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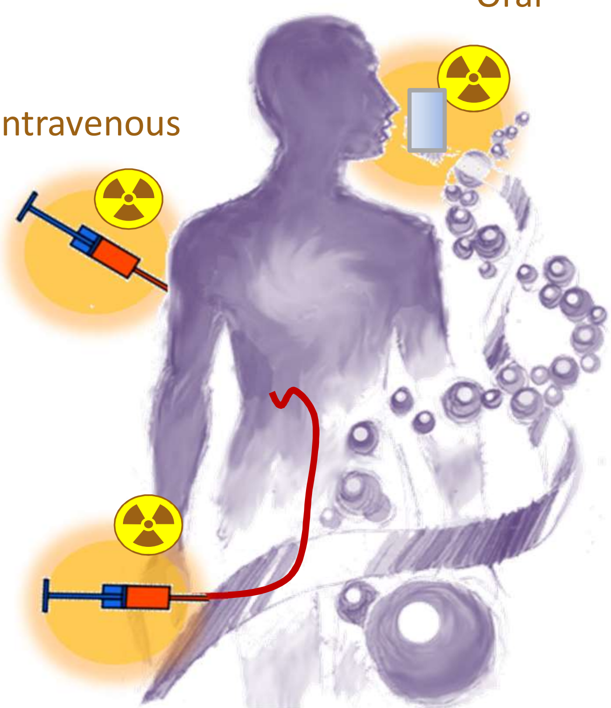
Dosimetry and dosimetric tools in radionuclide therapy, including results from a European survey

KATARINA SJÖGREEN GLEISNER
MEDICAL RADIATION PHYSICS, LUND UNIVERSITY, SWEDEN

Radionuclide therapies



- Thyroid
  - ^{131}I NaI for benign conditions
  - ^{131}I NaI for thyroid cancer
- Adult neuroendocrine disease
  - ^{131}I mIBG, ^{177}Lu or ^{90}Y radiopeptides
- Neuroblastoma - ^{131}I mIBG
- Non-Hodgkins lymphoma
  - ^{177}Lu or ^{90}Y labelled mAbs
- Bone metastases - ^{153}Sm, ^{89}Sr, ^{223}Ra
- Prostate cancer - ^{177}Lu-PSMA (trial)
- Myeloproliferative disease - ^{32}P
- Intra-arterial treatment in liver :
  - ^{90}Y microspheres, ^{166}Ho
- Joints - Radiation synovectomy ^{90}Y, ^{186}Re, ^{169}Er
- ^{169}Er, ^{67}Cu, ^{188}Re, ^{227}Th, ^{225}Ac, ^{211}At ....

Systemically administered

- Thyroid
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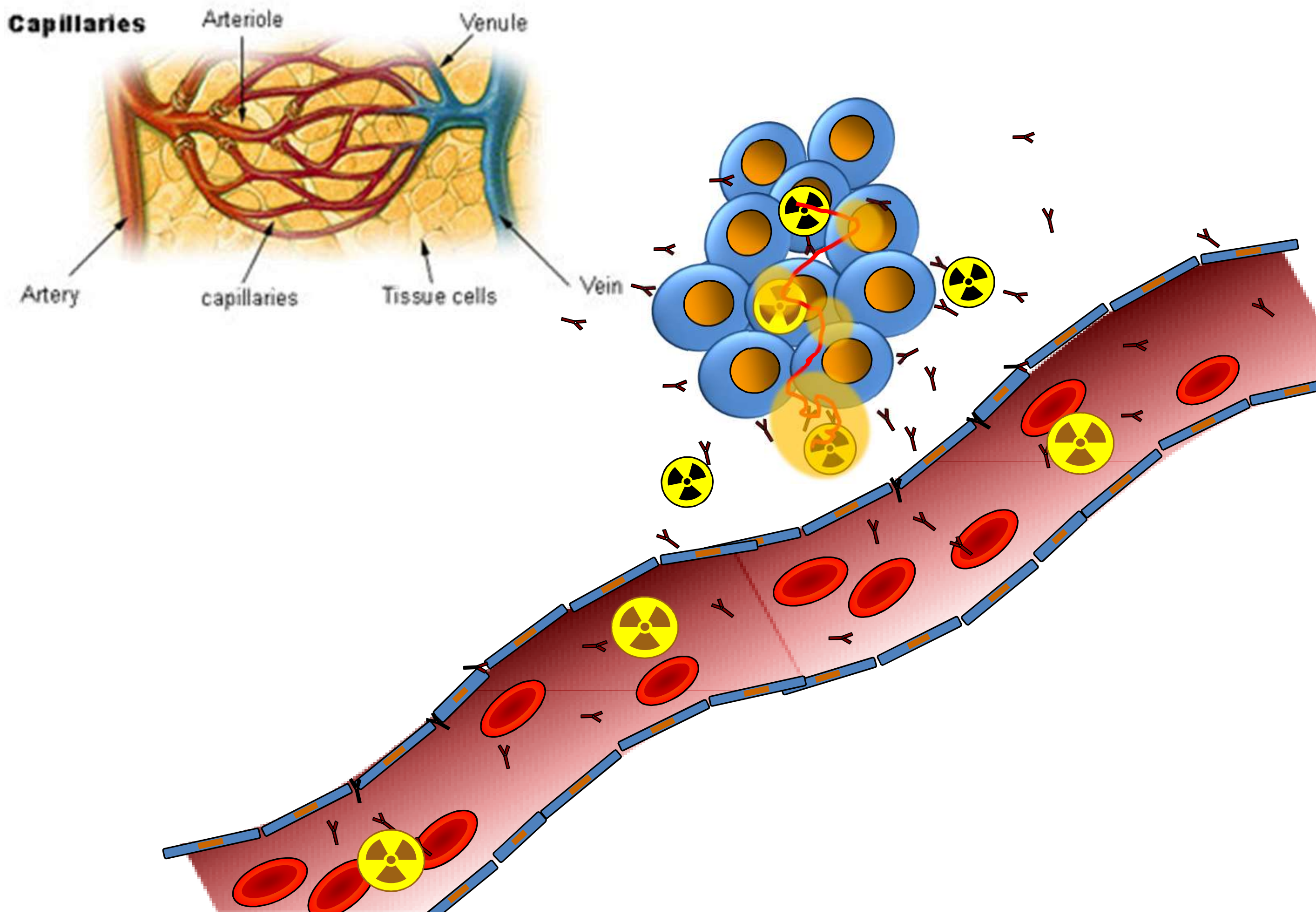
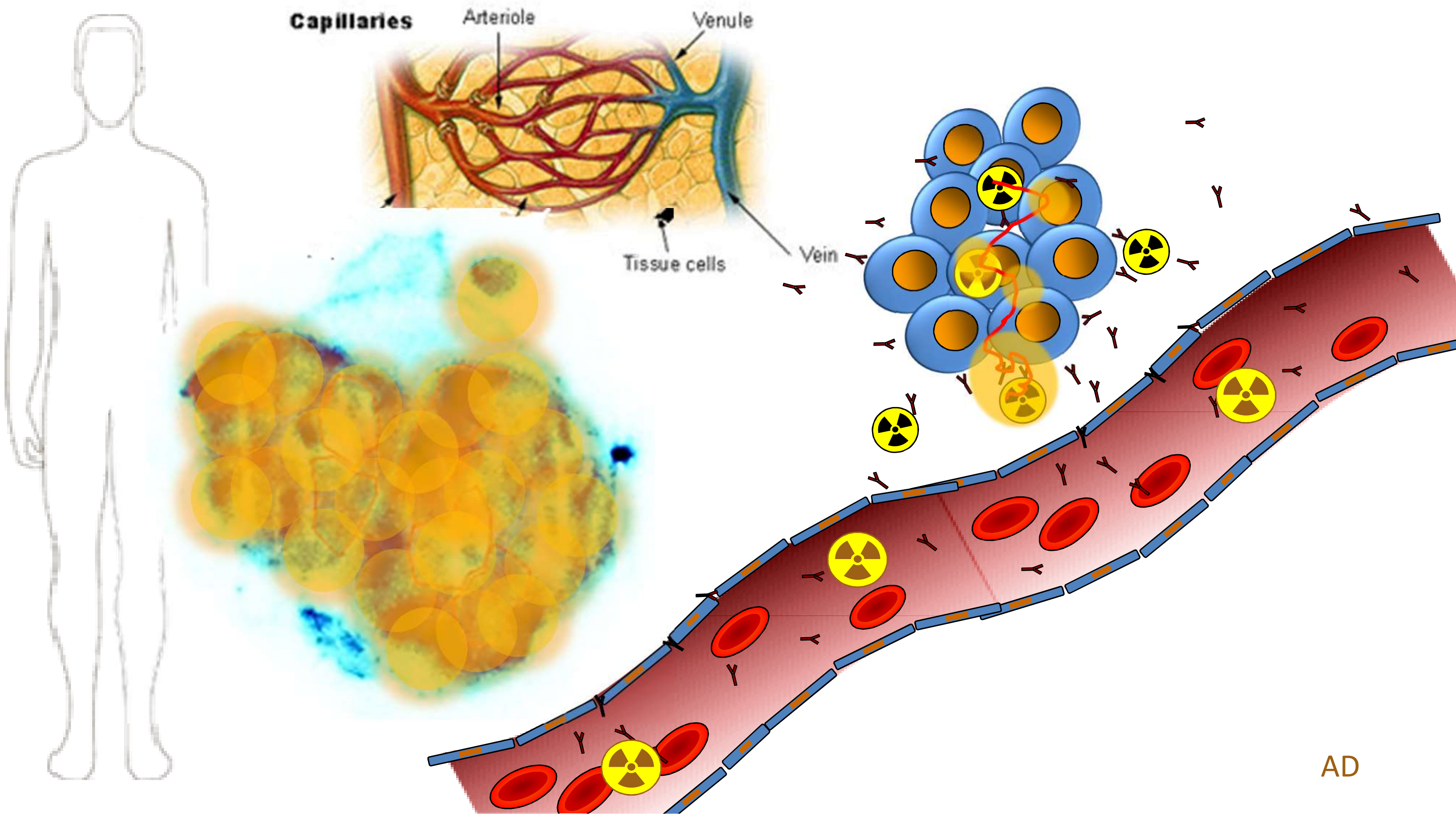


Systemically administered



Autoradiography: intratumoral distribution of monoclonal antibody in rat

Örbom et al
J Nucl Med 2013

AD

Definition of absorbed dose (ICRU 85 and 86)

- The absorbed dose is the mean energy imparted, $\mathrm{d}\bar{\varepsilon}$, to the matter in an infinitesimal volume, $\mathrm{d}V$, with mass $\mathrm{d}m$

$$D = \frac{\mathrm{d}\bar{\varepsilon}}{\mathrm{d}m}$$

unit gray (Gy) ; 1 Gy = 1 J/kg.

