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METROLOGY TO SUPPORT INNOVATION IN MOLECULAR RADIOTHERAPY

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CGPM 2018

ICR The Institute of Cancer Research

Overview

Current status

- Nuclear Medicine enables imaging of the function of organs and the diagnosis of malignancies
- Molecular radiotherapy uniquely treats cancers systemically with radiotherapeutics
- International standardisation of measurements of radioactivity enables safer, more effective procedures and provides the confidence for international clinical trials
- Molecular radiotherapy is undergoing a revolution – rapid increase in radioactive drugs, treatments, methods of administration. Promises significant benefit in healthcare.

Ongoing developments

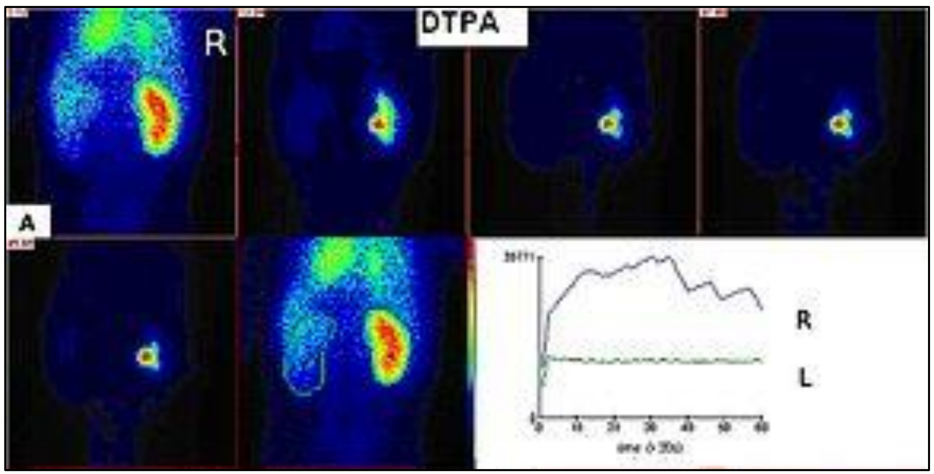
- Standards for new radiotherapeutics
- Research into measurements of activity to calculate radiation doses delivered to tumours and organs in individual patients

Nuclear Medicine

Nuclear Medicine uses injected radionuclides that localise in selected tissues

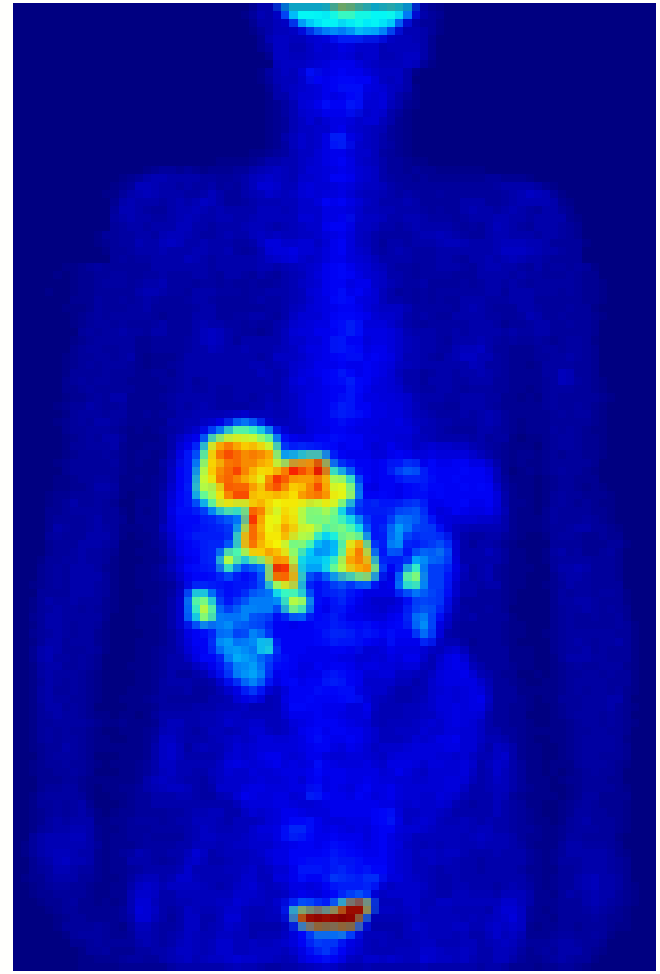
Diagnostic Nuclear Medicine scans are used to image normal organs or an abnormal growth

Nuclear Medicine scans show function, for example of heart and kidneys



Renal imaging and analysis with Tc-99m DTPA

~5,000,000 nuclear medicine scans are performed in Europe each year


F-18 FDG scan
A large metastatic tumour mass from colon cancer is seen in the liver

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Molecular Radiotherapy

Tc-99m bone scan with abnormal uptake

Myohan at English Wikipedia, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=17270224)

A tracer level of a diagnostic agent can selectively localise in abnormal tissue.

