The ROYAL MARSDEN
NHS Foundation Trust

Current challenges in dosimetry: Trials, tribulations and transcendence

Glenn Flux

Radioisotope Physics Group
Royal Marsden Hospital &
Institute of Cancer Research
Sutton UK

ICR

In the beginning

Saul Hertz (endocrinologist) treated benign thyroid disease and thyroid cancer 80 years ago.

Arthur Roberts (physicist) measured excretion and external count rates

TABLE II - ANALYSIS OF 20 CASES "CURED" BY Ra-I + KI
ON BASIS OF EXAMINATION MARCH 31, 1946

SERIES NO.	CASE-HOSP. NO.	DOSE OF I^{130} and DATE OF ADMINISTRATION	BMR BEFORE I^{130}	BMR LEVEL OFF IODIDES	TIME OFF IODIDES	THYROID SIZE '46	ESTIMATED THYROID WT. (gm.)	% OF Ra-I EXCRETED 72-HOURS	ESTIMATED THYROID IRRIDIATION (r) 12 HOUR	8 DAYS*
6	MICHAEL K. MGH-227382	2.3mC 7-24-'41 1.7mC 7-30-'41 } 4.0 mC	+45	DEC.-'42 (-9) MAY-'43 (-16) JAN.-'46 (-7)	4 YRS.+	N	45	35 22	320 280	390 300
7	ALLISON D. (AET 9.) MGH-319927	1.4mC 9-19-'41 1.5mC 9-21-'41 } 2.9 mC	+65	1-8-'46 (-6)	4 YRS.	N	45	9 20 (?)	260 260 (?)	280 220 (?)
8	NAOMI K. (AET 9) MGH-321155	1.5mC 9-24-'41	+30	7-17-'45 (-3) 3-27-'46 (+4)	7 MOS	FIRM 2XN	40	15	300	250
9	MILDRED G. MGH-322935	4.9mC 11-26-'41	+30	5-8-'45 (-10)	4 YRS.	N	60	17	650	420
11	FRANCES H MGH-198910	5.8mC 4-9-'42	+37	7-9-'42 (-12) 2-24-'44 (+9) 2-3-'46 (-13)	3.5 YRS.	N	60	17	750	380
12	FERDINAND L. MGH-354330	7.5mC 5-15-'42	+55	'45 (+11) 2-3-'46 (-13)	3 YRS.	HARD 1.5XN	60-75	26	950	500

Courtesy Barbara Hertz

Leo Marinelli – father of dosimetry & radiobiology

1940s: Marinelli and Eve Curie: Radiobiology & Mme. Curie's Vision for Medicine

Courtesy Judith Marinelli

NOTE ON THE TIME-INTENSITY FACTOR IN RADIOBIOLOGY

By U. Fano and L. D. Marinelli

Carnegie Institution of Washington, Department of Genetics, Cold Spring Harbor, N. Y., and Memorial Hospital, New York, N. Y.

Communicated January 15, 1943

In many radiobiological reactions the effect of a given dosage of radiation is found to depend on the "time-intensity factor," that is, to be a direct function of the intensity ("intensity effect") and to be lower when the treatment is intermittent than when it is continuous, the intensity remaining the same ("fractionation effect"). This phenomenon has been generally attributed to recovery of the biological material from the action of the radiation. The intensity effects have been determined by comparing the results of continuous irradiation with constant dose and different inten-

JCI The Journal of Clinical Investigation

DOSAGE DETERMINATION IN THE USE OF RADIOACTIVE ISOTOPES

Leonidas D. Marinelli

J Clin Invest. 1949;28(6):1271-1280. https://doi.org/10.1172/JCI102194.

Research Article

$$D_\beta = 73.8\, C\, E_\beta\, T$$

Uses and misuses

A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 92 SEPTEMBER 1953 NUMBER 3

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USES AND MISUSES OF RADIOACTIVE IODINE IN TREATMENT OF CANCER OF THYROID

RULON W. RAWSON, M.D.
J. E. RALL, M.D.
AND
JACOB ROBBINS, M.D.
NEW YORK

THE EARLY studies with radioactive iodine by Hertz, Roberts, and Evans [1] and by Hamilton and Soley,[2] in which it was demonstrated that the natural avidity of the thyroid for iodine could be used to selectively deposit radioactive isotopes of iodine in thyroid tissues, led to the hopeful hypothesis that diseased thyroid tissue might be effectively irradiated by administering radioactive iodine to patients suffering with such maladies. Already it has been amply demonstrated in many

'Because the metastases were growing very rapidly, we very naively resorted to heroic measures and administered radioiodine in doses of 61 mc. on April 10, 1947; 10 mc. on June 16, 1947; 93 mc. on Nov. 6, 1947; 184 mc. on Dec. 31, 1947, and 250 mc. on May 29, 1948'.

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‘Finally a pancytopenia developed and the patient died.’

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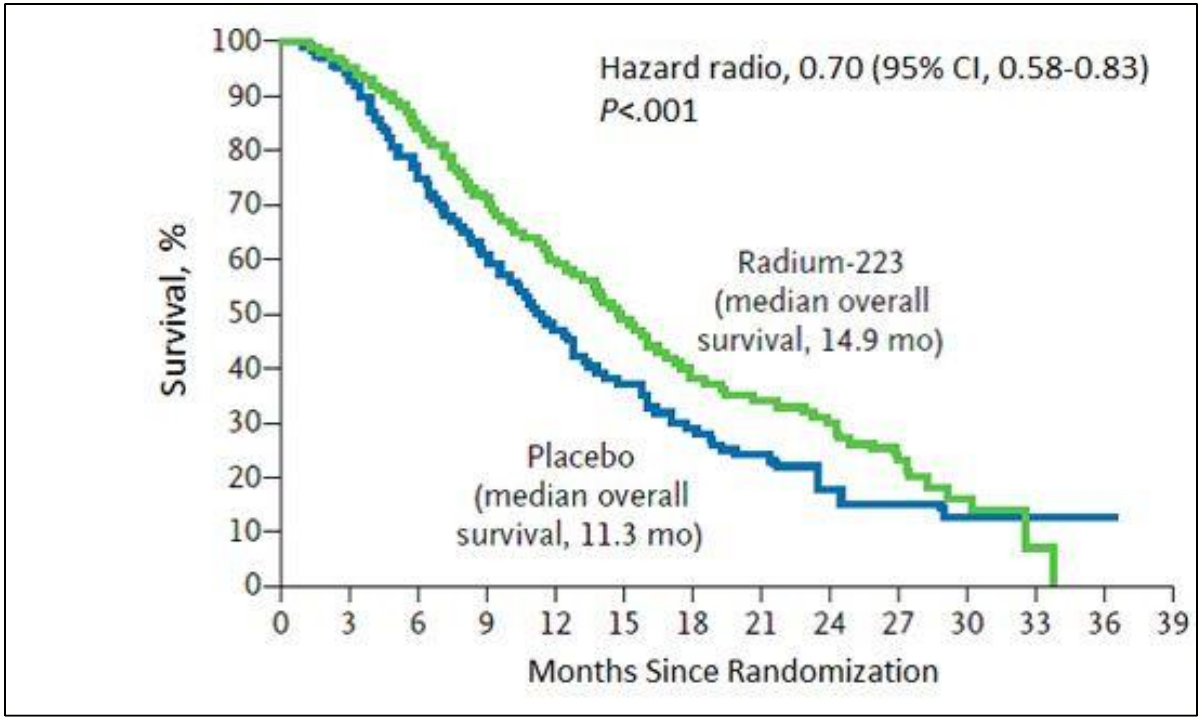
'Unfortunately, we are seeing patients who have been treated empirically with frequent comparatively small doses of radioactive iodine by the calendar rather than by considerations of the capacity of such tumors to concentrate radioiodine or of the radiosensitivity of the tumors'

Ra-223 (Xofigo)

The ALSYMPCA trial

55 kBq/kg x 6 over 6 months

3.6 months increase in overall survival



Parker New Engl J Med 2013

The changing landscape…

#DEALS FEBRUARY 24, 2014 / 8:50 AM / 4 YEARS AGO

Bayer clinches $2.9 billion deal for Norway's Algeta

Reuters Staff

2 MIN READ

OSLO/FRANKFURT (Reuters) - German drug firm Bayer (BAYGn.DE) has clinched a $2.9 billion deal to take over Norwegian cancer drug maker Algeta ALGETA.OL after being tendered 92.17 percent of the shares in a cash offer, the companies said on Monday.

Bayer extended the acceptance deadline by two days to Wednesday, February 26, to eliminate any remaining uncertainty.

The changing landscape…

#DEALS FEBRUARY 24, 2014 / 8:50 AM / 4 YEARS AGO

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2 MIN READ

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…two days to Wednesday, February 26, to eliminate

#BUSINESS NEWS NOVEMBER 3, 2017 / 7:12 AM / 3 MONTHS AGO

Novartis to buy French cancer specialist AAA for $3.9 billion

4 MIN READ

John Miller

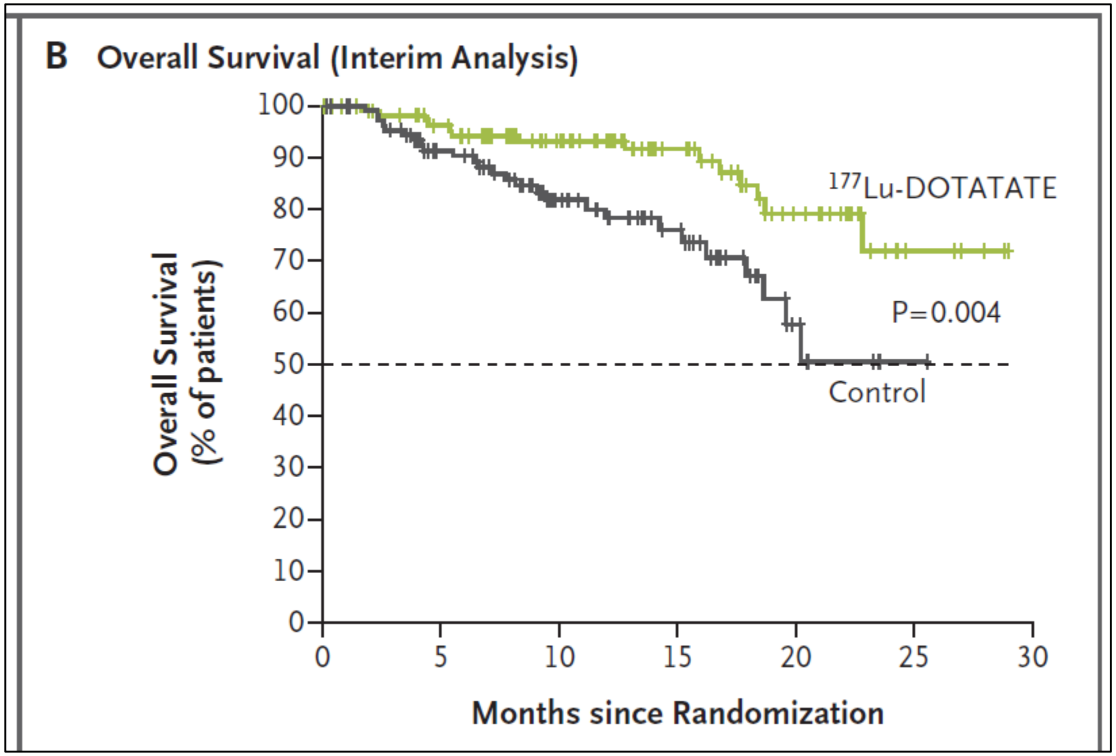
ZURICH (Reuters) - Novartis (NOVN.S) has agreed to buy French-based Advanced Accelerator Applications (AAA) (AAAP.O) for $3.9 billion (2.99 billion pounds), giving it a platform in radiopharmaceuticals and access to a new therapy for the kind of cancer that killed Steve Jobs.