- The **mean absorbed dose** in a target region r_T with mass $M(r_T)$

$$D(r_T) = \frac{1}{M(r_T)} \int_{\mathcal{M}} D \, \mathrm{d}m$$

*ICRU Report 85: Fundamental quantities and units for ionizing radiation, Journal of the ICRU **11** 1 (2011).*
*ICRU Report 86: Quantification and reporting of low-dose and other heterogeneous exposures, Journal of the ICRU **11** 2 (2011).*

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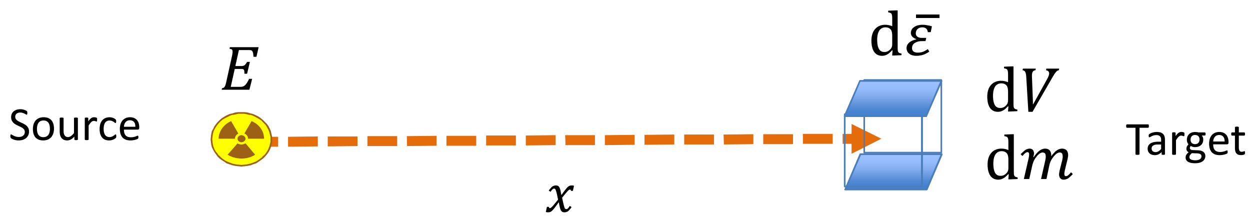
Internal dosimetry - The absorbed fraction

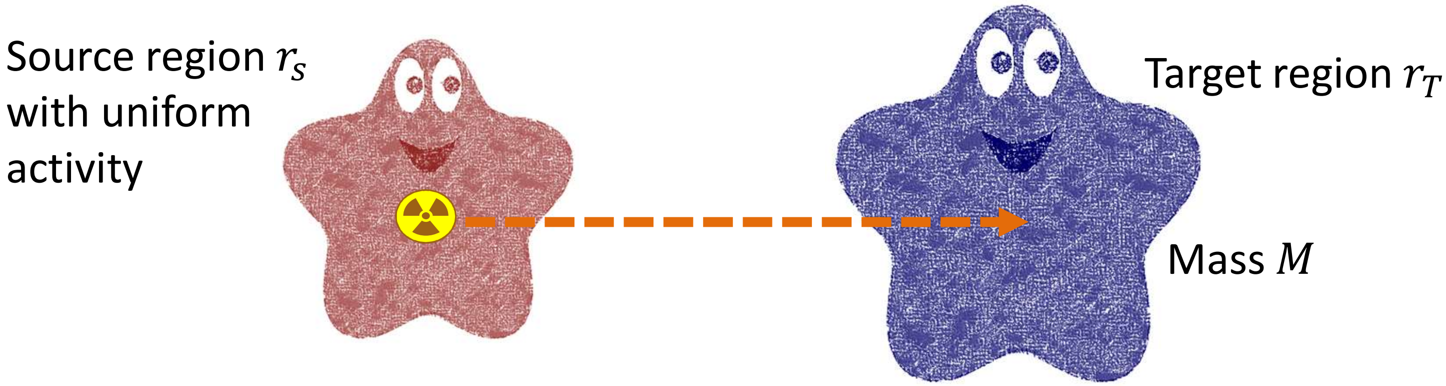
$$D = \frac{\mathrm{d}\bar{\varepsilon}}{\mathrm{d}m}$$



$$\mathrm{d}\bar{\varepsilon} = E \cdot \phi(x, E)$$

$\phi(x, E)$ is the absorbed fraction, i.e. the fraction of radiation energy emitted from the source (E) that is absorbed in the target.
$\phi(x, E)$ is dimensionless and $0 \leq \phi(x, E) \leq 1$.

Internal dosimetry - The absorbed fraction



The absorbed fraction $\phi(r_T \leftarrow r_S)$ is in this case the fraction of radiation energy emitted from the **source region** that is absorbed in the **target region**.

The mean absorbed dose;

$$D(r_T) = \frac{1}{M(r_T)} \int_{\mathcal{M}} D \, \mathrm{d}m = \frac{1}{M(r_T)} \int_{\mathcal{M}} \left(\frac{\mathrm{d}\bar{\varepsilon}}{\mathrm{d}m} \right) \mathrm{d}m = \frac{1}{M(r_T)} \int_{\mathcal{M}} \frac{E \cdot \phi(r_T \leftarrow r_S, E)}{\mathrm{d}m} \, \mathrm{d}m$$

$$= \frac{1}{M(r_T)} \cdot E \cdot \phi(r_T \leftarrow r_S, E)$$

Internal dosimetry - The *S* value

The S value states the mean absorbed dose to the target region r_T per radioactive decay in the source region r_S

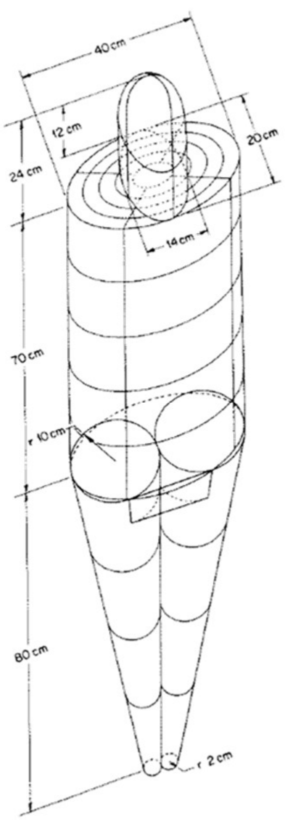
$$S(r_T \leftarrow r_S) = \frac{1}{M}\sum_i E_i \cdot Y_i \cdot \phi(r_T \leftarrow r_S, E_i)$$

$$\frac{1}{M(r_T)} \cdot E \cdot \phi(r_T \leftarrow r_S, E)$$

E_i	mean (or individual) energy of the ith nuclear transition	Radionuclide data
Y_i	the yield, i.e. the number of ith nuclear transitions per nuclear transformation (number of emitted particles or photons per decay)	

Absorbed fractions and S values and are calculated by Monte Carlo radiation-energy transport calculations.

Absorbed fractions and *S* values



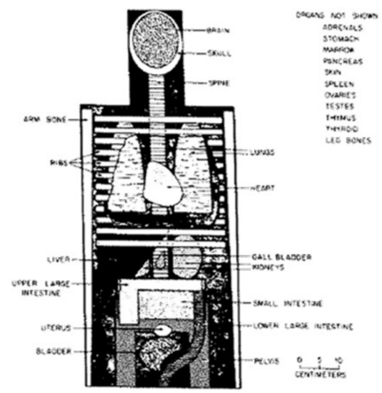


FIG. B-2. Anterior view of the principal organs in the head and trunk of the phantom.

minus sign the right. The total volume of both legs is 20,776 cm³ and the mass is 21,901 g. It is apparent that the leg region does not join smoothly to the trunk region, because the legs protrude slightly beyond the ellipse defining the trunk in the plane z=0.

The genitalia (male) of the phantom consist of the region specified by

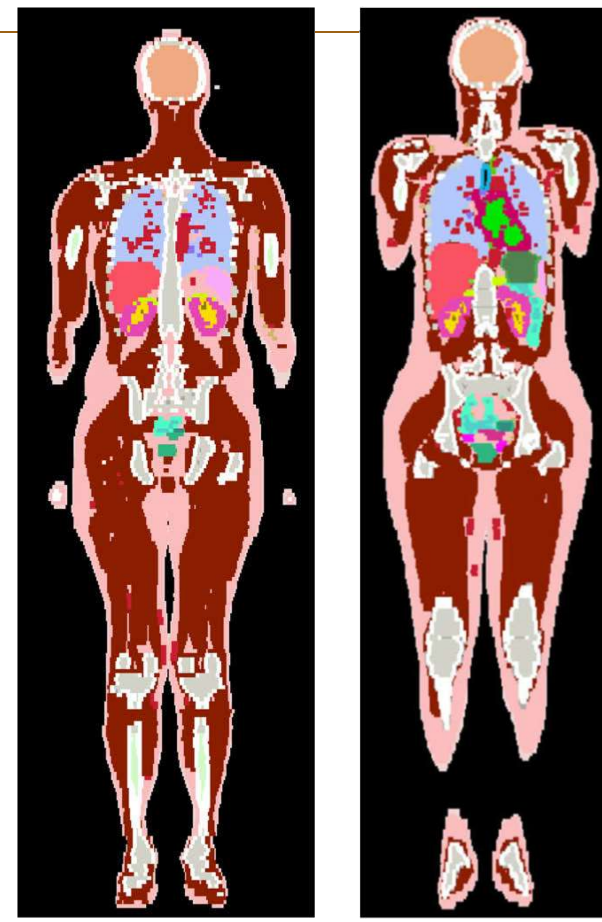
$$-4.8 \leqq z \leqq 0, \quad -\left(10+\frac{z}{10}\right) \leqq x \leqq 10+\frac{z}{10},$$