A high level of a therapeutic agent can therefore selectively target abnormal tissue with radiation.

Molecular Radiotherapy (MRT) is the treatment of cancer or benign disease with therapeutic radiopharmaceuticals – high energies, high activities.

Used for the treatment of hyperthyroid conditions, thyroid cancer, bone metastases from prostate cancer, neuroendocrine tumours, neuroblastoma in children, liver tumours…

New treatments for lung tumours and breast cancer

MRT is the only medical treatment that allows imaging of the drug in real time!

Uptake of Ra-223 in bone metastases

Hindorf Nucl Med Comun 2012

Chittender
Nucl Med 2

The radiotherapeutics revolution

MEDraysintell

Press Release

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

RADIOTHERAPEUTICS ARE DRIVING UP THE NUCLEAR MEDICINE MARKET

n the last few weeks two leading companies proved that radiotherapeutics are becoming the driving orces 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 market is expected to grow 26% annually between 2014 and 2030.'

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The radiotherapeutics revolution

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

Novartis to buy French cancer specialist AAA for $3.9 billion

John Miller

4 MIN READ

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.

The radiotherapeutics revolution

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#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.

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The radiotherapeutics revolution

MEDraysintell

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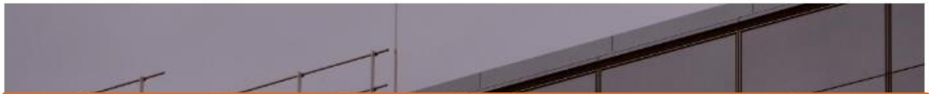

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Chinese firm makes last-minute $1.4 billion offer for Australia's Sirtex, trumps Varian: Reuters

May 4, 2018 By Reuters News

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Chinese private equity firm **CDH Investments** lobbed a last-minute $1.4 billion offer for Australian liver-cancer treatment firm **Sirtex Medical** (SRX.AX), trumping **Varian Medical Systems** (VAR.N) days before the U.S. firm was set to seal a takeover deal.

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Growth in radiotherapeutics

MEDraysintell

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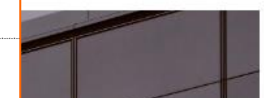

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Bloomberg

Deals

Novartis to Buy Cancer Drugmaker Endocyte for $2.1 Billion

By James Paton

18 October 2018 06:28 *Updated on 18 October 2018 06:59*

#DEALS FEBRUARY 24, 2

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Norway's

Reuters Staff

OSLO/FRANKFURT (Reu
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.4 billion
umps Varian:

last-minute $1.4 billion
offer for Australian liver-cancer treatment firm **Sirtex Medical** (SRX.AX), trumping
seal a

October 2018

Lu-177 PSMA for bone metastases from prostate cancer

Unprecedented opportunities and challenges!

Pioneers & Visionaries

Karl Compton

Saul Hertz

Cancer has been treated with radiotherapeutics for nearly 80 years.

1936 – Dr Karl Compton gives a lunchtime lecture at Harvard medical school:

"What Physics Can Do for Biology & Medicine"

Saul Hertz (endocrinologist) asked if it would be possible to synthesise radioactive iodine

Arthur Roberts (physicist)
Glenn Seaborg (radiochemist)

Led to the first treatment of hyperthyroidism with radioiodine in 1941, and soon after thyroid cancer.

Leo Marinelli devised a system for calculating the absorbed dose delivered.

Led to the birth of nuclear medicine.

Glenn Seaborg

Arthur Roberts

Leo Marinel

Current standardisation: 'Radioactive chemotherapy':

Current practice is to treat according to the level of activity administered:

Examples:

- 7400 MBq radioiodine for thyroid therapy
- 7400 MBq I-131 mIBG, Y-90 DOTATATE, Lu-177 DOTATATE for neuroendocrine tumours

Biokinetics vary from patient to patient affecting uptake and retention of the radiotherapeutics. Therefore a large range of absorbed doses are delivered from fixed activities of radiation:

Examples:

- Normal bone from Ra-223: 2 – 8 Gy (Chittenden *J Nucl Med* 2015)
- Red marrow from I-131 radioiodine: 38 – 375 mGy/GBq (Bianchi *Q J Nucl Med* 2013)
- Thyroid remnants from I-131 radioiodine: 7 – 570 Gy (Flux *Eur J Nucl Med* 2010)

In general, radiation doses to normal organs vary by an order of magnitude

Radiation doses to tumours vary by two orders of magnitude

Current research investigating treatment according to radiation dose. Paradigm shift!

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Internal dosimetry

There is ongoing development to standardise the radiation doses delivered to patients. The basic equation for patient dosimetry combines physics & biology:

$$\bar{D} = \tilde{A}.S$$

$\bar{D} = The\ mean\ radiation\ dose\ delivered\ to\ an\ organ\ or\ tumour$

$\tilde{A} = The\ total\ number\ of\ radioactive\ decays\ in\ an\ organ\ or\ tumour$

$S = The\ radiation\ dose\ delivered\ for\ each\ radioactive\ decay$

The meeting of physics and biology!

