Highlights of the EANM 2004 congress and dosimetry symposium, Helsinki, Finland Sept 4-8, 2004

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Nashville, TN, USA

History

Medical Radionuclides: Radiation Dose and Effects
Oak Ridge Associated Universities
Oak Ridge, TN
December 8-11, 1969
Proceedings: U.S. Atomic Energy Commission, AEC Symposium Series 20, CONF-691212, 1970

Radiopharmaceutical Dosimetry Symposium
Oak Ridge Associated Universities
Oak Ridge, TN
April 26-29, 1976
Proceedings: U.S. Food and Drug Administration, HEW Publication (FDA) 76-8044, 1976

Third International Radiopharmaceutical Dosimetry Symposium
Oak Ridge Associated Universities
Oak Ridge, TN
October 7-10, 1980
Proceedings: U.S. Dept of Health and Human Services, HHS Publication FDA 81-8166, 1981

History

Fourth International Radiopharmaceutical Dosimetry Symposium
Oak Ridge Associated Universities
Oak Ridge, TN
November 5-8, 1985
Proceedings: Oak Ridge Associated Unversities, 1986

Fifth International Radiopharmaceutical Dosimetry Symposium
Oak Ridge Associated Universities
Oak Ridge, TN
May 7-10, 1991
Proceedings: Oak Ridge Associated Universities, 1992

Sixth International Radiopharmaceutical Dosimetry Symposium
Oak Ridge Associated Universities
Oak Ridge, TN
May 7-10, 1996
Proceedings: Oak Ridge Associated Universities, 1999

History

Seventh International Radiopharmaceutical Dosimetry Symposium
Vanderbilt University
Nashville, TN
April 17-19, 2002
Proceedings: 3 issues of Cancer Biotherapy and Radiopharmaceuticals, 2003

Web site: http://www.doseinfo-radar.com/symphome.html

1st International Symposium on Radionuclide Therapy and Radiopharmaceutical Dosimetry

Helsinki, Finland

Sept 4-8, 2004

Congress web site: http://www.eanm.org/eanm2004/index.html

Dosimetry/Radiobiology Track

- Radiobiology
- Radionuclide Therapy & Dosimetry: Radioimmunotherapy
- Radionuclide Therapy & Dosimetry: mIBG and Peptides
- Radionuclide Therapy & Dosimetry: Quantitative Analysis & Treatment Planning

Dosimetry/Radiobiology Track

- Radionuclide Therapy & Dosimetry: Dosimetric Models
- Radionuclide Therapy & Dosimetry: Thyroid, Bone Pain Pallation & Misc.
- Radionuclide Therapy & Dosimetry: Animal and In-Vitro Studies

Multidisciplinary Education/Discussion Sessions

Therapy/Dosimetry Multidisciplinary I: Controversies in Radioimmunotherapy

- Physics. S.-E. Strand (SE)
- Clinical. FV. Lewington (UK)

Therapy/ Dosimetry Multidisciplinary II: The Way Forward lies in Individual Patient Dosimetry

- The Way Forward lies in Individual Patient Dosimetry. M. Stabin (USA)
- Physics. G. Flux (UK)
- Clinical. B. Brans (BE)

Multidisciplinary Education/Discussion Sessions

Therapy/ Dosimetry Multidisciplinary III: Therapy of Thyroid diseases - How important is stunning? How necessary is Dosimetry?

- Therapy of Thyroid Diseases. M. Luster (GE)
- Physics. M. Lassmann (GE)
- Clinical. S. Clarke (UK)

Erasmus MC
University Medical Center Rotterdam

Ultrasound microbubbles promoted internalisation of radiolabelled peptides

Marion de Jong, Eric Krenning, Bert Bernard, Ayache Bouakaz, Folkert ten Cate, Nico de Jong, Annemieke van Wamel

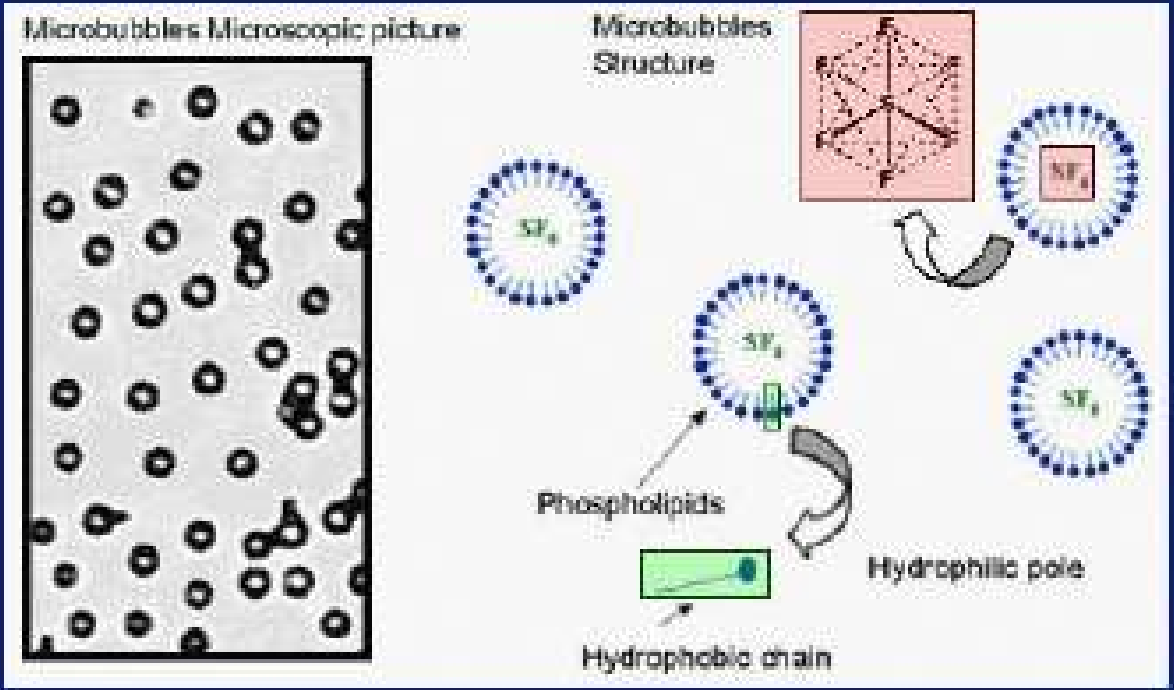
Nuclear Medicine
Experimental Echocardiography

- 111In-DOTA-Tyr3-octreotate (10^{-10}M) internalisation was investigated in CA20948 rat pancreatic tumour cells in vitro (12-well membrane inserts, 10^5 cells/well).
- The normal internalisation levels of the radiolabelled peptide were compared to the levels in cells treated with ultrasound and contrast microbubbles (SonovueTM), gas microbubbles encapsulated in a phospholipid-shell (mean size 2.5 µm).
- The cell cultures were positioned at a distance of 75 mm from the transducer, the temperature of the medium was kept constant 37°C.
- Ultrasound exposure consisted of a burst of 10 µs length, 1 MHz frequency and 420 kPa amplitude repeated each 75 ms. Microbubbles were added in a microbubble-cell ratio of 1:1.

Ultrasound Contrast Agent Microbubbles

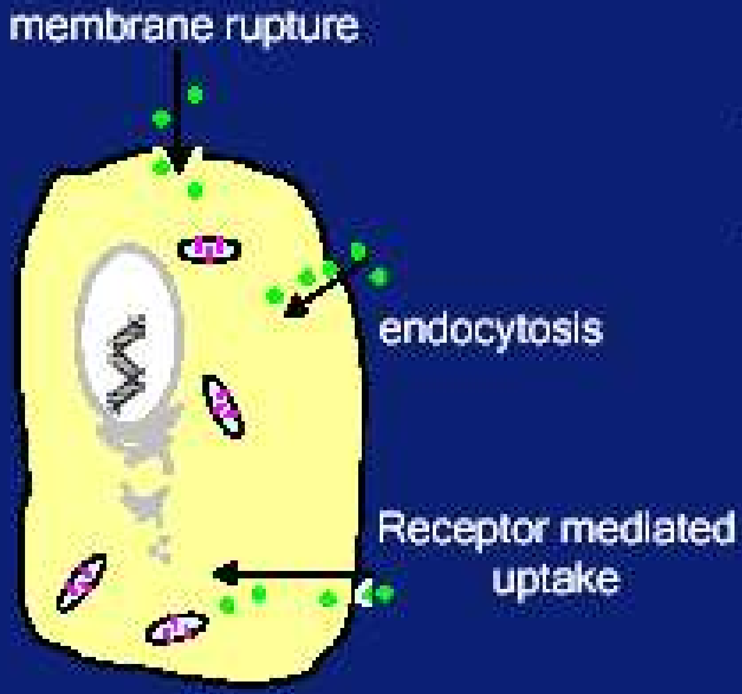
Characteristics

- Gas bubbles encapsulated in a shell (stability)
- Shell: albumin, phospholipid or polymer
- Gas: air/N_2/SF_6 or Perfluorocarbon (c_nf_{2n+2})