$$-\left(10+\frac{z}{10}\right) \leqq y \leqq 0,$$

and

$$\left[x \pm \left(10+\frac{z}{10}\right)\right]^2 + y^2 \geqq \left(10+\frac{z}{10}\right)^2,$$

and this last inequality must hold for either choice of



1975: MIRD phamplet 5

ICRP report 110, 2009

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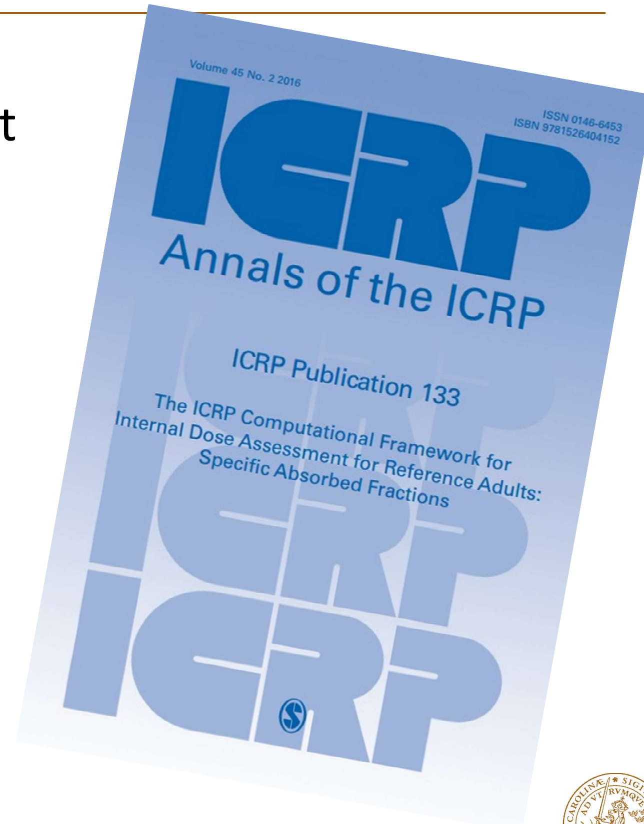
ICRP and IDAC-Dose 2.1

- ICRP Publication 133: ICRP, 2016. The ICRP computational framework for internal dose assessment for reference adults: specific absorbed fractions. ICRP Publication 133. Ann. ICRP 45(2), 1–74.
- IDAC-Dose2.1, developed based on the ICRP specific absorbed fractions and computational framework of internal dose assessment given for reference adults in ICRP Publication 133.
- Free-ware: http://www.idac-dose.org/



- *Andersson M., Johansson L., Eckerman K. and Mattsson S. IDAC-Dose 2.1, an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms. EJNMMI Research 2017*

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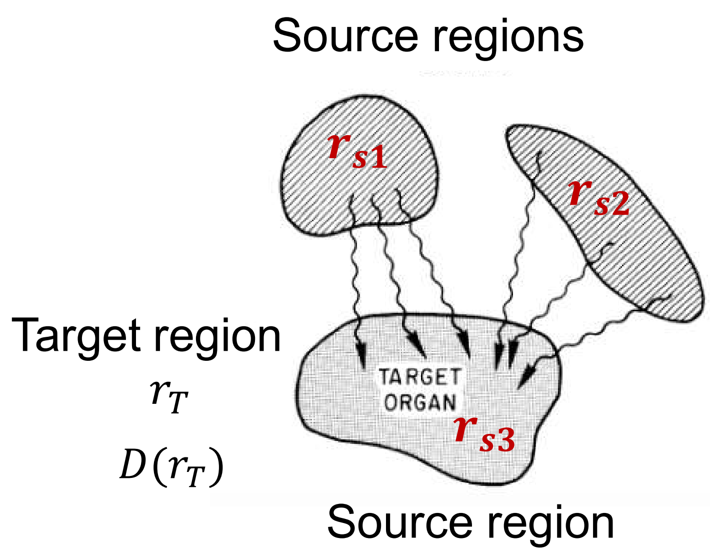
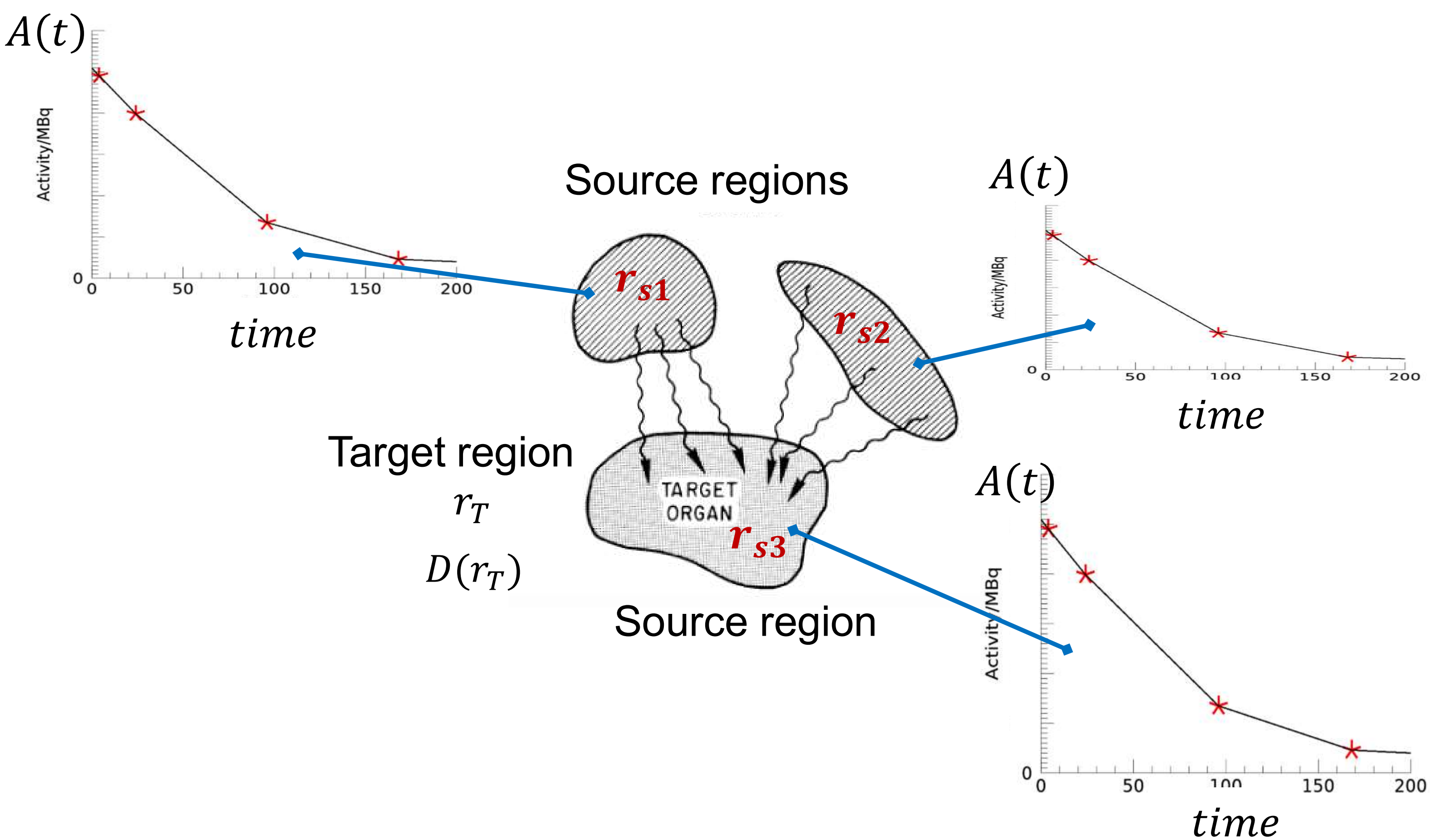
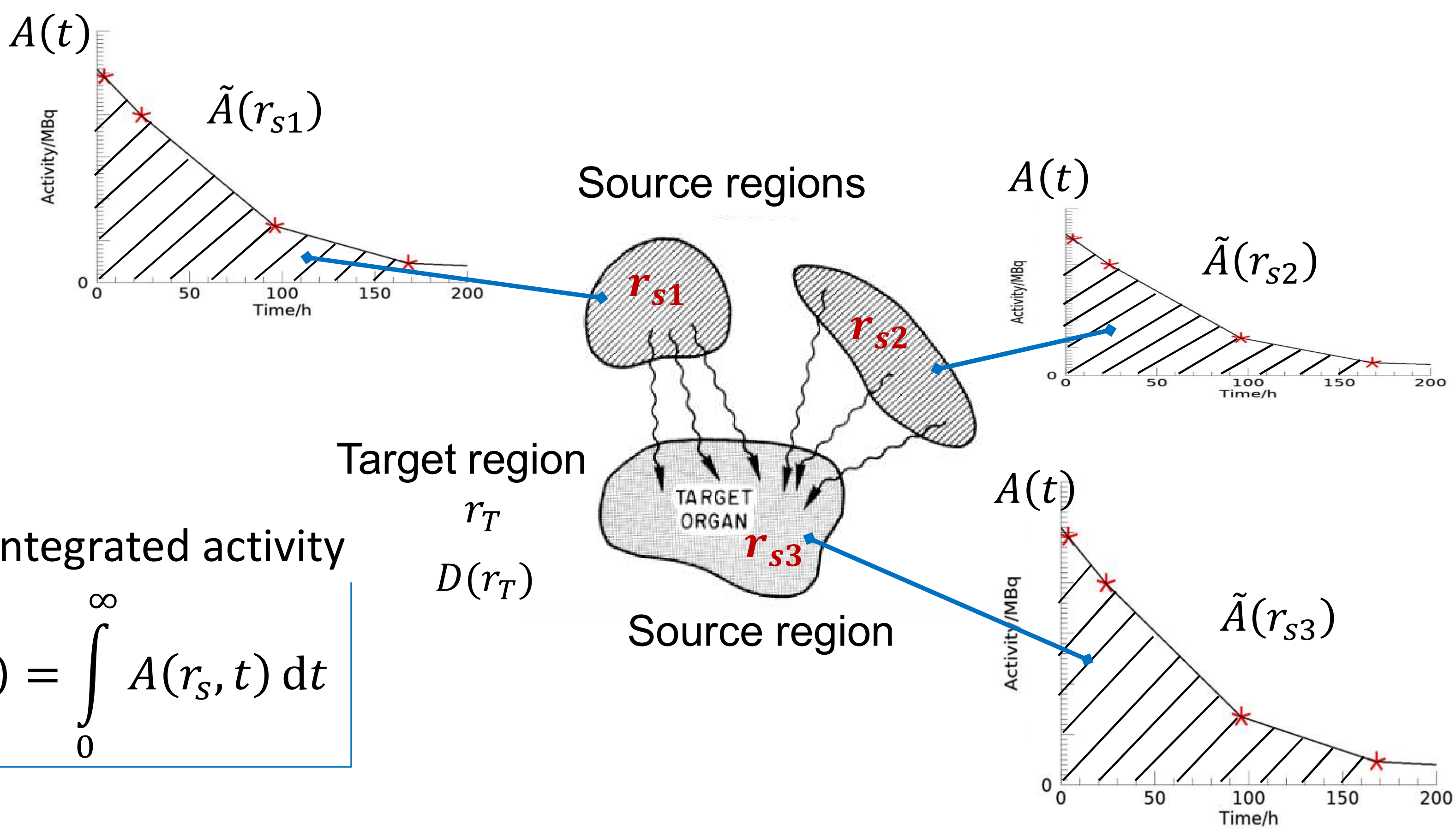
The MIRD formalism for internal dosimetry