The onus on the medical physicist is to measure the number of radioactive decays occurring within a tumour or normal organ.

Obtained from several scans after administration to track the distribution of activity over time

Standardisation of activity measurements

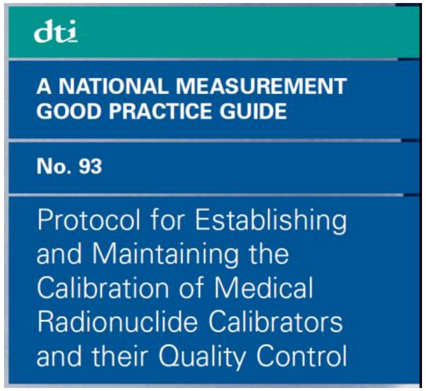
The CIPM MRA ensures that activity measurements made by the NMIs are standardised internationally (104 signatories from 59 member states covering 159 institutes). The KCDB of measurements is maintained by the BIPM.

This ensures that primary standards of radioactivity are equivalent in different countries and that patients are administered the same activity.

Table 2.2 Typical state-of-the-art uncertainties for primary standards

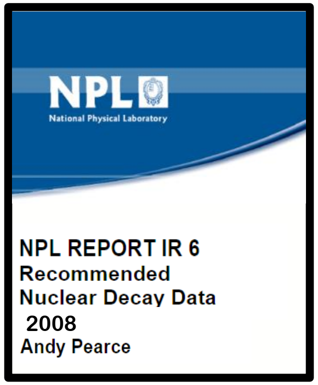
Nuclide	Uncertainty (%) (k=2)	Nuclide	Uncertainty (%) (k=2)
^{32}P*	1.50	^{99m}Tc	2.0
^{51}Cr	1.0	^{111}In	1.5
^{57}Co	2.0	^{123}I**	1.5
^{67}Ga	2.5	^{125}I**	3.0
^{89}Sr*	1.0	^{131}I	1.0
^{90}Y*	1.0	^{201}Tl	1.50

* Pure beta emitter
**Low-energy photon



Isotope	Half life (days)	Uncertainty (%)
I-131	8.02	0.02
Lu-177	6.65	0.06
Ra-223	11.43	0.44
I-124	4.16	1.44
Y-90	2.67	0.05
P-32	14.28	0.3

Measurement of physical half-lives



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Uncertainties

GUIDELINES

EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations

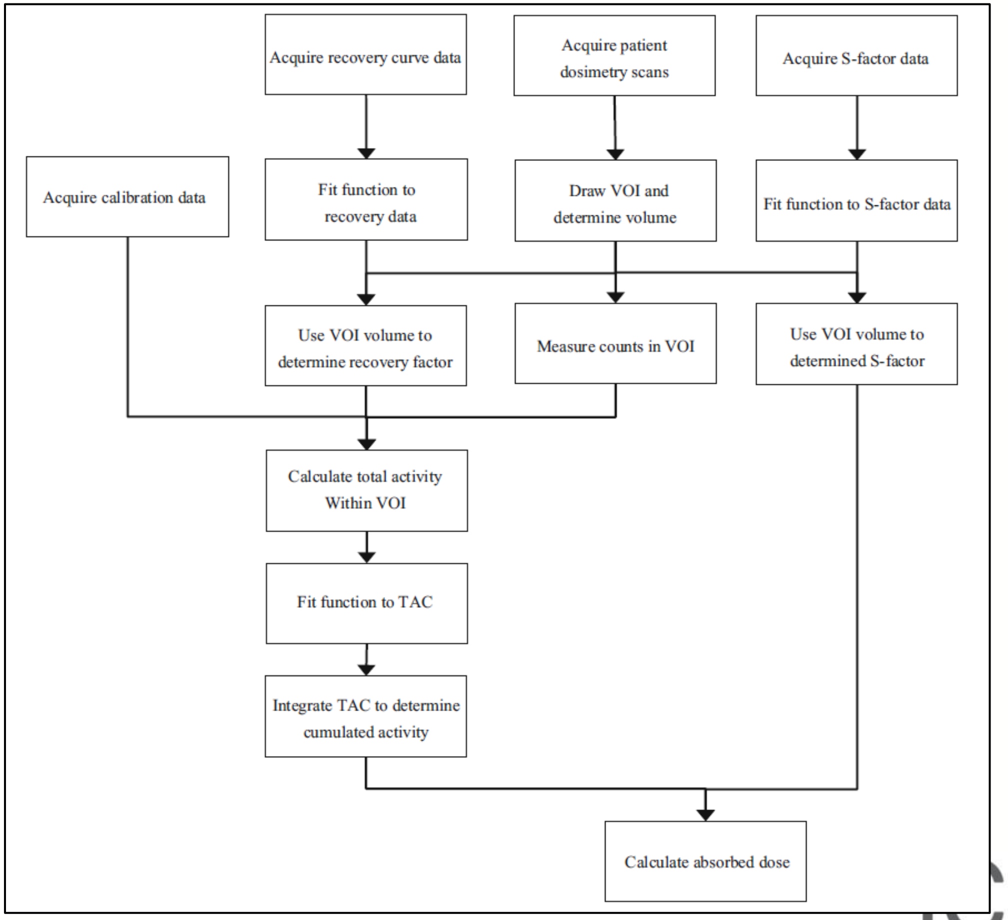
Jonathan I. Gear[1] • Maurice G. Cox[2] • Johan Gustafsson[3] • Katarina Sjögreen Gleisner[3] • Iain Murray[1] • Gerhard Glatting[4] • Mark Konijnenberg[5] • Glenn D. Flux[1]