Erasmus MC

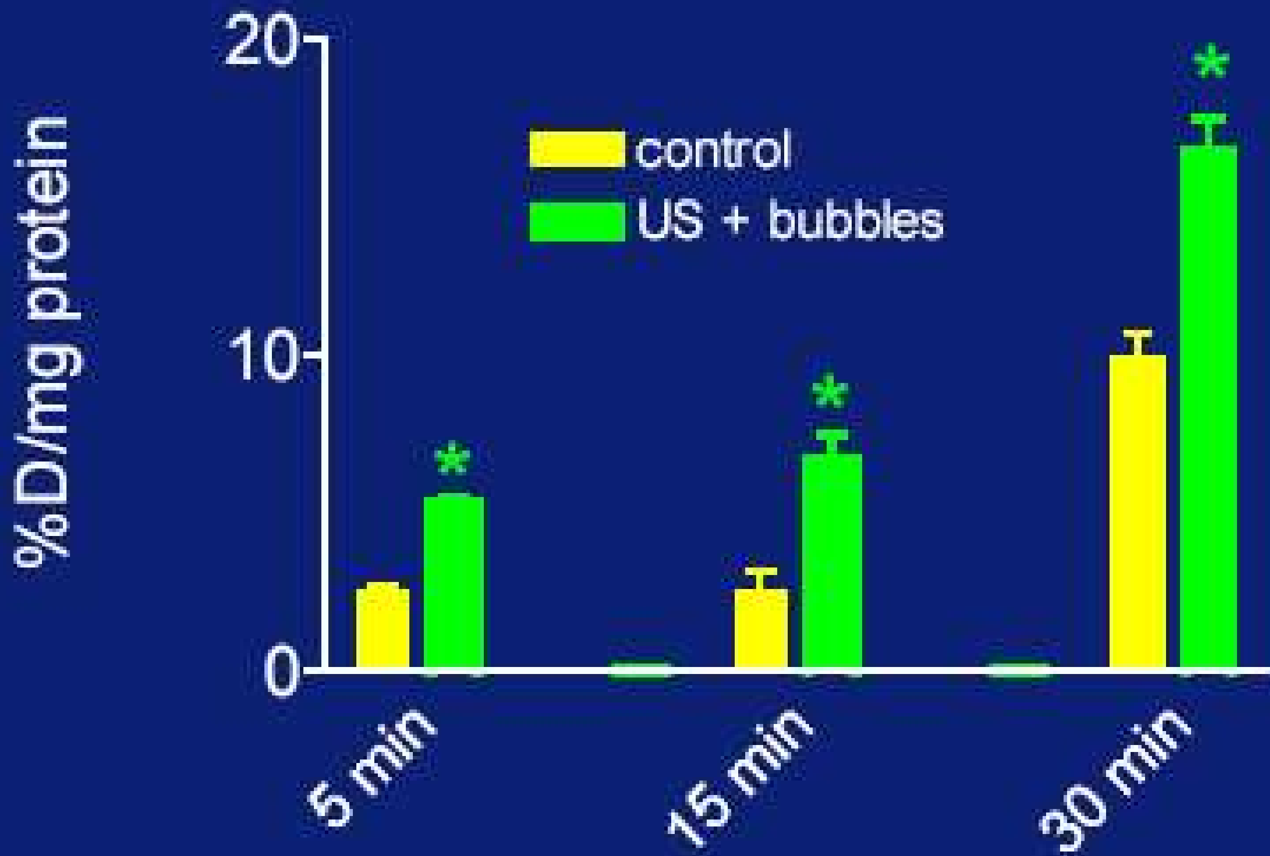
Ultrasound and microbubbles increase peptide uptake through enhanced cell membrane permeabilization?



using oscillating and/or collapsing microbubbles:

- create membrane rupture / pores: sonoporation
- stimulate endocytosis
- stimulate receptor-mediated uptake

US and bubbles enhanced ^{111}In-DOTA-Tyr^3-octreotate internalization *in vitro*



n = 4 and * P ≤ 0.05

Erasmus MC

- **Results** showed that already after 5 minutes of ultrasound and microbubbles treatment internalisation of ^{111}In-DOTA-Tyr3-octreotate was doubled compared to control.
- The highest increase in internalisation of ^{111}In-DOTA-Tyr3-octreotate was found after 15 minutes of combined ultrasound and microbubbles treatment.
- These results demonstrate that additional ultrasound and microbubbles treatment improved the uptake of the radiolabelled peptide up to 260% in an in vitro set-up.
- These results hold great promise for improvement of the therapeutic index during PRRT as with a lower systemic dose a higher tumour uptake can be reached by using ultrasound and by microbubble sonoporation at the tumour site only.

In-vivo uses of thermoluminescent dosimetric threads: validation for internal radiotherapy and external irradiation uses.

D. JARNET*, **B. DENIZOT***, A. BITAR**, M.BARDIES**, A.LISBONA***, P.JALLET*

* Inserm U646, 10, rue A. Boquel, 49100 ANGERS, FRANCE

** Inserm U601, quai Moncousu, 44100 NANTES, FRANCE

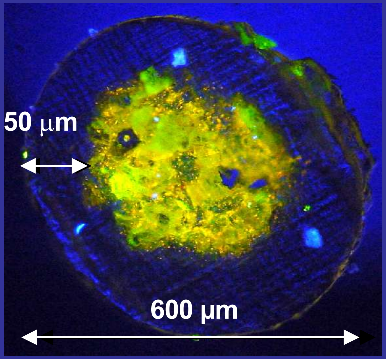
*** CRLCC René Gauducheau, Boulevard Monod, 44805 SAINT-HERBLAIN, FRANCE

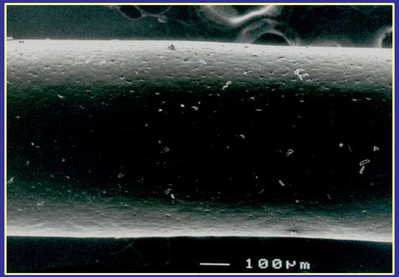
Inserm

Institut national
de la santé et de la recherche médicale

Co- extruded thermoluminescent threads

- Core
  - LiF : Mg, Cu, P (GR200P, China)
  - Plasticizers, Polypropylene
- Protective shell : Polypropylene





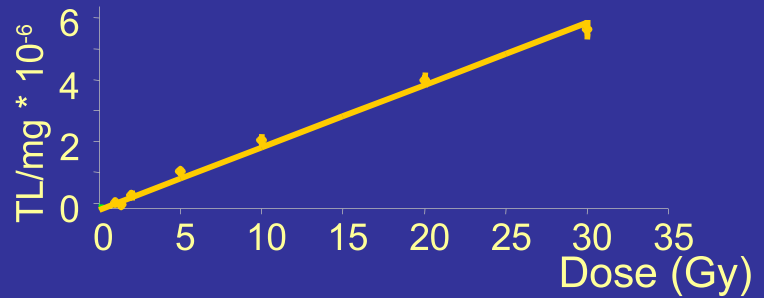
- Minimum reliable size : 5 mm length
- Sterilizable by autoclave (134°C / 18 min.)

1.5 cm dosimeter

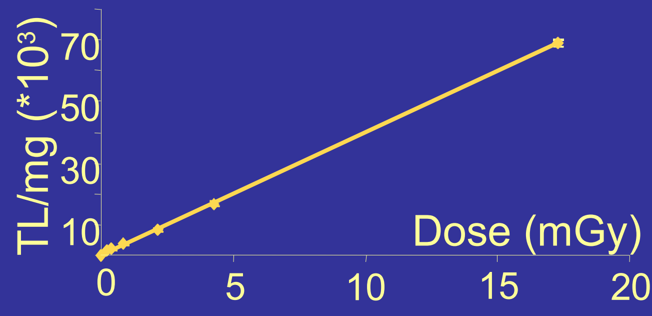
Patents: Fr 99, WO 00, US 03

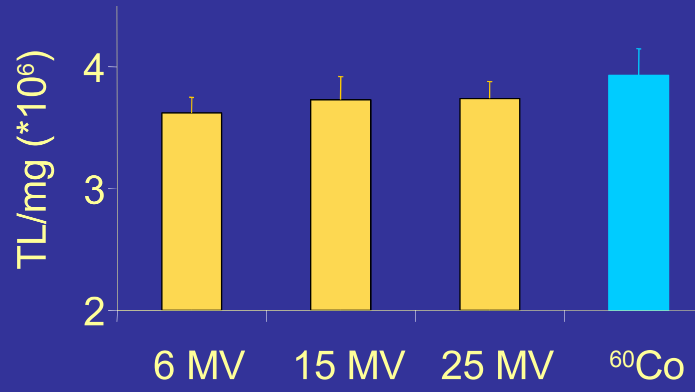
Thread calibration

- Reference : ^{60}Co



- External irradiations :
  - low energy X rays (85 kV)
    - Minimal threshold: ≈ 100 µGy
  - high energy X rays (from 6 to 25 MV)
  - electron beams (from 6 to 20 MeV)

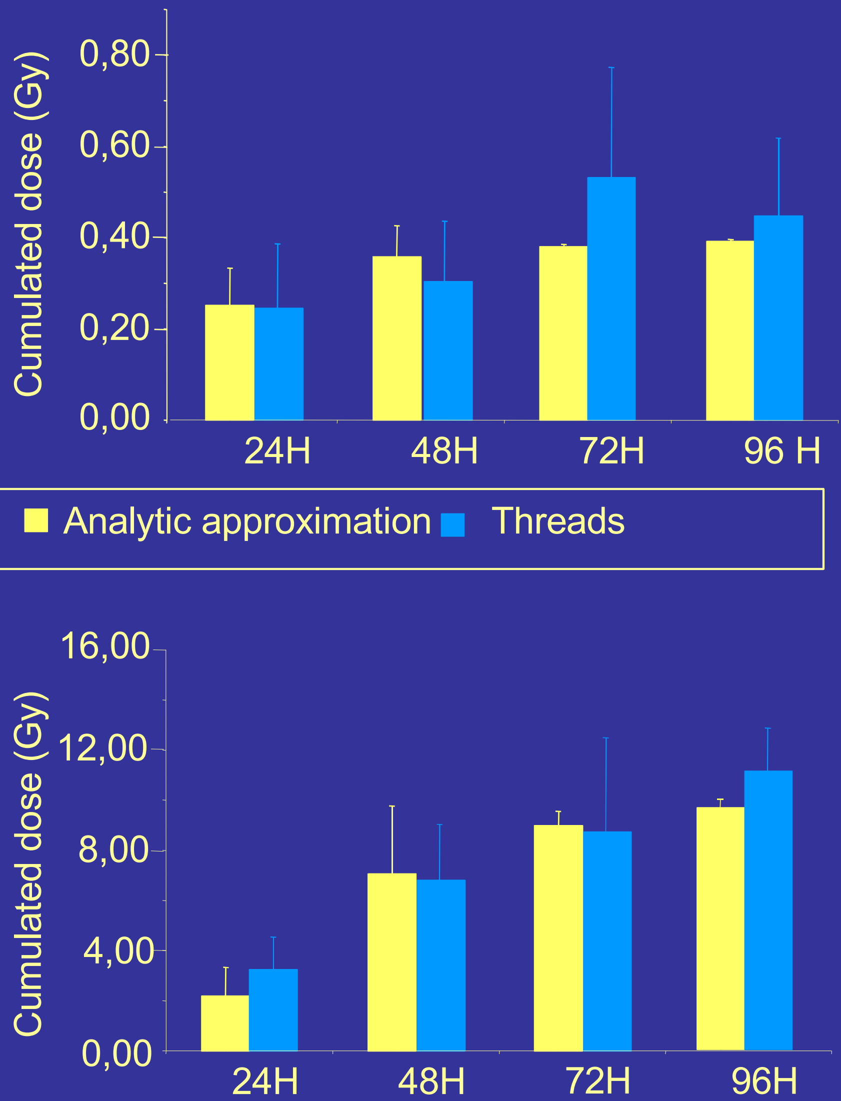




Internal radiotherapy validation: Results

Liver

Tumor



Dose (calculation)