The MIRD formalism for internal dosimetry



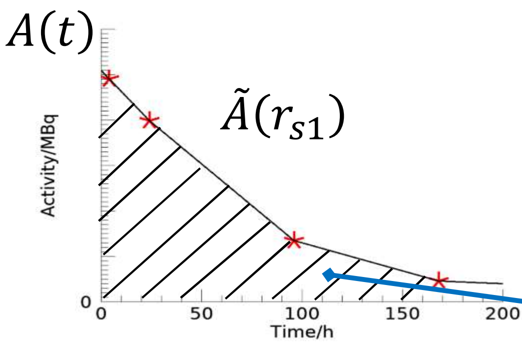
The MIRD formalism for internal dosimetry

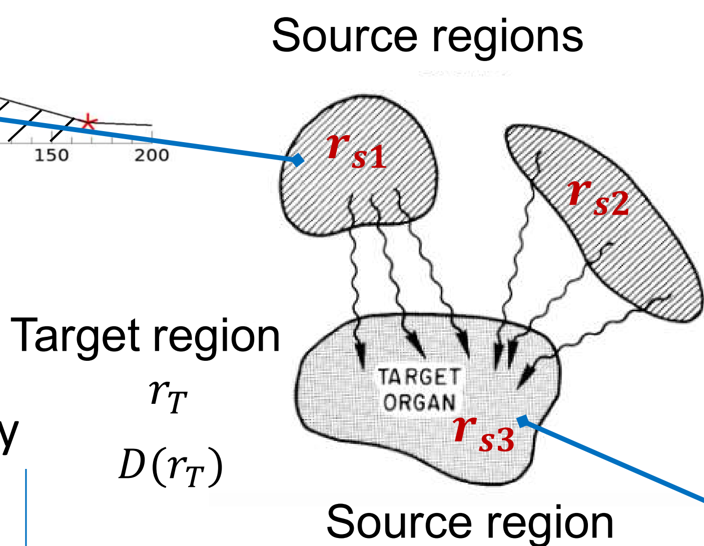


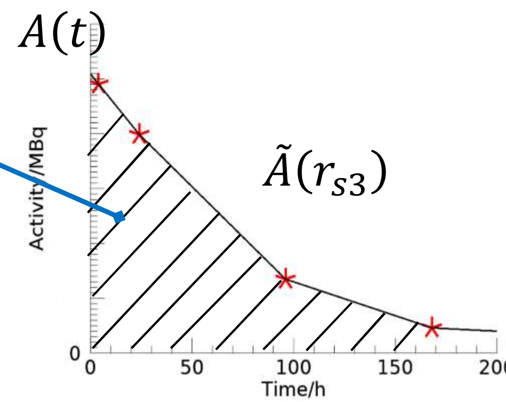
Time-integrated activity

$$\tilde{A}(r_s) = \int_0^\infty A(r_s, t)\, \mathrm{d}t$$

The MIRD formalism for internal dosimetry







$$D(r_T) = \sum_{r_S} \tilde{A}(r_s)\ S(r_T \leftarrow r_S)$$

Total number of radioactive decays in source region r_S

mean absorbed dose to r_T per radioactive decay in source region r_S

Time-integrated activity

$$\tilde{A}(r_s) = \int_0^\infty A(r_s, t)\, \mathrm{d}t$$

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Radionuclide therapy - Patient-specific internal dosimetry

- Absorbed doses range between one, tenths, or hundreds of Gy.
- Absorbed doses vary between individual patients.
- The primary objective is to understand the risks of deterministic tissue reactions and the probability of disease control for the individual patient.

- Patient-specific dosimetry requires patient-specific estimates of
  - Time-integrated activity in relevant source regions
  - S values

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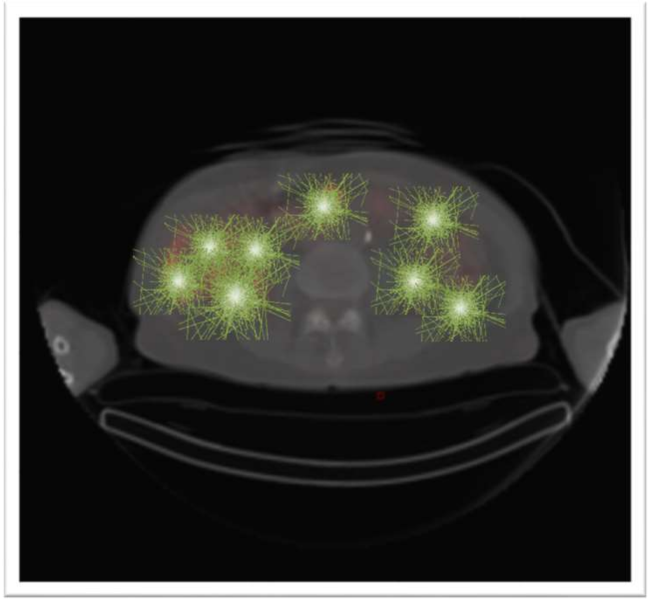
Patient-specific *S* values

- Mass scaling of precompiled S values, between reference phantom mass and patient tissue mass,
  for particle radiation; $S(r_T \leftarrow r_S)_{pa} = \frac{M_{ref}(r_T)}{M_{pat}(r_T)} \cdot S(r_T \leftarrow r_S)_{ref}$

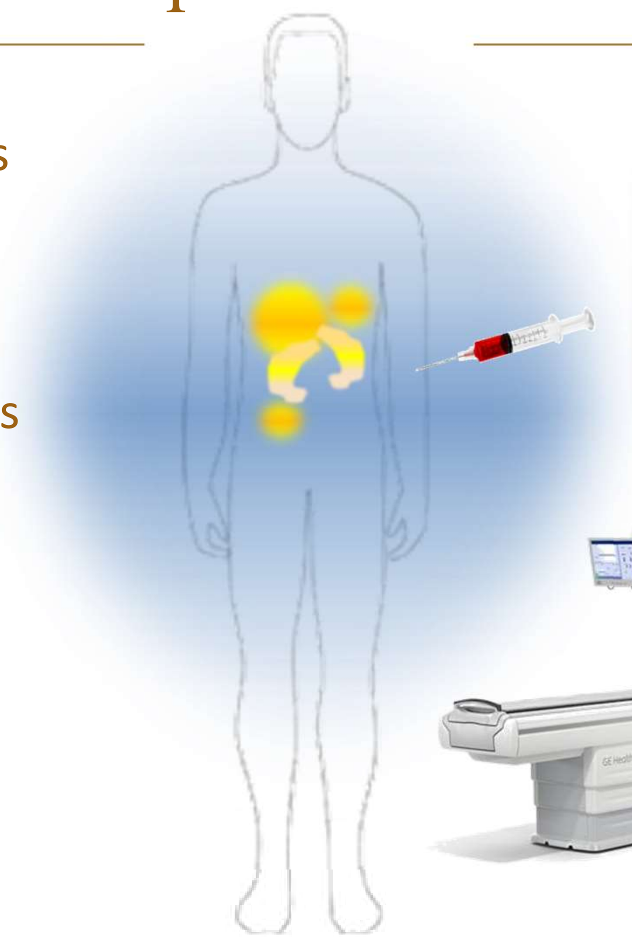
- Calculation in the voxel geometry defined by the patient images
  - Local deposition of emitted energy in the same voxel where it is emitted
  - Monte-Carlo based radiation-energy transport calculation