Received: 9 August 2018 / Accepted: 14 August 2018

Eur J Nucl Med 2018

Uncertainties due to:

- Instrumentation
- Operator (target outlining)
- Quantification



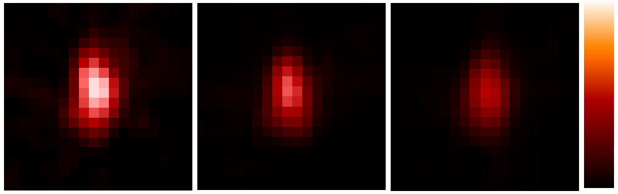
Standardisation of quantitative imaging

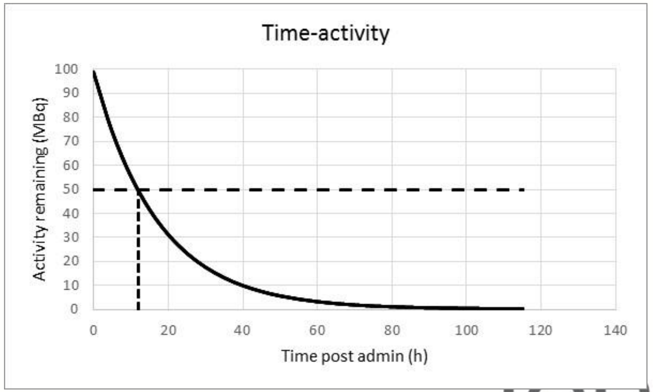
Nuclear medicine gamma cameras are designed to image small quantities of low energy gamma emitters for *qualitative* diagnosis.

Therapy imaging requires *quantitative* imaging of high energy, high activity radionuclides.

Cameras must be calibrated to convert the counts acquired into absolute measurements of activity and to make corrections for 'deadtime' if there is a higher count rate than then the system can handle.

Not simple, and requires standardisation for multicentre trials





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Standardisation of quantitative imaging

Comparison of ^{90}Y and ^{177}Lu measurement capability in UK and European hospitals

Andrew Fenwick*, Michaela Baker, Kelley Ferreira, John Keightley

National Physical Laboratory, Hampton Road, Teddington TW11 0LW, UK

H I G H L I G H T S

- ^{90}Y and ^{177}Lu measurement accuracy in UK and European hospitals is presented.
- 40% of participants are able to measure ^{90}Y to within 5%.
- 81% of participants are able to measure ^{177}Lu to within 5%.
- Geometry dependence is identified in radionuclide calibrator measurements of ^{90}Y.