=

Dose (threads)

Patient-Specific Dosimetry for Internal Emitters:

- Necessary?
- Helpful?
- Advisable?

Problems and complaints:

1. “Patient-specific dosimetry is wildly inaccurate”

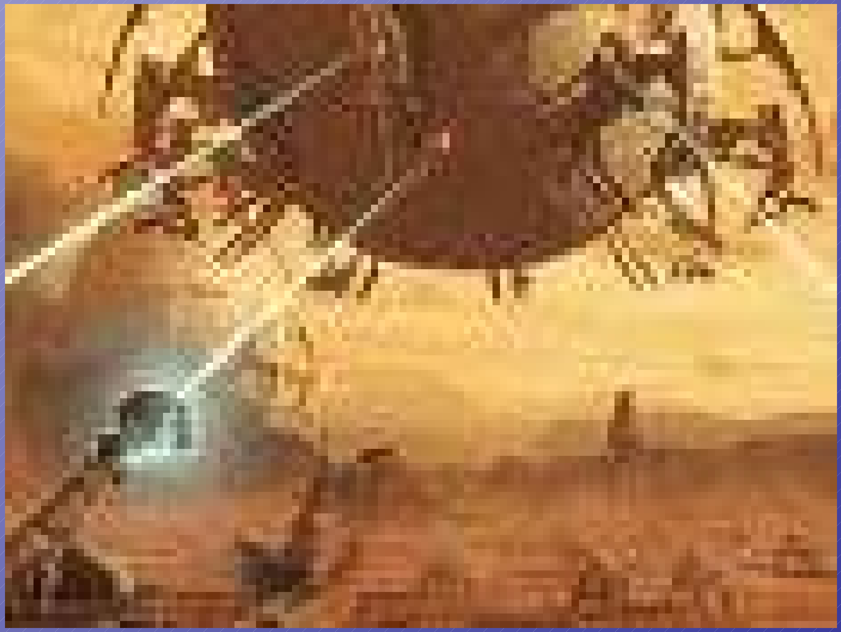
3. “Dosimetry requires too many resources”

5. “Everybody does it differently”

Internal Emitter Therapy

Sophistication

External Beam Therapy
Treatment Planning



Accuracy

Difficulty

Success Rate

The Role of Dosimetry in Radionuclide Therapy

- The options:
  - NO dosimetry (most common)
  - BAD dosimetry (the state of the art)
  - GOOD dosimetry (sometimes observed)
  - EXCELLENT dosimetry (still a research area)

Rules and regs…

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COUNCIL DIRECTIVE 97/43/EURATOM

of 30 June 1997

on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom

THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the Commission, drawn up after obtaining the opinion of a group of persons appointed by the Scientific and Technical Committee,

Having regard to the opinion of the European Parliament[1],

Having regard to the opinion of the Economic and Social Committee[2],

(1) Whereas the Council has adopted Directives laying down the basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation, as last amended by Directive 96/29/Euratom[3];

protection applied to medical exposure, the International Commission on Radiological Protection reviewed the subject in its 1990 and 1996 recommendations;

(6) Whereas such developments make it necessary to repeal Directive 84/466/Euratom;

(7) Whereas Directive 96/29/Euratom lays down basic safety standards for the protection of the workers administering the medical exposure and of the members of the public; whereas the same Directive ensures that the total of contributions to the exposure of the population as a whole, is kept under review;

(8) Whereas health and safety requirements, including radiation protection aspects, regarding the design, manufacture and placing on the market of the medical devices are dealt with by Council Directive 93/42/EEC of 14 June 1993 concerning medical devices[5]; whereas pursuant to Article 1 (8) of that Directive, the relevant

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information, taking into account economic and social factors.

(b) For all medical exposure of individuals for radiotherapeutic purposes, as mentioned in Article 1 (2) (a), exposures of target volumes shall be individually planned; taking into account that doses of non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

2. Member States shall:

(a) promote the establishment and the use of diagnostic reference levels for radiodiagnostic examinations as referred to in Article 1 (2) (a)

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- Radiological installation: a facility containing radiological equipment.

- Radiodiagnostic: pertaining to *in vivo* diagnostic nuclear medicine, medical diagnostic radiology, and dental radiology.

- Radiotherapeutic: pertaining to radiotherapy including nuclear medicine for therapeutic purposes.

Article 3

Justification

The UK Ionising Radiation (Medical Exposures) Regulations 2000

Optimisation

(2) In relation to all medical exposures for radiotherapeutic purposes the practitioner shall ensure that exposures of target volumes are individually planned, taking into account that doses of non-target volumes and tissues shall be as low as reasonably practicable and consistent with the intended radiotherapeutic purpose of the exposure

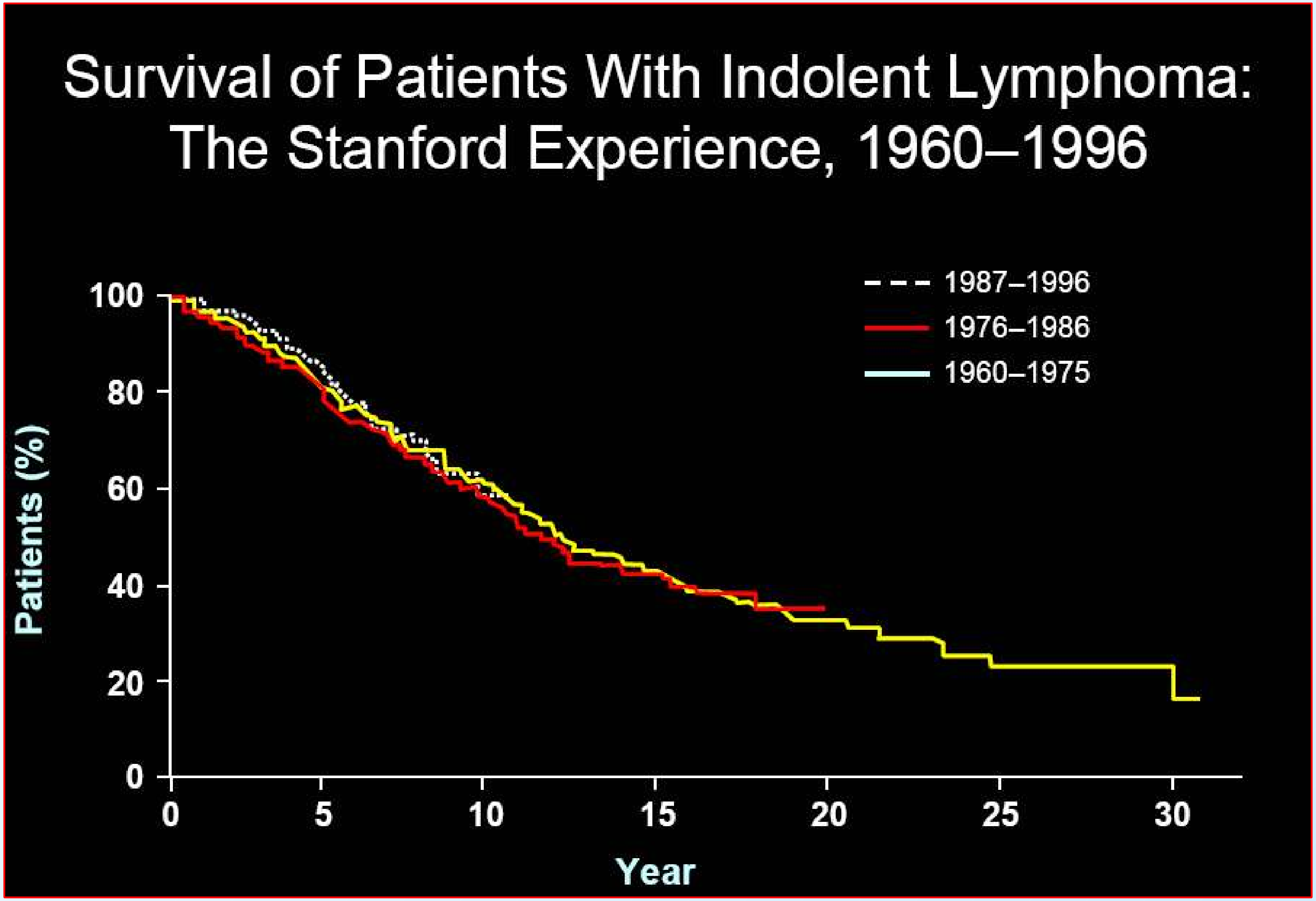
(3) Without prejudice to paragraphs (1) and (2), the operator shall select equipment and methods to ensure that for each medical exposure the dose of ionising radiation to the individual undergoing the exposure is as low as reasonably practicable and consistent with the intended diagnostic or therapeutic purpose and in doing so shall pay special attention to -

(a) quality assurance;
(b) assessment of patient dose or administered activity; and
(c) adherence to diagnostic reference levels for radiodiagnostic examinations falling within

Efficacy

	^{131}I anti CD20 75cGy WBD	^{90}Y anti CD20 0.4 mCi/kg
ORR %	71	67
CR %	34	25
TTP (m)	12	>12.9

Potential impact of RIT ?