Lu-177 DOTATATE for midgut neuroendocrine tumours

The NETTER trial

4 x 7400 MBq over 6 months

Improvement in progression free survival

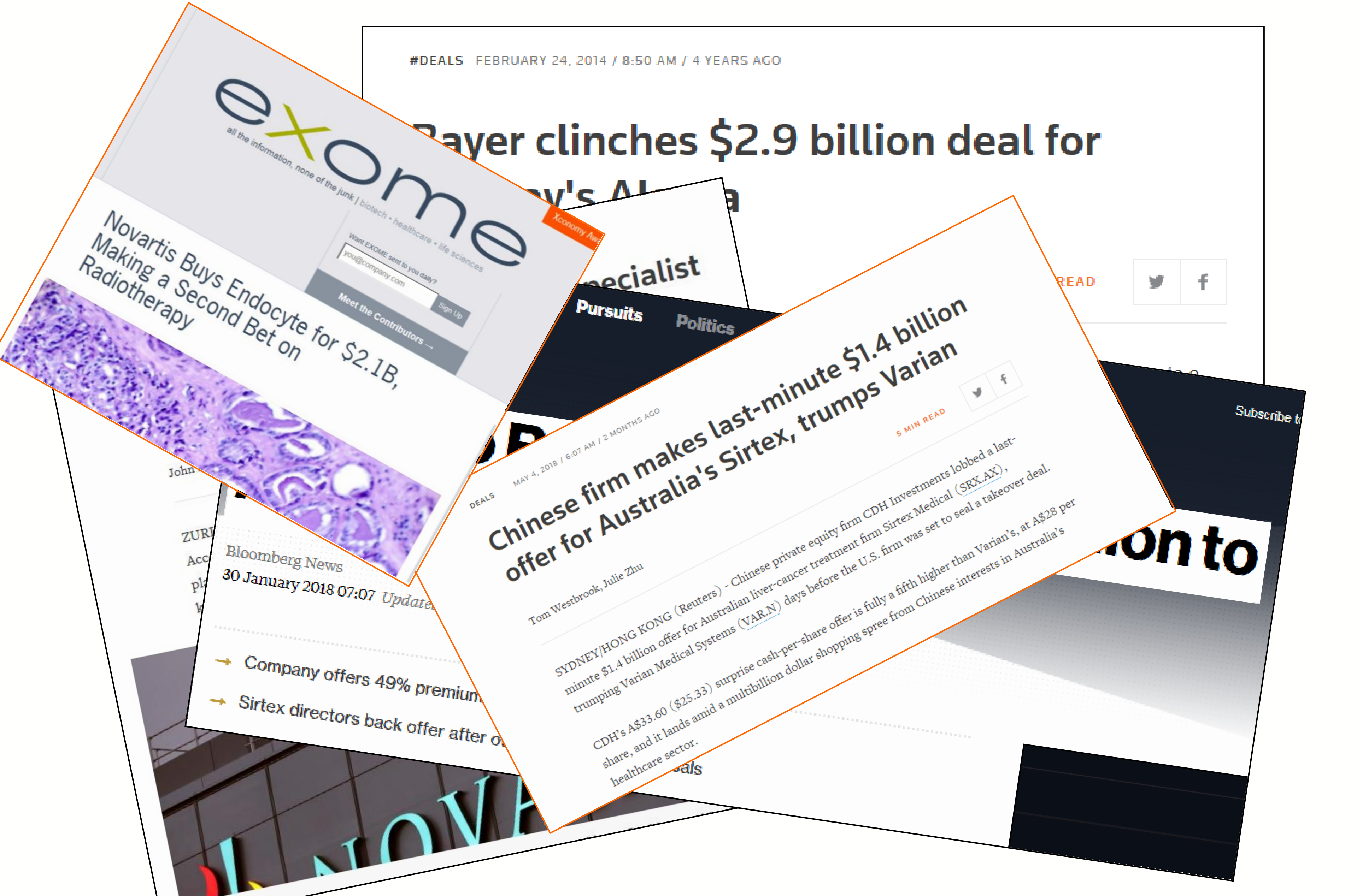


Strosberg New Engl J Med 2017

The changing landscape…

The changing landscape…

The changing landscape…



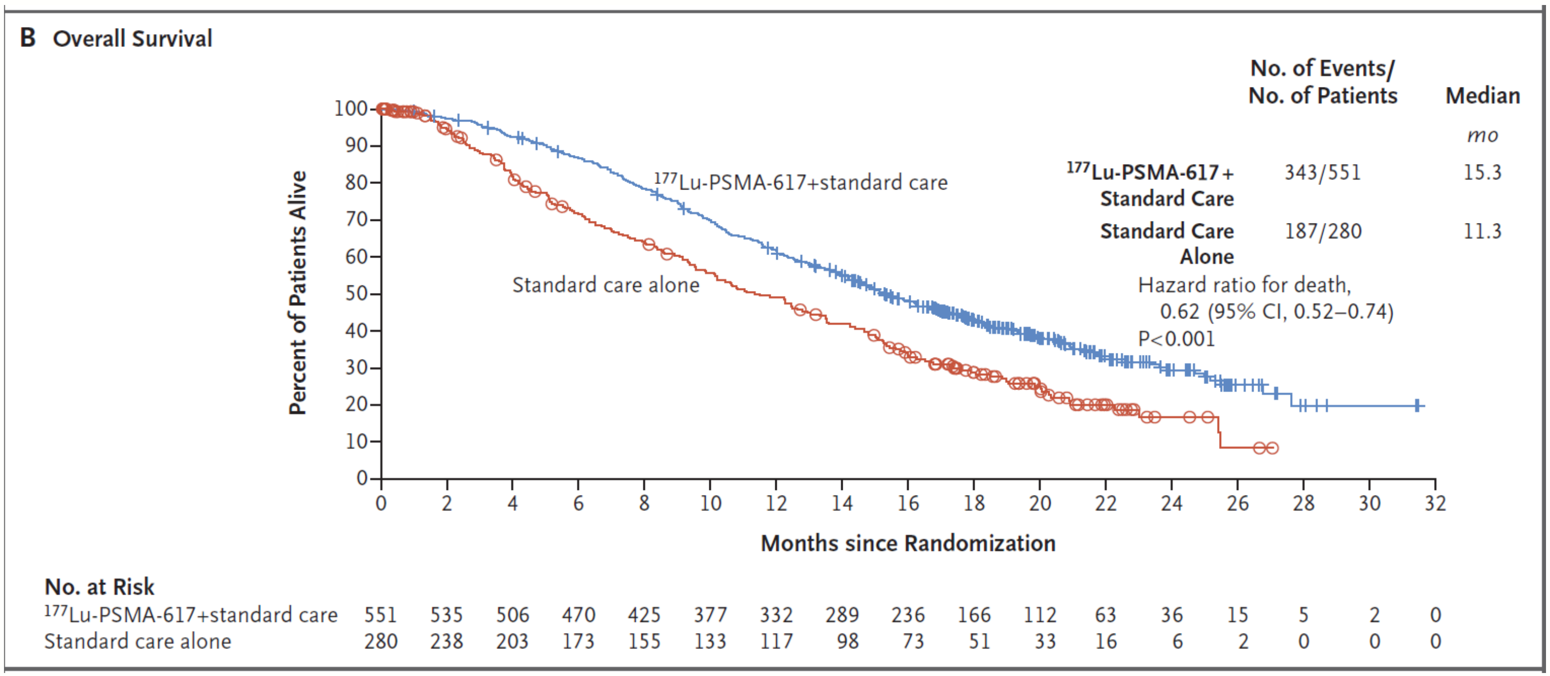
Lu-177 PSMA for mCRPC

The VISION trial

6 x 7400 MBq over 6 months

4 months survival compared with ‘permitted standard of care’

Currently under evaluation by FDA, EMA



Sartor, de Bono New Engl J Med 2021

The changing landscape…

MEDraysintell

Press Release

Louvain-la-Neuve, Belgium and Lalaye, France – November 17, 2015

RADIOTHERAPEUTICS ARE DRIVING UP THE NUCLEAR MEDICINE MARKET

In the last few weeks two leading companies proved that radiotherapeutics are becoming the driving forces of the nuclear medicine market.

Earlier this month, Bayer published once again strong results for its Xofigo (radium-223 dichloride), a product introduced on the US market in 2013 and used in the treatment of prostate and bone cancers, that is now reaching US$ 210 million for the first nine months of 2015, growing by almost 50% from 2014.

Last week, Advanced Accelerator Applications S.A. (NASDAQ: AAAP) made its IPO at US$16 and saw its stock surged to US$ 25.02 (+56%) in just four days of trading. AAA is developing a radiotherapeutic, Lutathera (Lutetium-177 DOTATATE), intended for use in the treatment of patients with gastro-enteropancreatic neuroendocrine tumors (GEP-NET). Lutathera just completed its phase III clinical phase and is expected to be on the market by early 2017.

MEDraysintell recently showed in its report "Nuclear Medicine World Market Report and Directory" that new opportunities lie ahead in nuclear medicine, especially in the radiotherapeutic area with new products to reach the market before end of 2020. The global Nuclear Medicine market is expected to reach US$ 24 billion in 2030, showing an annual average growth of 11%. The diagnostic radiopharmaceutical market is expected to grow, on average by 6% a year, mainly driven by volume but limited impact from new tracers, while the therapeutic radiopharmaceutical market is expected to grow 26% annually between 2014 and 2030.

The therapeutic radiopharmaceutical market is expected to grow 26% annually between 2014 and 2030

Where next?