MRT DOSIMETRY

Metrology for clinical implementation of dosimetry in molecular radiotherapy

COMMENTARY

SELIMETRY—a multicentre I-131 dosimetry trial: a clinical perspective

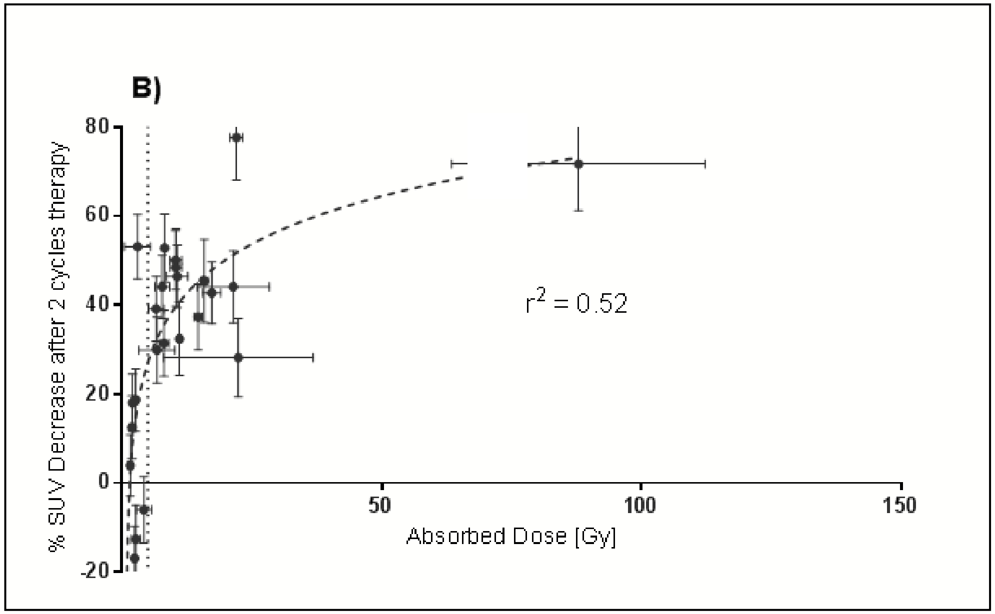
[1]JONATHAN WADSLEY, MRCP, FRCR, MA, [2]REBECCA GREGORY, PhD, [2]GLENN FLUX, PhD, [3]KATE NEWBOLD, MRCP, FRCR, MD, [3]YONG DU, FRCP, PhD, [4]LAURA MOSS, FRCP, FRCR, LLM, [5]ANDREW HALL, MSc, [5]LOUISE FLANAGAN, PhD and [5]SARAH R BROWN, PhD

[1]Weston Park Hospital, Sheffield, UK
[2]Department of Physics, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK
[3]Royal Marsden Hospital, London, UK
[4]Velindre Hospital, Cardiff, Wales
[5]CTRU, University of Leeds, Leeds, UK

Ongoing initiatives to standardise cameras across European centres: MRTDosimetry & Medirad

Absorbed dose relationship

- Ra-223 for bone metastases: Relationship between lesion absorbed dose and % change in fluoride-18 uptake



Murray EJNMMI 2017

- The function of the tumours decreases with increasing radiation dose

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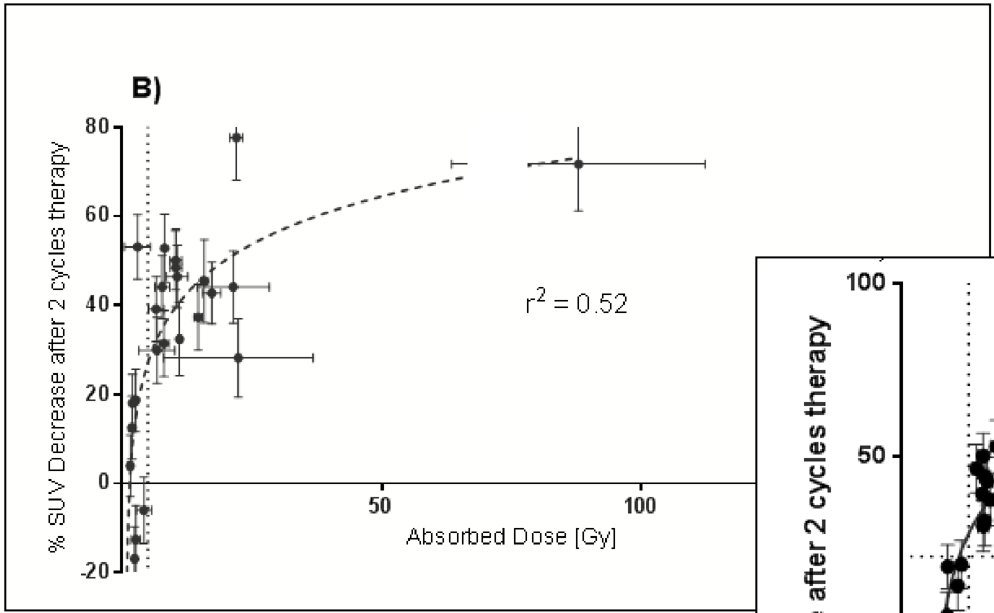
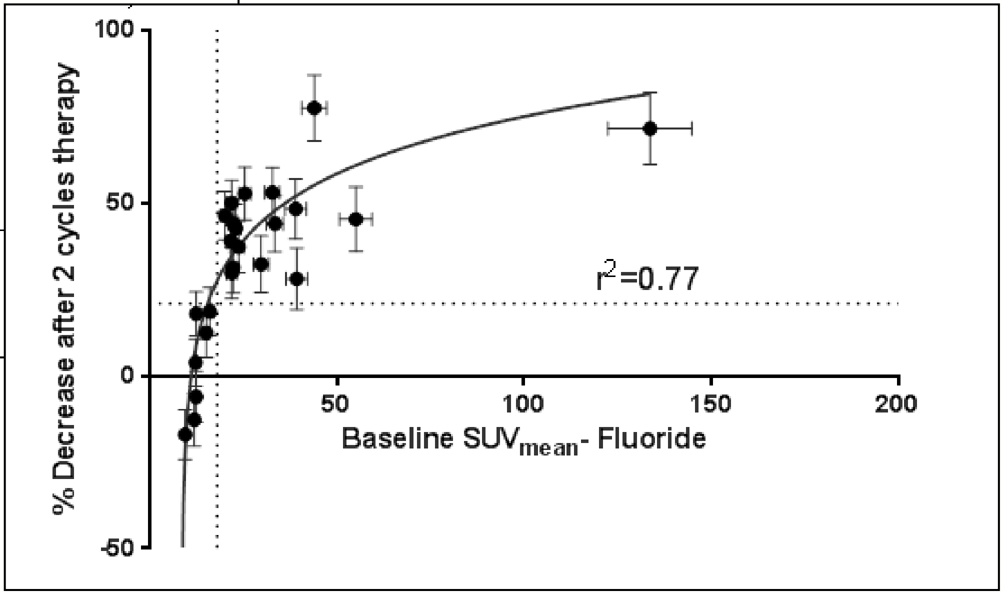
Absorbed dose relationship

