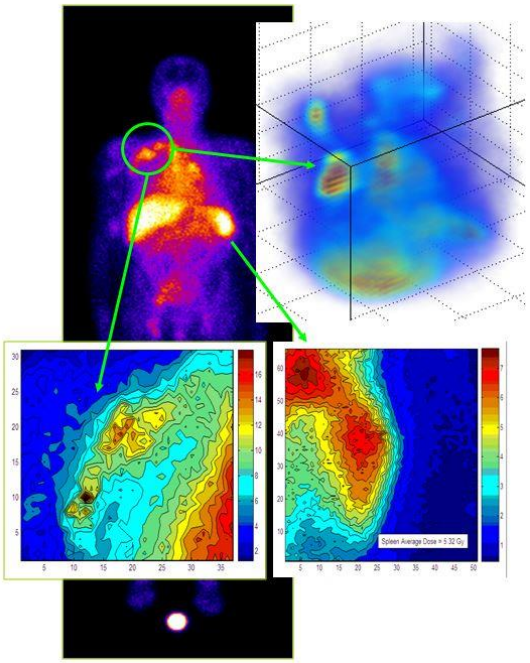
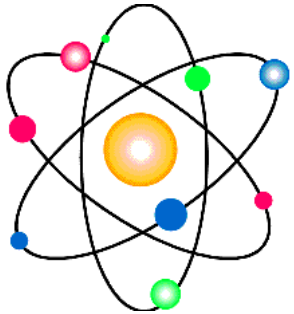
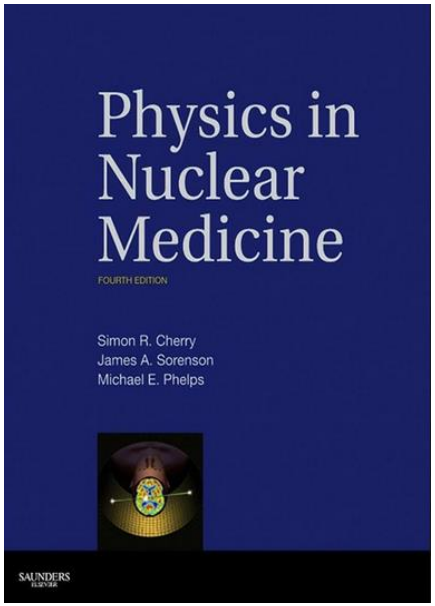
Physics in Nuclear Medicine



Francesco Cicone, MD





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Faculté de biologie et de médecine

Historical introduction

Current perspectives

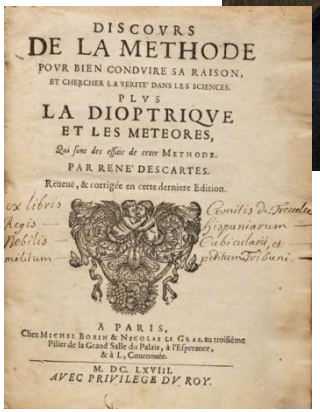
Technology

Radiation protection

(New radionuclides)

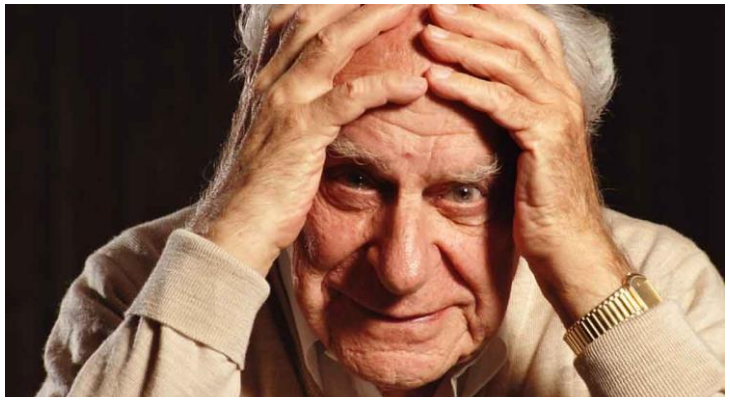
Internal Dosimetry

The history of (nuclear) medicine is history of human mind



René Descartes
(1596-1650)

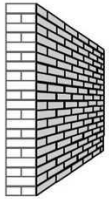
Karl Popper
(1902-1994)



Cartesian Dualism

Mind

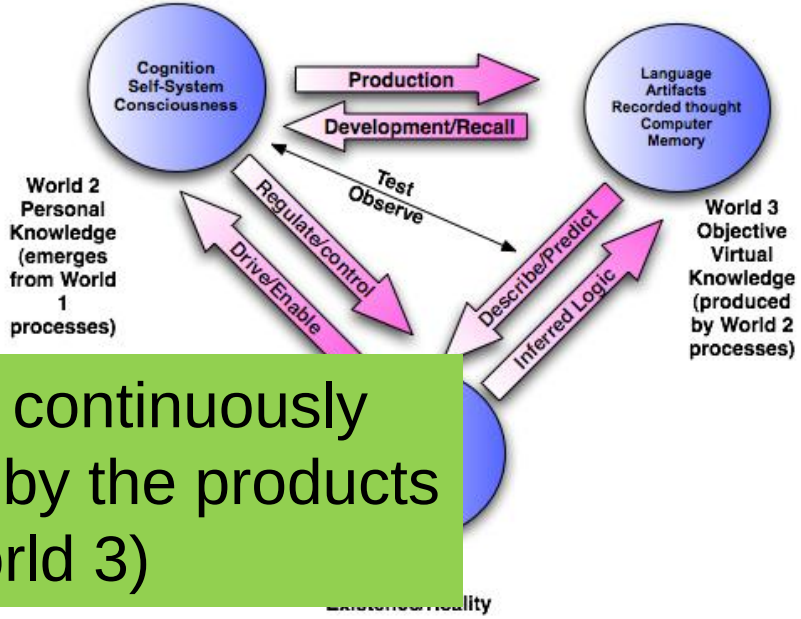
« Res cogitans »



Matter

« Res extensa »

Karl Popper's Three Worlds of Knowledge



The physical world (World 1) is continuously changed, modeled and reshaped by the products of the human mind (World 3)

Milestones of Nuclear Medicine

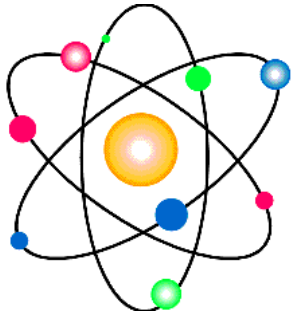


Table 1 The pioneers of nuclear medicine

1895	X-rays	Wilhelm C. Roentgen	German physicist	1845 to 1923
1896	Radioactivity	Antoine H. Becquerel	French physicist	1852 to 1908
1898	Polonium, radium,thorium	Marie Sklodowska Curie	French physicist	1867 to 1934
1923	Tracer principle	Georg V. Hevesy	Hungarian chemist	1885 to 1966
1927	Circulation times	Hermann L. Blumgart	German doctor	1895 to 1977
1928	Counter	Johannes W. Geiger	German physicist	1882 to 1945
		Walther Mueller	German physicist	1905 to 1979
1932	Cyclotron	Ernest O. Lawrence	American physicist	1901 to 1958

Table 2 The early years of nuclear medicine

1934	First radioactive ^{128}I	Enrico Fermi	Italian physicist	1901 to 1954
1936	Production of ^{99m}Tc	Emilio G. Segre	Italian physicist	1905 to 1989
1936	First therapy with ^{32}P	John H. Lawrence	American physicist	1904 to 1991
1938	Discovery of ^{131}I	Glenn Seaborg	American chemist	1912 to 1999
1942	Therapy of benign thyroid disease	Saul Hertz	American physician	1905 to 1950
		Robley D. Evans	American physicist	1907 to 1995
1946	First therapy of thyroid cancer	S. M. Seidlin	American physician	1895 to 1955
		Leo D. Marinelli	American physicist	1886 to 1995
1949	First therapy of thyroid			
	Carcinoma in Europe	Cuno Winkler	German physician	1919 to 2003
		Eric E. Pochin	British physician	1909 to 1990

Ell P *EJNMMI Physics* 2014, 1:3

Fahey *et al. EJNMMI Physics* (2017) 4:15
DOI 10.1186/s40658-017-0182-7

EJNMMI Physics

COMMENTARY Open Access

Saul Hertz, MD, and the birth of radionuclide therapy

Frederic H. Fahey[1,2*], Frederick D. Grant[1,2,3] and James H. Thrall[1,4]

1936 - K Compton « What physics can do for biology and medicine? »

S. Herz: « Could iodine be made radioactive artificially? »

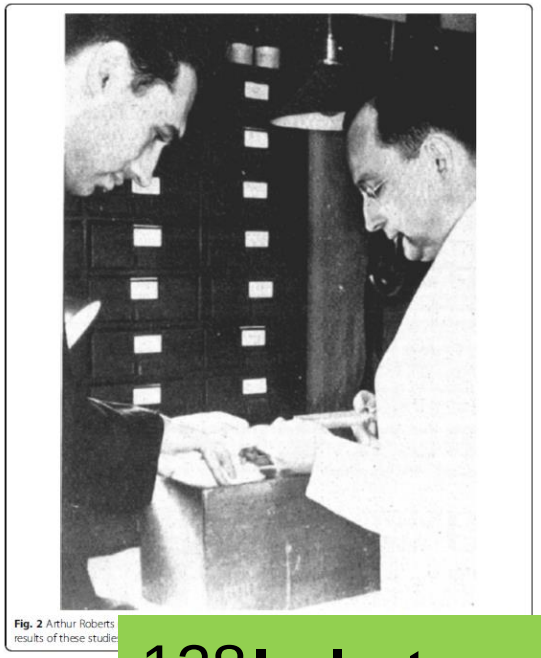
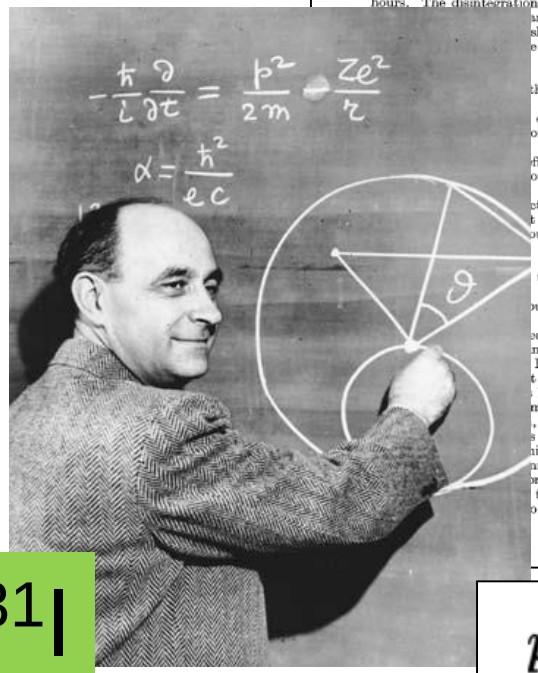


Fig. 2 Arthur Roberts
results of these studie



MAY 19, 1934 NATURE 757

Letters to the Editor

[*The Editor does not hold himself responsible for opinions expressed by his correspondents. Neither can he undertake to return, nor to correspond with the writers of, rejected manuscripts intended for this or any other part of* NATURE. *No notice is taken of anonymous communications.*]

Radioactivity Induced by Neutron Bombardment

EXPERIMENTS have been carried out to ascertain whether neutron bombardment can produce an induced radioactivity, giving rise to unstable products which disintegrate with emission of β-particles. Preliminary results have been communicated in a letter to *La Ricerca Scientifica*, 5, 282; 1934.

The source of neutrons is a beryllium tube containing radium emanation and powdered beryllium, the amount of radium emanation varying in the different experiments from 30 to 630 millicuries. We are much indebted to Prof. G. C. Trabacchi, Laboratorio Fisico della Sanità Pubblica, for putting at our disposal such strong sources.

[illegible] irradiation with the source for a period which varied from a few minutes to several hours, they were put around a Geiger counter with walls of thin aluminium foil (about 0·2 mm. thickness) and the number of impulses per minute was registered.

So far, we have obtained an effect with the following elements:

Phosphorus—Strong effect. Half-period about 3 hours. The disintegration electrons could be photo-[illegible]mber. Chemical separation showed that the unstable [illegible] bombardment is probably

[illegible] hours. As the result of the active product, this is

[illegible] effect. Period about 3 [illegible]otographed in the Wilson

[illegible]ffect. Period about 12 [illegible]otographed in the Wilson

[illegible]t with a period much longer [illegible] investigated at present.

[illegible]ut 5 minutes.

[illegible] small. Period about 6

[illegible] two days.

Period about 2 minutes.
[illegible]ut 1 hour.

Period about 30 minutes.
[illegible]ct. Period about 6 minutes.
[illegible]n the Wilson chamber.

Period about 2 minutes.
[illegible] 10 seconds.

[illegible] have also given indication [illegible] magnesium, titanium, zir-[illegible], antimony, selenium and [illegible] give indication of having [illegible]ich may be partly due to [illegible]ats and partly to successive [illegible]ons. The experiments are [illegible] to verify these results and [illegible] other elements.

The nuclear reaction which causes these phenomena may be different in different cases. The chemical separation effected in the cases of iron and phosphorus seems to indicate that, at least in these two cases, the neutron is absorbed and a proton emitted. The unstable product, by the emission of a β-particle, returns to the original element.

The chemical separations have been carried out by Dr. O. D'Agostino. Dr. E. Amaldi and Dr. E. Segrè have collaborated in the physical research.

ENRICO FERMI.

Physical Institute,
Royal University, Rome.
April 10.

Induced Radioactivity

CURIE and Joliot[1] and [illegible] and Henderson[2] have [illegible] the [illegible] high energy α-particles. They noted, further, that the positrons could be detected after the α-particle bombardment had ceased. It was therefore assumed that these electrons were produced by the radio-activity of [illegible] nuclei resulting from the [illegible] the expulsion of the [illegible] and Lawy[3] obtained similar results when they bombarded nitrogen with α-particles.

In order to account for the results obtained by bombarding certain ammonium salts in which hydrogen was in part replaced by diplogen with diplons, Oliphant, Harteck and Rutherford[4] assumed that a helium nucleus of mass 4 and charge 2 was formed by the union of two diplons, which differed from the ordinary α-particle in having a large excess energy and being in consequence unstable. It is the purpose of this note to point out that in a similar manner the radioactivity of the light elements is due to the formation, within their nuclei, of an unstable proton of excess energy which disintegrates by emitting a positron. It is suggested that the similarity of the disintegration phenomena observed is due to the radioactivity of this 'radioproton'.

It has been shown[5] that the emission of protons from neon, magnesium, silicon, sulphur and argon can be explained by assuming that pairs of electrons are formed by the interaction of α-particles and nuclei as suggested by a formula due to F. Perrin[6]. By assuming that the positron of the pair unites with a neutron to form a proton, it was found possible to retain the hypothesis of stability of nuclei of mass $4n$, the feeble proton emission of the elements mentioned being due to the less abundant isotopes. The mechanism was extended to the other proton-emitting elements and the conclusion arrived at in a previous paper[7] was confirmed, namely, that there are no 'free protons' in nuclei, these particles being combined with neutrons either as α-particles or diplons. This hypothesis will account for the induced radioactivity as follows.