- Many more radiotherapeutics on the way…

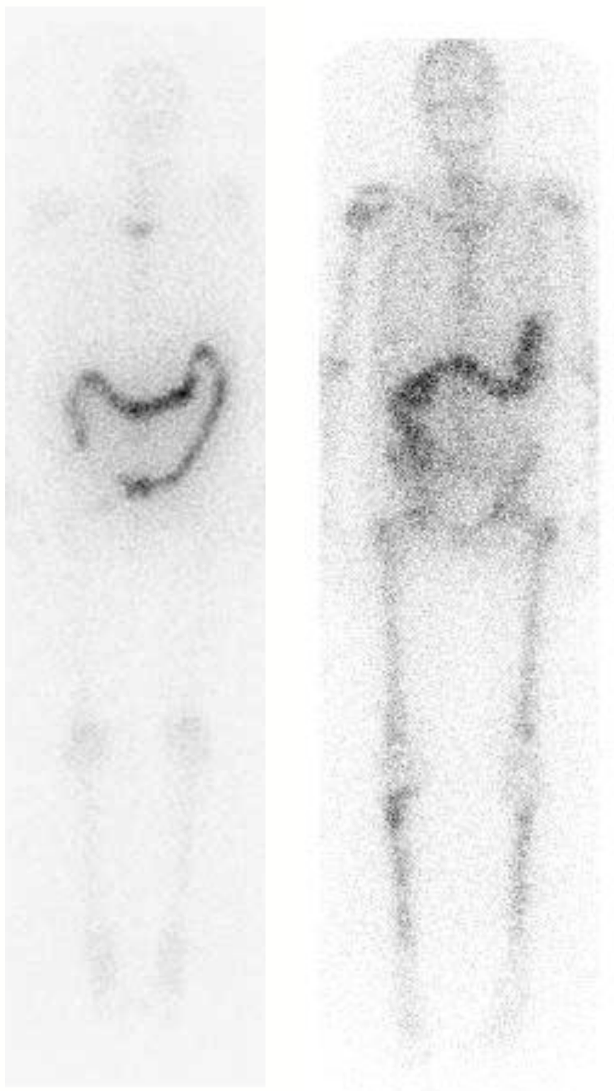
Table 1 | PSMA-targeted radiotherapeutics in clinical development

Drug	Lead sponsor	Radioactive isotope	PSMA-targeting agent	Clinical stage
^{177}Lu-PSMA-617	Novartis	Lutetium-177	Small molecule	Phase 3
PNT2002	Point Biopharma	Lutetium-177	Small molecule	Phase 3
TLX591	Telix Pharmaceuticals	Lutetium-177	mAb	Phase 3
I-131-1095	Progenics Pharmaceuticals	Iodine-131	Small molecule	Phase 2
^{177}Lu-PSMA-R2	Novartis	Lutetium-177	Small molecule	Phase 1/2
TLX592	Telix Pharmaceuticals	Actinium-225	mAb	Phase 1
BAY 2315497	Bayer	Thorium-227	mAb	Phase 1
^{225}Ac-PSMA-617	Novartis	Actinium-225	Small molecule	Phase 1
CTT1403	Cancer Targeted Technology	Lutetium-177	Small molecule	Phase 1

Nature article 2021 https://doi.org/10.1038/s41587-021-00954-z

- Can we do better?
- No imaging or dosimetry for any of these trials.
- Can we treat according to the radiation doses delivered as for radiotherapy?
- What would be the cost/benefit?

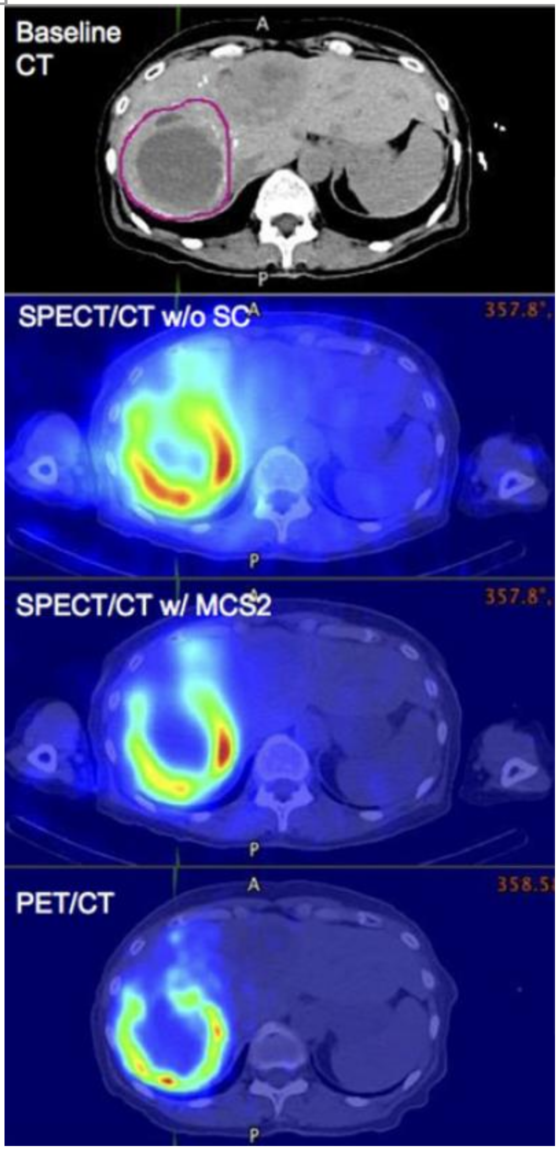
Imagng - The power of nuclear medicine



Ra-223 imaging
Hindorf Nucl Med Comun 2012

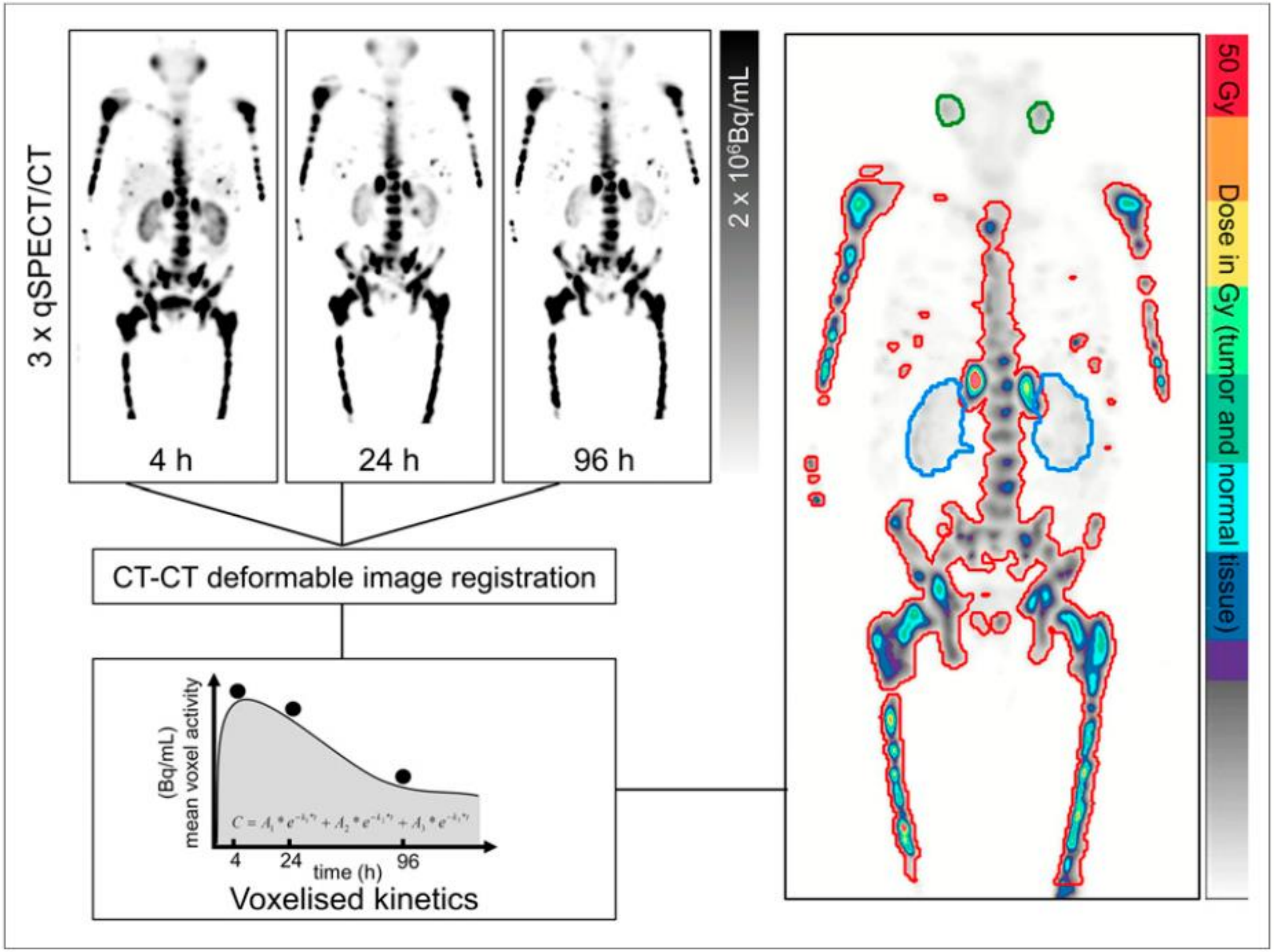
Imaging therapeutic drugs *in vivo* in real time

Nuclear medicine image provides information not available for ‘cold chemotherapeutics’



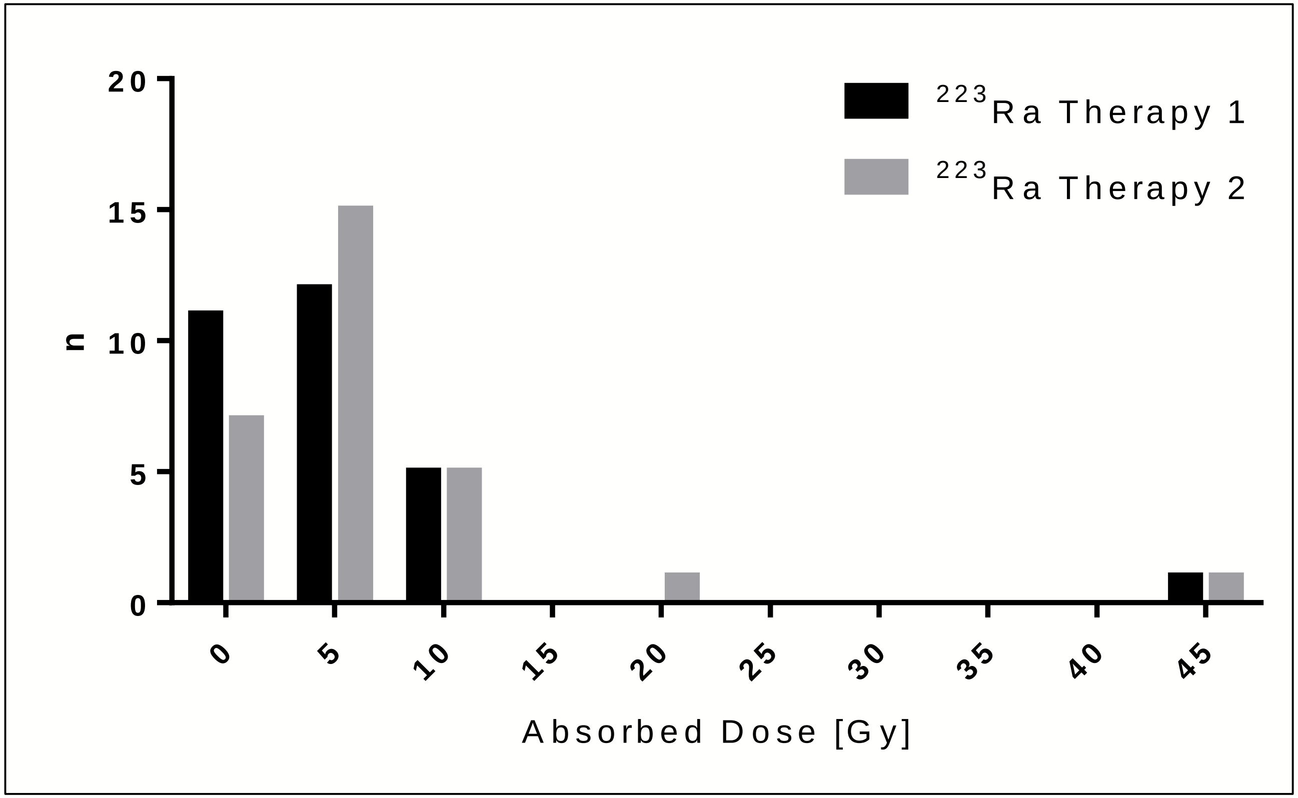
Bremstrahlung imaging
Dewaraja Med Phys 2017