- Ra-223 for bone metastases: Relationship between lesion absorbed dose and % change in fluoride-18 uptake





Murray EJNMMI 2017

- Baseline PET predicts the dose and could be used for initial treatment planning – administration could be increased

I-131 mIBG for neuroblastoma

Case study – Vienna, 22 year old female

Neuroblastoma is a cancer of the neuroendocrine system found in children and young adults.

Conventional treatment is 7400 MBq I-131 mIBG

'Veritas' protocol (Dr Simon Meller, RMH):

Administer according to a 4 Gy whole-body radiation dose in 2 fractions.

Fraction 1: According to weight

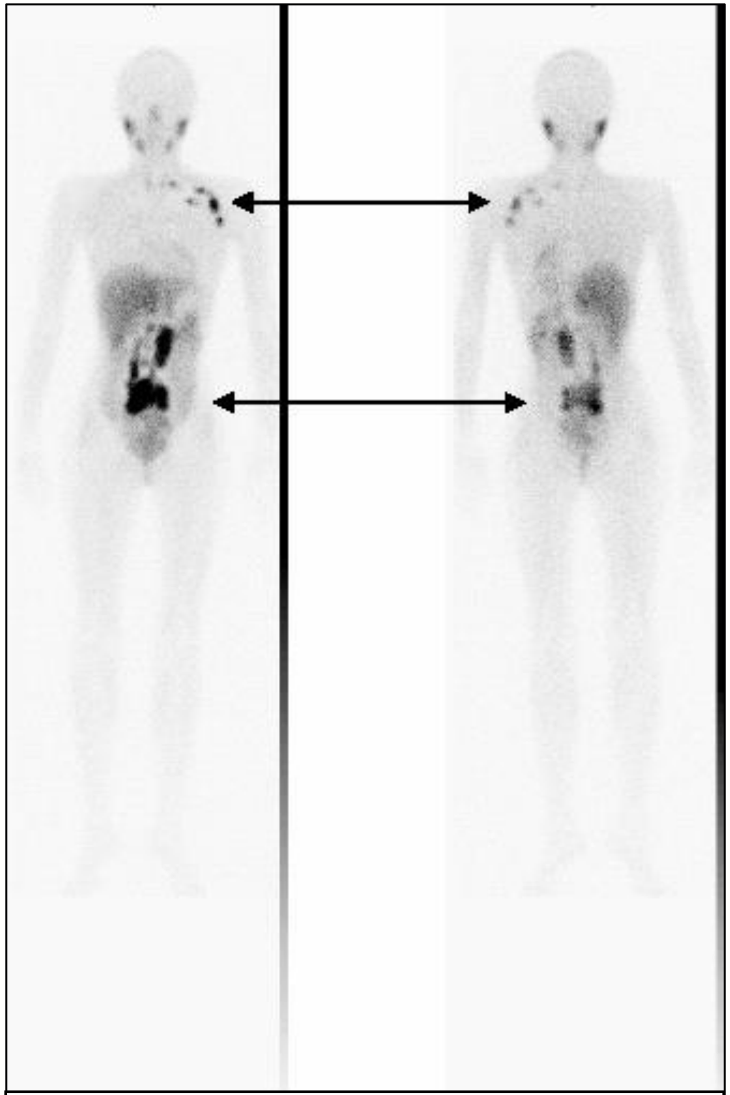
Fraction 2: Modified according to dosimetry

At presentation:

Post CDDP/VP16+ HD CAV, rapid COJEC

Post surgery

Post radiotherapy



Becherer & Ladensten

St Anna's children's hospital, Vienna

At presentation

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I-131 mIBG for neuroblastoma