Controversy 1

Current practice fails to exploit the potential of RIT

Efficacy **Safety**

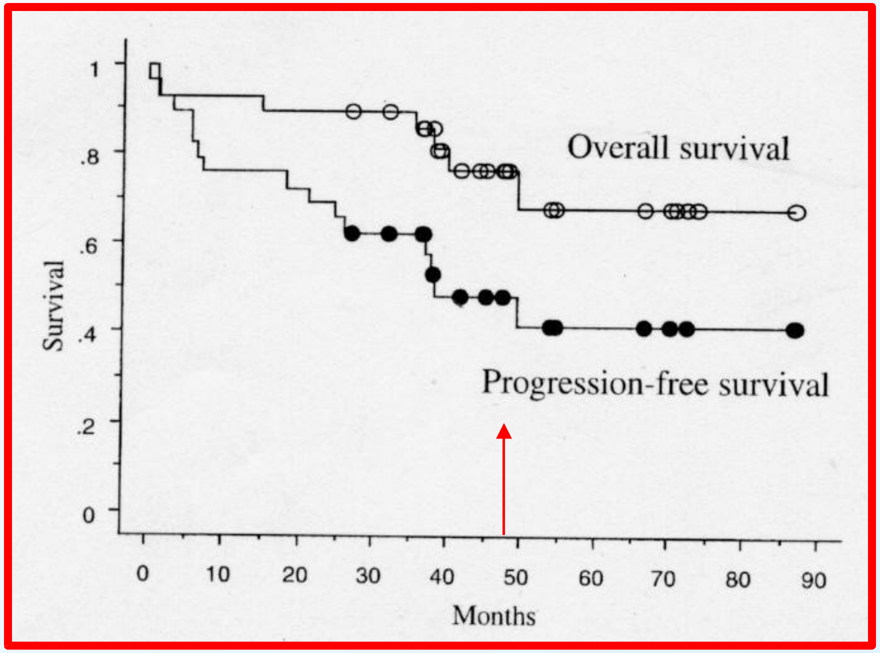
Myeloablative ^{131}I tositumomab
Refractory NHL

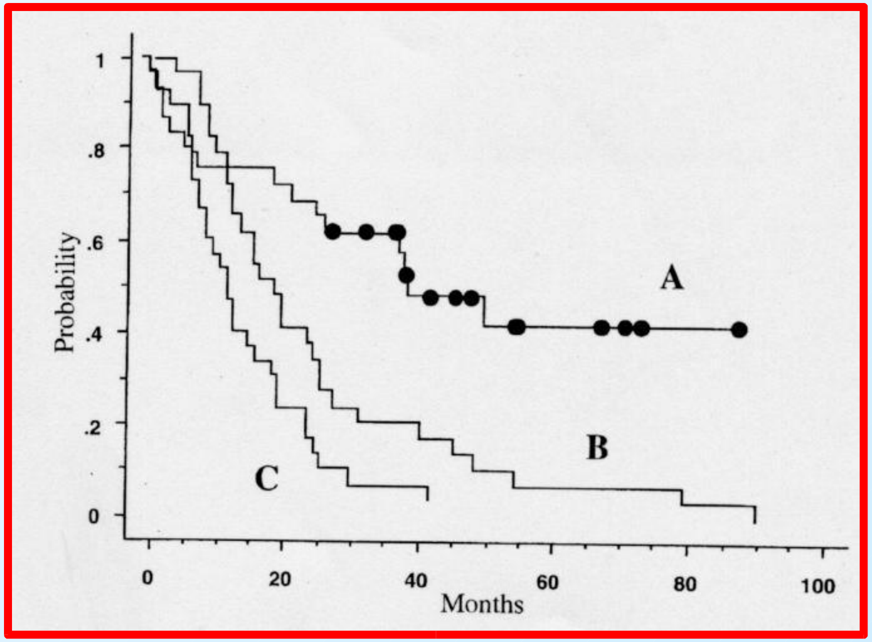
66% low grade	34% intermediate/high
Stage III/IV	96%
median prior Rx	3

ORR %	86
CR %	79

Press OW et al. Lancet 1995
Liu SY et al. JCO 1998

Myeloablative anti B1 therapy





Overall & Progression Free survival

n=29

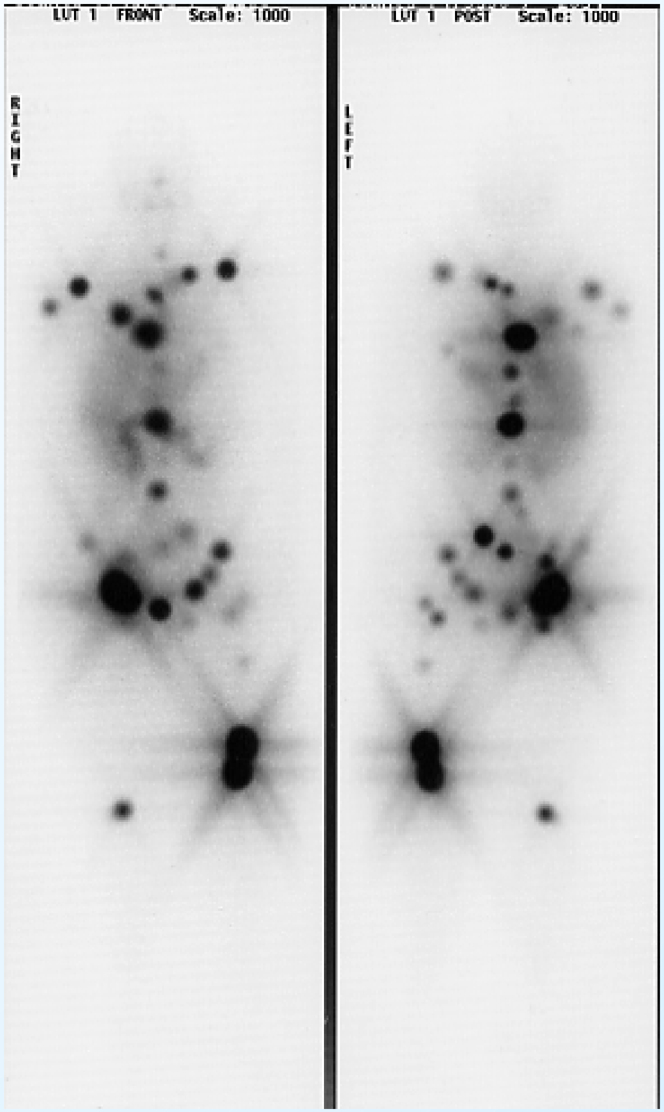
PFS after RIT (A)   Best previous Rx (B)
Last previous chemoRx (C)

Liu et al. JCO 1998

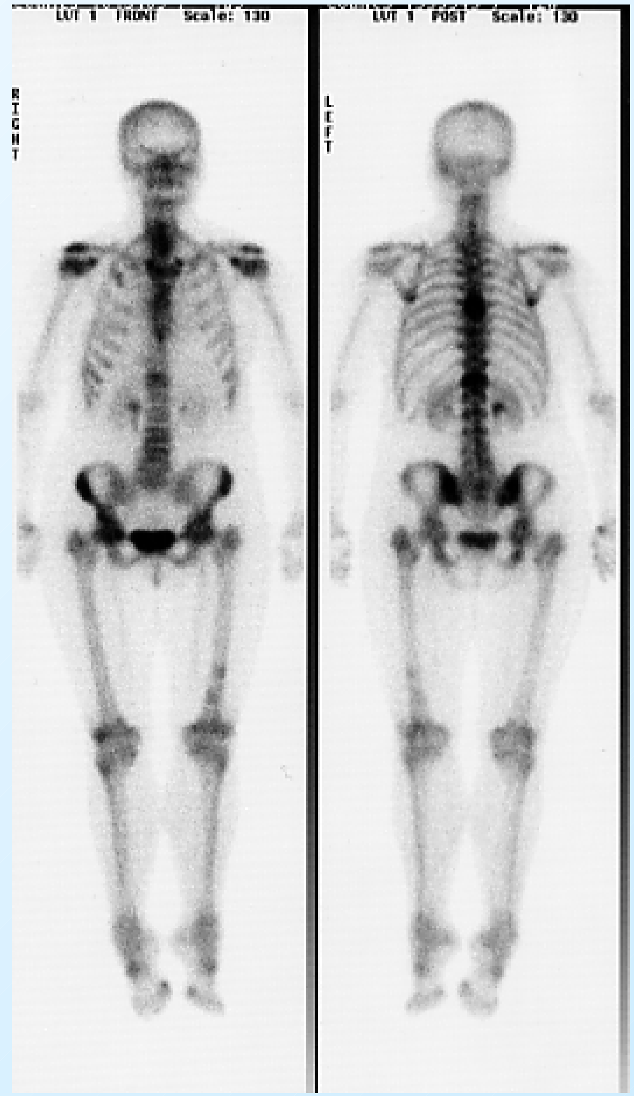
Conclusions
How to improve outcome

2. Measure dose
3. Establish optimal tumour dose
4. Define optimal administration protocol
5. Abandon monotherapy
6. Exploit cold antibody effect