Lu-177 PSMA 617



Violet J Nuc Med 2019

Dosimetry for lesions – Ra-223

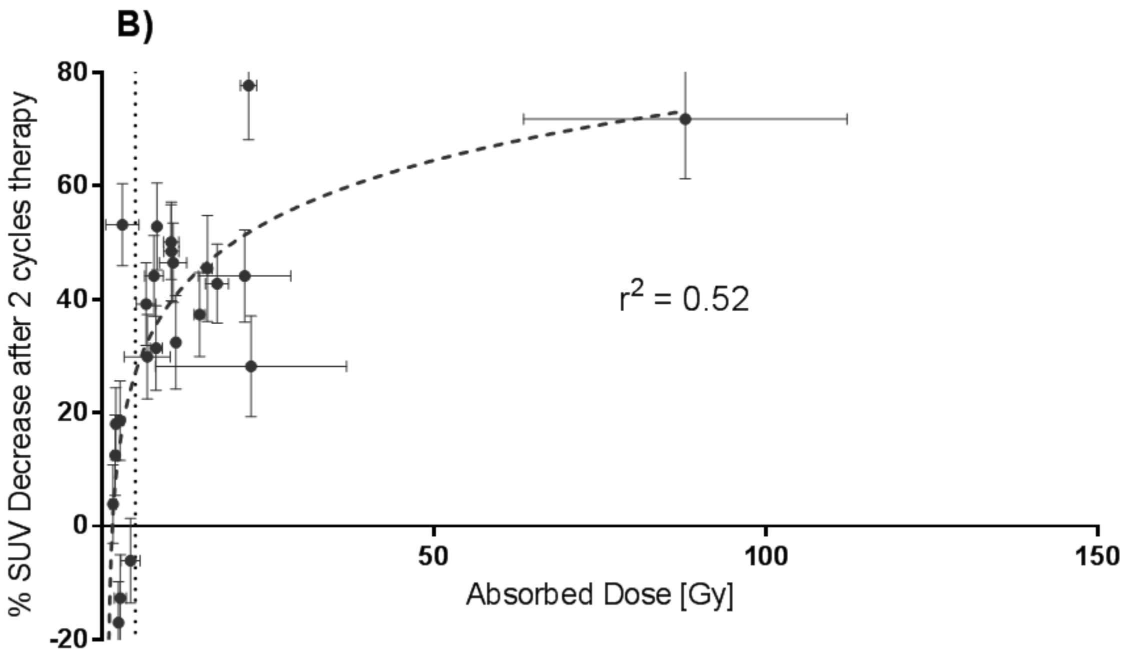


29 lesions identified in 6 patients

Tumour absorbed doses ranged from 0.6 – 44 Gy

Murray *et al* EJNMMI 2017

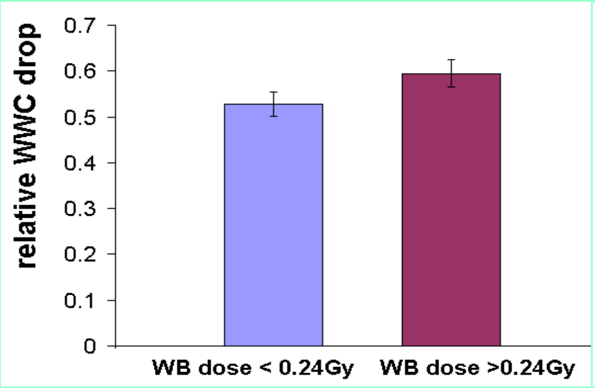
Absorbed dose lesion response for Ra-223

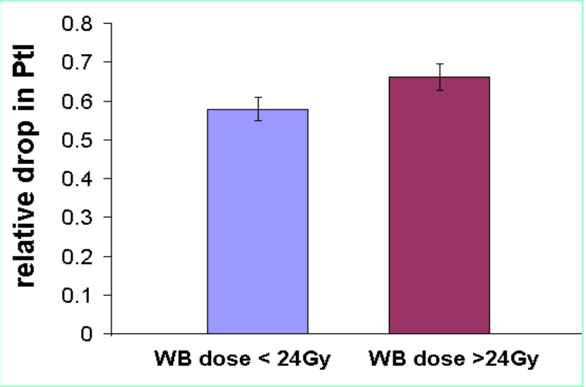


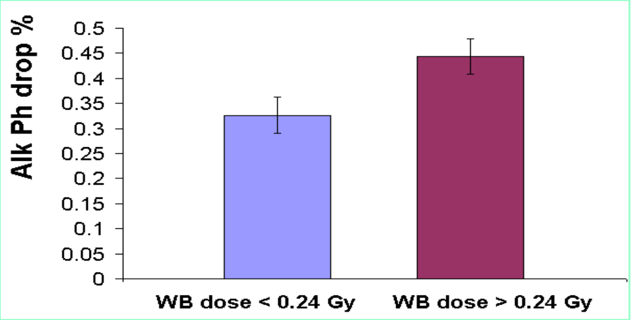
Decrease in SUV as a function of absorbed dose. Below a ‘dose threshold’ the SUV increases.

Dose-toxicity response for Re-186 HEDP

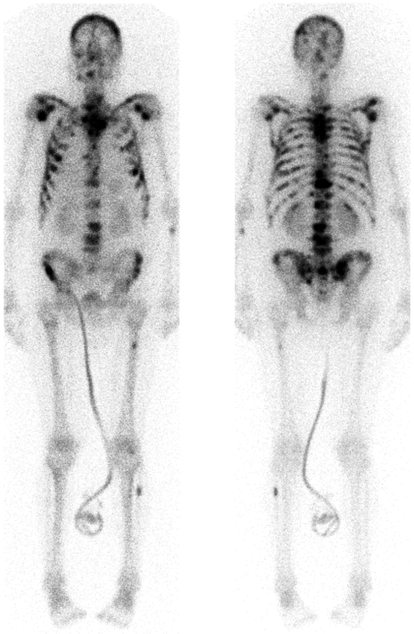
Short term toxicity







WB dose correlates with drop in WCC, platelet count, alkaline phosphatase ($p<0.05$)

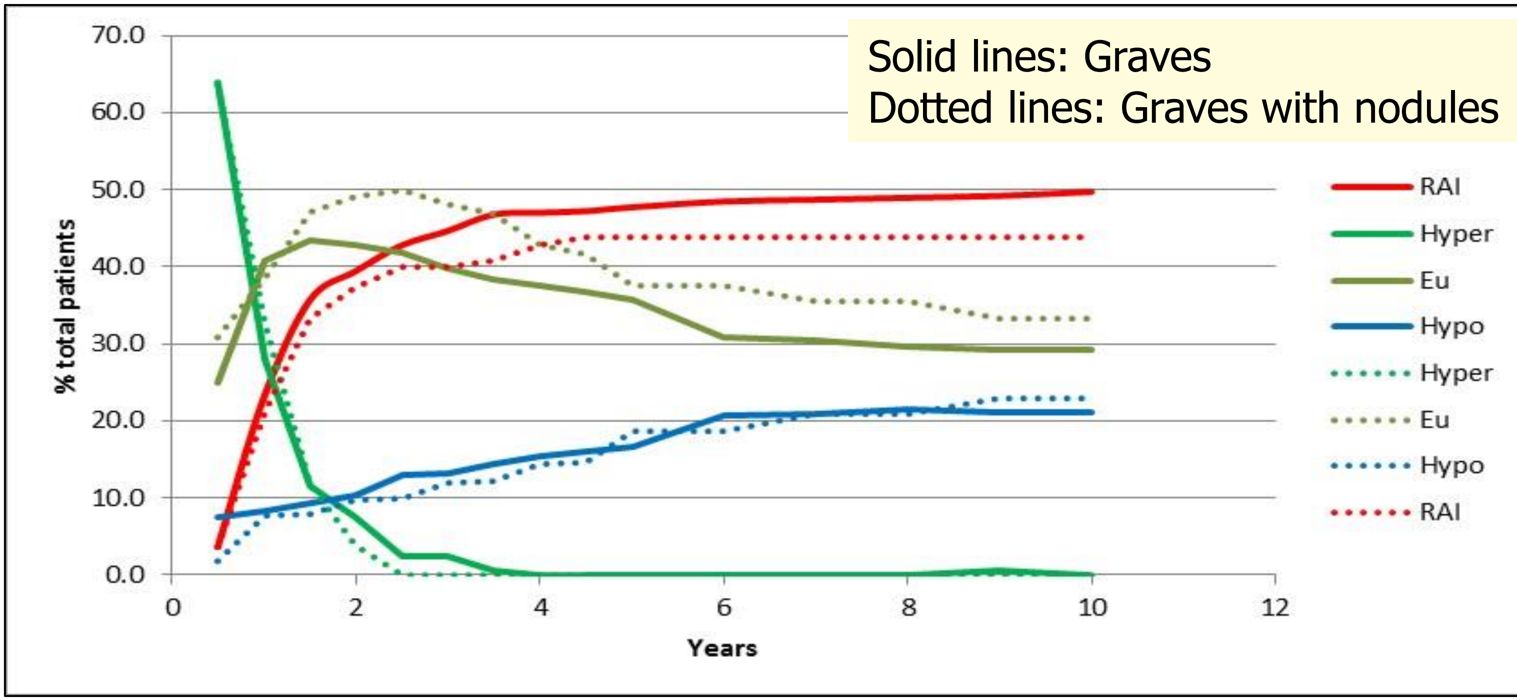


Short term toxicity

Francesca Buffa
Eur J Nucl Med (2003)

I-131 for benign thyroid disease

RMH: Study of 300 patients treated to deliver 60 Gy. Mean administered activity ~ 100 MBq, range of 17 – 1400 MBq).