Initial treatment

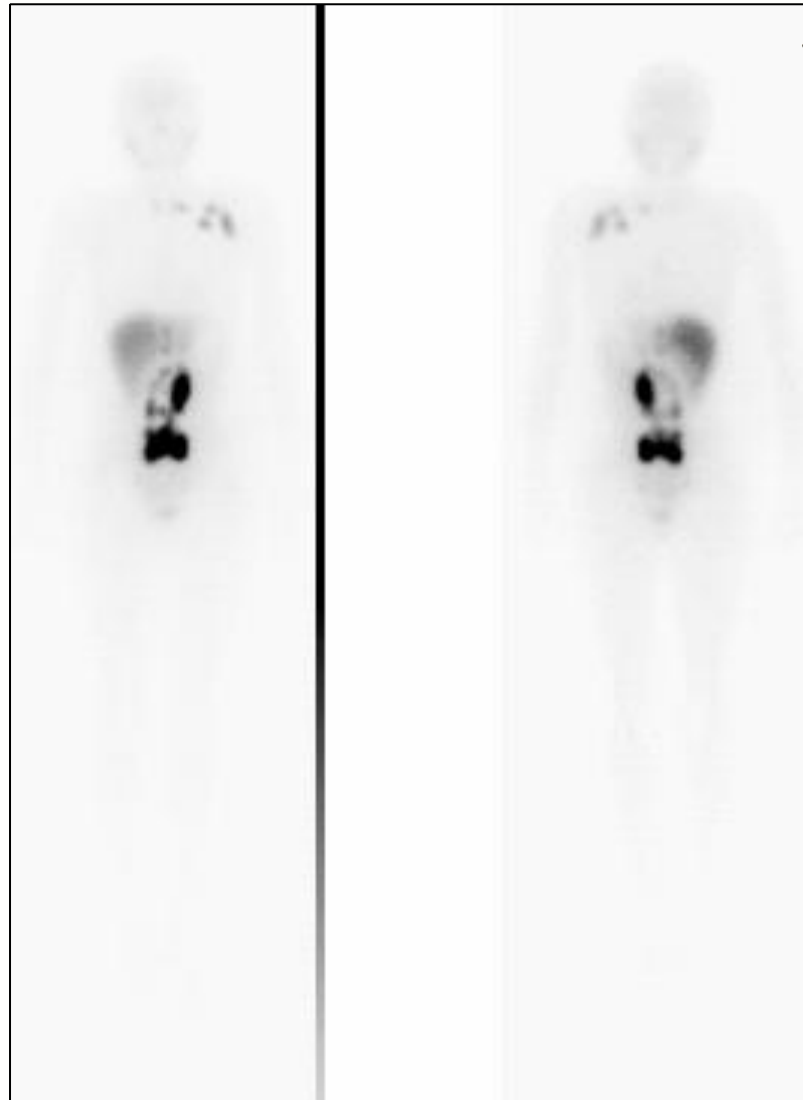
8.7 GBq (1 Gy WB dose)

+

19.7 GBq (2.3 Gy WB dose)

Slightly under target

(new technique)