Consider, for example, the case of aluminium. It is supposed that the proton emission is caused by the positron of the electron pair uniting with the free neutron, the negative electron combining with the positron of the diplon to produce a quantum of γ-radiation and leaving the stable nucleus $_{14}Si^{29}$. When the energy of the α-particle increases beyond a critical value, it is supposed that the neutron is emitted before the high energy positron unites with it. The radioproton is formed, however, as the positron unites with one of the two neutrons produced

^{128}I, later… ^{131}I

$$p \rightarrow n + e^{+} + \nu$$

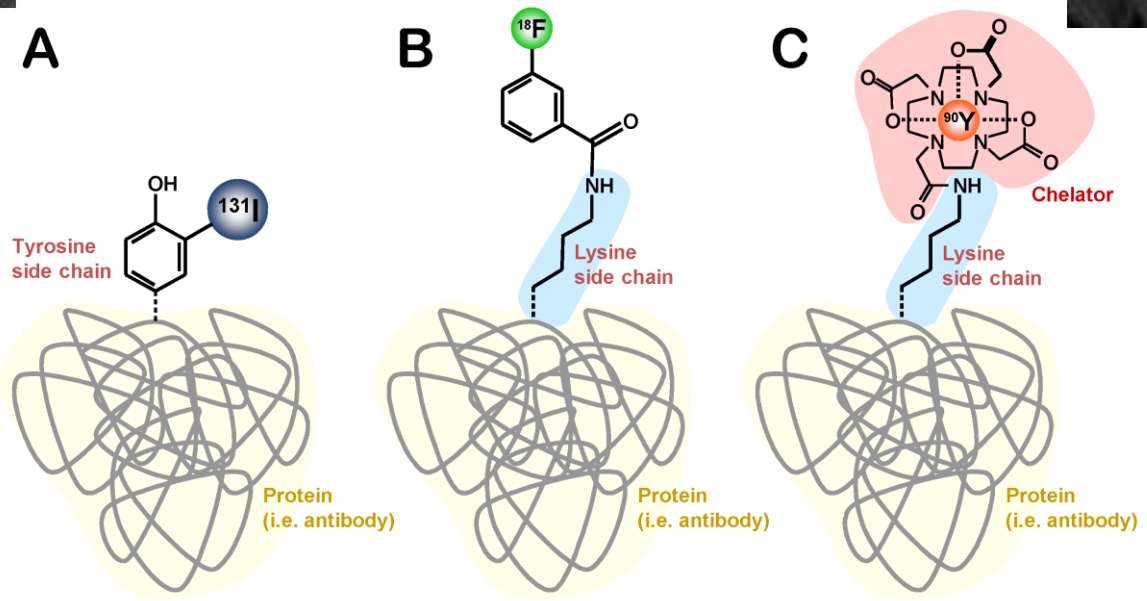
Nuclear Medicine is the concrete achievement of brilliant products of the human mind

The tracer principle

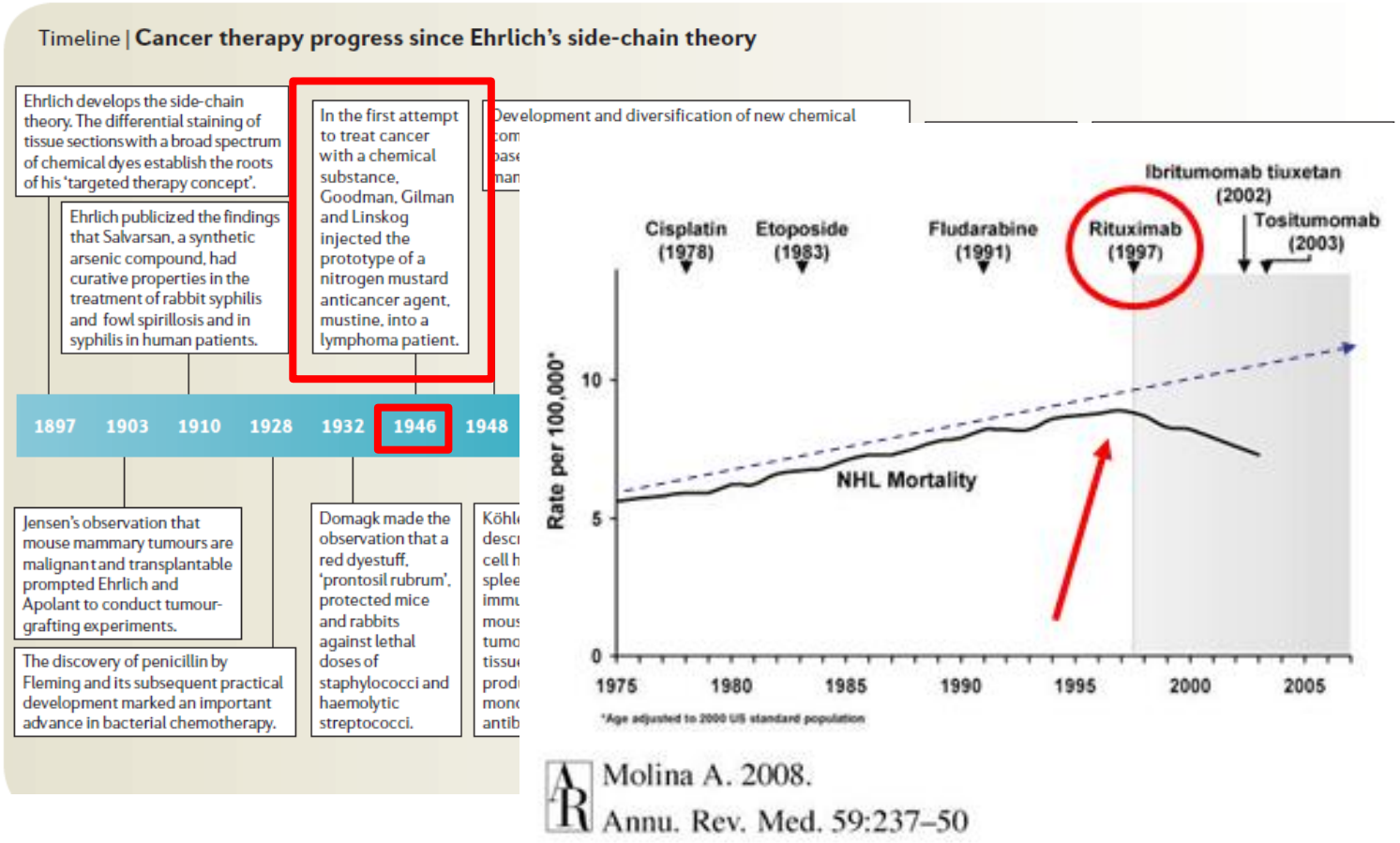
G. de Hevesy
(1885-1966)

The « magic bullet »

P. Ehrlich
(1854-1915)



Sugiura et al. *Molecules* 2014, 19; 2135-2165

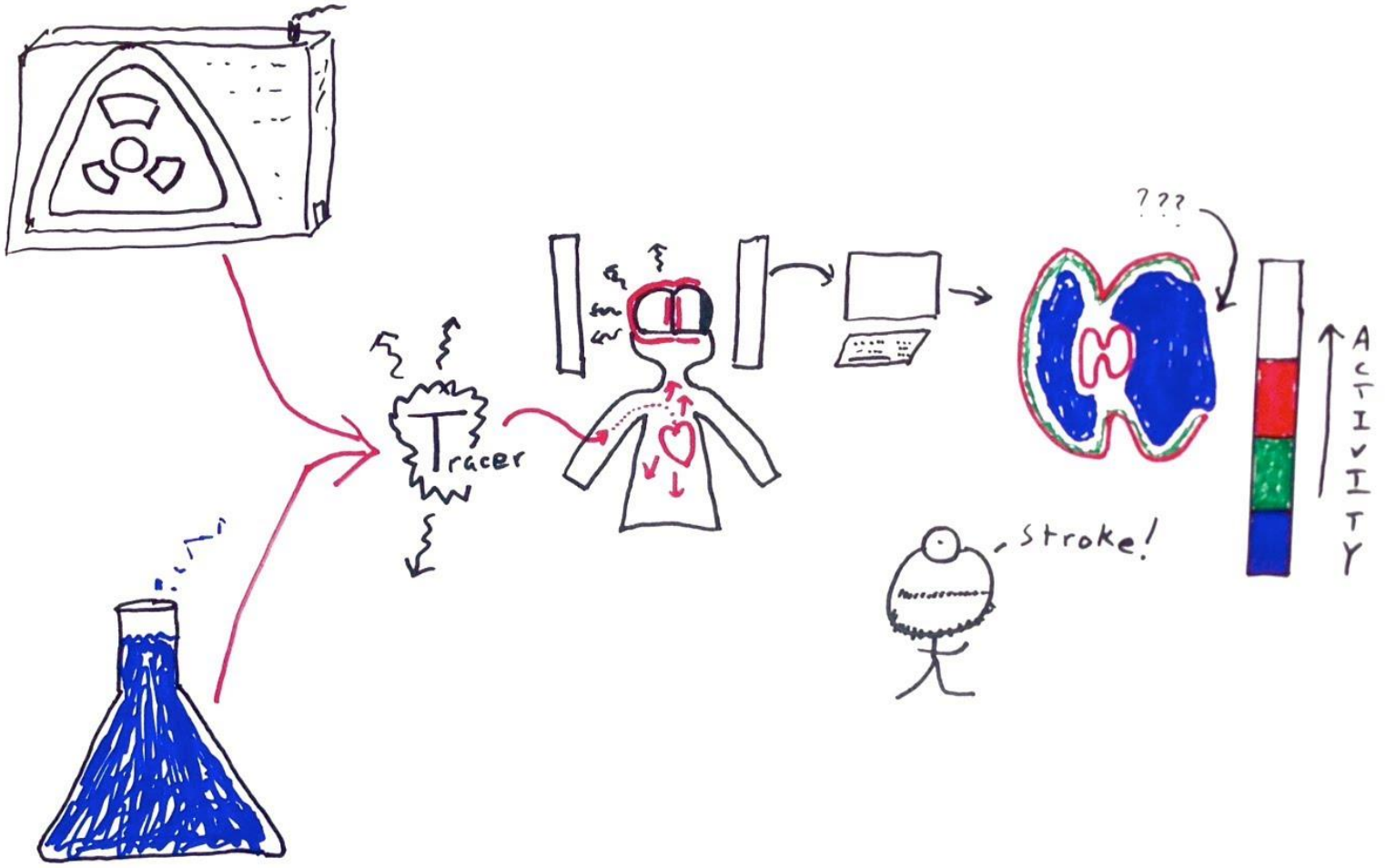


Molina A. 2008.
Annu. Rev. Med. 59:237–50

Ehrlich's ideal of « aiming precisely » using drugs with high efficacy dominates modern drug discovery

Strebhardt K & Ullrich A *Nat Rev Cancer 2008;*8:473-480

Radioactivity for medical use



What do we need more?

THE REVIEW OF SCIENTIFIC INSTRUMENTS VOLUME 29, NUMBER 1 JANUARY, 1958

Scintillation Camera

HAL O. ANGER
Donner Laboratory of Biophysics and Medical Physics and Radiation Laboratory, University of California, Berkeley, California
(Received August 19, 1957; and in final form, October 21, 1957)

A new and more sensitive gamma-ray camera for visualizing sources of radioactivity is described. It consists of a lead shield with a pinhole aperture, a scintillating crystal within the shield viewed by a bank of seven photomultiplier tubes, a signal matrix circuit, a pulse-height selector, and a cathode-ray oscilloscope. Scintillations that fall in a certain range of brightness, such as the photopeak scintillations from a gamma-ray-emitting isotope, are reproduced as point flashes of light on the cathode-ray tube screen in approximately the same relative positions as the original scintillations in the crystal. A time exposure of the screen is taken with an oscilloscope camera, during which time a gamma-ray image of the subject is formed from the flashes that occur. One of many medical and industrial uses is described, namely the visualization of the thyroid gland with I^{131}.

1950 - S Seidling: If a metastasis has high uptake, we can destroy it. Now, for God's sake, when will physicists learn to measure ^{131}I uptake? L. Marinelli: « As soon as physicians decide how much uptake is *high* »

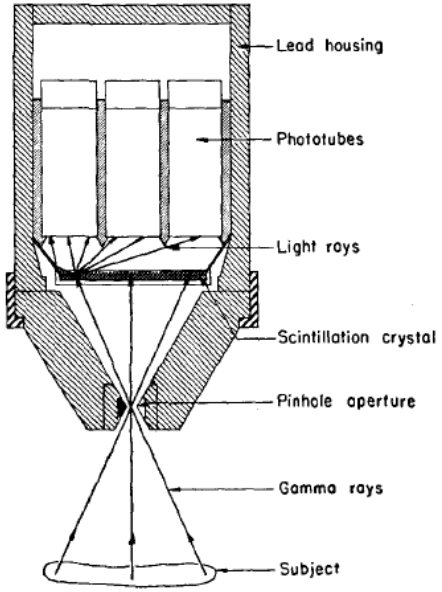


FIG. 1. Sectional drawing of scintillation camera.

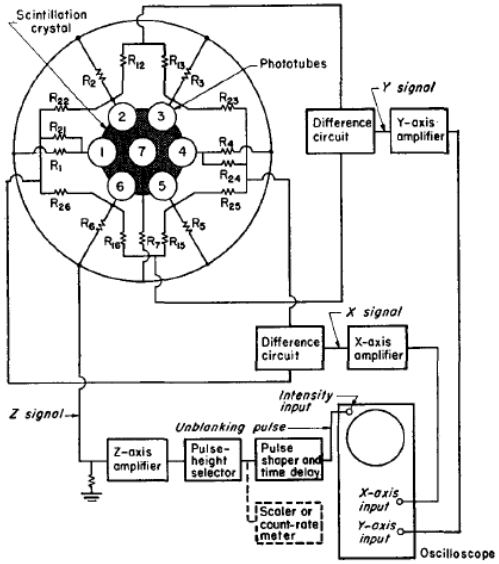


FIG. 2. Block diagram of electronic circuit.

H. Anger
(1920-2005)

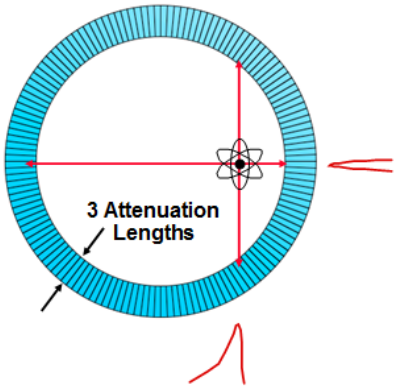
Evolving technologies

Properties of PET Scintillators

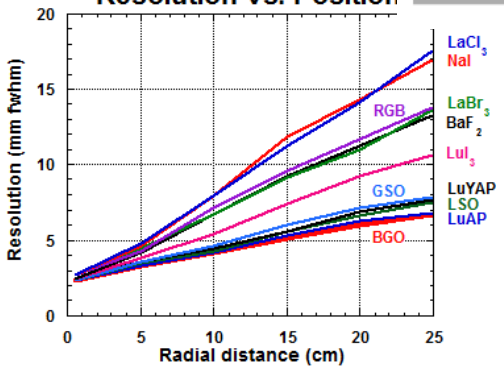
Scintillator	τ (ns)	Luminosity (photons/MeV)	I_0 (phot/MeV/ns)	I_0 (pe/ns)
BGO	300	8,200	27	1.6
BaF_2 (fast)	0.8	1,800	2250	132
LSO / LYSO	42	25,000	595	35
$LaBr_3$	30	60,000	2000	118
LuI_3	23	100,000	4348	256

Low Density ⇒ Radial Elongation

Penetration Blurs Image



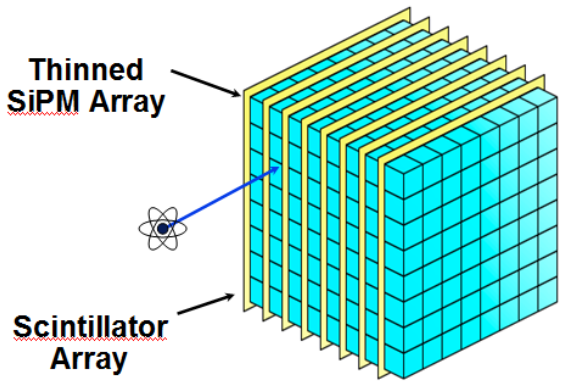
Resolution vs. Position



$LaBr_3$ (& BaF_2) Have More Degradation Than LSO

- New Scintillators Have Enabled TOF PET
- Timing Is Not the Only Important Property for PET

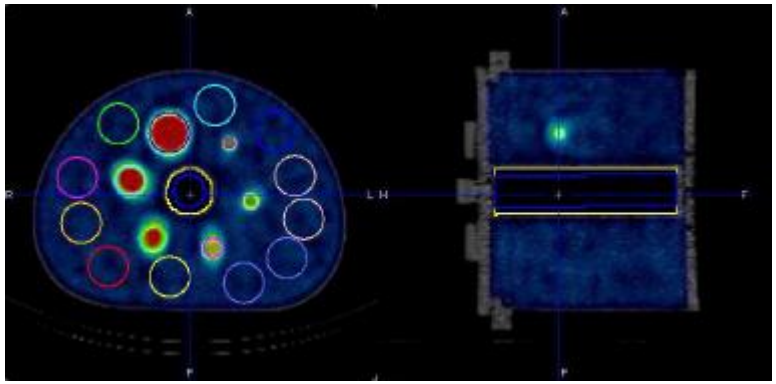
Future TOF PET Design?