After 10 years:

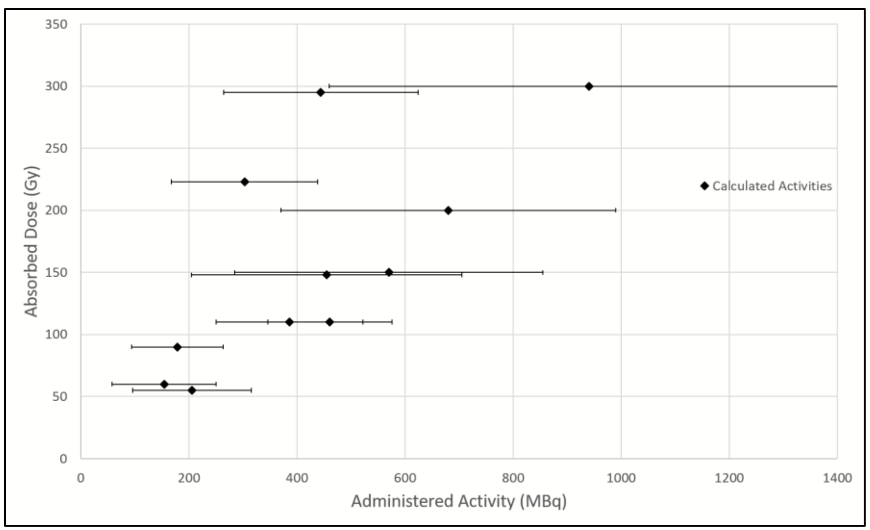
50% of patients needed more radioiodine
20% patients became hypothyroid
30% of patients naturally euthyroid

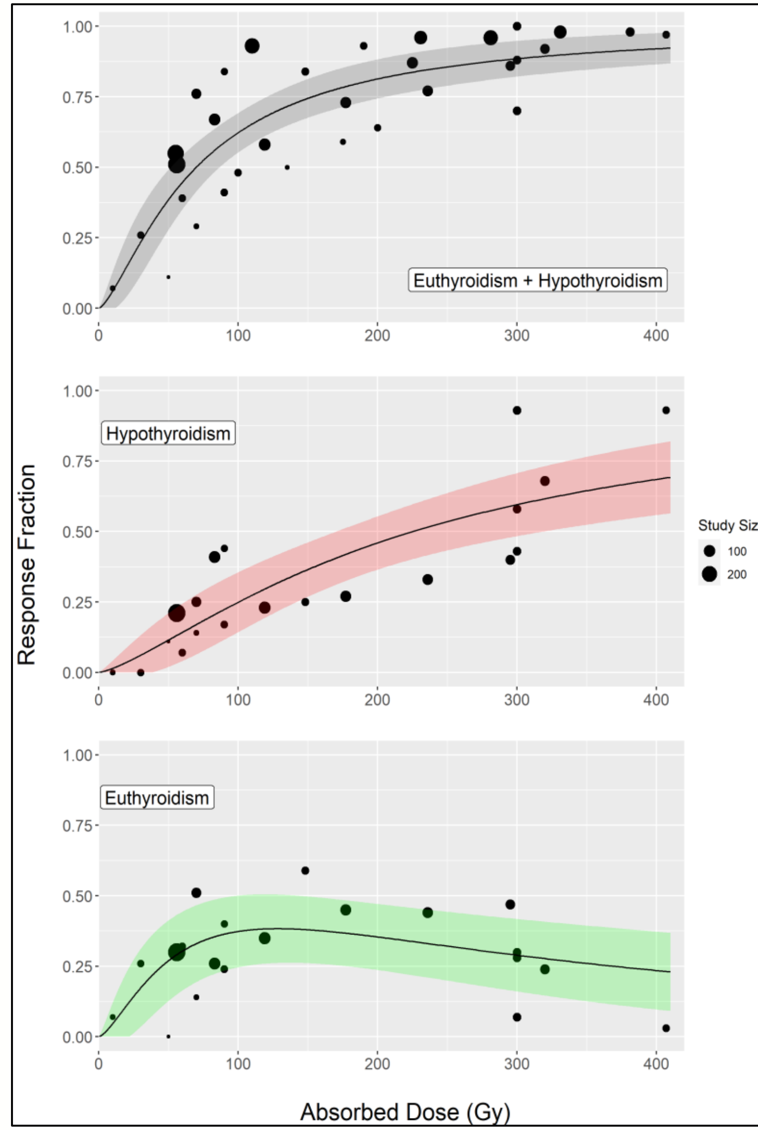
Hyer *et al* Nucl Med Commun 2018

Radioiodine for benign thyroid disease

Systematic review: 1122 papers mentioning dosimetry. Fifteen eligible for meta-analysis (>2000 patients)

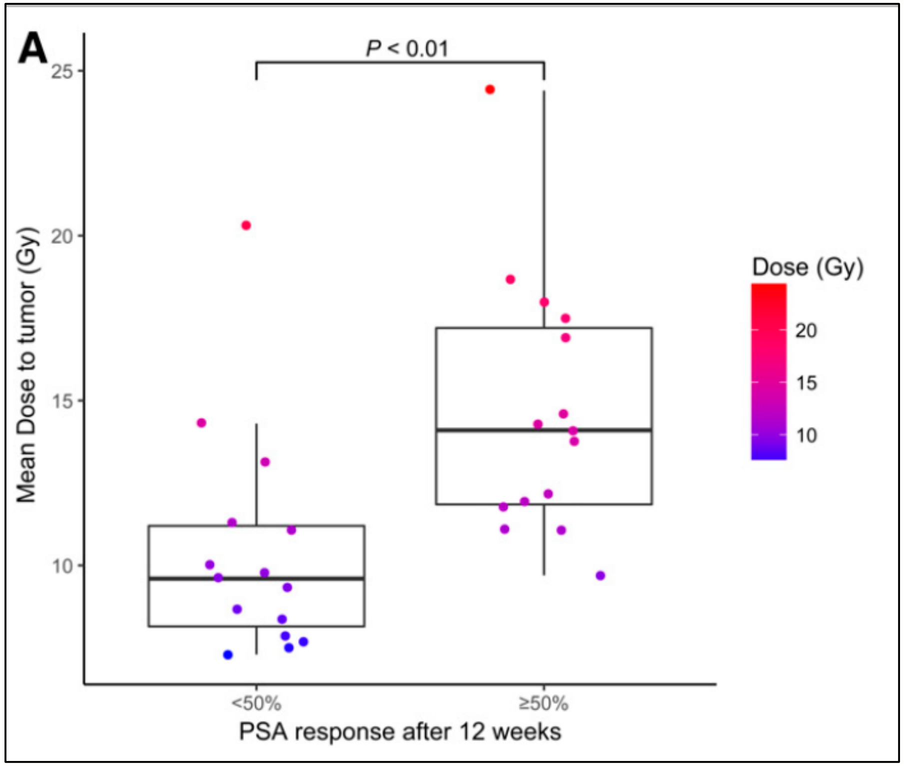
Probability of euthyroid response highest at 128 Gy (38%)





Range of activities to deliver the same radiation dose

Lu-177 PSMA

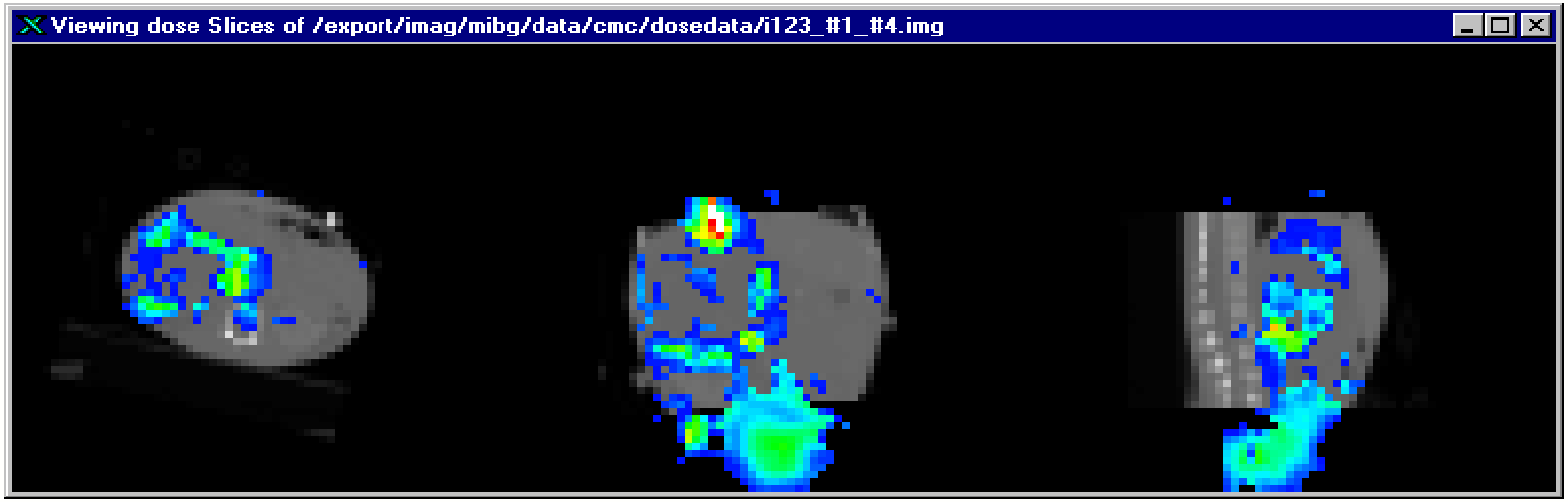


Violet J Nuc Med 2019

Tumour dose was associated with PSA response with a median dose of 14.1 Gy in patients achieving a PSA decline of at least 50%, versus 9.6 Gy for those achieving a PSA decline of less than 50% (P , 0.01).

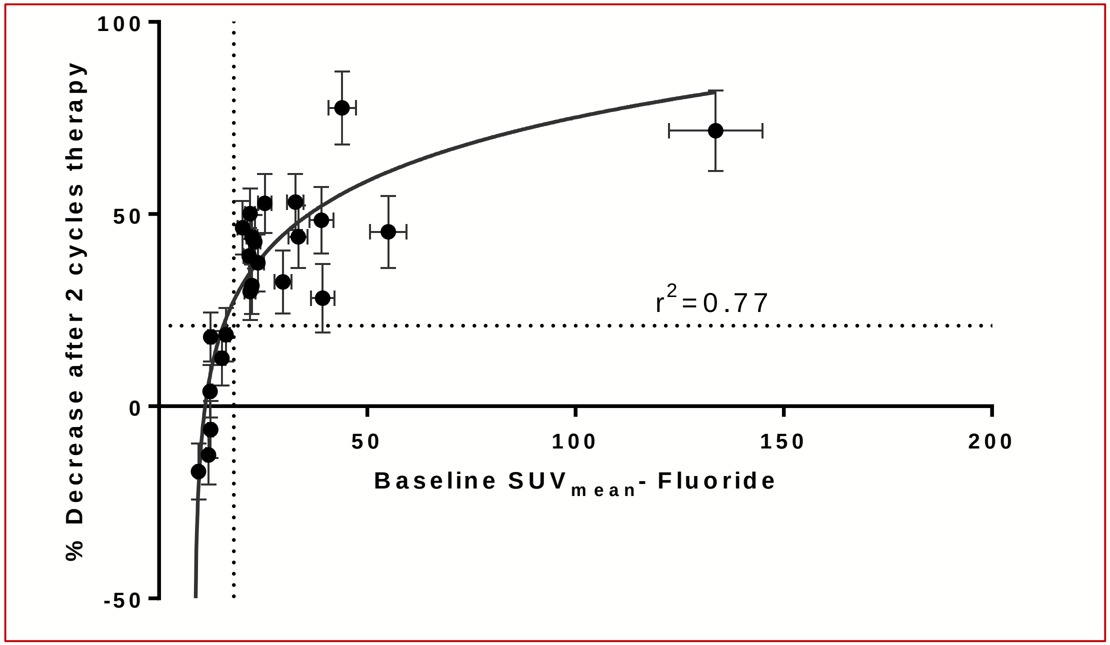
Treatment planning – pre-therapy

Transaxial Coronal Sagittal



Predicted I-131 radiation dose map from I-123 tracer in neuroblastoma treated with I-131 mIBG