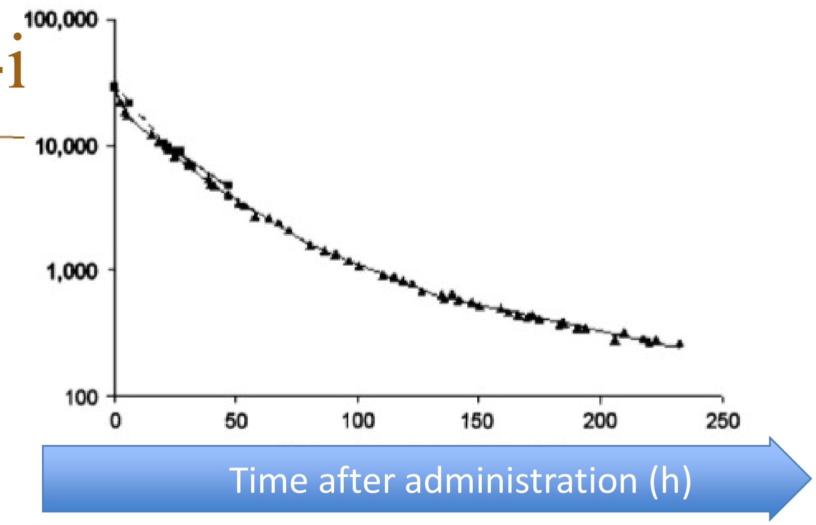


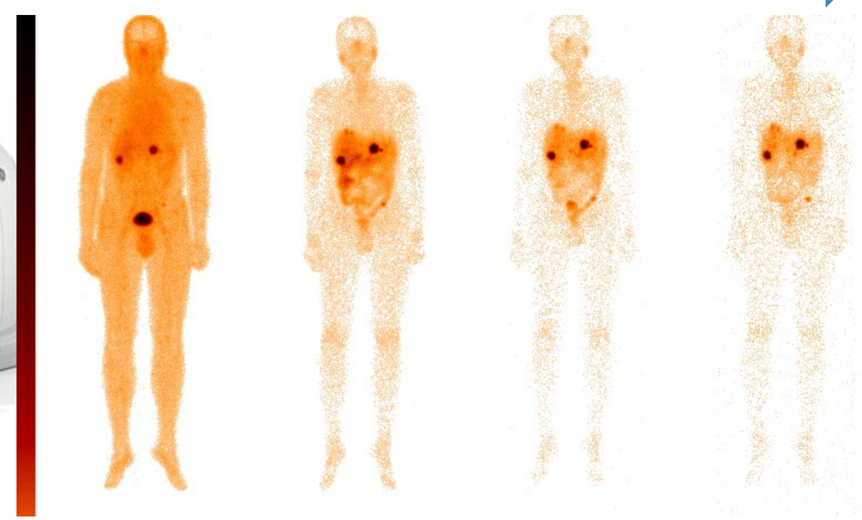
Patient-specific estimate of the time-i

photons

particles
(β^-, α)







Examples of dosimetry-guided radionuclide therapies, and metrological techniques used

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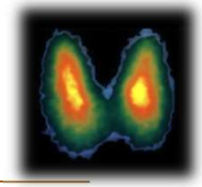
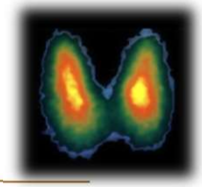
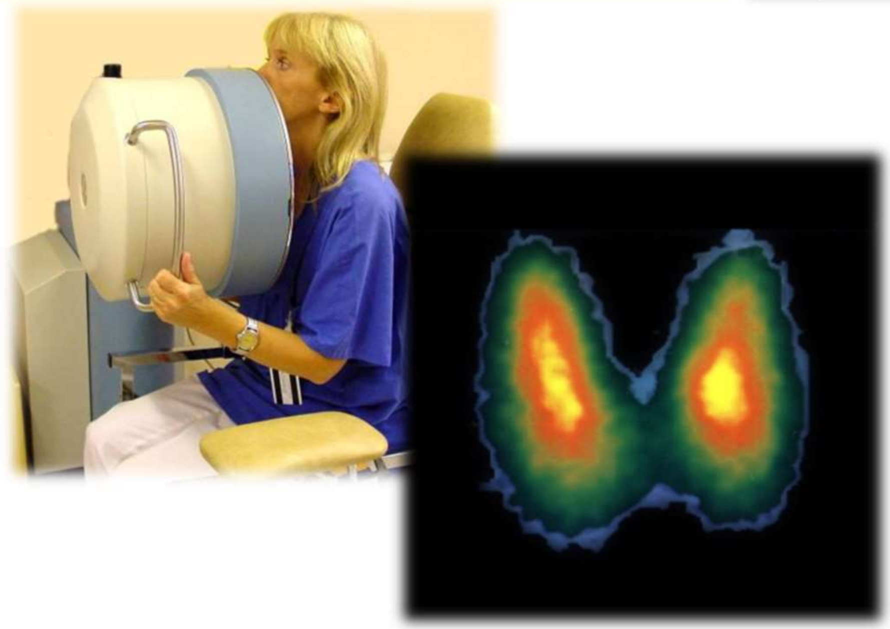
^{131}I-NaI treatment planning of benign thyroid diseases, probe activity measurements



131-I	
Half-life	8.02 d
Decay	β^-
Max energy	606 keV
Gamma Energy (yield)	364 keV (81%)

^{131}I-NaI treatment planning of benign thyroid diseases, probe activity measurements





- Tracer administration of ^{131}I
- measurements (detector count rate) on different days

- Known amount of ^{131}I inserted in neck phantom, calibration Count rate to activity

Thyroid mass from scintigraphy or ultrasound, -> $M_{pat}(thyr)$

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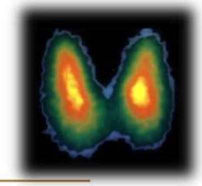
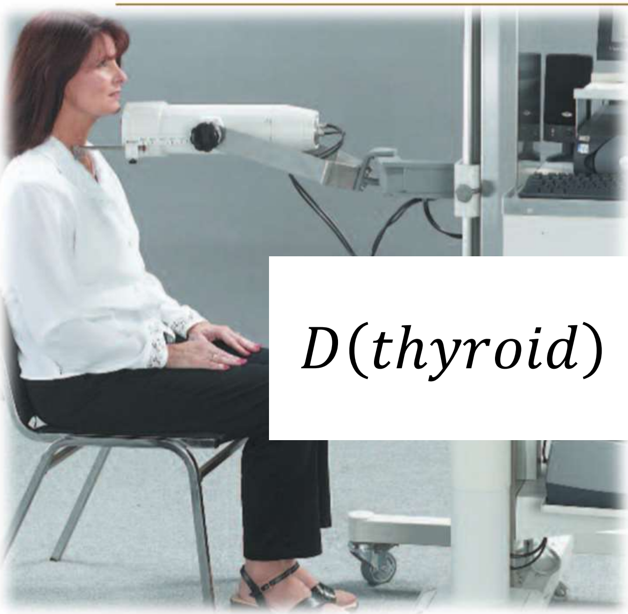
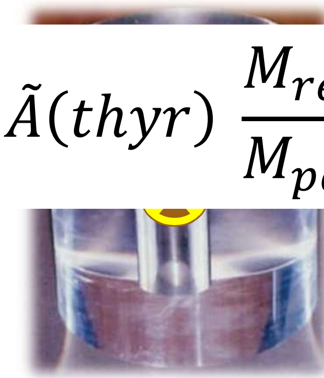
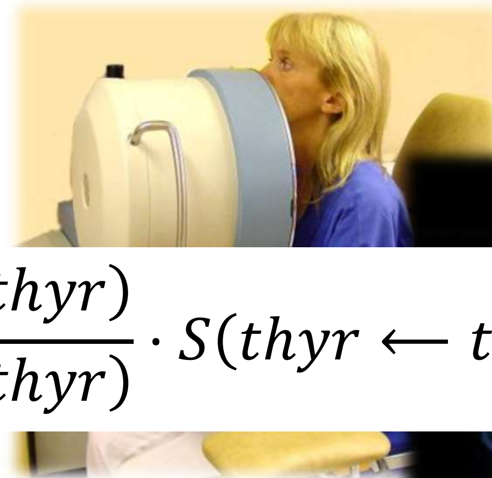
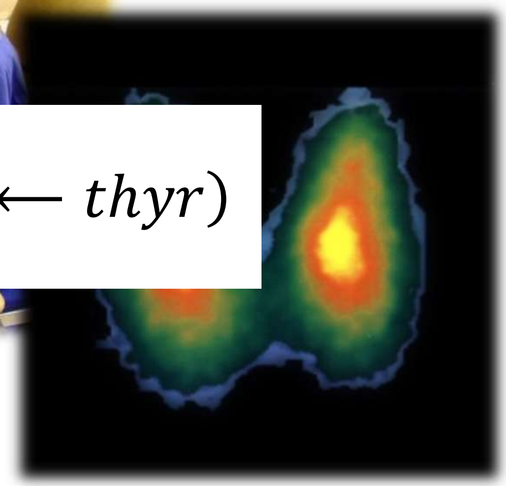
^{131}I-NaI treatment planning of benign thyroid diseases, probe activity measurements











$$D(thyroid) = \tilde{A}(thyr)\,\frac{M_{ref}(thyr)}{M_{pat}(thyr)} \cdot S(thyr \leftarrow thyr)$$

- Tracer administration of ^{131}I
- measurements (detector count rate) on different days

- Known amount of ^{131}I inserted in neck phantom, calibration Count rate to activity

Thyroid mass from scintigraphy or ultrasound, -> $M_{pat}(thyr)$

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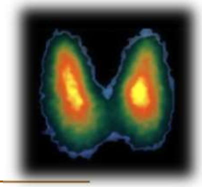
^{131}I-NaI treatment planning of benign thyroid diseases, probe activity measurements



Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-013-2387-x

GUIDELINES

EANM Dosimetry Committee Series on Standard Operational Procedures for Pre-Therapeutic Dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases

Heribert Hänscheid · Cristina Canzi · Wolfgang Eschner · Glenn Flux · Markus Luster · Lidia Strigari · Michael Lassmann