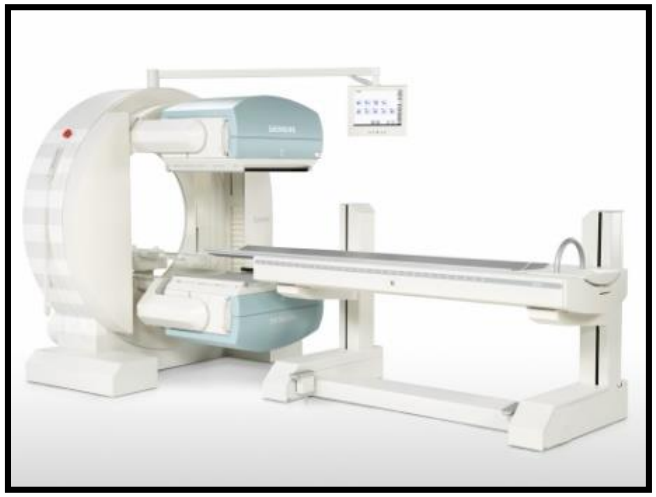


- Depth of Interaction & 150 ps Timing Resolution
- 11x Reduction in Variance in Practical Geometry

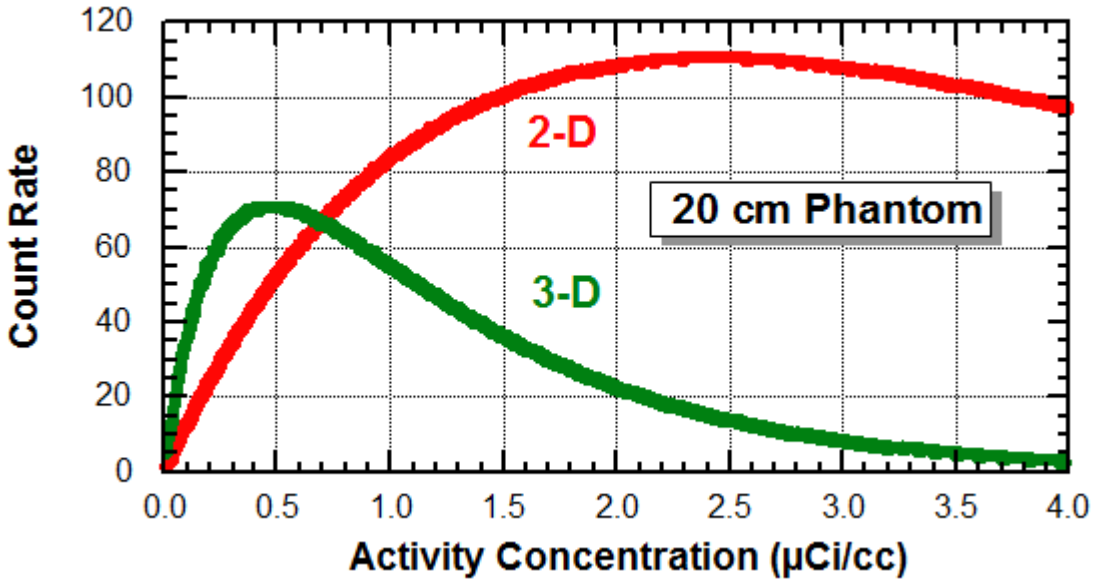
Courtesy of *Moses WW*

Instrumentation:QC and performance evaluation





$$NECR = \frac{T^2}{T + S + 2R}$$



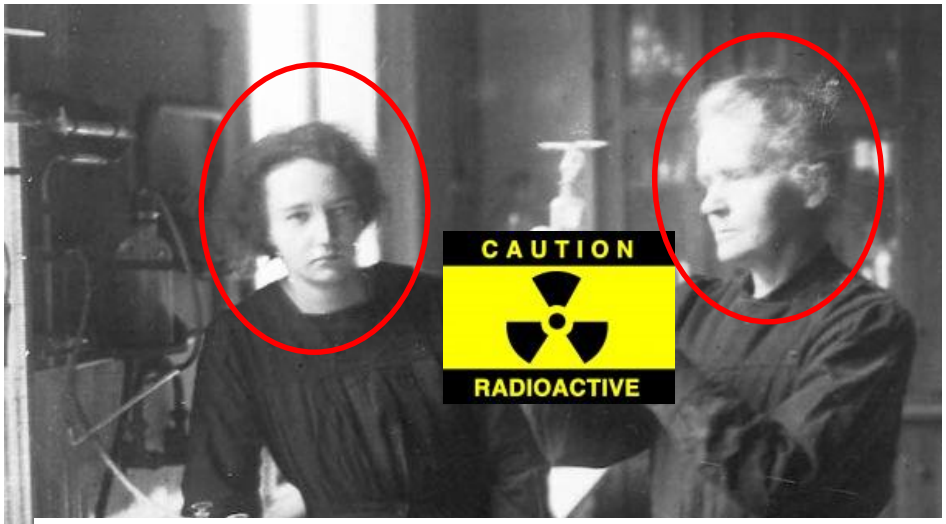
… a change of perspective:

from Technology to Biology !

1) Radiation Protection

2) Dosimetry

1) Radiation Protection



Marie Sklodowska-Curie (1867-1934)

Nobel Prize Physics 1903 (with P. Curie & H. Bequerel)
Nobel Prize Chemistry 1911

of aplastic anemia

Irene Curie-Joliot (1897-1956)

Nobel Prize Chemistry 1935 (with F. Joliot)

of leukemia

Marie Curie's century-old radioactive notebook still requires lead box

Adam Clark Estes
8/04/14 2:00pm · Filed to: SCIENCE

56.0K 34 6

"One of our joys was to go into our workroom at night; we then perceived on all sides the feebly luminous silhouettes of the bottles of capsules containing our products. It was really a lovely sight and one always new to us. The glowing tubes looked like faint, fairy lights."

Linear-no threshold and ALARA ?

OPINION PAPER/COMMENTARY

Time to Reject the Linear-No Threshold Hypothesis and Accept Thresholds and Hormesis: A Petition to the U.S. Nuclear Regulatory Commission

Carol S. Marcus, PhD, MD

Abstract: On February 9, 2015, I submitted a petition to the U.S. Nuclear Regulatory Commission (NRC) to reject the linear-no threshold (LNT) hypothesis and ALARA as the bases for radiation safety regulation in the United States, using instead threshold and hormesis evidence. In this article, I will briefly review the history of LNT and its use by regulators, the lack of evidence supporting LNT, and the large body of evidence supporting thresholds and hormesis. Physician acceptance of cancer risk from low dose radiation based upon federal regulatory claims is unfortunate and needs to be reevaluated. This is dangerous to patients and impedes good medical care. A link to my petition is available: http://radiationeffects.org/wp-content/uploads/2015/03/Hormesis-Petition-to-NRC-02-09-15.pdf, and support by individual physicians once the public comment period begins would be extremely important.

Key Words: linear no-threshold hypothesis, radiation hormesis

(*Clin Nucl Med* 2015;40: 617–619)

The linear-no threshold (LNT) hypothesis states that all radiation absorbed doses, no matter how small, have a finite probability of causing cancer. The lower the radiation absorbed dose, the lower the probability that a cancer may be caused, but the probability is never zero. The dose rate is irrelevant, and all absorbed doses are additive. That this is not the case is evidenced by the practices of radiation oncology and of nuclear medicine therapy. The threshold concept is that no cancer will be produced until a certain radiation absorbed dose is reached. The hormesis concept is that low radiation doses are *beneficial* because the repair mechanisms that are stimulated by the low dose radiation reverses the initial damage and continues to protect the organism from more radiation or other noxious exposures that might otherwise lead to cancer. Eventually, there is a radiation dose high enough so that damage reversal is incomplete, and there we see the deleterious effect of radiation resulting in excess cancer production.

Prof. Edward J. Calabrese has traced the origin of LNT to shocking scientific misconduct by the nation's leading geneticists beginning in 1956.[1–3] Some members of the U.S. National Academy of Sciences Biological Effects of Atomic Radiation I (BEAR I) Genetics Panel were motivated by self-interest to exaggerate risks to promote their science and the probability of grants. Combined with the antinuclear agenda of many during the Cold War era, in which lies to produce fear of any dose of radiation were commonplace, the LNT concept caught on. Radiation regulators used the LNT as the basis of radiation safety regulation "to be conservative", and eventually NRC added "ALARA". LNT became a religion, not a scientifically based concept. On May 17, 2001, the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health created a national uproar by stating that CT scans were causing many cases of cancer, and tried to stop self-referral of patients for CT scans to rule out early cancer and cardiac calcifications that can predict heart disease. FDA's claims were based upon LNT. Surprisingly, physician groups such as the American College of Radiology and the Society of Nuclear Medicine did not contest any of it and meekly went along with the idea that low doses from CT and diagnostic radiopharmaceuticals could cause cancer. The race began to get radiation doses down. There was never any evidence that these groups were examining the data upon which FDA's dire predictions were based. Also, in 2001, the NCRP published Report no. 136 entitled "Evaluation of the Linear-Nonthreshold Dose–response Model for Ionizing Radiation"[4] in which they upheld the LNT. This NCRP study was funded by the NRC. In 2003, Zbigniew Jaworowski of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and a past Chair of that group, and Michael Waligorski, destroyed that Report's credibility with an astonishing exposé of scientific misconduct.[5]

Biological organisms are exceedingly complex and have evolved in a world of stressors, particularly oxygen, and also low dose background radiation. More than 150 genes have thus far been found that are involved in the defense of organisms against noxious stimuli.[6] There are several thousand papers relating to hormesis, and two textbooks in the field. This is a whole field of science that regulators pretend does not exist. Let us review some human studies whose data support radiation hormesis.

The most commonly used data are those of the Life Span Study of the Radiation Effects Research Foundation which studies the Japanese atomic bomb survivors. Recent data[7] show a hormetic effect for all solid cancers in the 0.3–0.7 *Gy* (30–70 rad) dose range, and the study of leukemia rates in the 96,000 survivors[8] showed hormesis at low doses with a threshold at about 500 mSv (50 rem).

Nuclear power plant workers comprise the largest study of radiation workers, 400,000 from 154 power plants in 15 countries,[9,10] and the study showed a decrease in the risk of all cancers including leukemia. In trying to explain this, the National Academy of Sciences Biological Effects of Ionizing Radiation (BEIR) VII Committee hypothesized the "healthy worker effect". The idea is that people who work with radiation are healthier than the general population, and get less cancer, anyway. A little thought will show the fallacy here.[11] Most radiation workers begin work when they are young, when most people are healthy. Cancer is largely a disease of older people, with half the cases occurring in people over 65 years old.[12] So, you have to be healthy to get old enough to get cancer. Sickly people often die young, of something other than cancer. People with hyperlipidemia die young of myocardial infarctions, people with cystic fibrosis often die early of infections, and people with juvenile onset diabetes often die early from infections, myocardial infarctions, or renal failure. The "healthy worker effect" is backwards. Hormesis is a perfectly good explanation.

Female tuberculosis patients in Canadian sanatoriums from 1930 to 1952 were followed with fluoroscopy. There were 31,710 patients

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From the David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles, CA.
Conflicts of interest and sources of funding: none declared.
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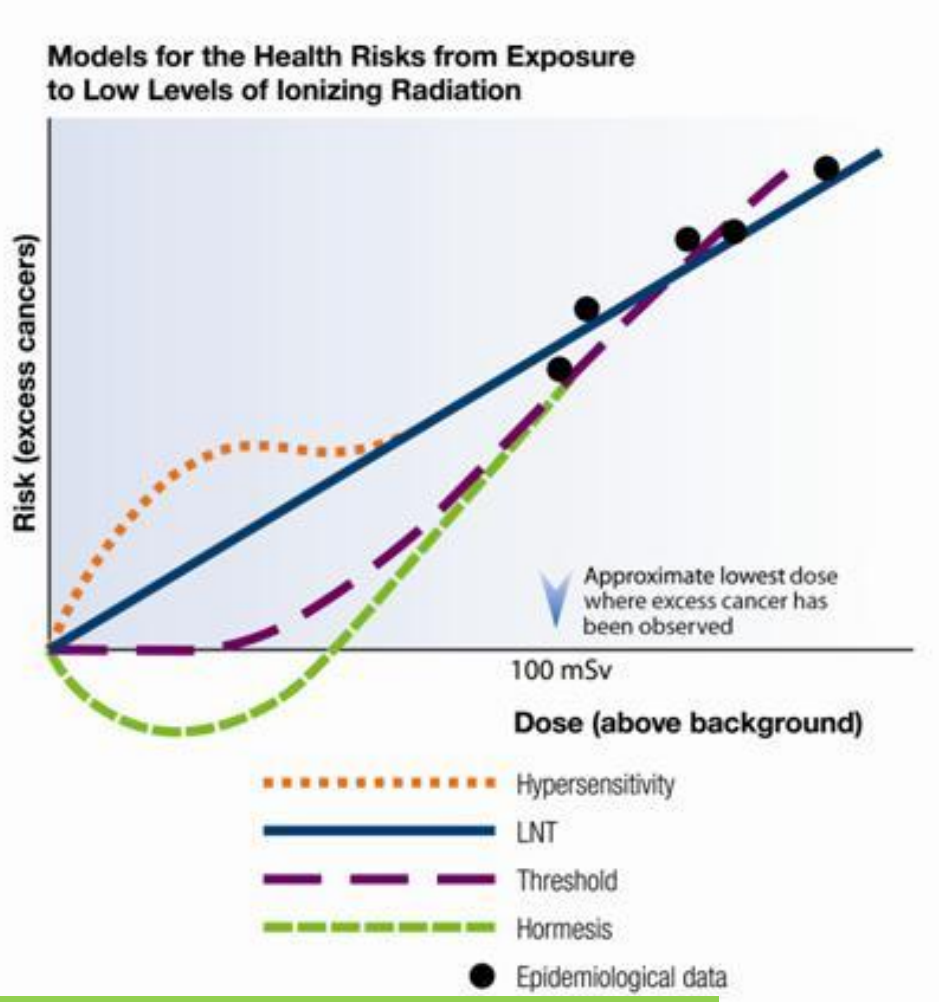
ISSN: 0363-9762/15/4007–0617



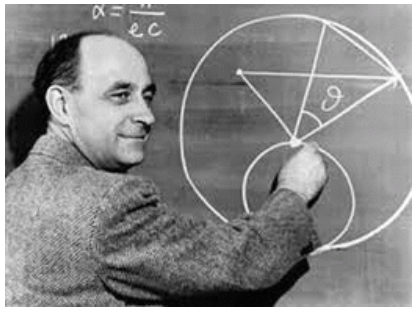
« ALARA should be removed entirely from the regulations as it makes no sense to decrease radiation doses that are not only harmless but may me hormetic »

2) Dosimetry

$$\bar{D}(r_k \leftarrow r_h) = \sum_{h=0}^{N} \tilde{A}_h \cdot S(r_k \leftarrow r_h)$$

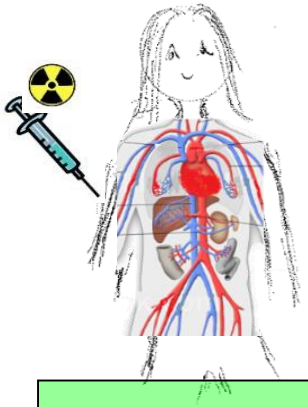
=

X

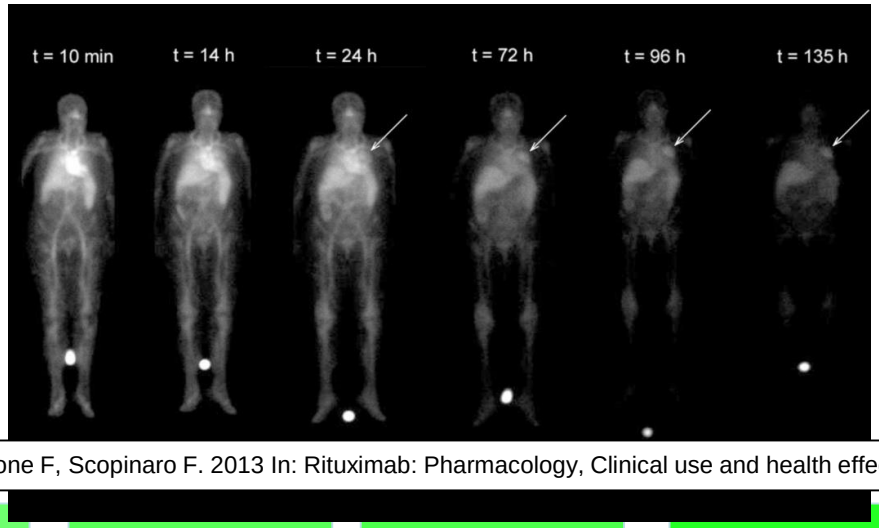


D (Gy): What effect on tissues?