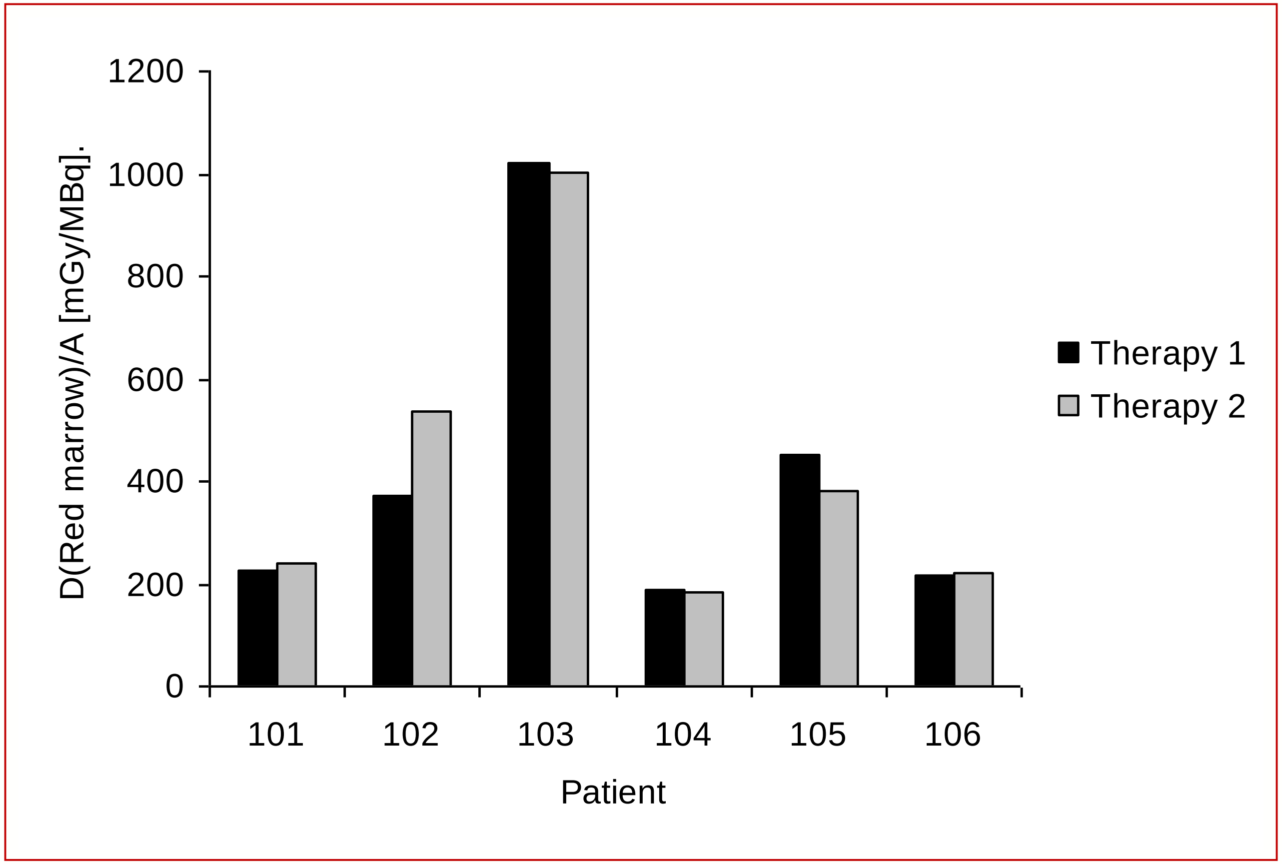
Treatment planning – Ra-223



- F-18 Fluoride uptake correlates with the Ra-223 uptake
- Ra-223 uptake correlates with radiation dose
- Dose correlates with response

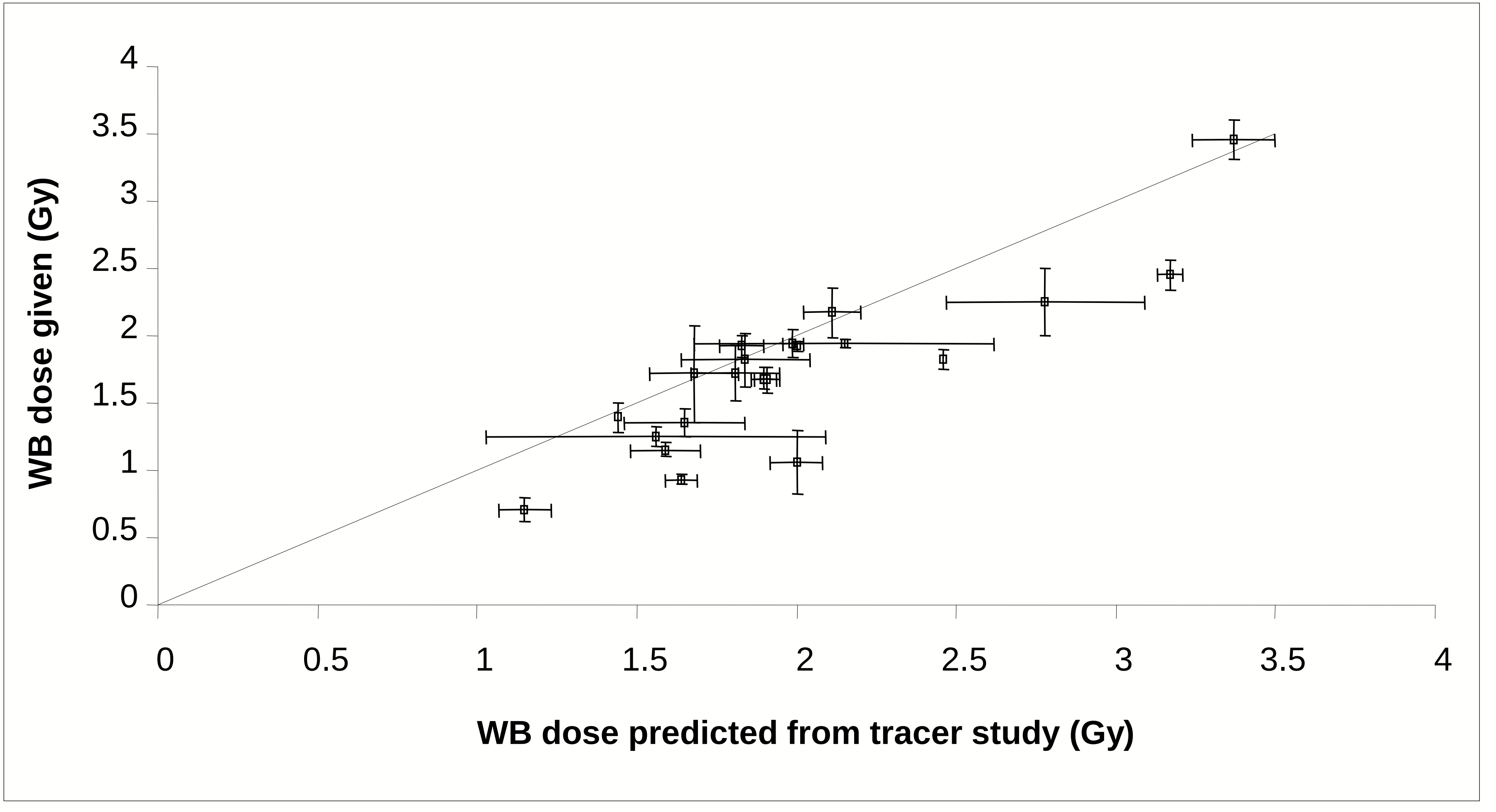
- F-18 Fluoride could predict outcome

Treatment planning – adaptive



Ra-223 - Red marrow absorbed dose: Main contribution from activity in bone, as blood activity disappears quickly: Range 1.7 – 7.7 Gy

Prediction of whole-body doses from tracer



Buckley JNM (50) 2009

ESIOP Veritas study (neuroblastoma)

- ESIOP phase 3 clinical trial for very high risk neuroblasoma: treatment with I-131 mIBG + topotecan vs High Dose Thiotepa.
- Wholebody absorbed dose calculated after first administration
- Second administration (2 weeks later) to deliver a total of 4 Gy
- Stem cell support
- 20 years to set up. No funding for physics.

Sel-i-metry

Aim of trial to investigate role of selumetinib in iodine negative thyroid cancer

Aim of physics: To collate imaging and dosimetry from 9 systems in 8 centres

Gamma cameras designed for diagnostic studies with 185 MBq Tc99m - Not for quantitative studies with GBq of therapeutic radionuclides!

Site visits to characterise each camera. Phantoms were scanned to see how many counts were recorded in response to levels of I-131

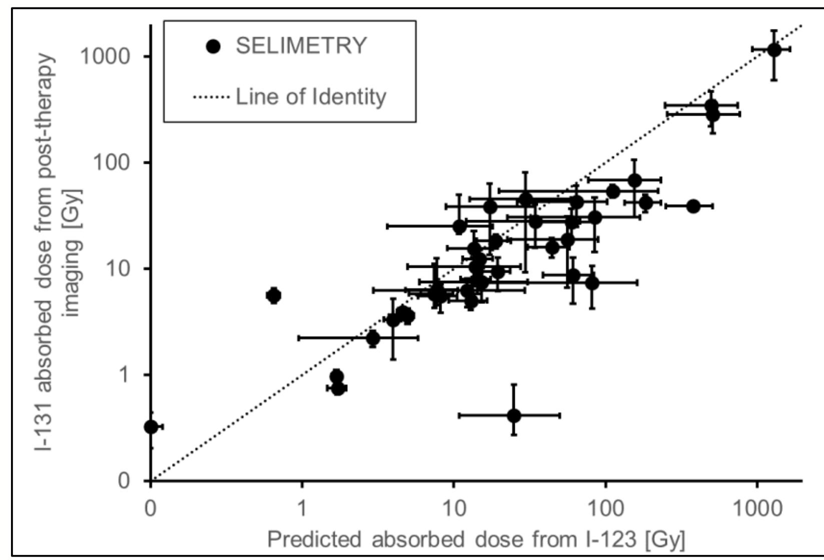
I-123 NaI pre-therapy dosimetry predicts I-131 dose delivered

Physics in Medicine & Biology   IPEM Institute of Physics and Engineering in Medicine

PAPER • OPEN ACCESS

Standardised quantitative radioiodine SPECT/CT Imaging for multicentre dosimetry trials in molecular radiotherapy

To cite this article: Rebecca A Gregory *et al* 2019 *Phys. Med. Biol.* **64** 245013



I-131 dose at therapy predicted from pre-therapy scans

Medirad

Horizon 2020

Observational study of radioiodine treatment of low & intermediate risk thyroid cancer

European centres:

Marburg
Wurzburg
Toulouse
RMH London

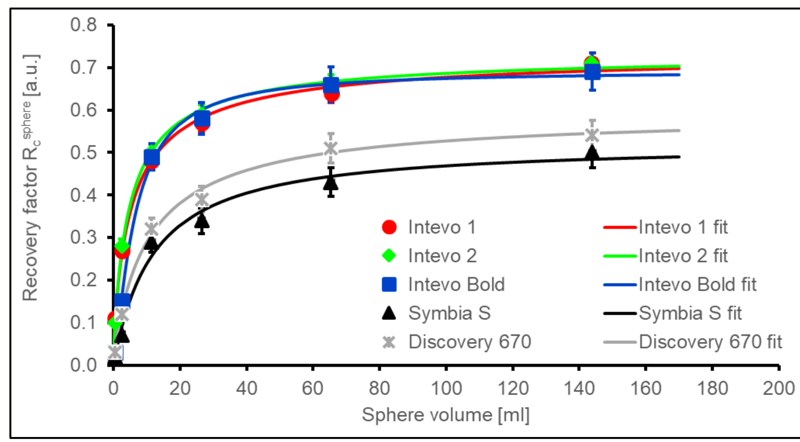
Cameras of same make and model have the same response

Good network
100 patients recruited throughout COVID lockdowns

ORIGINAL RESEARCH Open Access

Setting up a quantitative SPECT imaging network for a European multi-centre dosimetry study of radioiodine treatment for thyroid cancer as part of the MEDIRAD project

Jan Taprogge[1,2*], Francesca Leek[1,2], Tino Schurrat[3], Johannes Tran-Gia[4], Delphine Vallot[5], Manuel Bardiès[6], Uta Eberlein[4], Michael Lassmann[4], Susanne Schlögl[4], Alex Vergara Gil[6], the MEDIRAD WP3 Investigator Team and Glenn D. Flux[1,2]



Partial volume effect of different systems

Ongoing work - Quantitative imaging

SPECT & PET acquire images of the radiopharmaceutical. Imaging of function, not form.