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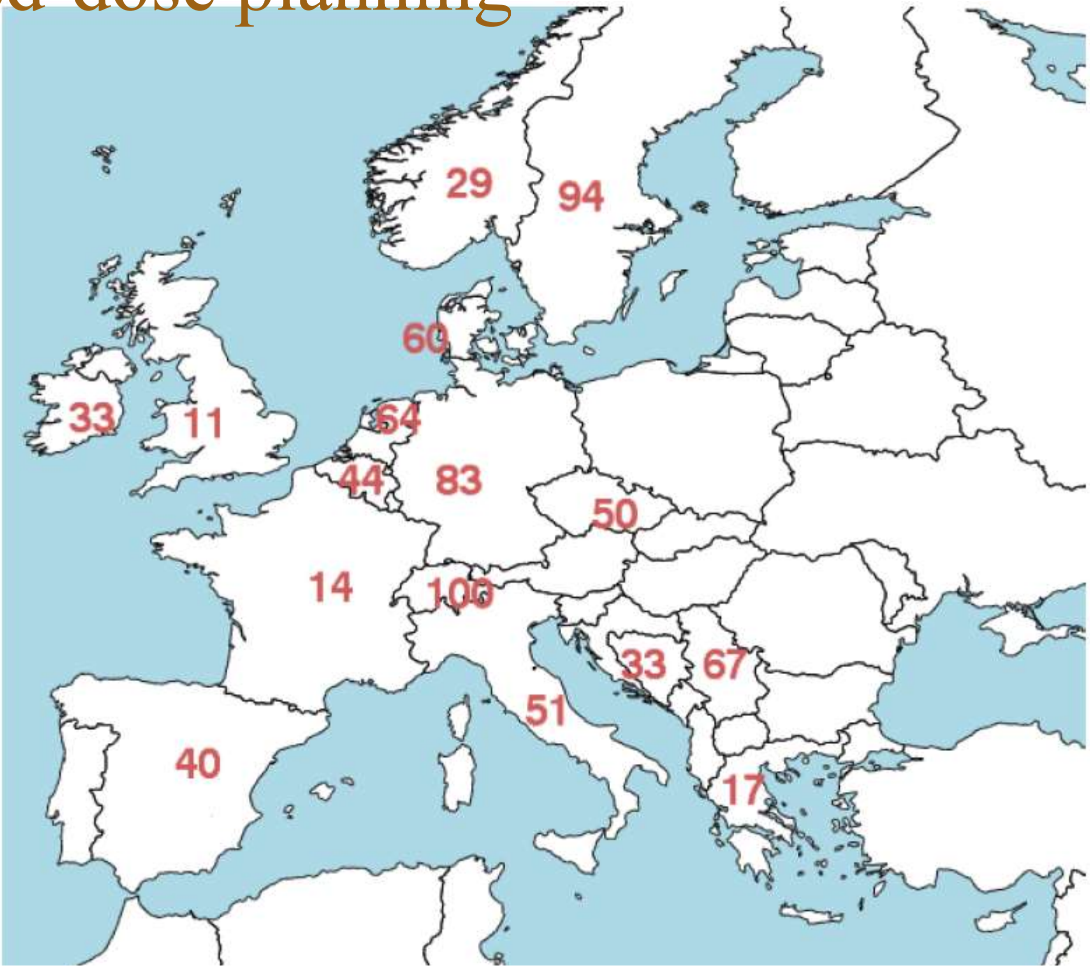
^{131}I-NaI treatment planning of benign thyroid diseases Frequency of absorbed-dose planning

Survey on 2015
% responders stating
Always or Majority
on the question
Is the absorbed dose individually planned for each patient?

More on the survey later in the presentation



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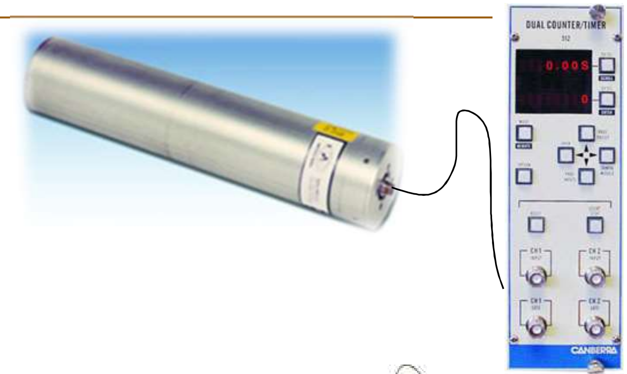
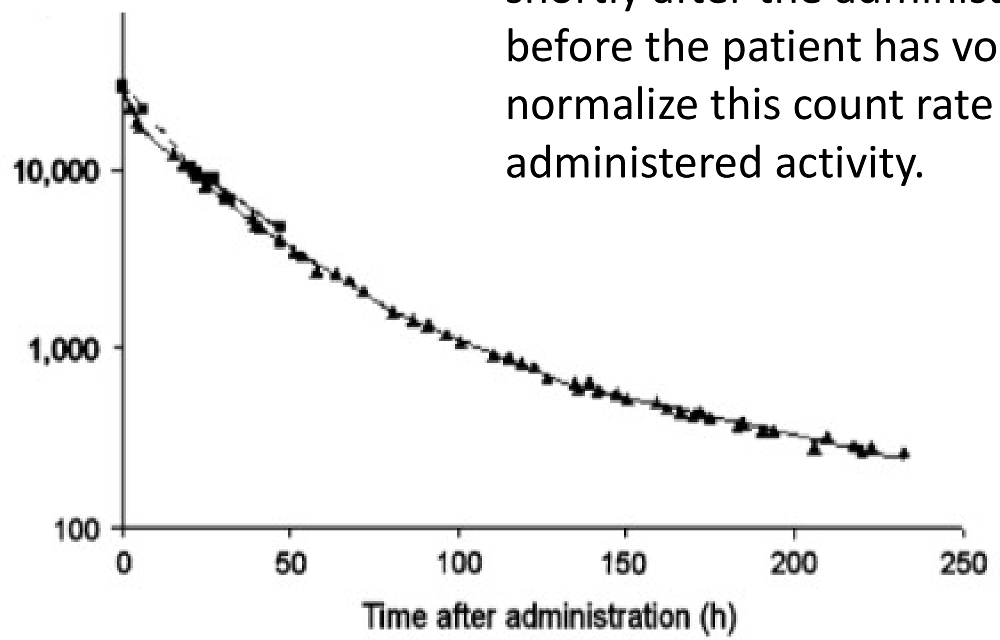
^{131}I-mIBG – neuroblastoma
Activity measurements with probe or whole-body scintigraphy

- The high yield of photon emission for ^{131}I results in an exposure of the whole body, including the radiosensitive bone marrow
- Normal-organ limit: 2 Gy to whole-body, as surrogate for red bone marrow.
- Whole-body measurements

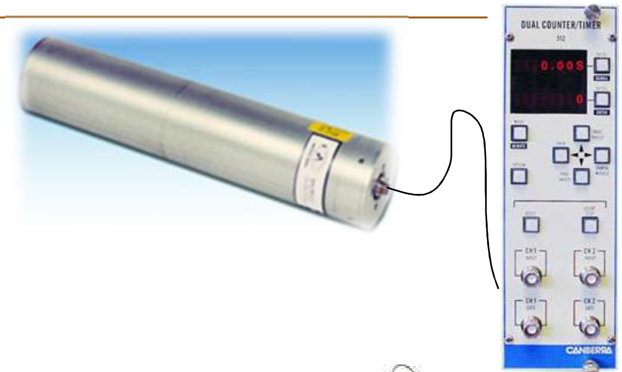


^{131}I-mIBG – neuroblastoma
Activity measurements with probe or whole-body scintigraphy

Whole-body count rate -> Whole-body Activity (MBq)

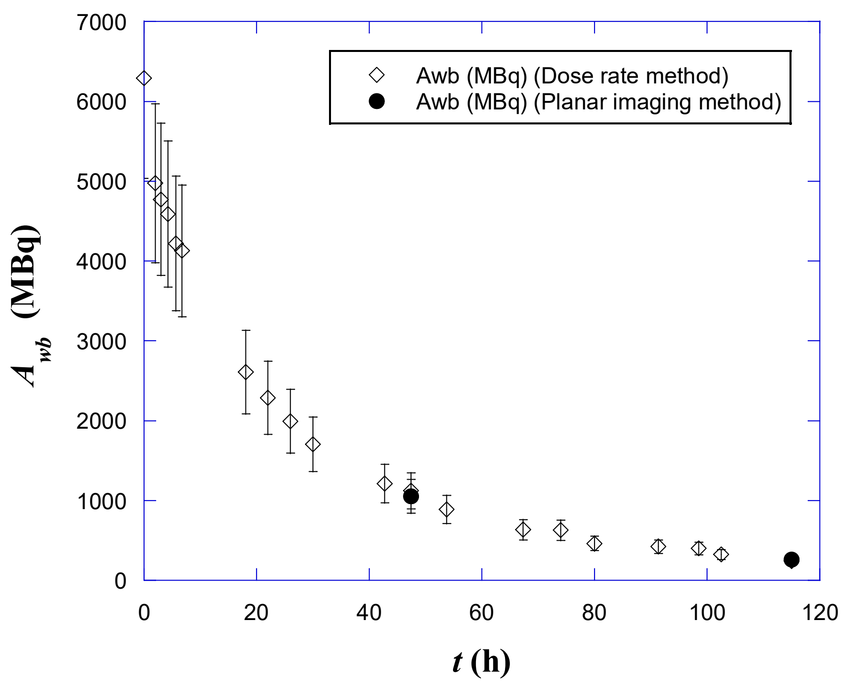


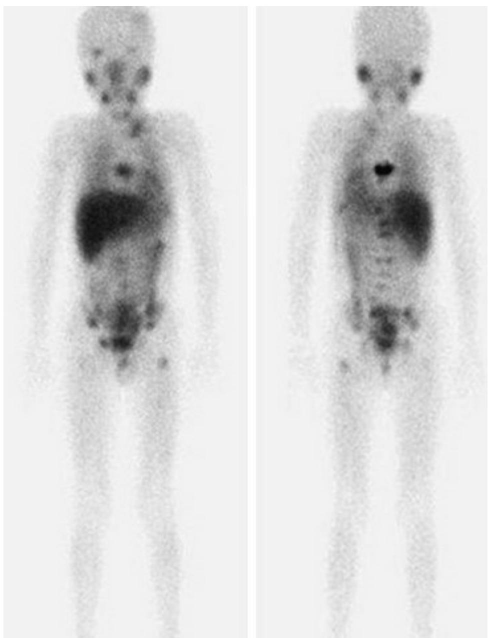
Calibration: A first measurement shortly after the administration, before the patient has voided, normalize this count rate to the administered activity.