RAI uptake in Bone Metastases

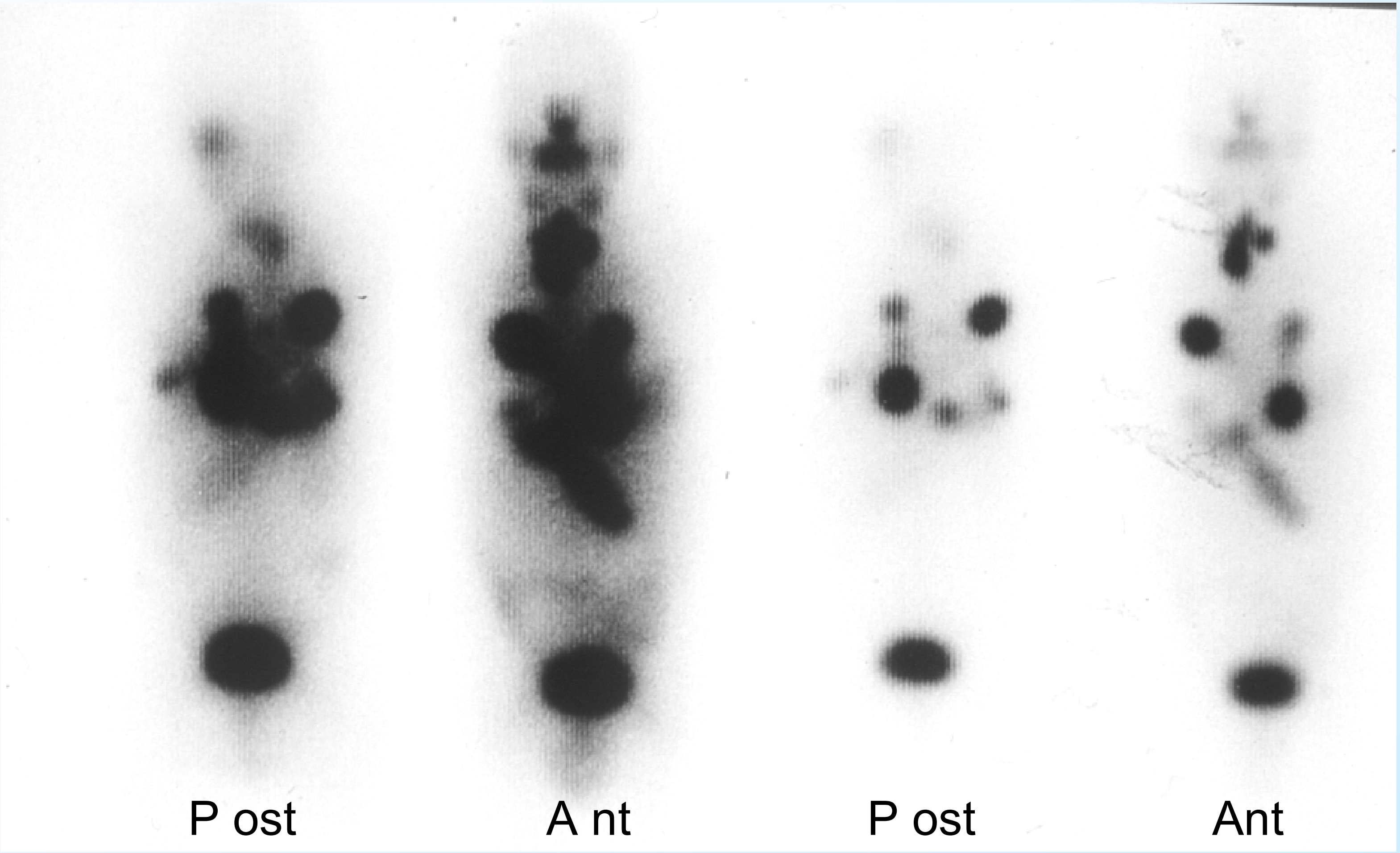


ant RAI post



ant TcMDP post

EXTENSIVE LUNG METASTASES



OUTCOMES OF DOSIMETRY

PRIMARY

- Improved thyroid/lesion ablation rate
- Reduction in doses to normal tissues

SECONDARY

- Compliance with legislation
- Consideration of environment (if activity levels reduced)
- Facilitation of research

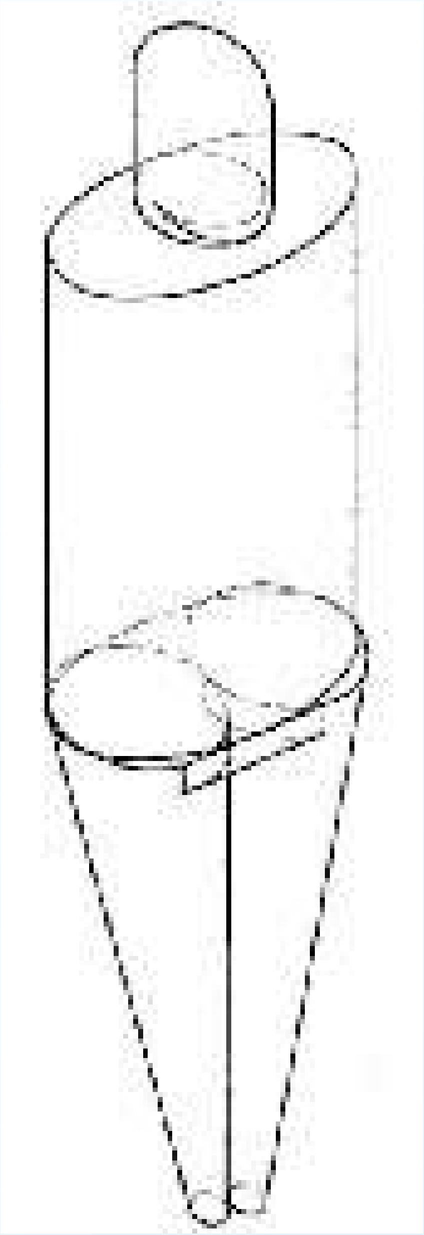
IMPACT OF VARYING ACTIVITIES ON OUTCOME OF REMNANT ABLATION

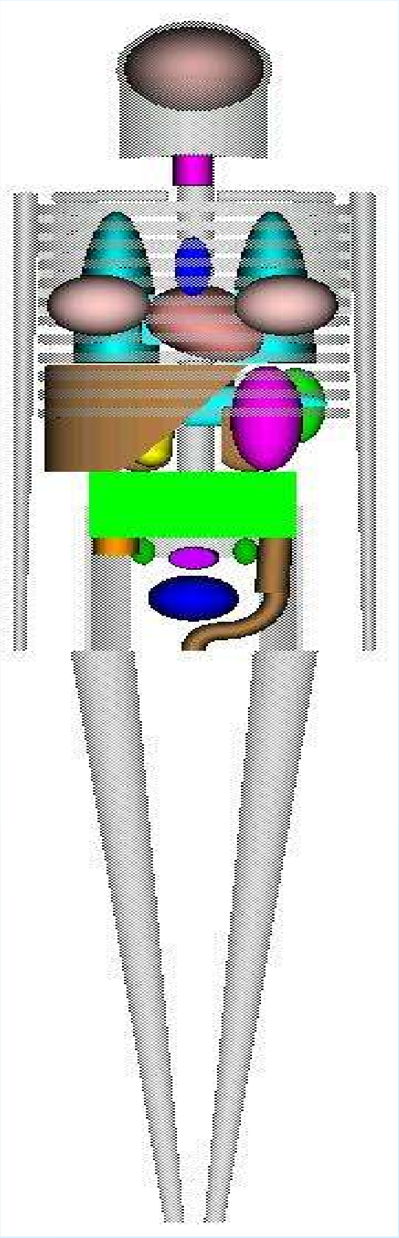
Activity (mCi)	25-35	35-64	65-119	120-200
n	27	54	38	30
Mean absorbed dose (cGy)	19,800 +/- 992	31,372 +/-3355	49,616 +/-7858	130,200 +/- 24,162
Success	63%	78%	74%	77%

Bal et al, 1994

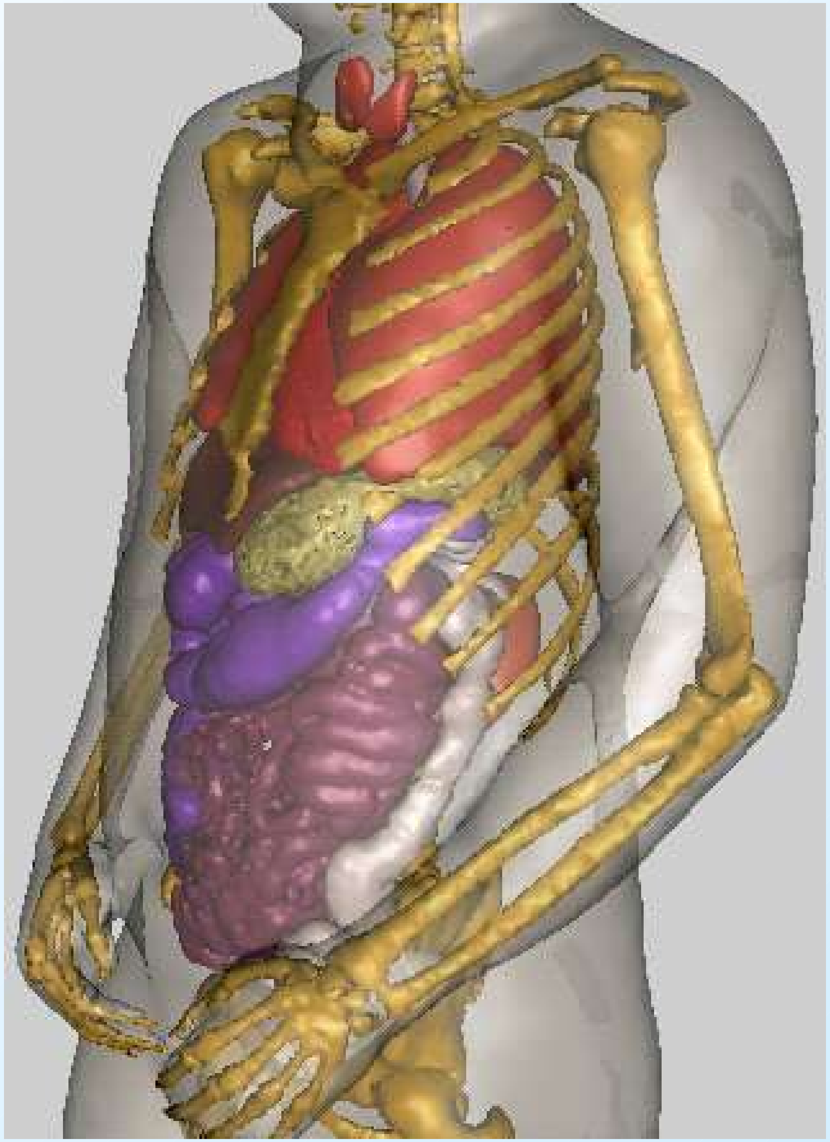
PROBLEMS WITH DOSIMETRY

- No standardised approach
- No reliable method
- Dosimetric studies may result in stunning
- Resource intensive
- Time consuming for patient
- Variable data on outcomes