Becherer & Ladensten

St Anna's children's hospital, Vienna

Scan after treatment 1

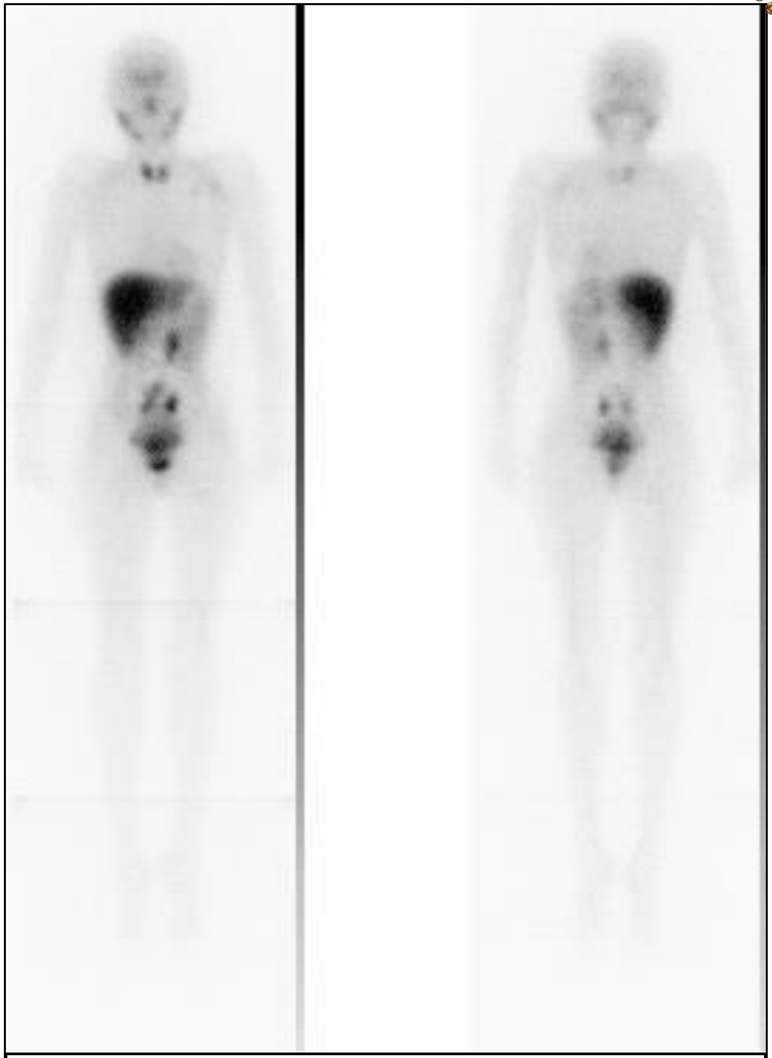
I-131 mIBG for neuroblastoma

Treatment well tolerated and showed response. Therefore a second cycle was given

18.5 GBq (1.7 Gy WB dose)

+

11.1 GBq (1.1 Gy WB dose)



Becherer & Ladensten

St Anna's children's hospital, Vienna

Scan after treatment 2

I-131 mIBG for neuroblastoma

7 months later.

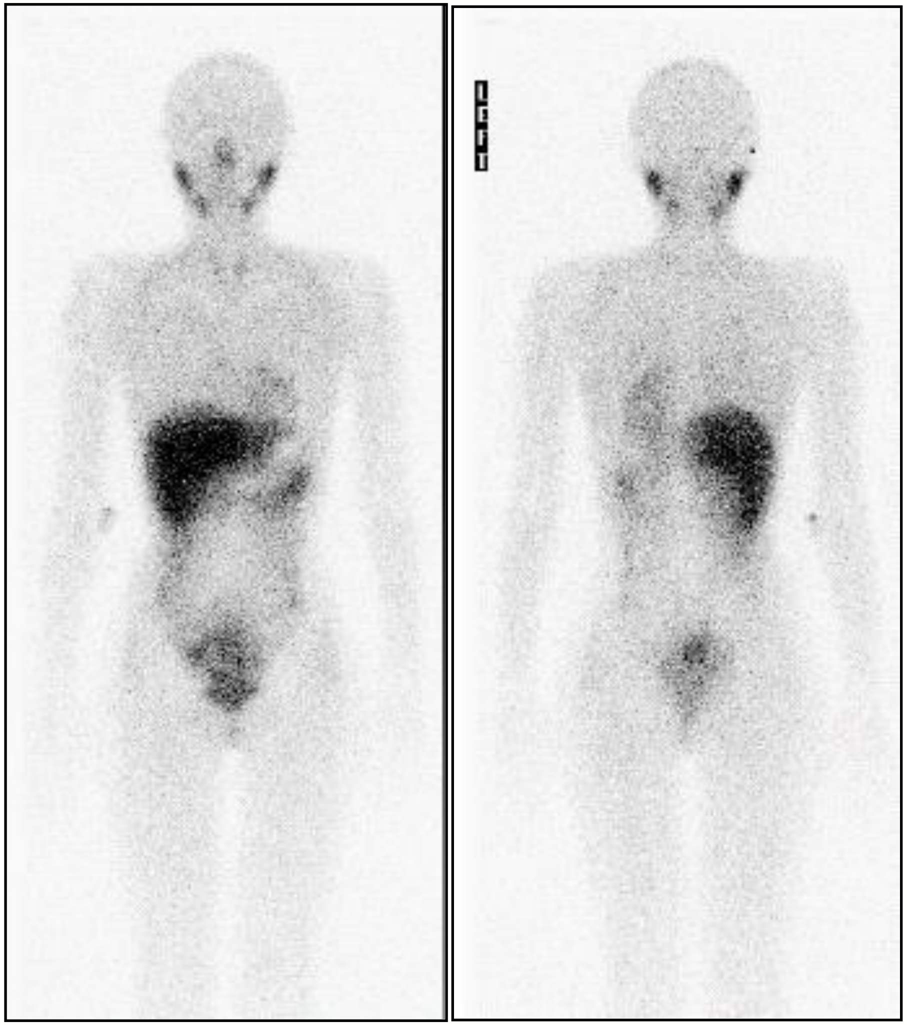
Clear.

Total of 58 GBq activity administered

~ 8 times more activity administered than in the absence of dosimetry

(mostly rapidly eliminated)

Combination of physics & clinical judgement



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Conclusions

Accurate and standardised measurement of radionuclides enables radiotherapeutics to be administered worldwide with equivalence

Emphasis is now on personalised treatments according to radiation dosimetry, as is standard practice for external beam radiotherapy

Treatment planning protocols are in development

International collaborations are being set up to standardise quantitative imaging and multicentre, multinational clinical trials are starting

Cost/benefit of treatments will improve with tailored treatments

Rapid progress in the field with metrology and the clinic working together to improve existing treatments and to make the next generation of drugs safer and more effective

Ackowledgements

Radioisotope Physics Group, RMH/ICR

Nuclear Medicine RMH

Patients (participation & involvement)