Image-based dosimetry



SPECT / CT
Image acquisition

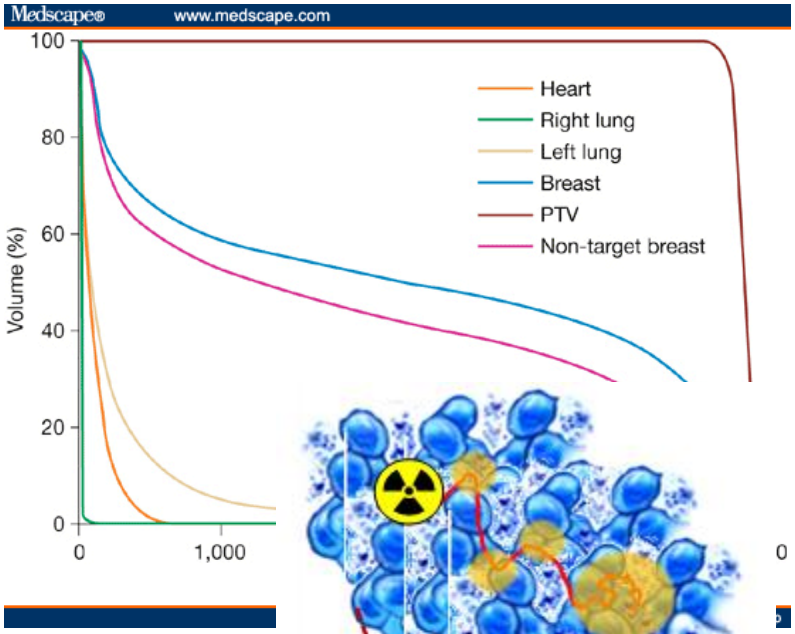


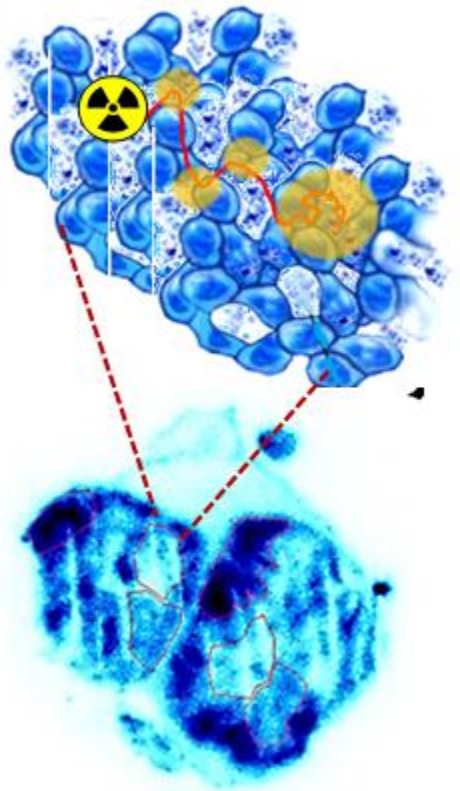
Cicone F, Scopinaro F. 2013 In: Rituximab: Pharmacology, Clinical use and health effects

Quantitative image reconstruction Attenuation and scatter corrections Coll. response	Camera-calibration factor → reconstructed cps to activity in each voxel	Delineation of 3D volumes of interest	Partial volume correction → Activity in organ	Mass of organ, or of voxels	Absorbed dose rate calculation Voxels or structures
CT-image as attenuation map	Camera calibration	CT-image information	Recovery coefficient	CT image volume and mass	CT image for mass

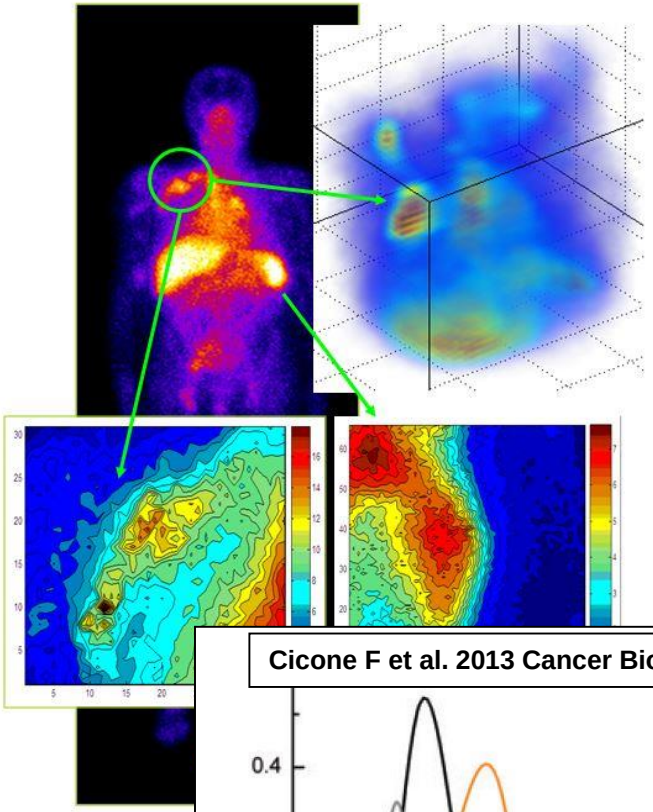
Courtesy of *Sjögreen Gleisner* K

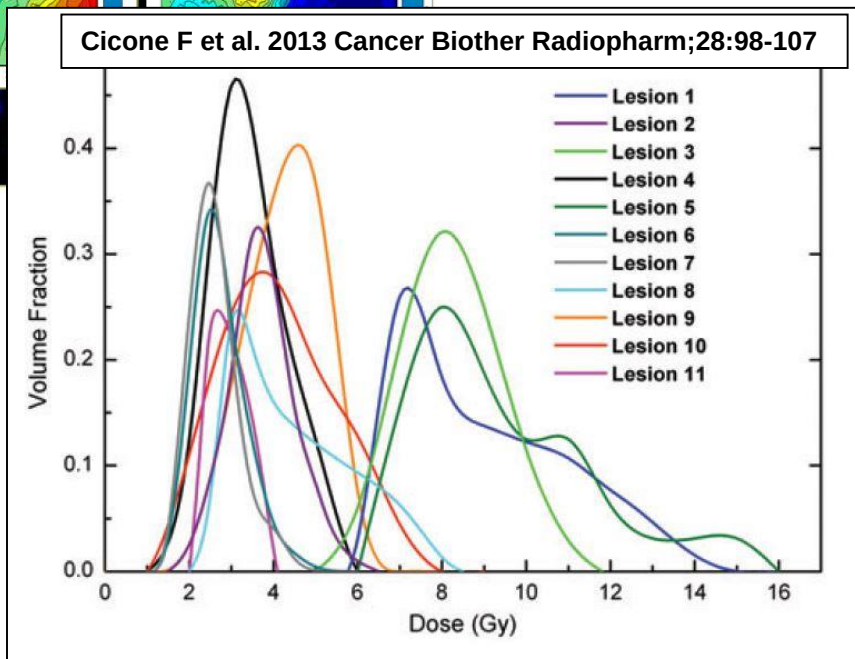
Tumour dosimetry: EBRT vs RIT





Örbom et al J Nucl Med 2013





EBRT vs RIT

Conventional External Beam Radiotherapy

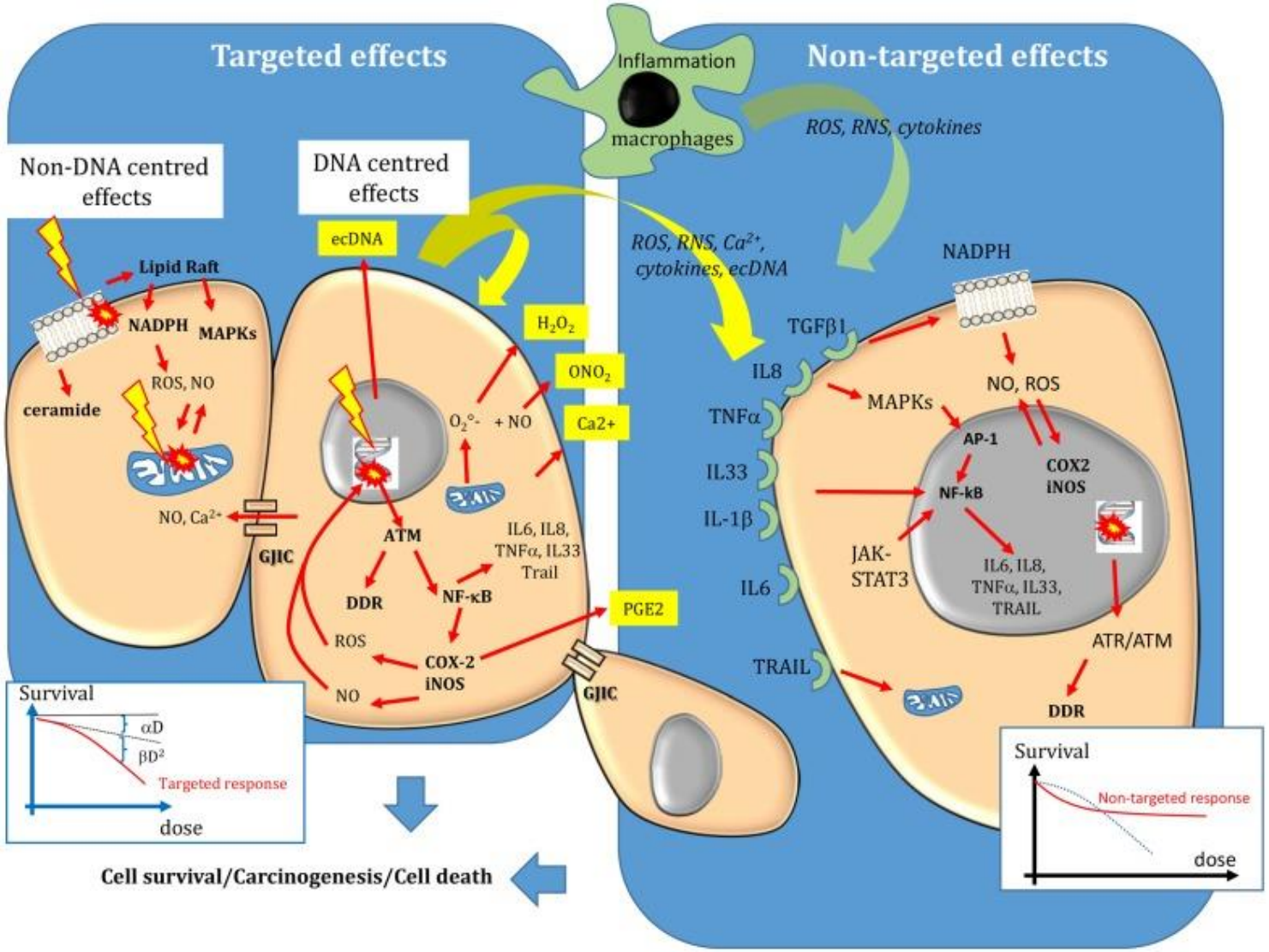
- ❑ Photons and electrons (6, 12, 18, 25 MeV)
- ❑ Low LET radiation : 0.2 keV/µm
- ❑Tumor (radiation sensitivity, microenvironment)
- ❑ Homogeneous irradiation field
- ❑ 2 Gy/fraction, multiple fractions
- ❑ Dose rate (60-120 Gy/h)
- ❑ Well defined dosimetry (50 Gy—80 Gy)

Targeted Radionuclide Therapy

- ❑ Antibody, peptides etc. (Pharmacokinetic/ Pharmacodynamic)
- ❑ Isotope ($T_{1/2Phys}$, specific activity decay spectrum)
  - Alpha particles: 40µm-92µm (e.g. Bi212)
  - Beta particles: µm- 1.2mm (e.g. Y90)
  - Auger electrons: nm-µm (e.g. Pt195m)
- ❑ Tumor (size, antigen density, radiation sensitivity, microenvironment)
- ❑ Heterogeneous dose distribution
- ❑ Protracted exposure (hours→ days)
- ❑ Low absorbed dose rate irradiation (<0.1—1.0 Gy/h)
- ❑ Mixed irradiation (low and high- LET radiation)
  - Alpha particles: 50-230keV/µm
  - Beta particles, γ, x-rays: 0.2 keV/µm
  - Auger electrons: 4-25 keV/µm
- ❑ MIRD Dosimetry (15— 30 Gy)

Pouget JP et al 2015 Front Med;17: 2-12

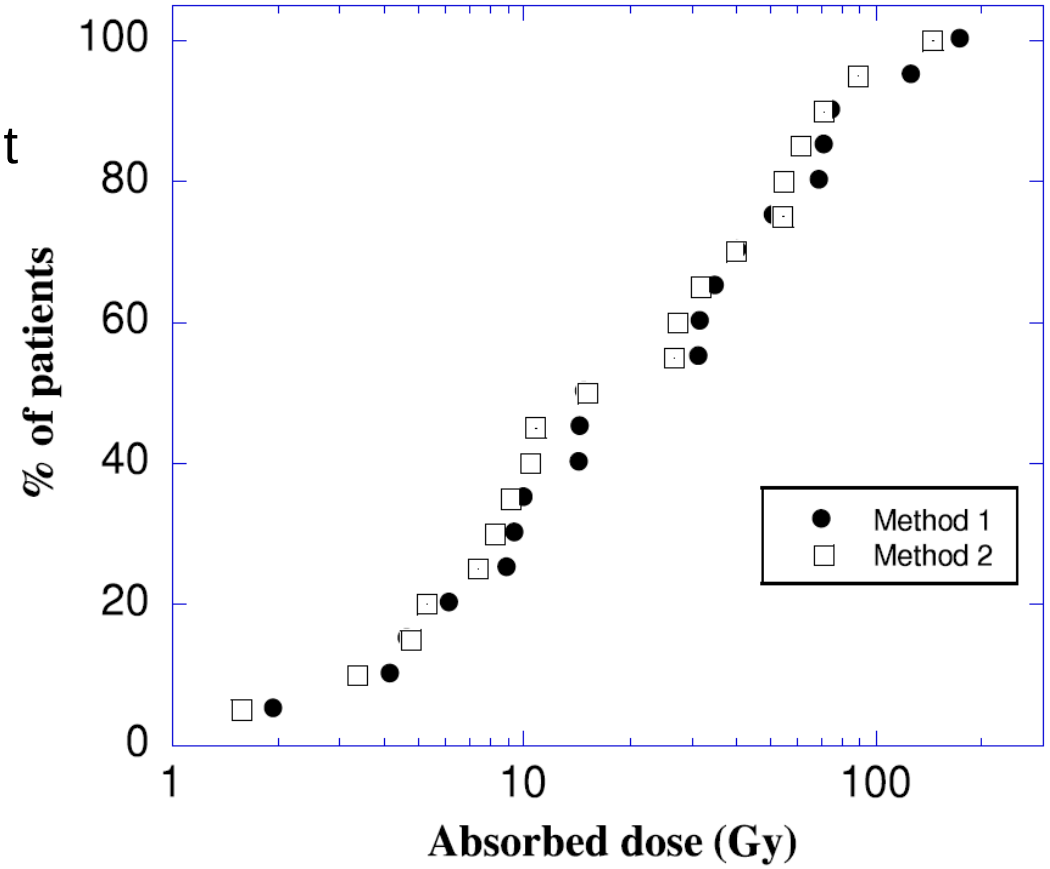
New paradigms in radiation biology



Biodistribution varies between patients

Same injected activity gives doses to remnant of **2-200 Gy**

Thyroid remnant ablation $Na^{131}I$



Minguez et al, Med Phys, 2016

Optimization of biodistribution: preloading

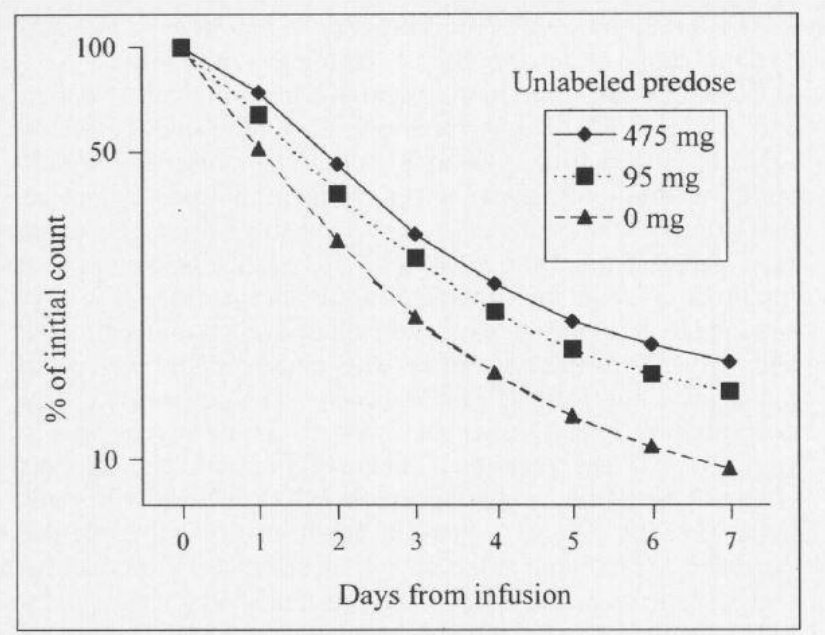


FIGURE 2. Relationship between total-body clearance and protein predose. The higher predose (475 mg) results in a much longer clearance than does no predose (0 mg).

Wahl RL et al. 1998 JNM;39(8 Suppl):21S-27S

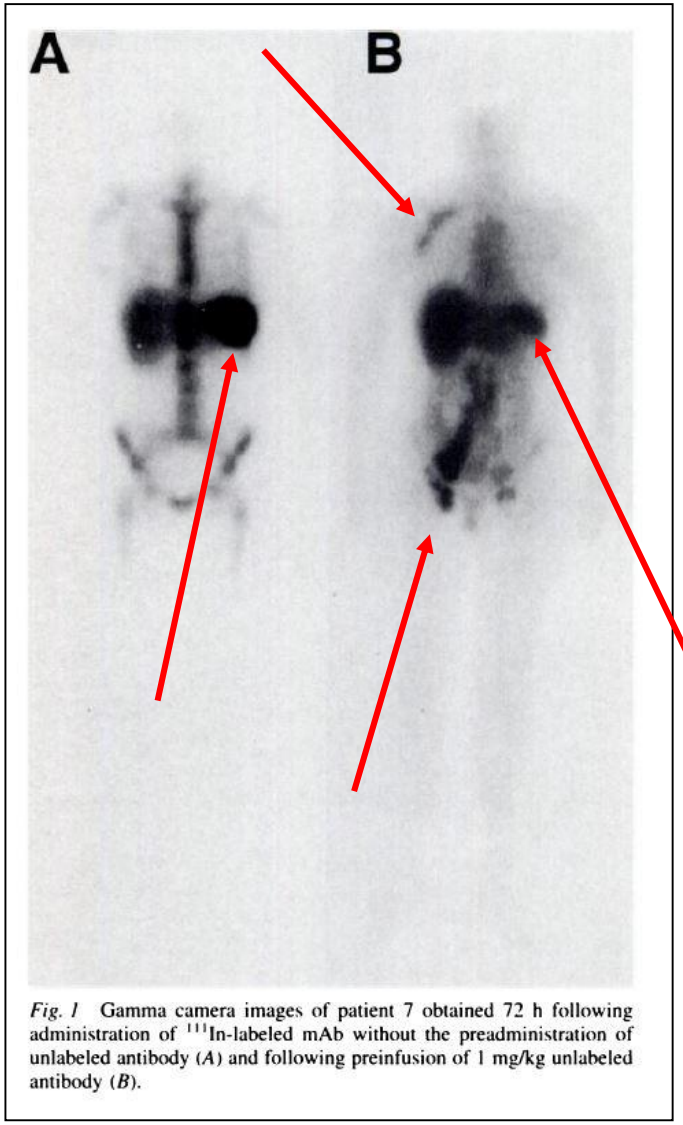


Fig. 1 Gamma camera images of patient 7 obtained 72 h following administration of ^{111}In-labeled mAb without the preadministration of unlabeled antibody (*A*) and following preinfusion of 1 mg/kg unlabeled antibody (*B*).