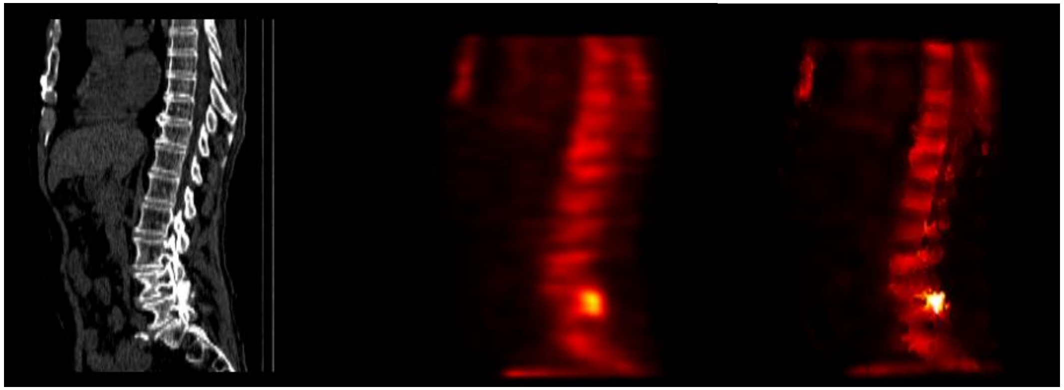
Imaging is qualitative - (can we see abnormal uptake?)

For dosimetry we need to quantify these images - (how much uptake?)

Image improvements and analysis obtained from image processing. Hybrid imaging (CT, MR + SPECT/PET can be used to correct for photon scatter and attenuation)

$$f^{i+1} = \frac{f^i \times \left(psf \otimes \left[\frac{g}{psf \otimes f^i} \right] \right)}{1 + \beta \frac{\partial U\left(f^k\right)}{\partial f^k}}$$

Penalised Deconvolution Algorithm



Localising CT

Original OSEM SPECT

Penalised Deconvolution

Tc99 MDP (bone agent)

Dr Iain Murray

Uncertainties & errors

Chain of uncertainties in theragnostics and dosimetry

$$\left[\frac{u(\bar{D})}{\bar{D}}\right]^2$$

$$= \left[\frac{u(A_0)}{A_0}\right]^2 + \left[\frac{u^2(\lambda)}{\lambda}\right]^2 - 2\frac{u(A_0,\lambda)}{A_0\lambda} + \left[\frac{u(Q)}{Q}\right]^2 + \left[\frac{u(R)}{R}\right]^2 + \left[\frac{u(C_i)}{C_i}\right]^2$$

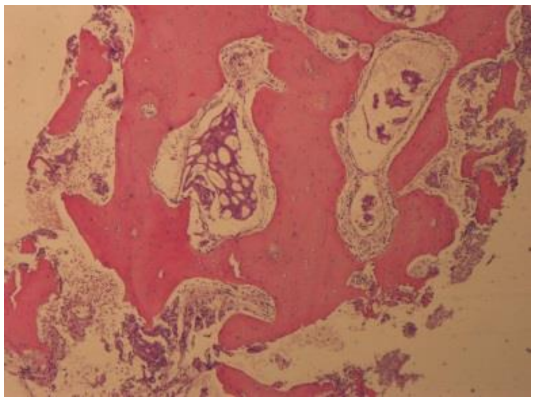
$$-\frac{\varphi}{R^2 v}\frac{\partial R}{\partial v}u^2(v) + |c_2|^2\left[\frac{u(v)}{v}\right]^2 - \frac{c_2}{Rv}\left(\frac{\varphi}{2v} - \frac{\partial R}{\partial v}\right)u^2(v)\frac{u(\tilde{A})}{\tilde{A}}\frac{A_i}{u(A_i)}$$

Uncertainty in mean radiation dose $\bar{D}$ as a function of
Initial activity A_0
Effective half-life λ
Volume v
Count rate C_i
Recovery coefficient R
Calibration factor Q

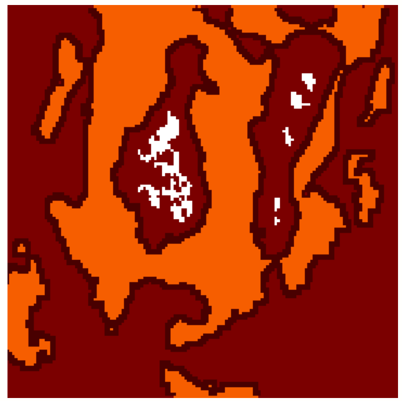
Gear *et al EANM guidelines* (*EJNMMI 2018)*

Ongoing work – Monte Carlo microdosimetry

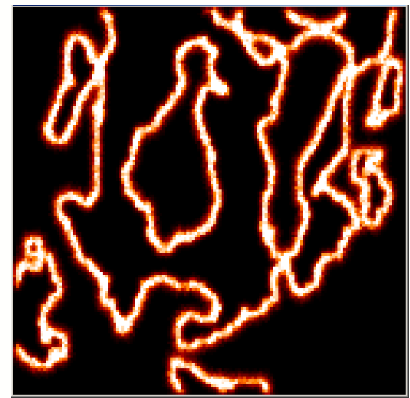
Histology



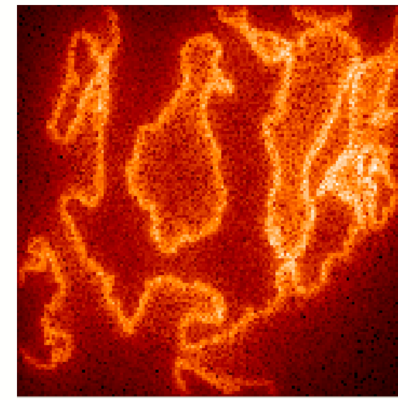
Segmentation



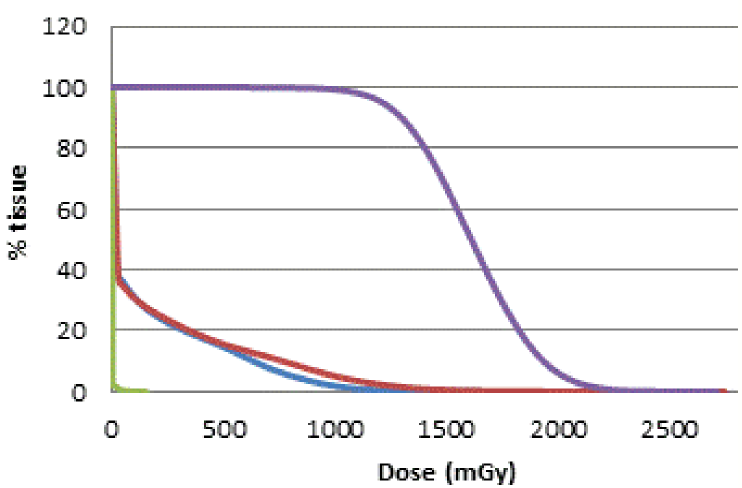
Dose map (α)



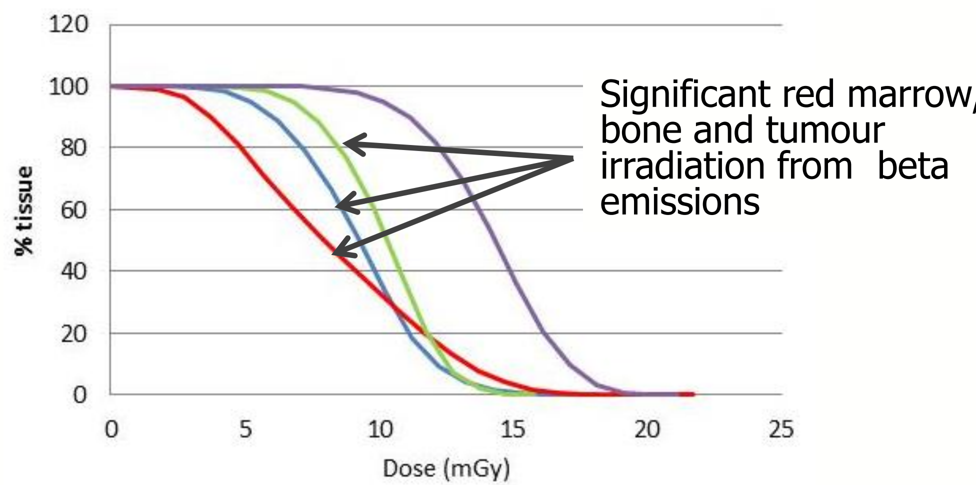
Dose map (β-γ)



Ra-223 alpha particles



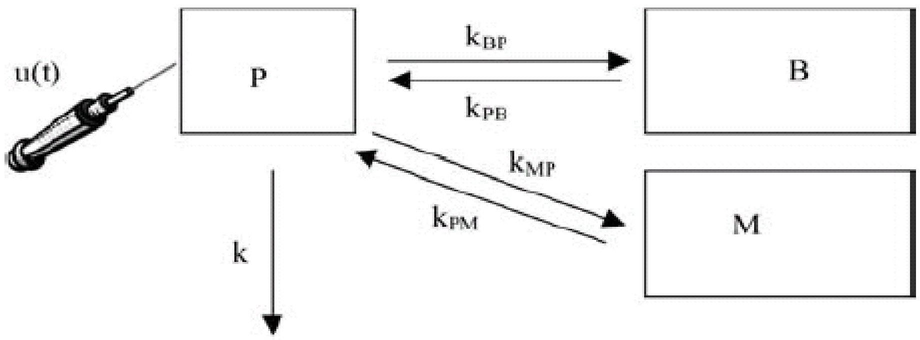
Ra-223 beta-gamma only



Endosteal layer **Trabecular bone** **Red marrow** **Tumour**

Antigoni Divoli

Predictive markers – Re-186 HEDP



Plasma
Normal bone
Metastatic bone

$$\begin{cases} A_P(t) = A_0 \cdot \exp(-(k + k_{MP} + k_{BP}) \cdot t) \cdot \exp(-\lambda \cdot t) \\ A_B(t) = \dfrac{k_{BP} \cdot A_0}{k + k_{BP} + k_{MP}} \cdot [1 - \exp(-(k + k_{MP} + k_{BP}) \cdot t)] \cdot \exp(-\lambda \cdot t) \\ A_M(t) = \dfrac{k_{MP} \cdot A_0}{k + k_{BP} + k_{MP}} \cdot [1 - \exp(-(k + k_{MP} + k_{BP}) \cdot t)] \cdot \exp(-\lambda \cdot t) \end{cases}$$