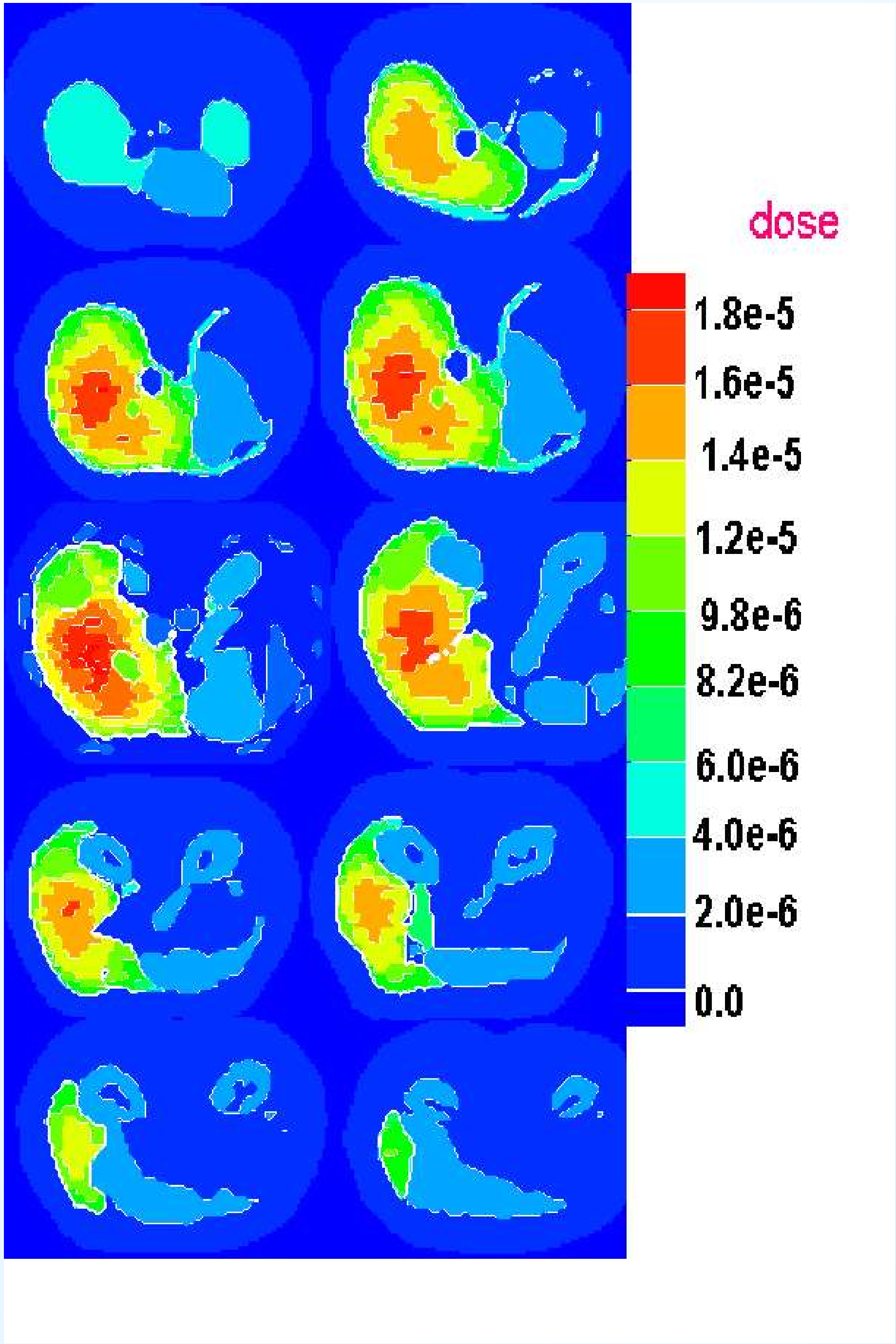




Adult equation- based model (MIRD/ICRP - 1975)

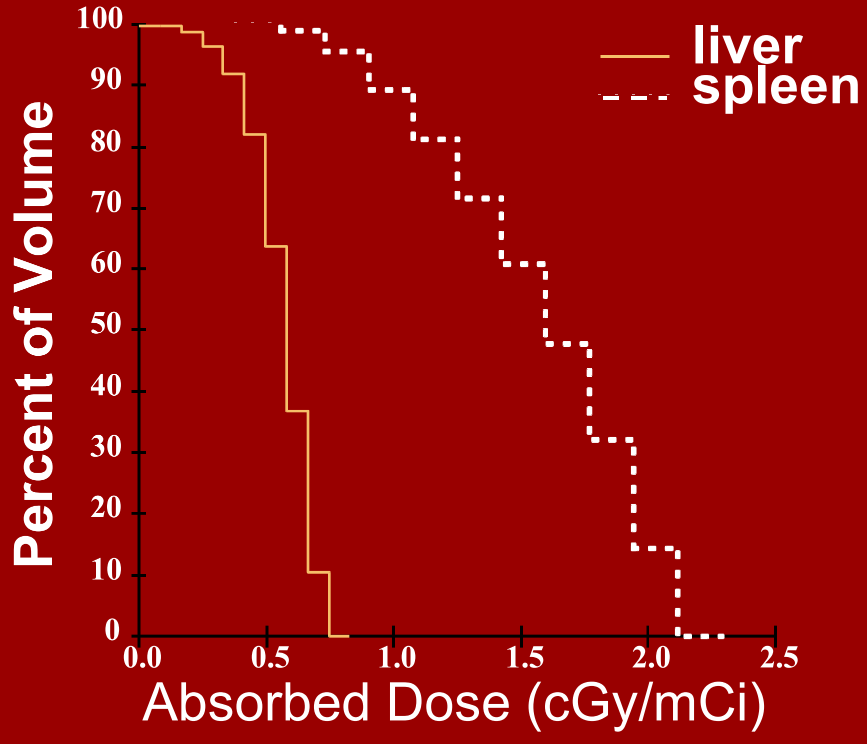


Exterior view of the VIP-Man phantom showing internal organs.

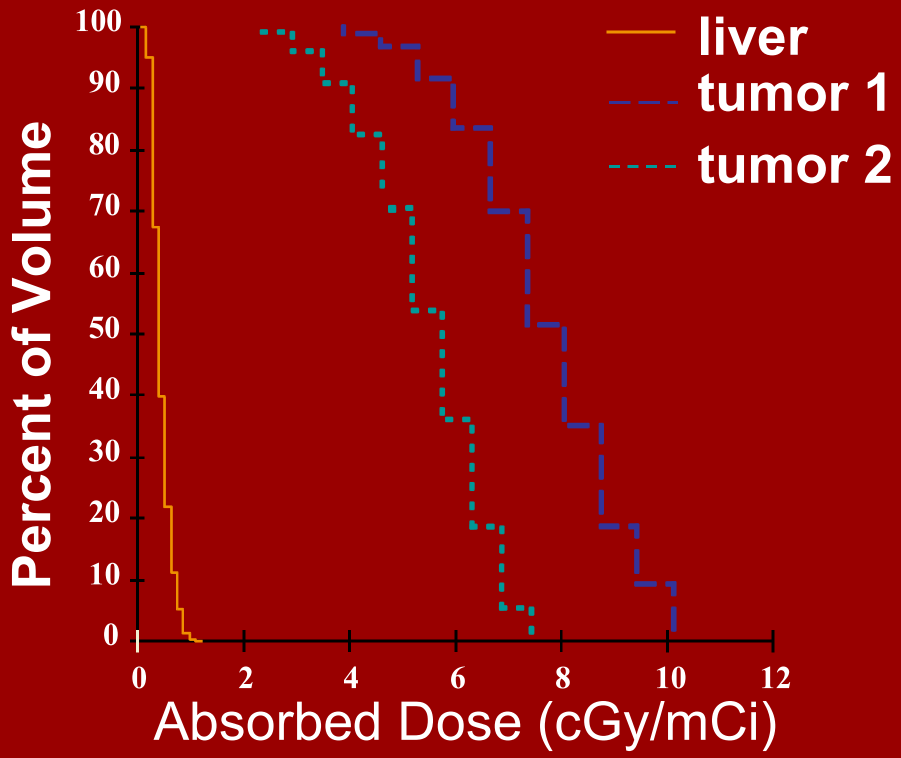


Dose distribution in the liver, uniform source distribution, 1.0 MeV photons. Dose units are (mGy/MBq.s).