Buckley et al, JNM 2009, 50; 1518 - 1524

^{131}I-mIBG – neuroblastoma
Activity measurements with probe or whole-body scintigraphy





$$D(wb) = \tilde{A}(wb)\,\frac{M_{ref}(wb)}{M_{pat}(wb)} \cdot S(wb \leftarrow wb)$$

Minguez et al, Medical Physics 42, 3969 (2015)

^{131}I-mIBG treatment of neuroblastoma (myeloablative)

Treatment to whole-body absorbed dose of 4 Gy, given in 2 treatment cycles, including bone-marrow stem-cell support

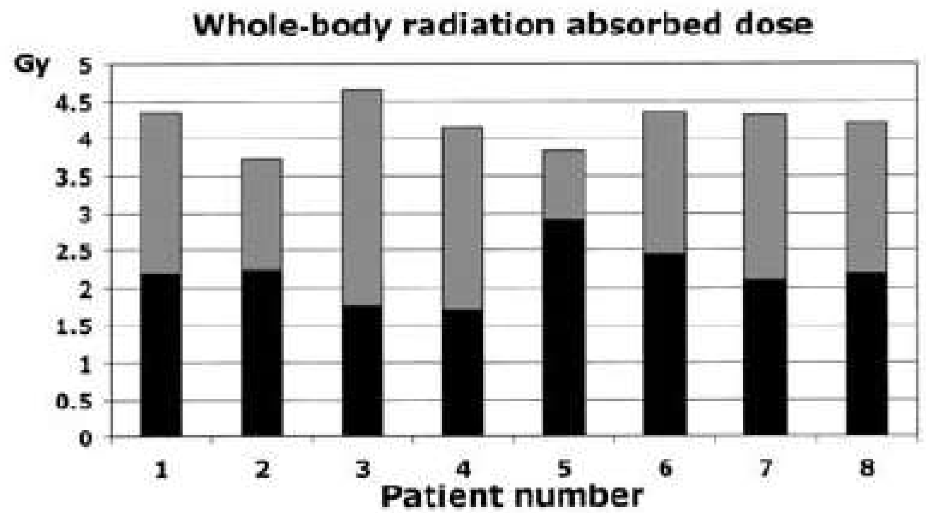


Figure 2. Whole-body dosimetry data following first (lower part of each bar) and second (upper part of each bar) administrations of ^{131}I-mIBG.

Gaze et al, CBR 2005, vol 20; no 2

Treatment of thyroid cancer ^{131}I-NaI

- Normal-organ limit: 2 Gy to blood (as surrogate for bone marrow)
- Estimated using whole-body measurements and blood sampling

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-008-0761-x

GUIDELINES

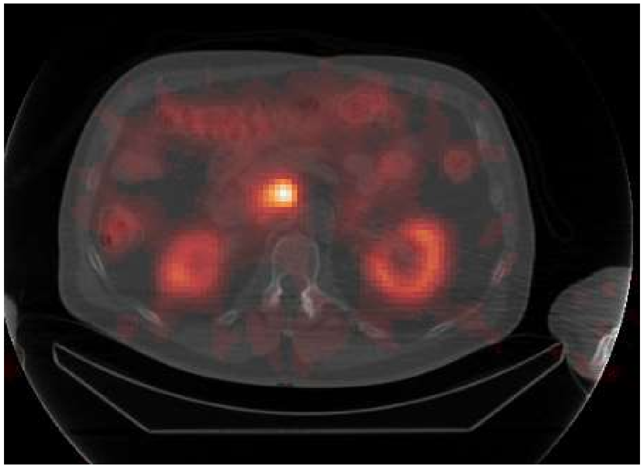
EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy

Michael Lassmann · Heribert Hänscheid ·
Carlo Chiesa · Cecilia Hindorf · Glenn Flux ·
Markus Luster

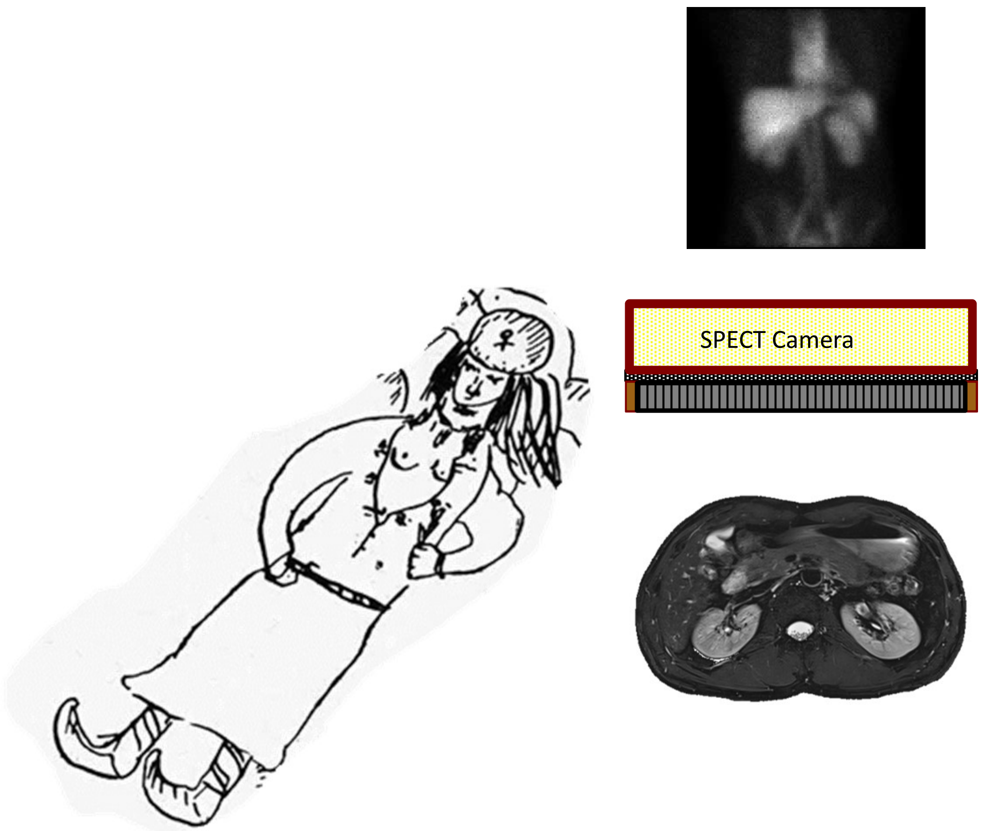
LUND UNIVERSITY

Dosimetry based on quantitative tomographic imaging

- SPECT/CT or PET/CT imaging
- Quantitative images with voxel values in unit of MBq or MBq/mL, at the time of image acquistion



Principle of tomographic measurement - SPECT

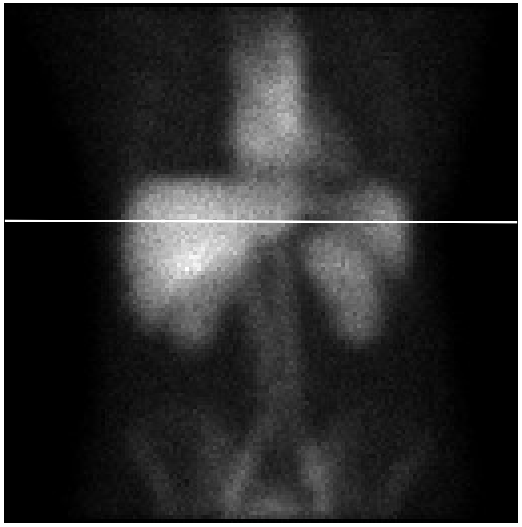


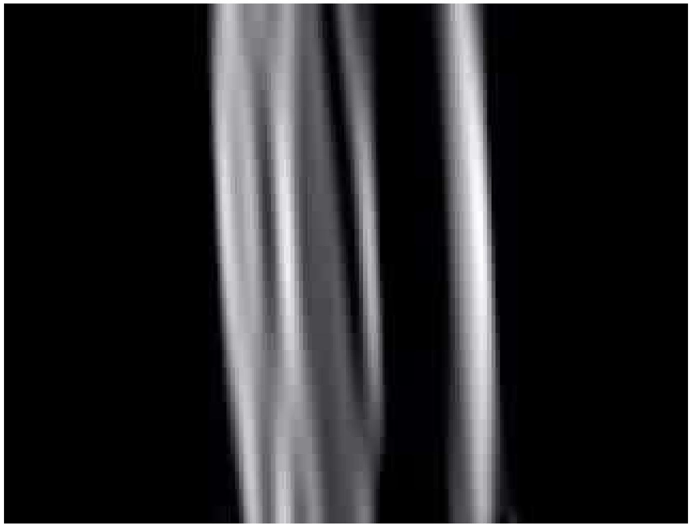
One measured projection image for each rotation angle of the camera head.

The measured number of counts in the projection images depend on the number of emitted photons.

Tomographic reconstruction

- For quantitative SPECT/CT and PET/CT imaging, a key element is an accurate tomographic reconstruction
- Reconstruction is a mathematical process in which the 3D source distribution is estimated from the projection images.