Knox SJ et al. 1996 Clin Canc Res;2:457-70

Is dosimetry useful?

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

REVIEW ARTICLE

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

Received: 15 May 2014 / Accepted: 19 May 2014

Tumor-Absorbed Dose Predicts Progression-Free Survival Following ^{131}I-Tositumomab Radioimmunotherapy

Yuni K. Dewaraja[1], Matthew J. Schipper[2], Jincheng Shen[3], Lauren B. Smith[4], Jure Murgic[5], Hatice Savas[1], Ehab Youssef[1], Denise Regan[1], Scott J. Wilderman[6], Peter L. Roberson[2], Mark S. Kaminski[7], and Anca M. Avram[1]

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Center Sestre Milosrdnice, Zagreb, C
and [7]Department of Internal Medici

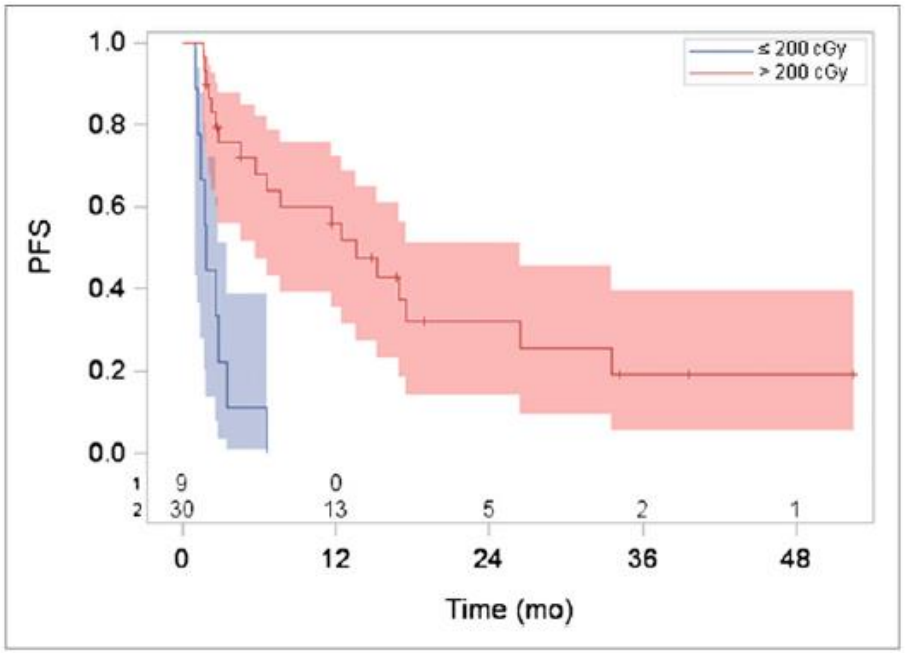
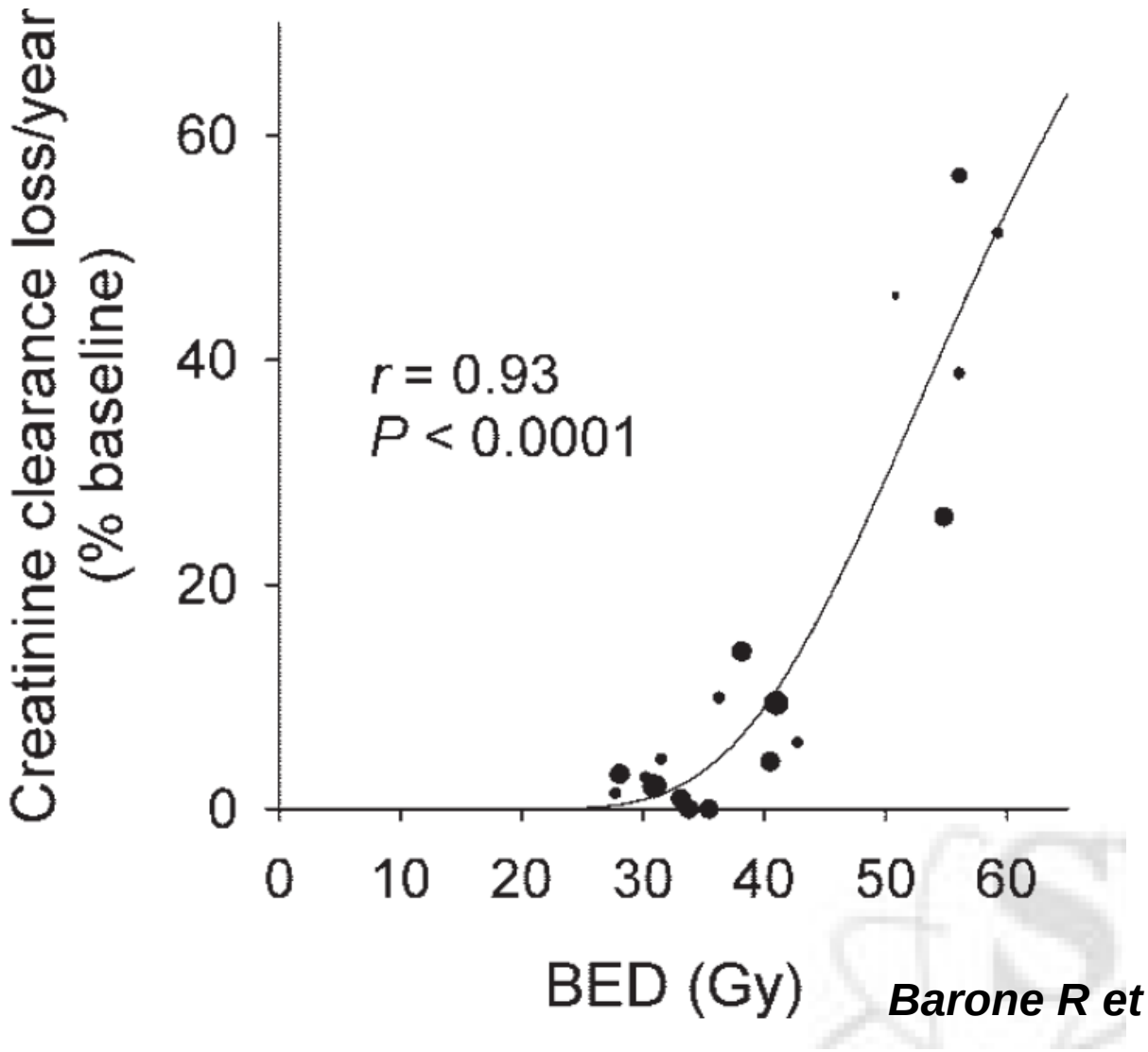


FIGURE 4. PFS (with number of subjects at risk and 95% confidence limits indicated) stratified by mean tumor-absorbed dose > 200 cGy and ≤ 200 cGy. Median PFS was 13.6 vs. 1.9 mo for the 2 dose groups (log-rank $P < 0.0001$).

JNM 2014;55:1047-1053

^{90}Y-PRRT of neuroendocrine tumours

Toxicity Grade kidneys



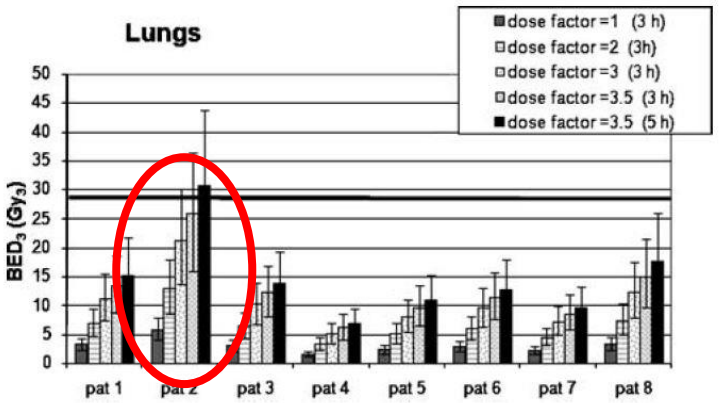
Barone R et al, JNM 2005

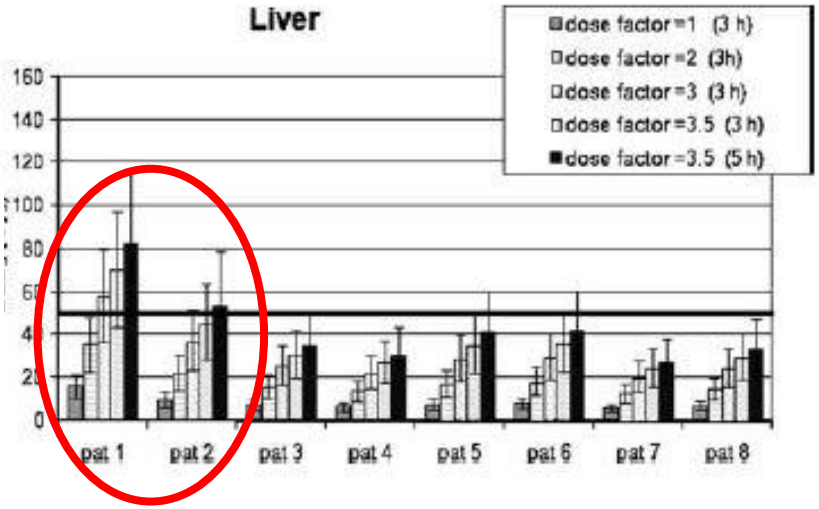
Eur J Nucl Med Mol Imaging (2010) 37:862–873
DOI 10.1007/s00259-009-1333-4

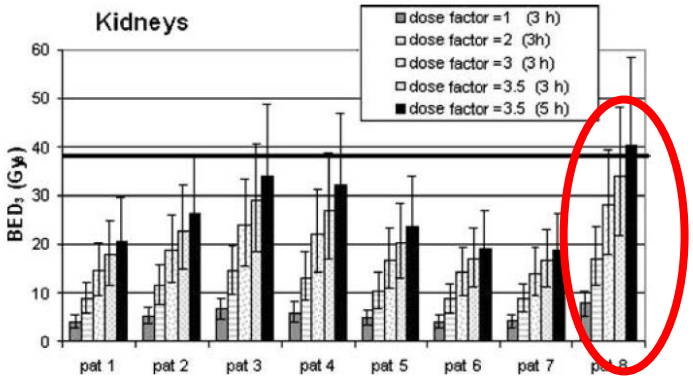
ORIGINAL ARTICLE

A theoretical dose-escalation study based on biological effective dose in radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan (Zevalin)

Massimiliano Pacilio · Margherita Betti · Francesco Cicone · Carolina Del Mastro · Livia Montani · Laura Chiacchiararelli · Alessia Monaco · Enrico Santini · Francesco Scopinaro







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Legislation

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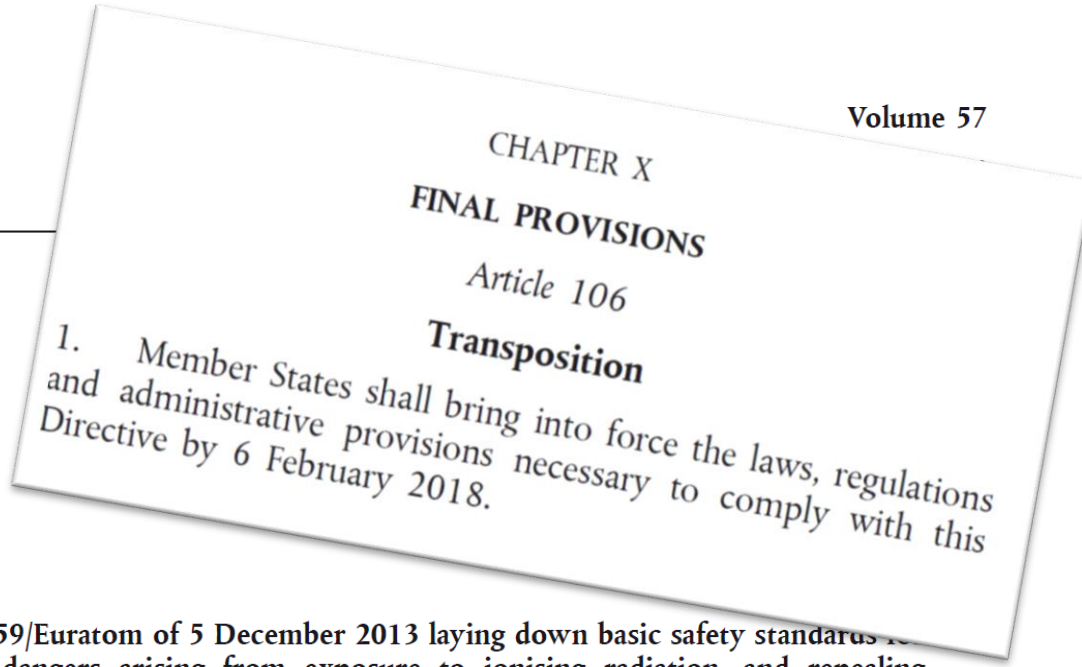


CHAPTER X

FINAL PROVISIONS

Article 106

Transposition

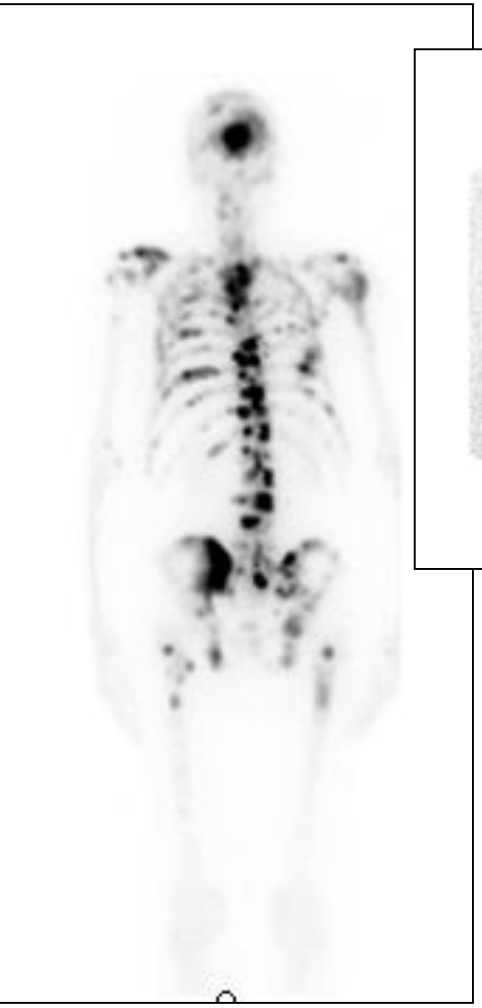
1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 6 February 2018.