Histogram representation



Patient 1



Patient 2

Dr. G. Sgouros, Memorial Sloan-Kettering Cancer Center, 2001

The Role of Dosimetry in Radionuclide Therapy

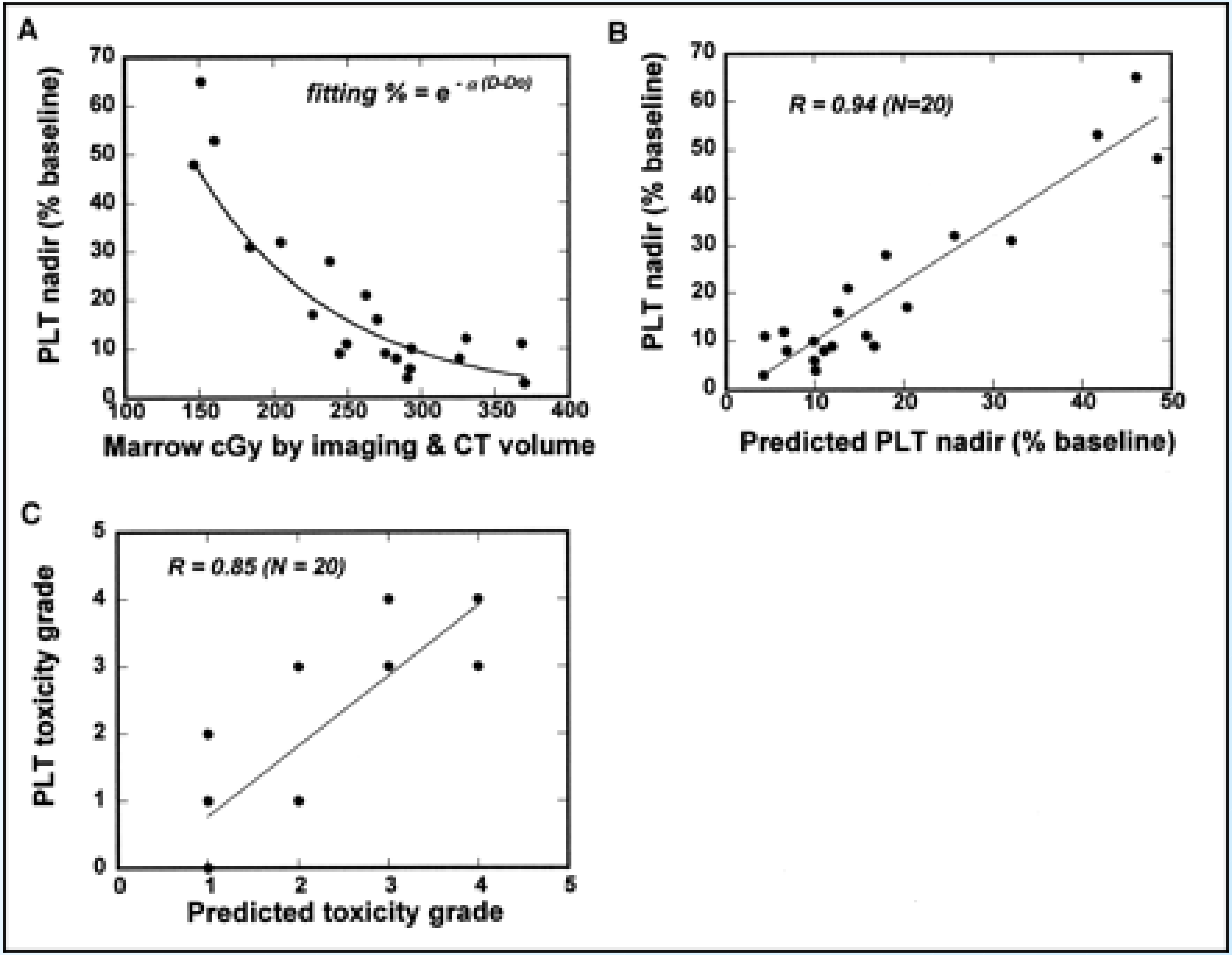
- Dosimetry models and methods
  - Standardized
  - Efficient
  - Reasonably accurate
- Patient-specific data:
  - Kinetics
  - Organ masses
- Link to patient-specific biology

Way forward

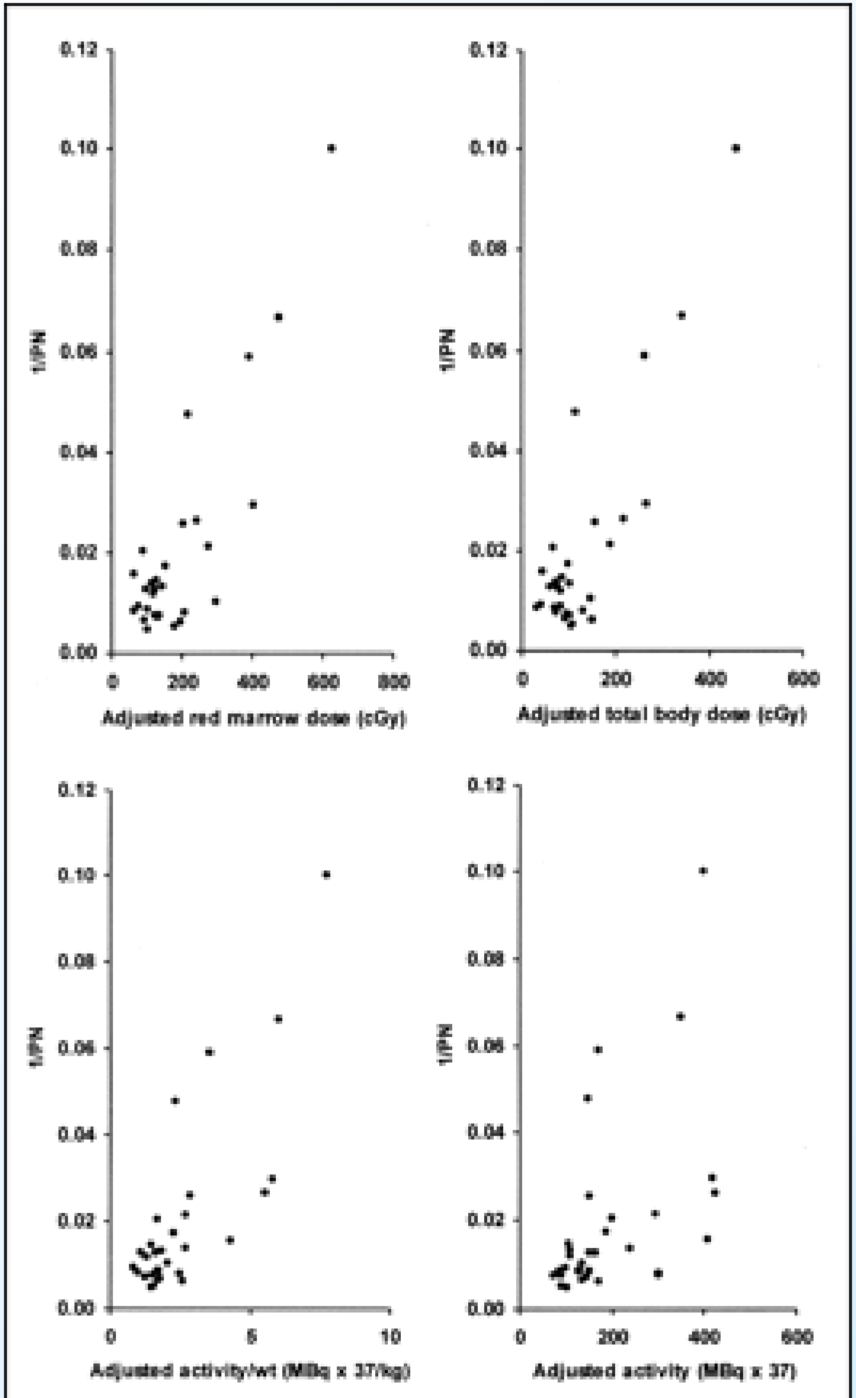
The Role of Dosimetry in Radionuclide Therapy

- Well done dosimetry may produce good correlations in the right populations, but...
- Radiation dose may not be the only influence on tumor response or toxic response of normal organs.
- Importance of **biology** is the key to success.
  - Disease/agent
  - Treatment/retreatment
  - Prior treatment
  - Inherent individual sensitivity