Compartmental modelling of transit of Re-186

Buffa FM et al: Eur J Nucl Med 2003;30:1114-1124

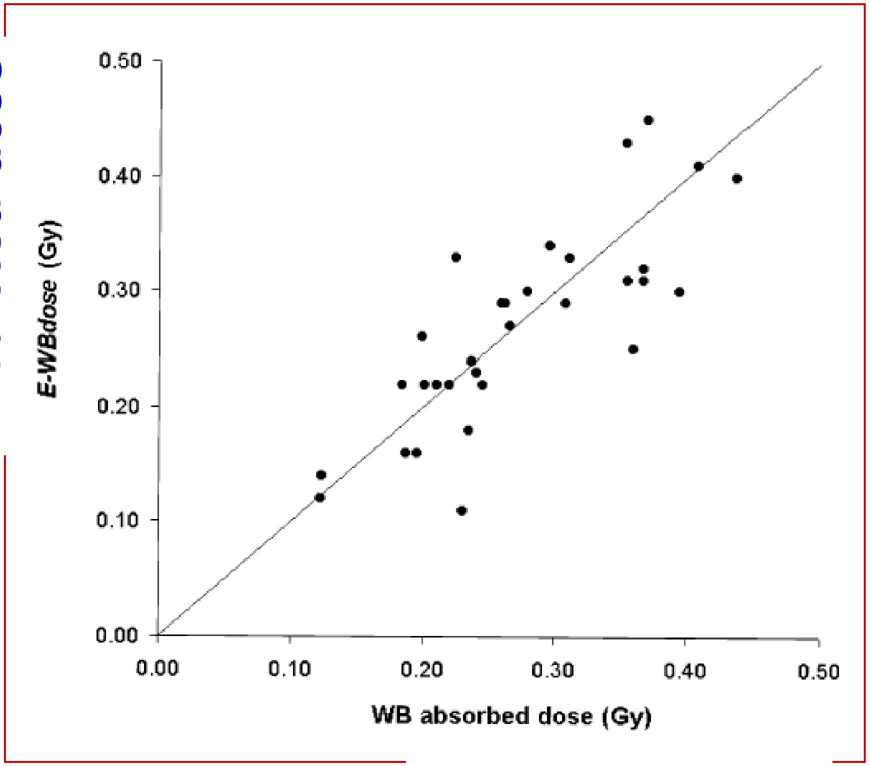
Treatment planning – modelling (Re-186 HEDP)

2003: Estimated WB dose accurately predicted from pre-therapy modelling based on kidney function, Alk Phos, patient weight

2016: WB dose correlates with survival

Can this be used for treatment planning?

Predicted dose



Delivered dose

$$E\text{-}WBdose \cong S \cdot \frac{70}{w} \cdot A_0 \cdot \frac{\left[\frac{c_1 \cdot {}^{51}\mathrm{Cr\text{-}EDTA}}{c_1 \cdot {}^{51}\mathrm{Cr\text{-}EDTA} + c_2 \cdot \mathrm{AlkPh} + \lambda} + \frac{c_2 \cdot \mathrm{AlkPh}}{\lambda}\right]}{\left(c_1 \cdot {}^{51}\mathrm{Cr\text{-}EDTA} + c_2 \cdot \mathrm{AlkPh}\right)}$$

Cost / benefit analysis (Back Of The Envelope…)

Current cost of Lu-177 PSMA treatment:
€12000 per administration, total of €72000 for full course of 6 treatments

Number of patients expected: 6000 per year

Total cost: €432m pa

Cost of 3 scans ~€600

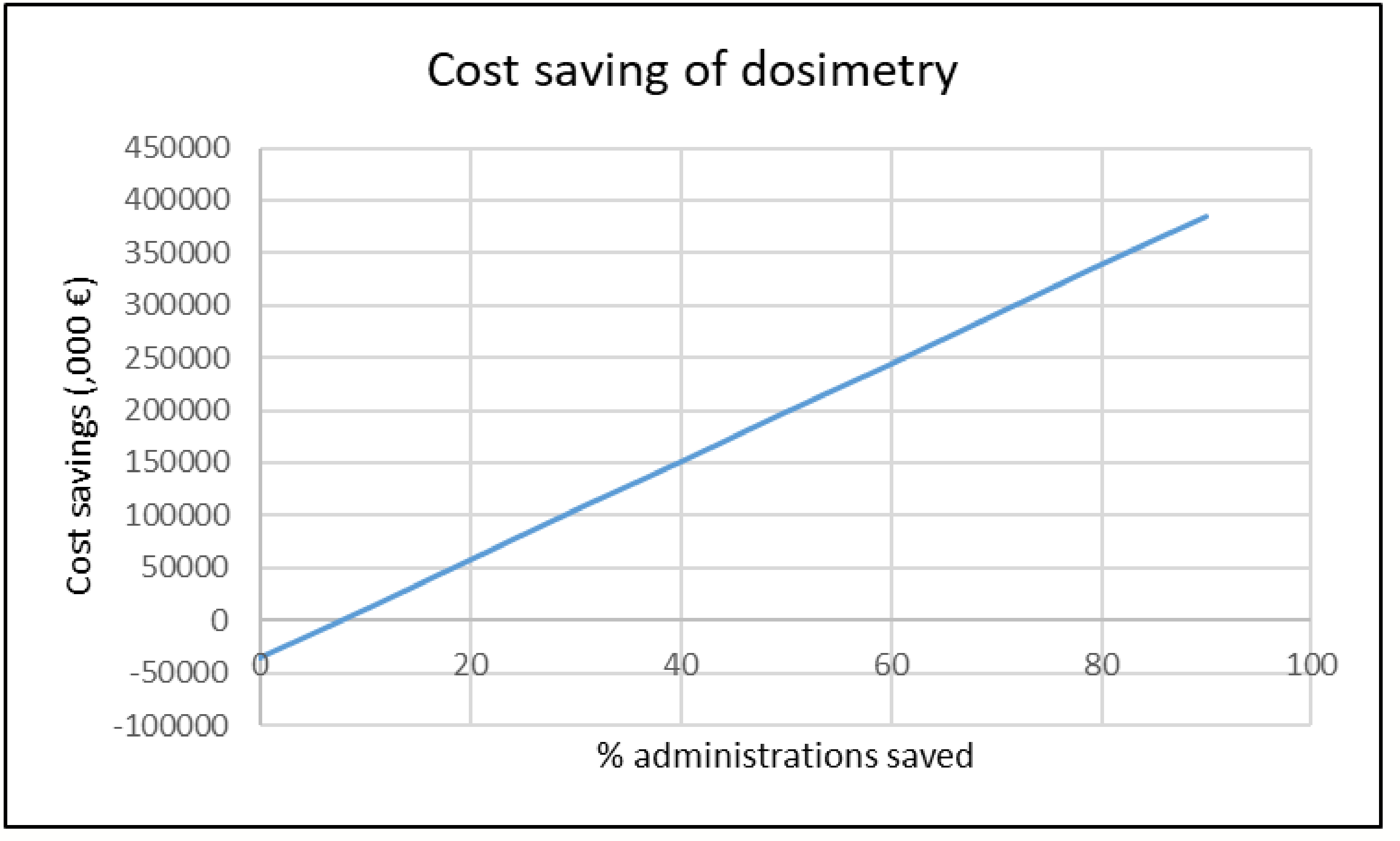
Allow 1-2 days for dosimetry: Cost ~€400

Total cost for full dosimetry: €1000 per administration

- 10% cost of drug.

Full dosimetry for 6000 pts could cost ~€36m

Cost / benefit analysis (Back Of The Envelope…)



Would need to save ~10% of administrations to be cost neutral

Cost/benefit of Lu-177 PSMA imaging

ADDING MEANINGFUL IMAGING REDUCES HEALTH CARE COSTS IN PRECISION NUCLEAR MEDICINE: ANECDOTAL EVIDENCE

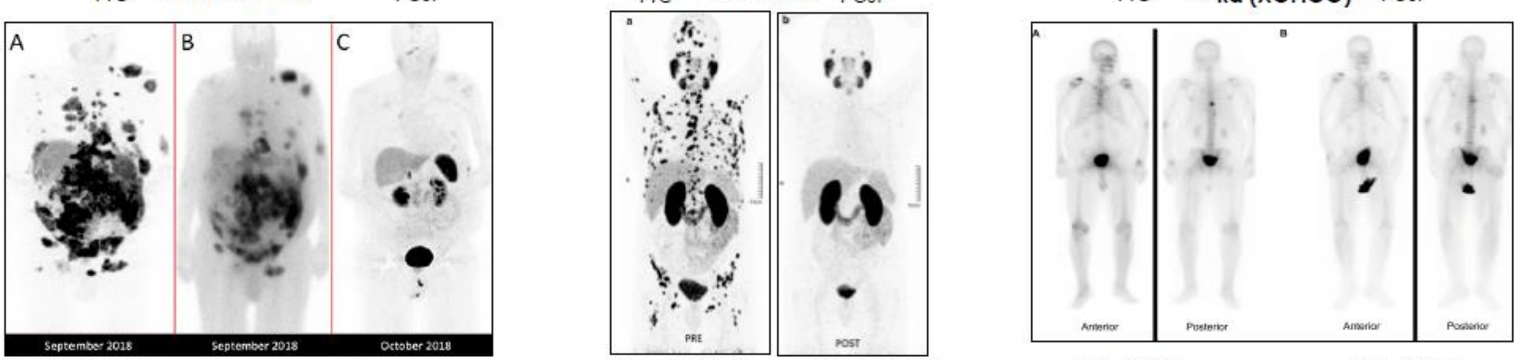
AHMANSON UCLA

THERAPY

$50 000 x 4 — Pre ^{177}Lu-DOTATATE Post

$50 000 x 3 — Pre ^{177}Lu-PSMA Post

$16 000 x 6 — Pre ^{223}Ra (XOFIGO) Post



^{68}Ga-DOTATATE ^{68}Ga-DOTATATE

^{68}Ga-PSMA11 ^{68}Ga-PSMA11

^{99}Tc-MDP ^{99}Tc-MDP

IMAGING $5000 $5000 $300

	Patients	PSMA scan ($5000/scan)	PSMA RLT ($/cycle)
No screening	40,000	$ 0	40,000 pts x $50,000 x 3 cycles = $6 Bill.
PSMA screening (-20%)	40,000	$200 Mil	32,000 pts x $50,000 x 3 cycles = $4.8 Bill.
		Adds $200 Mil. for IMAGING	Reduces THERAPEUTICS by $1.2 Bill

J. Czernin: PERSONALIZED NUCLEAR MEDICINE: THE COST OF IT ALL (Czernin ppt 11102021 (brolbrolbrol.com))

Conclusions

Dosimetry-based treatments with radiotherapeutics offer a level of personalised treatment that is not possible with other cancer drugs.

Again at the same fork in the road

Significant investment needed:

- Reimbursement for imaging and dosimetry (as for EBRT)
- Introduction of routine dosimetry (as for EBRT)
- Support for clinical physics
- Resourcing for research physics and radiobiology
- Multi-centre investigator led clinical trials

Aims:

- Characterise the radiation doses delivered
- Look for dose-effect correlations
- Develop dosimetry-based treatment planning

Potential huge benefit in cost savings and clinical efficacy

A great challenge (scientifically, logistically, politically) – but must be tried
Community effort!