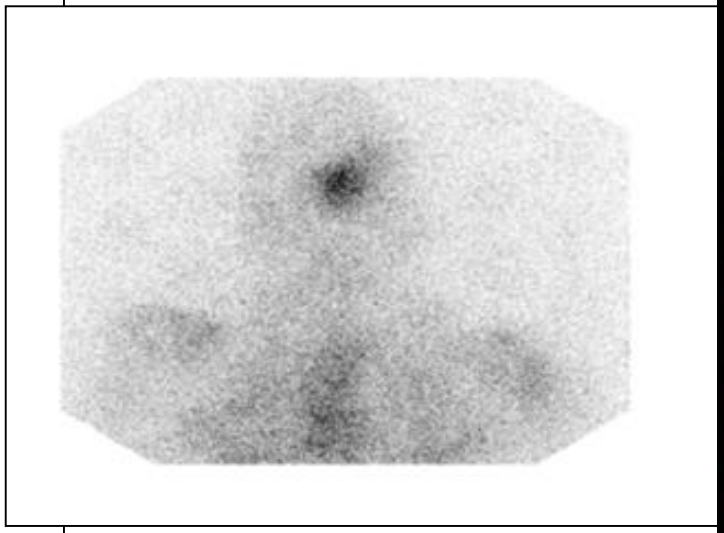
2013/59/Euratom

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

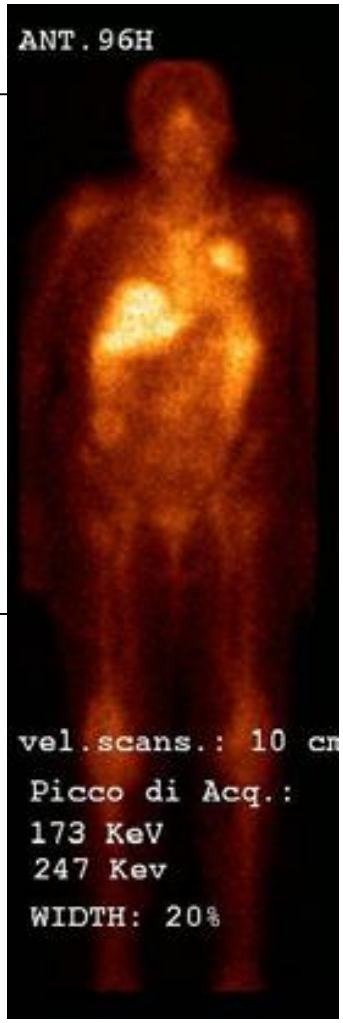
- (Chapter II, Definitions, Article 4, Definitions): " "radiotherapeutic" means pertaining to radiotherapy, **including nuclear medicine** for therapeutic purposes".

Verification of dose delivery: challenges for radionuclide imaging





$^{223}RaCl_2$



^{90}Y-Zevalin

Eur J Nucl Med Mol Imaging (2017) 44:1783–1786
DOI 10.1007/s00259-017-3707-3

EDITORIAL

The conflict between treatment optimization and registration of radiopharmaceuticals with fixed activity posology in oncological nuclear medicine therapy

C. Chiesa[1] · K. Sjogreen Gleisner[2] · G. Flux[3] · J. Gear[3] · S. Walrand[4] · K. Bacher[5] · U. Eberlein[6] · E. P. Visser[7] · N. Chouin[8] · M. Ljungberg[2] · M. Bardiès[9] · M. Lassmann[6] · L. Strigari[10] · M. W. Konijnenberg[11]

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3820-3

LETTER TO THE EDITOR

Dosimetry in clinical radionuclide therapy: the devil is in the detail

Francesco Giammarile[1,2] · Kristoff Muylle[1,3] · Roberto Delgado Bolton[1,4] · Jolanta Kunikowska[1,5] · Uwe Haberkorn[6,7,8] · Wim Oyen[1,9]

Eur J Nucl Med Mol Imaging (2018) 45:152–154
https://doi.org/10.1007/s00259-017-3859-1

LETTER TO THE EDITOR

From fixed activities to personalized treatments in radionuclide therapy: lost in translation?

G. D. Flux[1] · K. Sjogreen Gleisner[2] · C. Chiesa[3] · M. Lassmann[4] · N. Chouin[5,6] · J. Gear[1] · M. Bardiès[7] · S. Walrand[8] · K. Bacher[9] · U. Eberlein[3] · M. Ljungberg[2] · L. Strigari[10] · E. Visser[11] · M. W. Konijnenberg[12]

Internal Dosimetry Task Force

Sjögreen Gleisner *et al. EJNMMI Physics* (2017) 4:28
DOI 10.1186/s40658-017-0193-4

EJNMMI Physics

ORIGINAL RESEARCH Open Ac

Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey

Katarina Sjögreen Gleisner[1*], Emiliano Spezi[2], Pavel Solny[3], Pablo Minguez Gabina[4], Francesco Cicone[5], Caroline Stokke[6], Carlo Chiesa[7], Maria Paphiti[8], Boudewijn Brans[9], Mattias Sandström[10], Jill Tipping[11], Mark Konijnenberg[12] and Glenn Flux[13]

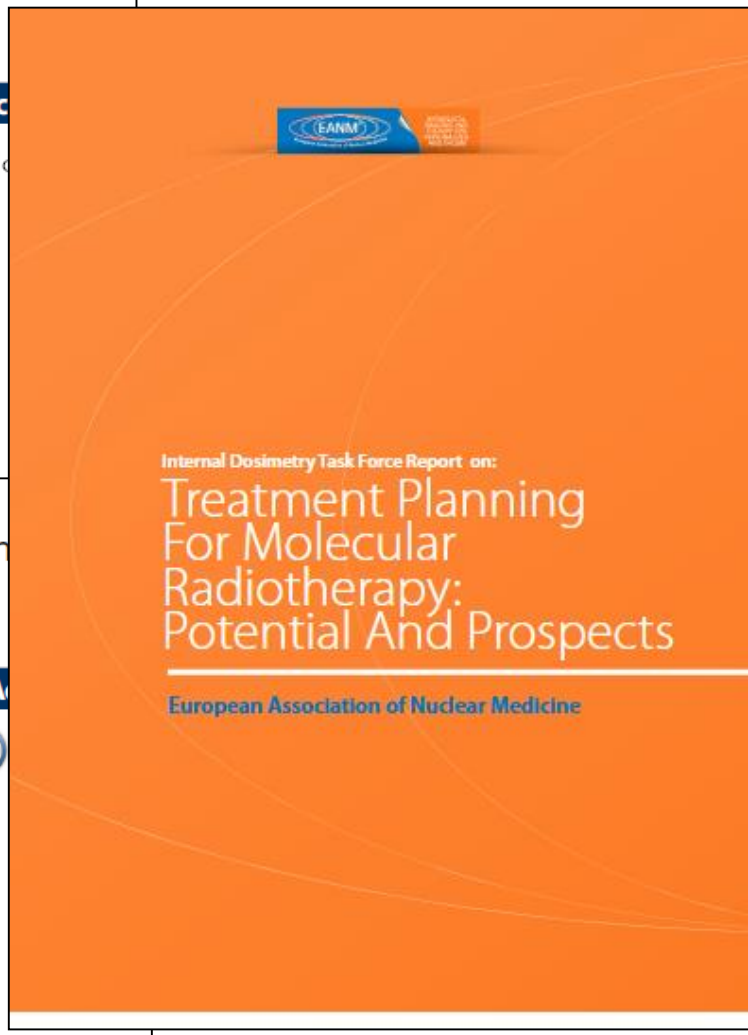
Stokke *et al. EJNMMI Physics* (2017) 4:27
DOI 10.1186/s40658-017-0194-3

EJNMMI Ph

ORIGINAL RESEARCH Open A

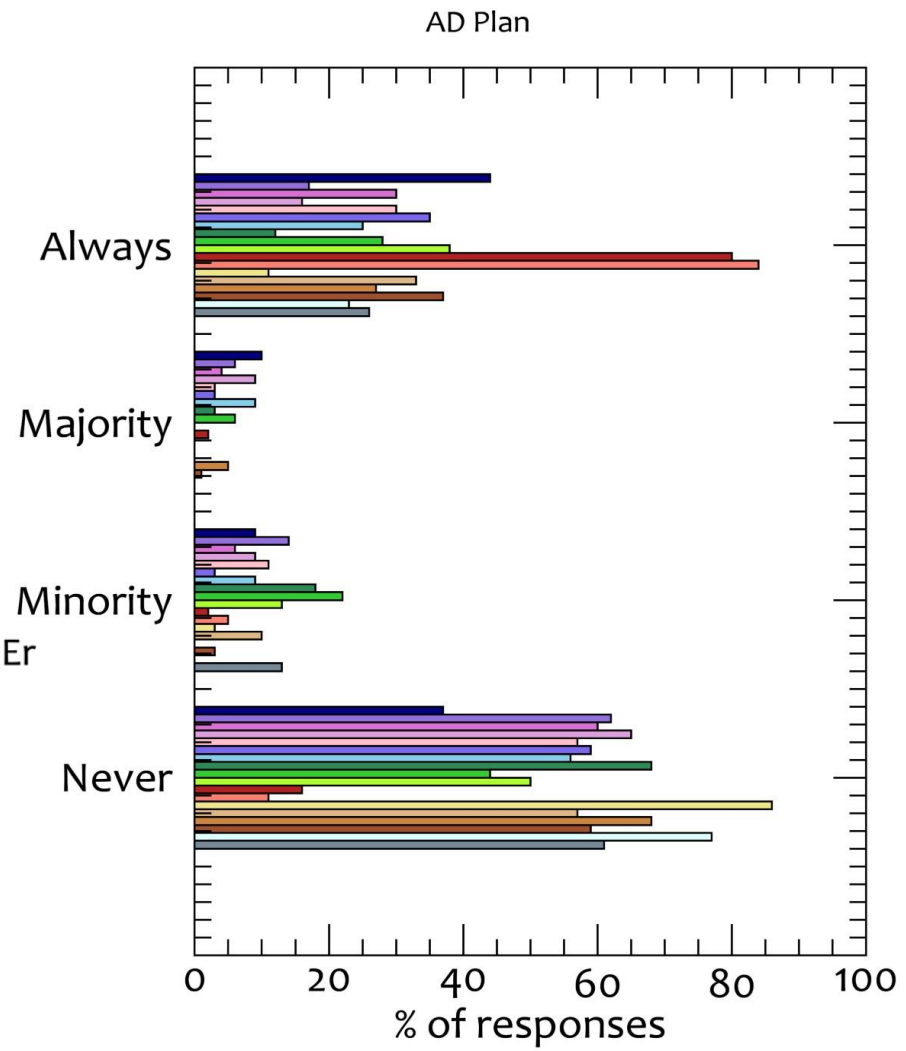
Dosimetry-based treatment planning for molecular radiotherapy: a summary of the 2017 report from the Internal Dosimetry Task Force

Caroline Stokke[1*], Pablo Minguez Gabiña[2], Pavel Solný[3], Francesco Cicone[4], Mattias Sandström[5], Katarina Sjögreen Gleisner[6], Carlo Chiesa[7], Emiliano Spezi[8], Maria Paphiti[9], Mark Konijnenberg[10], Matt Aldridge[11], Jill Tipping[12], Michael Wissmeyer[13], Boudewijn Brans[14], Klaus Bacher[15], Carsten Kobe[16] and Glenn Flux[17]



Is the absorbed dose individually planned for each patient?

- 131I NaI for benign thyroid diseases
- 131I NaI for thyroid ablation of adults
- 131I NaI for thyroid ablation of young
- 131I NaI for thyroid cancer therapy for adults
- 131I NaI for thyroid cancer therapy for young
- 131I mIBG for neuroblastoma
- 131I mIBG for adult neuroendocrine tumours
- 177Lu Somatostatin receptor PRRT
- Y90 Somatostatin receptor PRRT
- 177Lu PSMA therapy of prostate cancer
- 90Y resin microspheres in liver
- 90Y glass microspheres in liver
- Radiation synovectomy using 90Y 186Re or 169Er
- 153Sm for bone metastases
- 89Sr for bone metastases
- 223Ra for bone metastases
- 32P phosphate for myeloproliferative diseases
- 90Y Zevalin for B-cell lymphoma



^{90}Y somatostatin analogues for the treatment of neuro-endocrine tumours

6

DOSIMETRY FOR THERAPY PROCEDURES

INTRODUCTION

^{90}Y-DOTATOC was the first somatostatin analogue developed for treatment of patients with somatostatin receptor positive neuroendocrine tumours. Phase 1 clinical trials were dosimetry guided by using prospective ^{90}Y-DOTATOC quantitative PET imaging (1). The conclusion in this study was that individual patient dosimetry was needed as both kidney and tumour absorbed doses showed extreme variability. In the phase 2 trial for this compound no dosimetry was performed and patients were administered with a single or several administrations of 3.7 GBq/m² (2). Treatment protocols are mostly based on fixed activity or activity per body surface area (typically at 1.85 - 3.7 GBq/m²) administration schemes, which are repeated with a 6-8 week interval, depending on response and quite often adapted to (bone marrow) toxicity after previous treatment. This leads to the huge range in reported cumulative activities of 1.1 – 26.5 GBq (3).

EFFECTIVENESS

In the clinical phase 2 single-centre open-label trial overall 60% of the patients showed clinical response, biochemical response, and/or morphologic disease control after a single administration of 3.7 GBq/m² ^{90}Y-DOTATOC with amino-acid infusion (2). No randomised comparative studies have been performed for ^{90}Y DOTATOC. Several studies have been performed to compare ^{90}Y-labeled som
bination of ^{90}Y and ^{177}Lu peptides (4, 5). These combination therapi
of both radionuclides, whereas over its cumulative decay ^{90}Y emits

IMAGING

As ^{90}Y is a pure beta-emitter, direct imaging of the therapy com
bremsstrahlung spectrum in planar whole body or SPECT (7). Pe
formed by using the 0.003%/decay positron emission from ^{90}Y, wh
tifying the uptake in the renal cortex (8). Theragnostic companio
tively quantify the ^{90}Y DOTATOC biodistribution, with the gamma-
^{90}Y-DOTATATE (10). When using a surrogate peptide it is of great in
of peptide as used in the therapeutic setting, or otherwise correc
binding affinity (11).

ORGANS AT RISK AND NORMAL TISSUE DOSIMETRY

Both single ^{90}Y-DOTATOC therapy and combination treatment wit
nent and sometimes even fatal renal toxicity (grade 4 and 5) (2, 5). K
after thesapy. When the peptide is cleared by the primary renal
peptides are reabsorbed and remain in the secondary filter elemen
18 patients with ^{90}Y-DOTATOC PET quantification showed interpati
per activity ranged between 1.2 – 5.1 Gy/GBq (1), a comparable va
based dosimetry: 1.3 – 4.9 Gy/GBq (9). Bone marrow dosimetry is
wese used with ^{90}Y-DOTATOC and a correlation was observed with
(12). In 21 patients the bone marrow absorbed dose ranged betw
MBq.

TUMOUR DOSIMETRY

Tumour dosimetry is seldom performed for ^{90}Y-DOTATOC, most probably due to the highly metastasised nature of the tumours. Nevertheless it has been performed using In-111 DOTATOC as a companion diagnostic (13) and in the initial phase 1 clinical trial, using ^{90}Y DOTATOC (14).

ABSORBED DOSE-EFFECT

Longer follow-up in a sub-group of patients treated in Belgium revealed a dose-response relation between renal toxicity and the Biologically Effective Dose (BED) when based on the actual kidney volume instead of the standard size (15). It was observed that the activity and hence absorbed dose per treatment cycle significantly influenced the incidence of renal toxicity (16). Late stage renal toxicity was shown to follow a classic sigmoidal shaped dose-effect curve with the BED (17). The threshold for late renal toxicity was found around a BED of 40 Gy for patients without additional risk factors for renal disease, including high blood pressure, diabetes, or prior chemotherapy. Reduction in tumour volume was shown to be significant above tumour absorbed doses of 200 Gy (14).

DOSIMETRY-BASED TREATMENT PLANNING

One study repeated administrations according to the 1.85 GBq/m² dosing scheme until a threshold dose of 37 Gy BED was reached, thereby preventing renal toxicity (18). The BED has been semi-empirically defined in MIRD pamphlet 20 by using a sub-lethal damage repair half-life of 2.8 h and the radiobiology parameter $\alpha/\beta = 2.5$ Gy for late renal toxicity (16). A multi-factorial dose-effect model for blood platelet response was defined, using prior platelet counts as additional weighting factor, leading to a correlation between the weighted bone marrow dose and platelet count nadir after therapy (12).

ISSUES TO CONSIDER

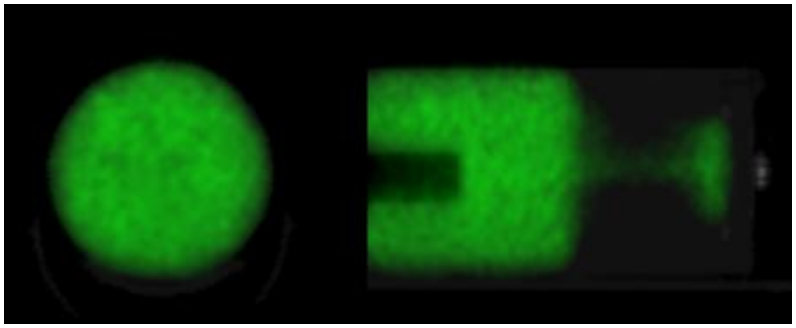
^{90}Y is a pure high energy beta emitter (mean energy 0.93 MeV), while a minute fraction (0.0032%) leads to internal pair production photons at 511 keV. Quantitative imaging of ^{90}Y is complex and prospective imaging with surrogate markers may deviate from the actual biodistribution.