Success Rate



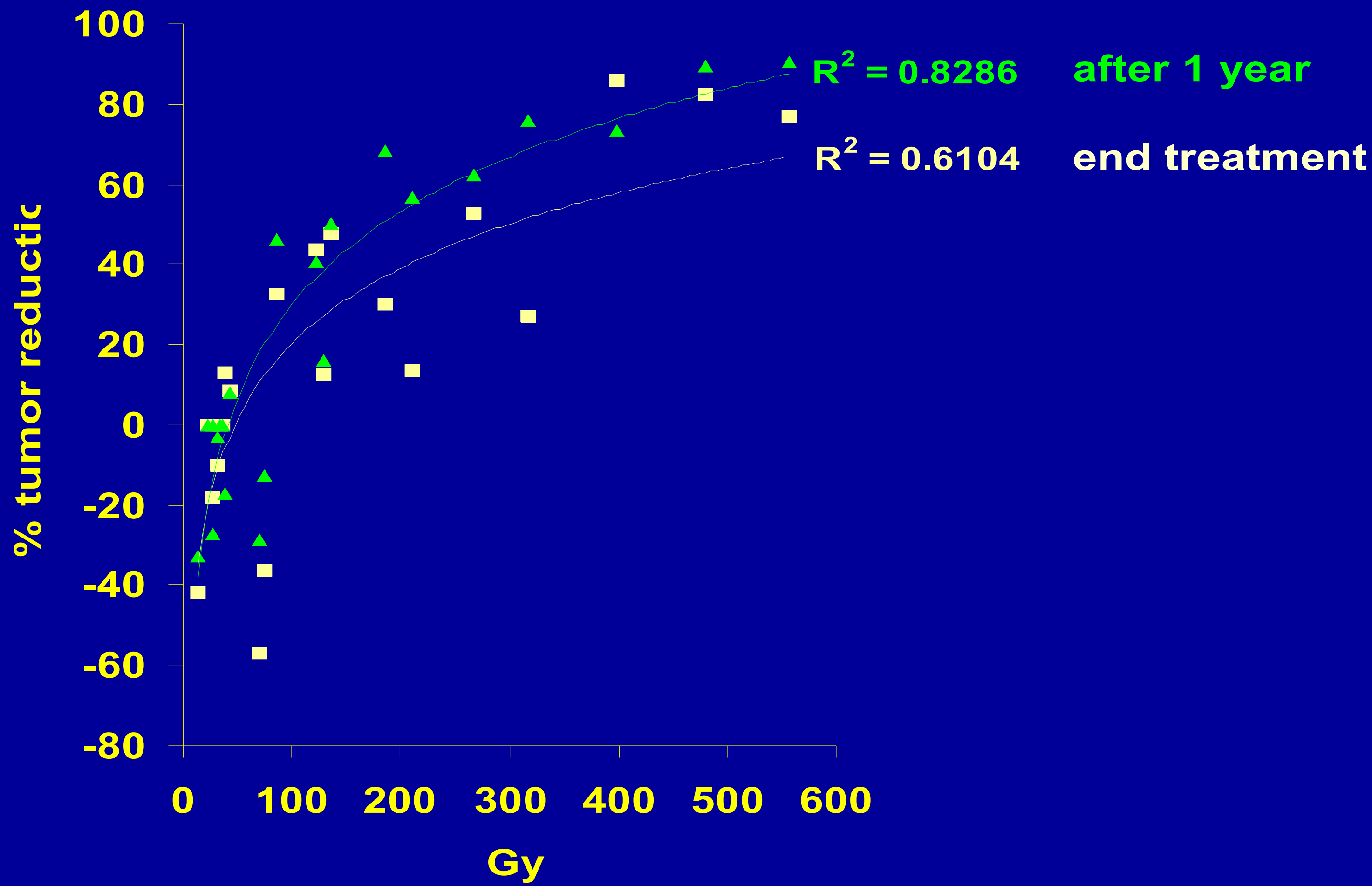
Shen et al. JNM 43 No. 9 1245-1253



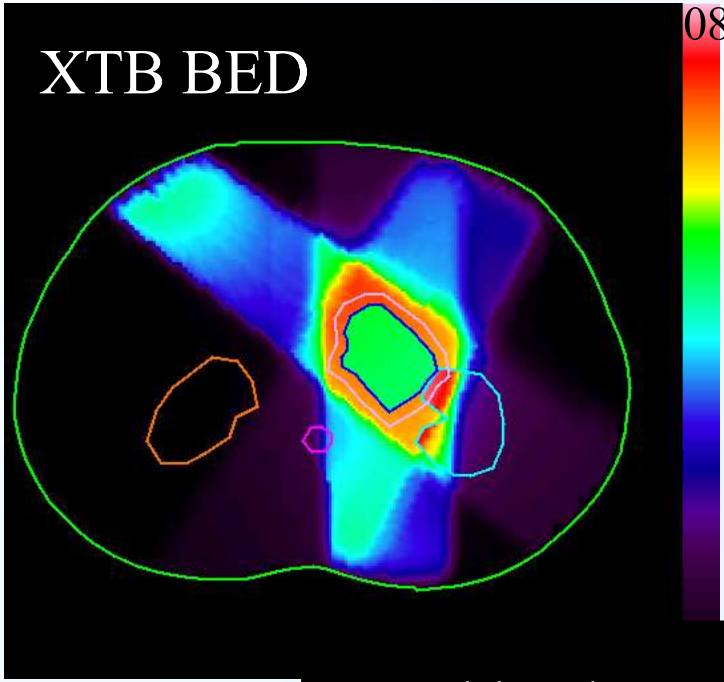
Siegel et al. JNM 44 (1): 67-76 –

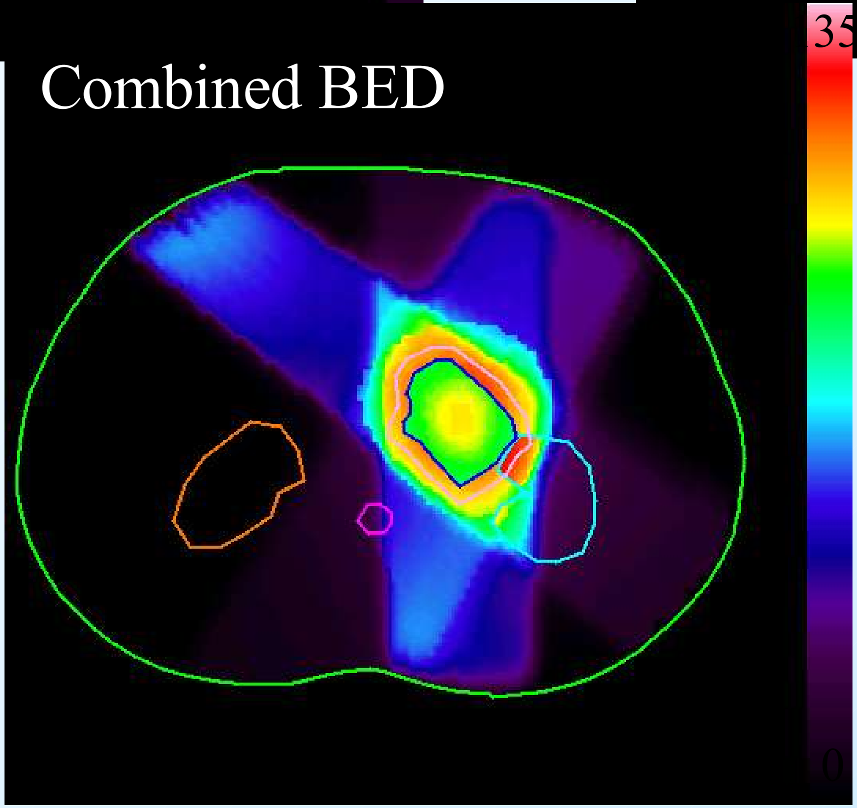
Patient-specific biomarker (FLT3-L) levels in blood used to adjust dosimetry.

Correlation tumor response vs dose (Gy)
^{90}Y Octreother, End of treatment and after 1 year
n = 22



Dr. S. Pauwels, 15th IRIST Meeting, Rotterdam, May-2002





Bodey, Flux and Evans (Royal Marsden Hospital, UK)

Dose rates and LQ model nephropathy

$$RE = 1 + \frac{R_0}{(\mu + \lambda_e)\frac{\alpha}{\beta}}; \quad T_\mu = 2h, \quad \frac{\alpha}{\beta} = 2.4\,Gy$$

therapy	N_{frac}	*A* (GBq)	*D* (Gy)	R_0 (Gy/h)	*RE*	*BED* (Gy)
^{90}Y Octreother	3	13.3	27	0.16	1.2	32
^{111}In Octreoscan	8	83	34	0.09	1.1	37
^{177}Lu Octreotate	4	29.6	26	0.04	1.0	27
^{166}Ho DOTMP	1	157	7.1	4	5.3	37
External beam	16		23	5	1.6	37
TBI + BMT	6		12	10	1.8	22

Cost comparisons

	Data acquisition	Processing	Output	Cost
WB Dose	20-30 timepoints	Curve splitting, Basic calculations ½ day	Whole-body dose	€200
1-D Dose	3 – 5 Planar scans	Outline VOI, sum counts, plot graph. 1 day. Good	Mean dose over the VOI	€1600
3-D Dose	3 – 5 SPECT scans	Reconstruct, register, 'black box' operation for dose. 3 days. Excellent	Dose distributions, DVH's, TCP's (if biological parameters known)	€5500
IMRT Plan	CT plan, MR? PET/SPECT?	Outlining, registration, beam shaping. 3 days.	Dose distributions, DVH's, TCP's (if biological parameters known)	€5500

The way forward

- Perform dose estimates for all patient treatments, as for external beam radiotherapy
- Proceeding with therapy with no knowledge of radiation dosimetry not in the best interests of patients (current or future).
- Patients given therapy with internal emitters do not deserve a lower standard of care than those treated with external radiation.
- Encourage standardisation of dosimetry
- Initiate multi-centre trials

- **Feasibility Of Dosimetry-Based High-Dose 131I-Meta-Iodobenzylguanidine With Topotecan As A Radiosensitiser In Children With Metastatic Neuroblastoma**

- The measured total whole body radiation absorbed dose ranged from 3.7 Gy to 4.7 Gy (mean 4.2 Gy).
- In vivo dosimetry allows a specified total whole body radiation dose to be delivered accurately.

- <u>How to Determine Blood Doses and Remnant Biokinetics for Thyroid Ablation Therapy of Differentiated Thyroid Cancer.</u> M. Lassmann, H. Hänscheid, M. Luster, C. Reiners; Dep. of Nuclear Medicine, University Wuerzburg, Wuerzburg, GERMANY.

- The proposed protocol can be easily implemented in a nuclear medicine department.
- Our protocol is well suited for multicenter clinical trials. It provides reproducible and standardized dose estimates for the ablation therapy of DTC.

- Individual Pixelwise Dosimetry in Glioma Patients Undergoing an Intratumoral 90Y-Substance P Brachytherapy. S. Kneifel1, A. Merlo2, H. R. Mäcke1, J. Müller-Brand1; 1Kantonsspital Basel, Universitätsklinik und -institut für Nuklearmedizin, Basel, SWITZERLAND, 2Kantonsspital Basel, Klinik für Neurochirurgie, Basel, SWITZERLAND.

- This method is feasible and delivers rather robust dose estimations.
- Due to the pixelwise computation, advanced evaluations such as dose-volume histograms are possible.