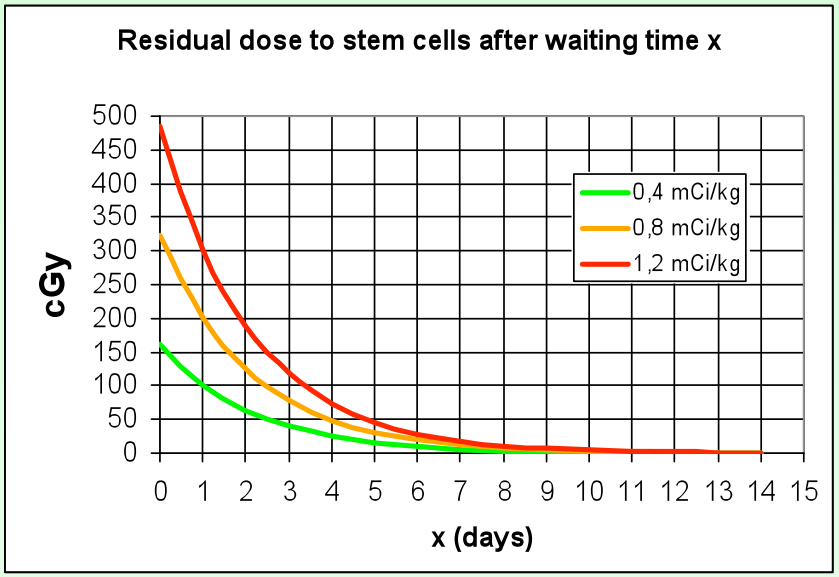
# Residual dose to stem cells

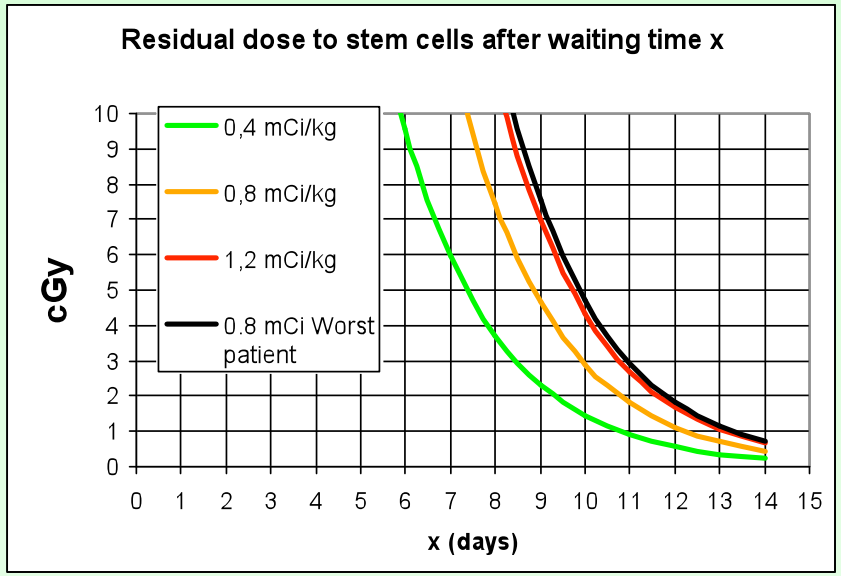
## x = waiting time bfore re-infusion

$$D(x)/ A_0 = \exp(- \lambda_{eff} x) / \lambda_{eff} * S_{RM \leftarrow RM} * RMBLR * FIA_{BL}(0) / mL * m_{RM}$$

- $S_{RM \leftarrow RM} = 5.87 \times 10^{-5}$ mGy/(MBq s)
- RMBLR = 0.34 [Sgouros Stabin et al Med. Phys 27(9) 2000]
- $m_{RM}$ = 1500 g [MIRD11]
- $FIA_{BL}(0)$ / mL: average from patient blood samples during $^{111}$In dosimetry
- $\lambda_{eff}$ : average from patient blood samples

# Residual dose to stem cells




- Of course it is only a model: the trend is correct, but the absolute value is an average.
- It is better to consider specific curves for each patient.
- It is better use ROI method for red marrw dosimetry
- **Marked difference in stem cells tolerable dose foud in literature:**
- **5 cGy or 75 cGy [Bartlett Eur. J. Nucl. Med. (2002) 29:1470-1477 ] ?**

# Progression free survival interval correlates with TB & RM dose

## Bishof Delaloye et al JNM 2009

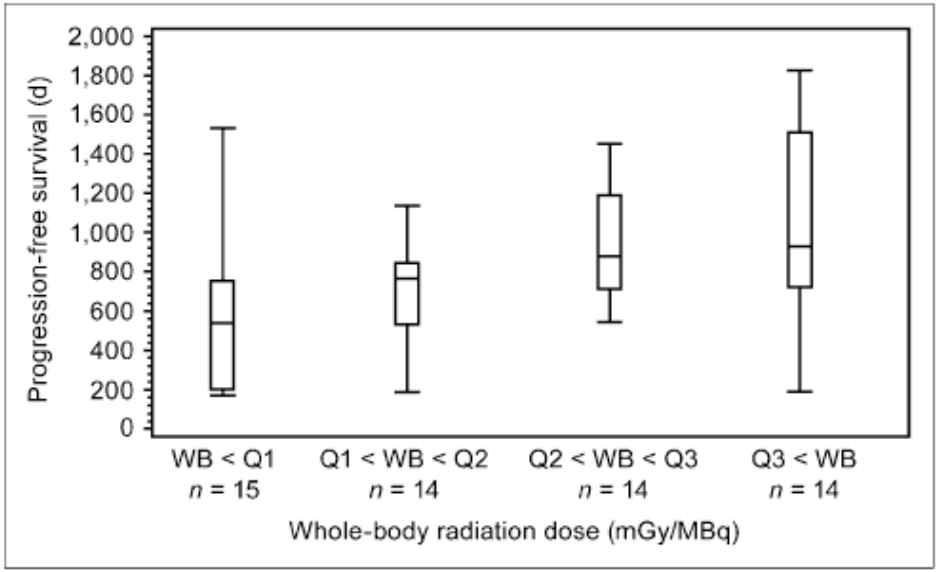



**FIGURE 3.** Correlation of PFS with whole-body (WB) radiation dose. Quartile 1 (Q1) = 0.55 mGy/MBq < WB radiation dose ≤ 0.62 mGy/MBq; quartile 2 (Q2) = 0.62 mGy/MBq < WB radiation dose ≤ 0.73 mGy/MBq; quartile 3 (Q3) = 0.73 mGy/MBq < WB radiation dose ≤ 0.83 mGy/MBq; quartile 4 (Q4) = 0.83 mGy/MBq < WB radiation dose ≤ 1.12 mGy/MBq.

# CONCLUSIONS

- Differences in obtained data seems to be attributable to many details, rather than to a single factor

- Improvement of accuracy and agrabout data eement in internal dosimetry will be reached after:
  - Deep attention to the details of the adopted methodology
  - Standardization and consensus about a practicable methodology

- Careful reporting these details in publications is necessary in this evolution process.

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