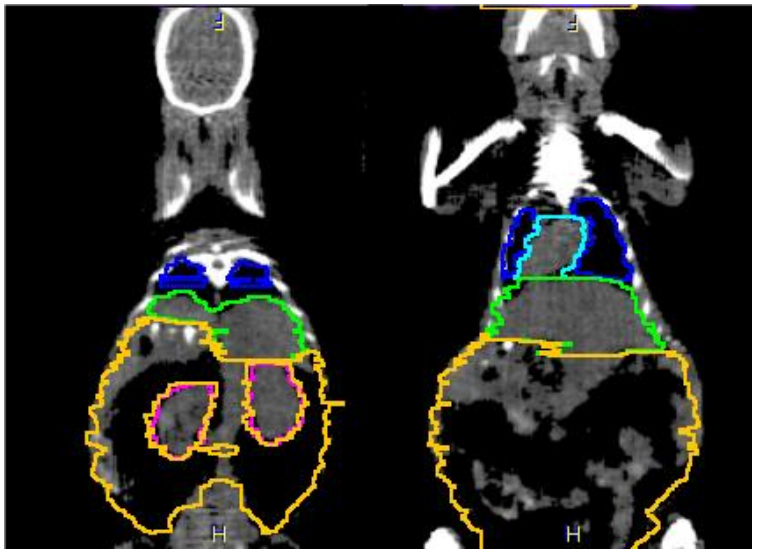
NEED FOR INVESTIGATION

Despite the clear relation between occurrence of late renal toxicity and absorbed dose this has not lead to clinical protocols using this concept. The longer range of the high-energy beta-particles from ^{90}Y results in relatively homogeneous dose distributions within uptake volumes. Still inhomogeneous uptake in tumours, by e.g. necrosis, could lead to inhomogeneity in dose distribution. This partly explains the high absorbed doses that are needed to lead to tumour volume reduction, but this needs to be further investigated. The radiation sensitivity of neuroendocrine tumours is not well known, but it is not considered to be extremely radio-resistant, considering the tumour dose of 50 Gy in neo-adjuvant external beam radiotherapy (19).

Additional challenges for radionuclide dosimetry (1): small animal dosimetry and new isotopes

µPET-based dosimetry of ^{152}Tb-CHX-A''-scFv78-Fc





^{152}Tb Dose (mSv/MBq)			
Target Organ	*Biodistribution*	*µPET*	*% dose difference*
Large Intestine	32.7	56.6	73
Small Intestine	33.6	62.325	85
Stomach Wall	49.8	45.975	-8
Heart	85.3	56.05	-34
Kidneys	**52.1**	**51.9**	**0**
Liver	**55.8**	**68.45**	**23**
Lungs	**46.2**	**80.35**	**74**
Pancreas	37.3	51.1	37
Spleen	51.4	35.225	-31
Bladder	16.7	37.6	125
Total Body	**20.6**	**33.175**	**61**

Cicone F, Denoël T, Viertl D et al. Oral presentation, EANM 2017

frontiers
Research Topics

Perspectives in Small Animal Radionuclide Imaging

For more information:
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http://fron.tiers.in/go/Tm1hJ9

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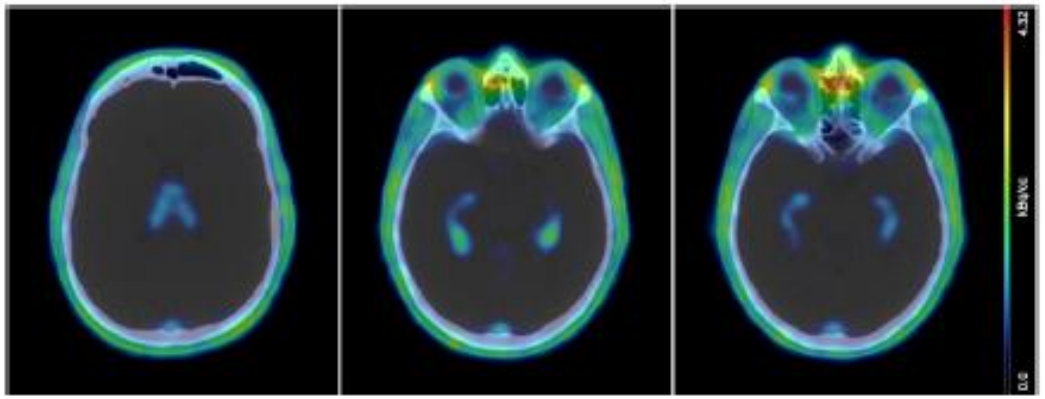
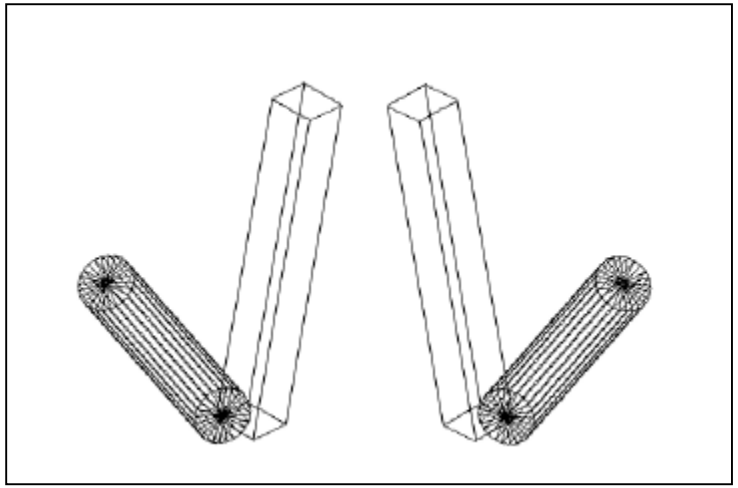
Genoa, Italy

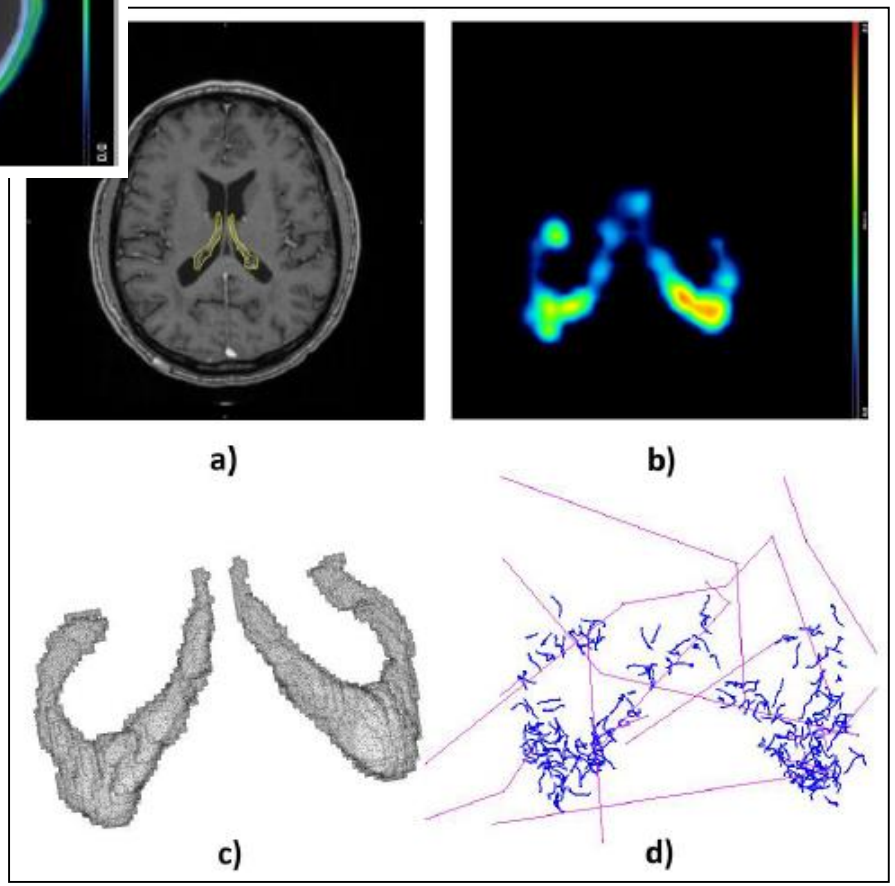
Frontiers in Medicine

Additional challenges for radionuclide dosimetry (2): new tracers and modelling of non-conventional organs



Gnesin S, Mitsakis P, Cicone F et al. EJNMMI Research 2017; 7:43





Amato E, Cicone F, Auditore L, Baldari S, Prior JO, Gnesin S (article in revision)

Conclusions

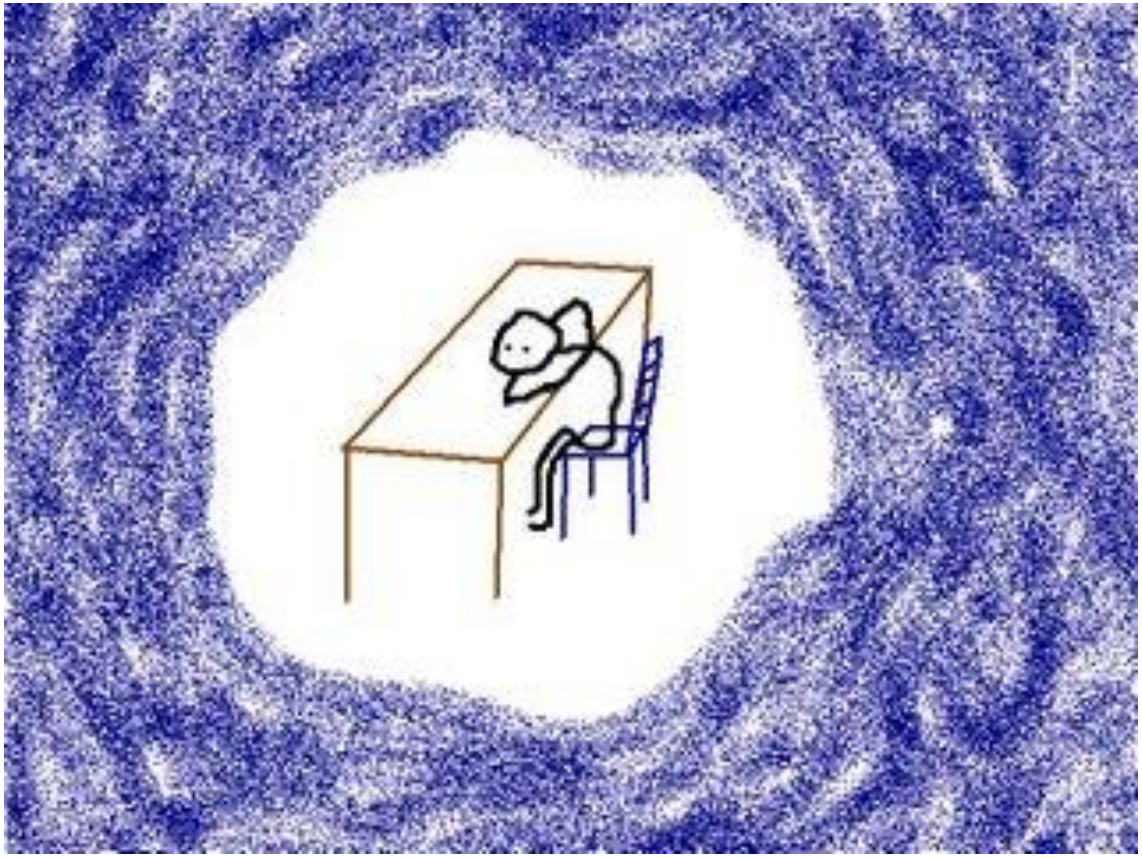
Nuclear medicine has developed thanks to the advancements of theoretical and applied physics

Many concepts that lead to such advancements are common to other medical specialities. Nowadays we talk about “precision medicine”, “personalised medicine” etc.

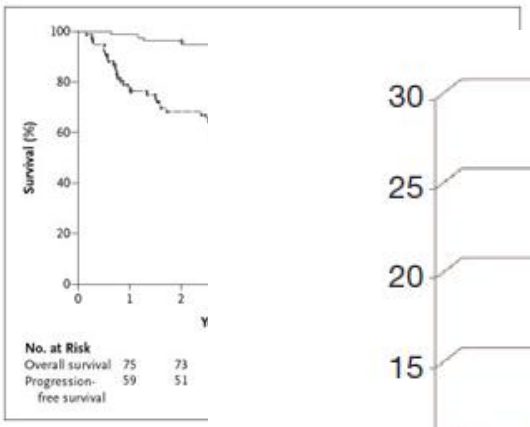
Internal dosimetry is becoming a standard in Nuclear Medicine Deparments, as it provides clinically useful results and fulfils newer regulatory requirements

Nuclear medicine physicians and medical physicists will need to sit together at the bedside to understand “personalised” (radio)biology

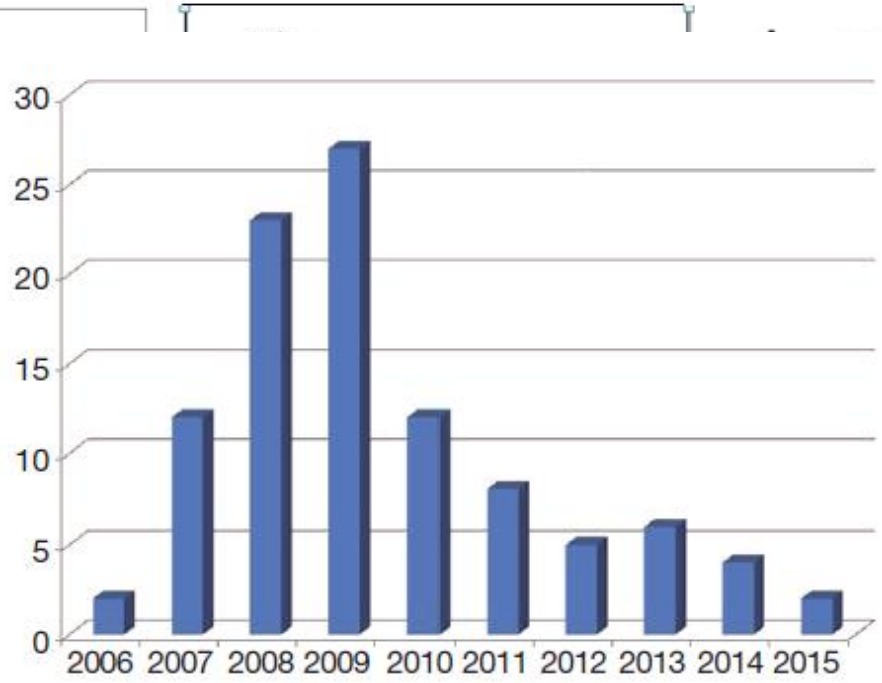
Thanks for your attention

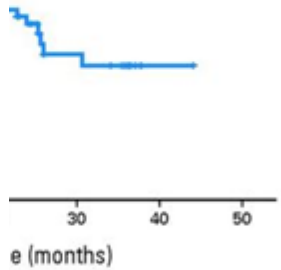


Having the magic bullet does not mean **Success**



Kaminski MS et al. N





;31:308-313

Figure 1 Distribution over time of a total of 101 radioimmunotherapy treatments with ^{90}Y-ibritumomab-tiuxetan (Zevalin®) performed at Sant'Andrea University Hospital of Rome, Italy, between July 2006 and October 2015.

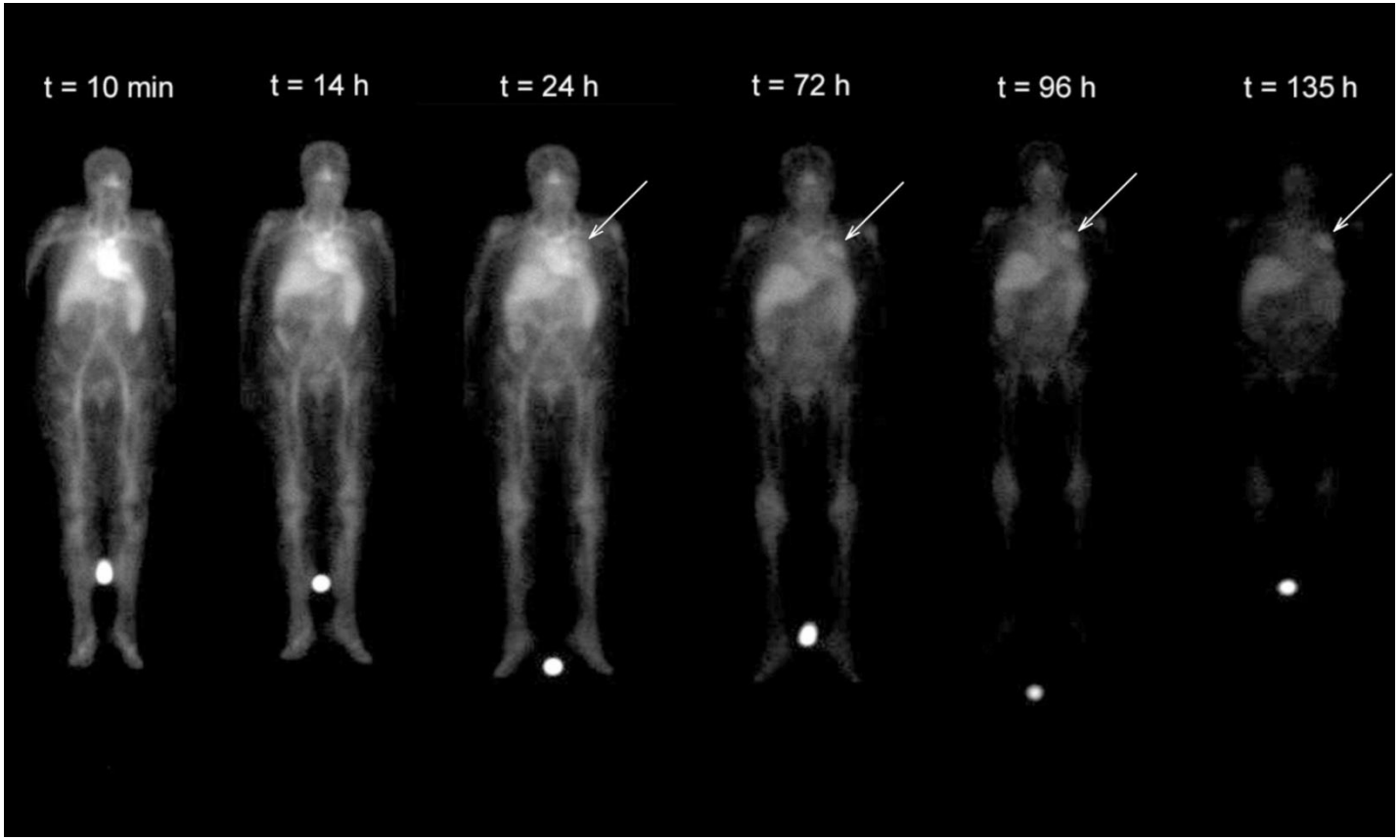
Cicone F et al. Trans Canc Res 2016

Is a medical physicist involved in each treatment?

- 131I NaI for benign thyroid diseases
- 131I NaI for thyroid ablation of adults
- 131I NaI for thyroid ablation of young
- 131I NaI for thyroid cancer therapy for adults
- 131I NaI for thyroid cancer therapy for young
- 131I mIBG for neuroblastoma
- 131I mIBG for adult neuroendocrine tumours
- 177Lu Somatostatin receptor PRRT
- Y90 Somatostatin receptor PRRT
- 177Lu PSMA therapy of prostate cancer
- 90Y resin microspheres in liver
- 90Y glass microspheres in liver
- Radiation synovectomy using 90Y 186Re or 169Er
- 153Sm for bone metastases
- 89Sr for bone metastases
- 223Ra for bone metastases
- 32P phosphate for myeloproliferative diseases
- 90Y Zevalin for B-cell lymphoma

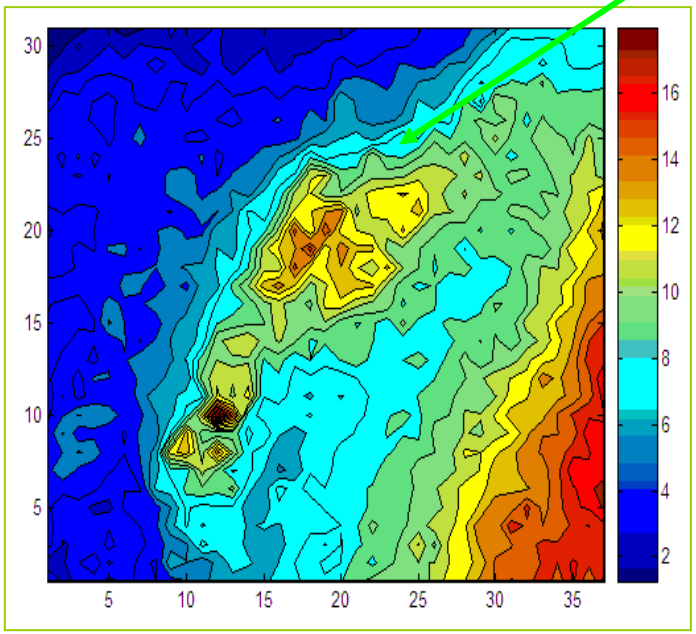
Dosimetria con surrogato ^{111}In- vs ^{90}Y-Zevalin:

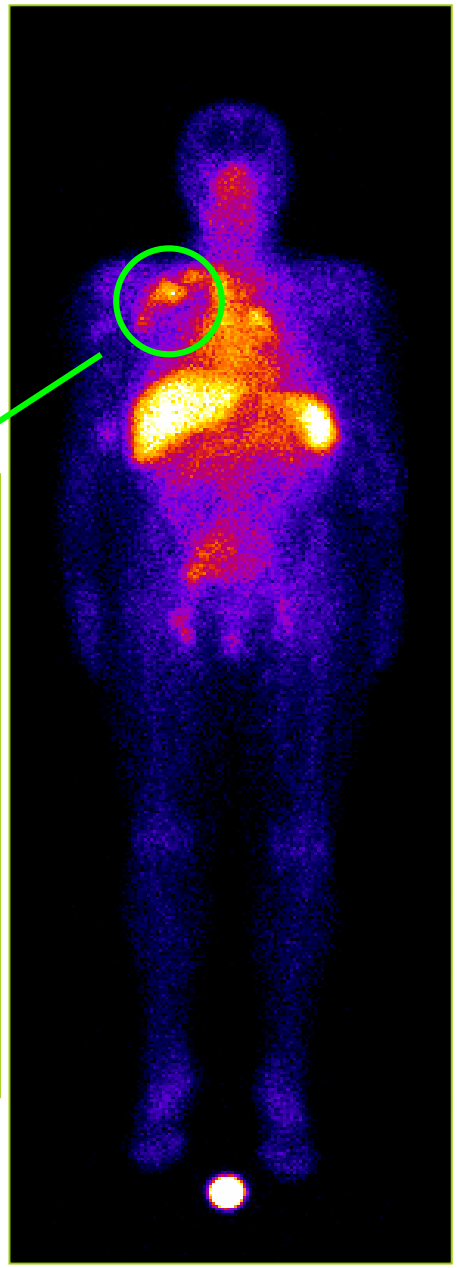
La (bio)distribuzione della radioattività nel tempo

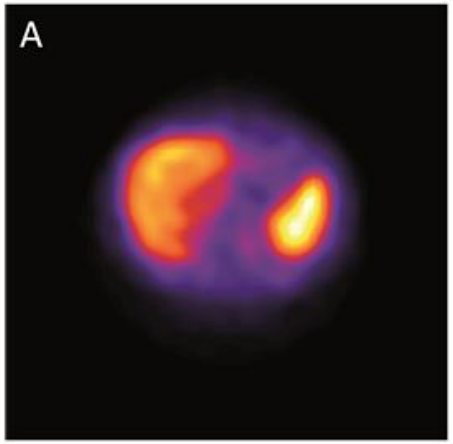


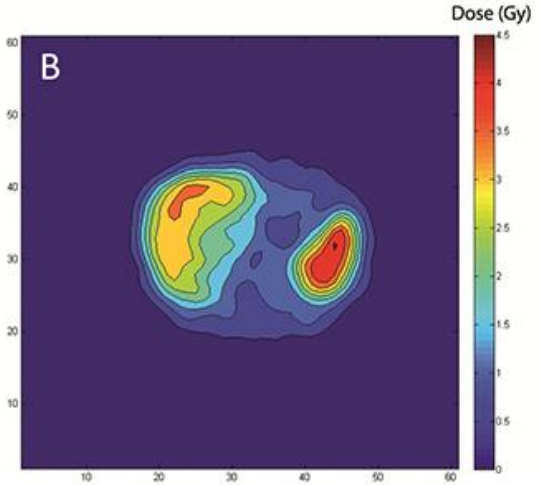
Cicone F, Scopinaro F 2013 In: Rituximab: Pharmacology, clinical use and health effects.

La distribuzione della radioattività nello spazio/tempo









D'Arienzo M et al. 2010 Radiother Oncol Abstr

^{90}Y microsphere treatment of hepatocellular carcinoma

NTCP
Liver

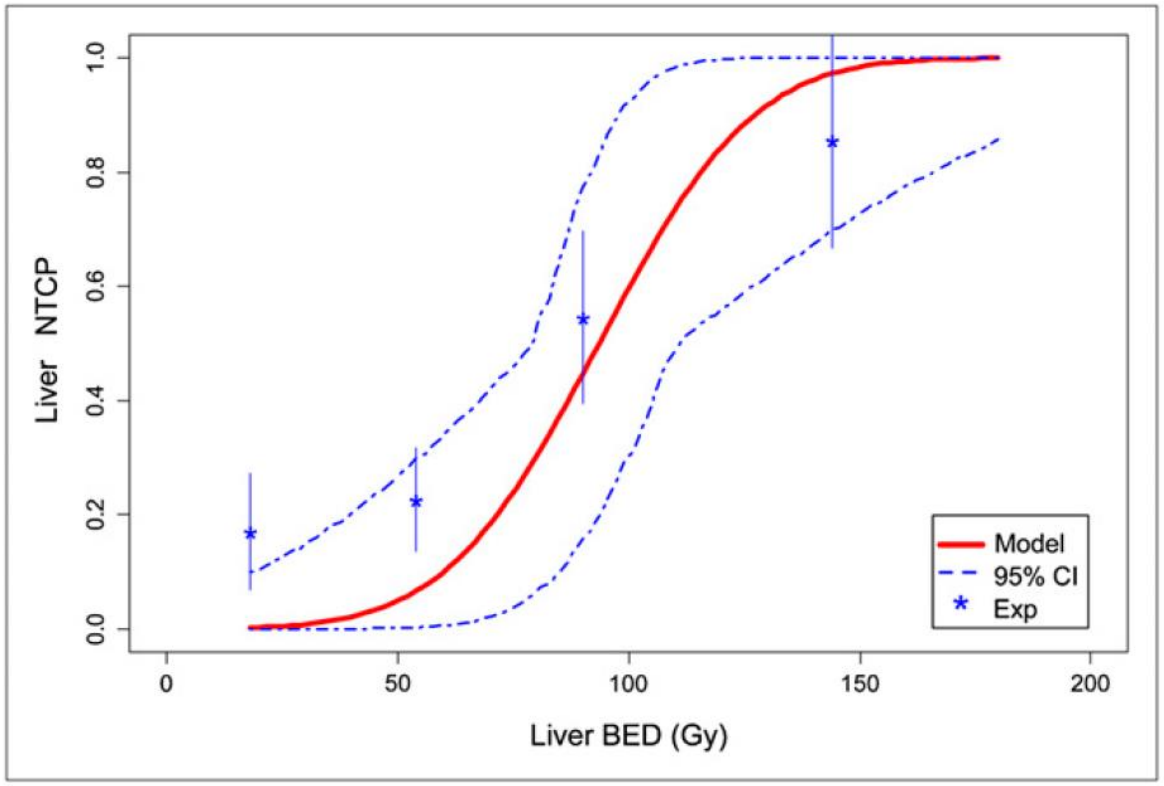
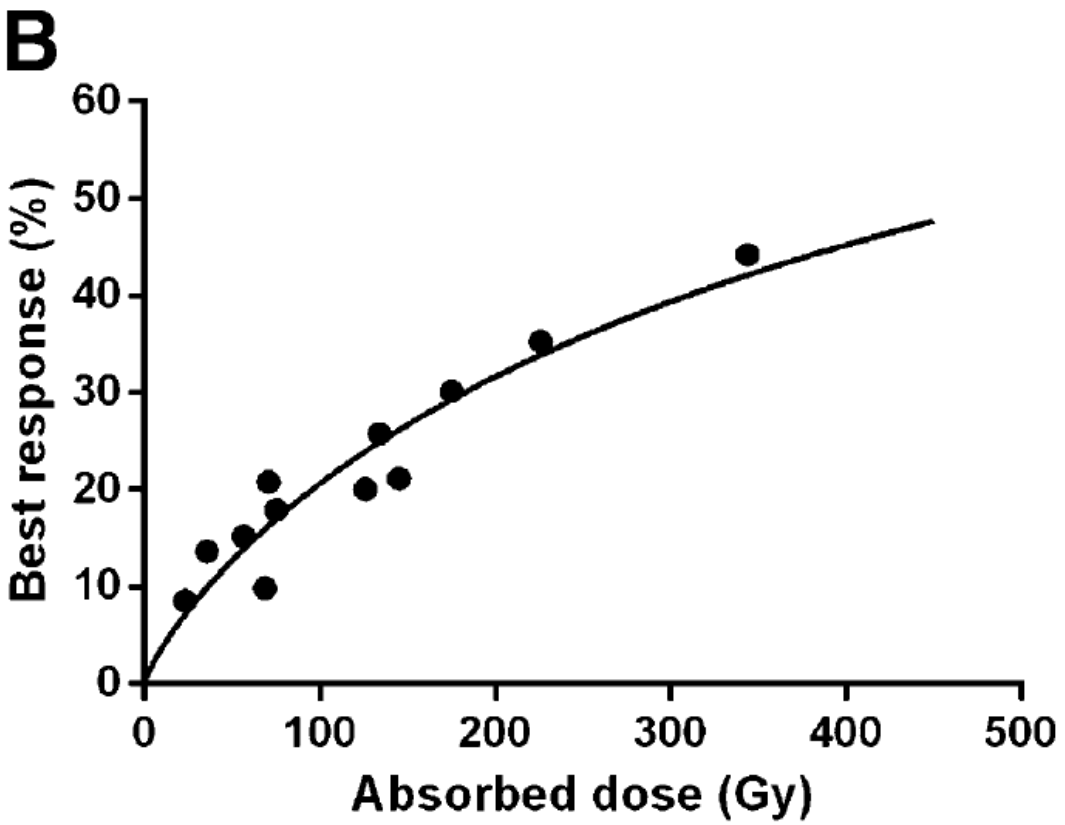


FIGURE 6. Normal-tissue complication probability of liver toxicity (solid line) vs. liver BED. Dashed line represents 95% CI. Vertical bars represent SD (caused by number of data in each group that created each point). Exp = experimental data.

Strigari et al, JNM, 2010

^{177}Lu-PRRT of neuroendocrine tumours

Tumour response



Ilan et al, JNM 2015

^{90}Y-PRRT of neuroendocrine tumours

Kidney NTCP

Comparison External beam and Radionuclide Therapy

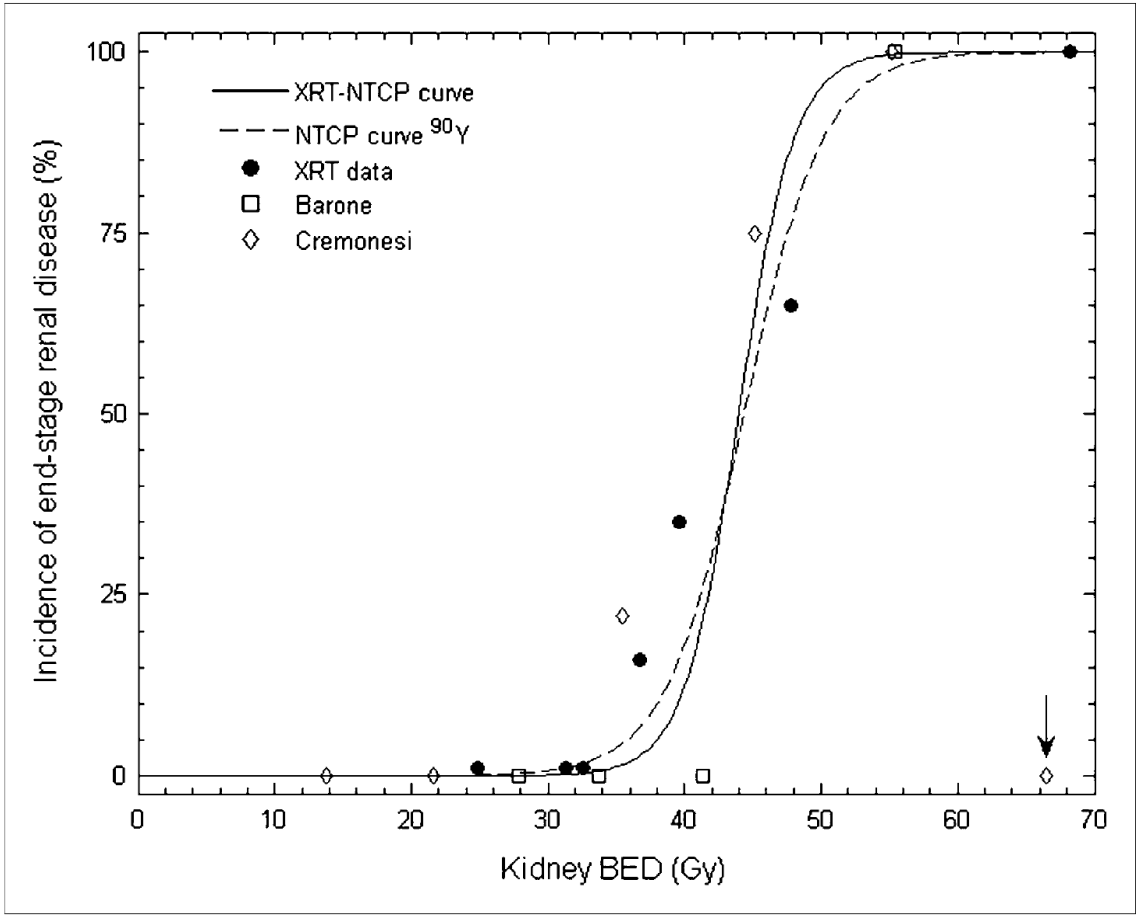


FIGURE 6. Dose–response curve for correlation between kidney BED and symptomatic radiation damage to kidneys for external-beam data, compared with ^{90}Y-DOTA-octreotide data.

Wessels et al, JNM 2008