Photon attenuation, scatter and collimator penetration

- Attenuation in body tissues, decreases count rate.
- Scattering and penetration of collimator septa add false counts
  - Scattered in the patient
  - Interacted in the collimator
  - Penetrated the collimator
  - Back-scattered in the camera housing
- Modern iterative reconstruction methods embed compensations for attenuation and scatter

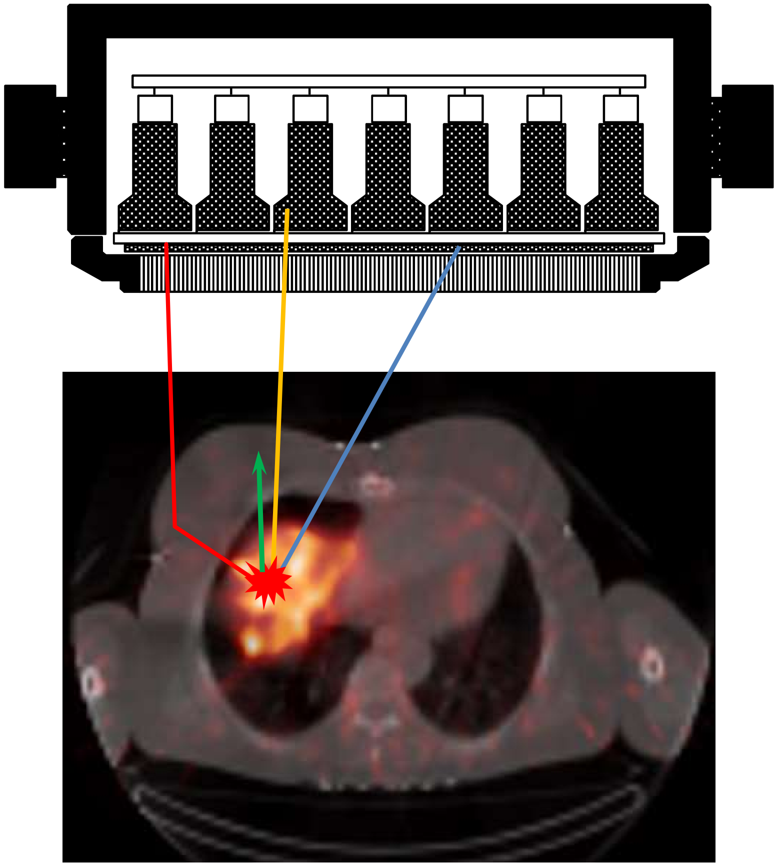


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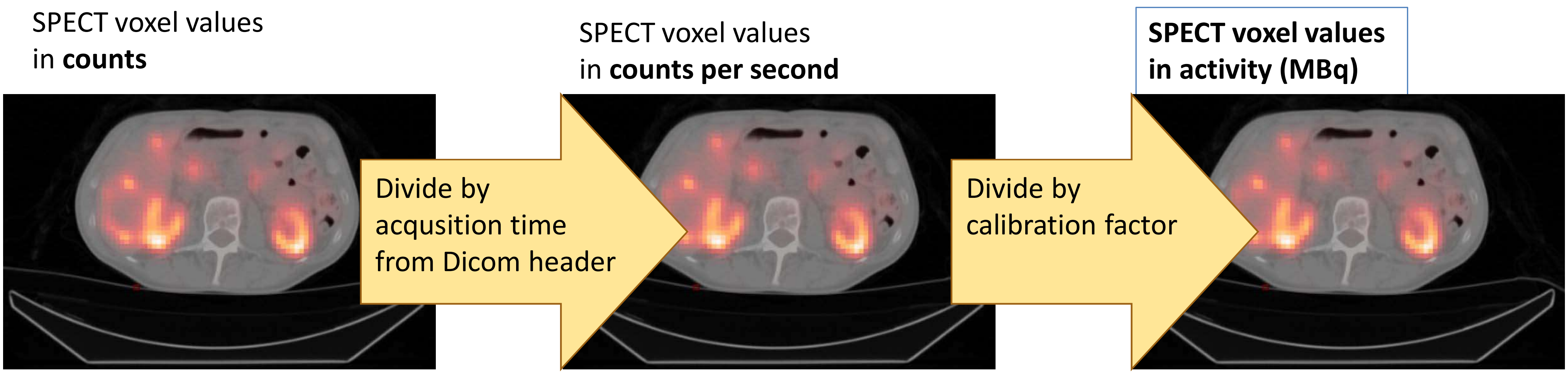
Image calibration factor

- For parallel-hole collimators the sensitivity is independent of the source-collimator distance, and approximately constant across the SPECT image.

- A single calibration factor can be used to convert from count rate to activity for all image values.

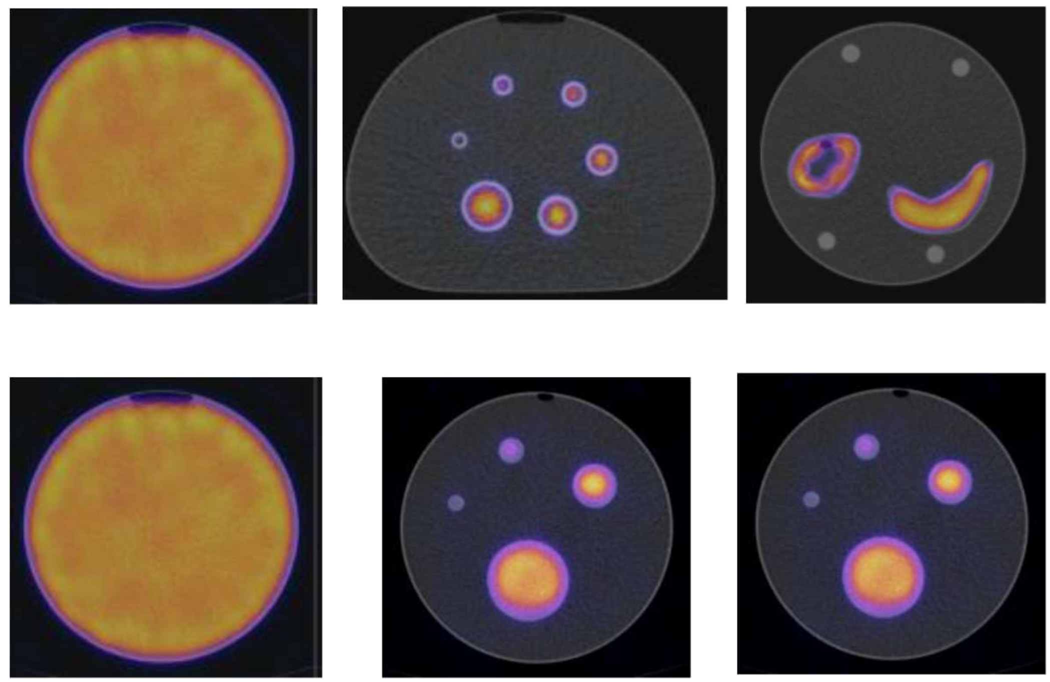


MRTDosimetry

http://mrtdosimetry-empir.eu/

- Calibration protocol and comparison excersizes:
- ^{177}Lu
- ^{133}Ba / ^{131}I

Calibration Corrections Tests



131I 131I 133Ba

The activity meter as a reference instrument

- The activity meter (dose calibrator) is used to
  - determine the injected activity to patients
  - calibrate instruments used for dosimetry.

- Accurate measurement of the activity in a solution is the starting point for treatments and dosimetry calculations.

- **Traceability** to standard laboratories in activity measurements is key;
  - ...traceability also for therapeutic radionuclides, such as ^{131}I, ^{177}Lu, or ^{90}Y.

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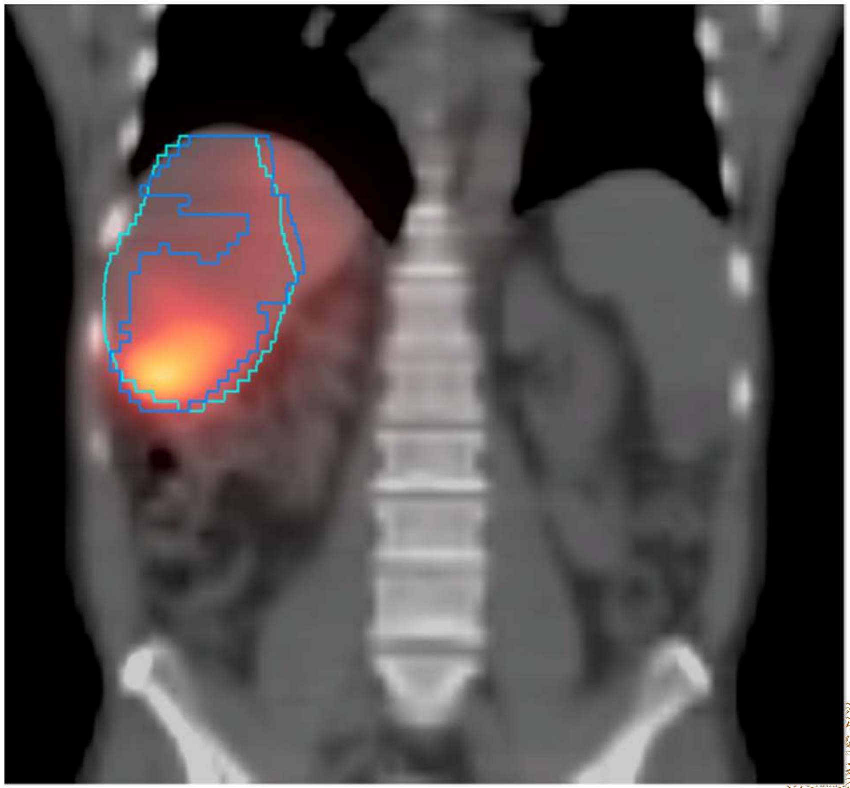
Examples:
^{90}Y-microsphere treatments in the liver

Half-life	2.67 d
Decay	β^-
beta energy (yield)	2297 keV (100%)
Positron yield	0.00638%

- Intra-arterially administered ^{90}Y-loaded microspheres
- Treatment of primary liver cancer and metastases in the liver
- Selection principle: different routes of blood supply to healthy liver tissue versus tumours



Bastiaannet et al. EJNMMI Physics (2018) 5:22

^{90}Y-microsphere treatments in the liver

- Need to monitor:
  - possible exrahepatic shunt (lungs)
  - mean absorbed dose to normal liver
  - mean absorbed dose to tumors

- Dose planning by ^{99m}Tc-MAA SPECT/CT

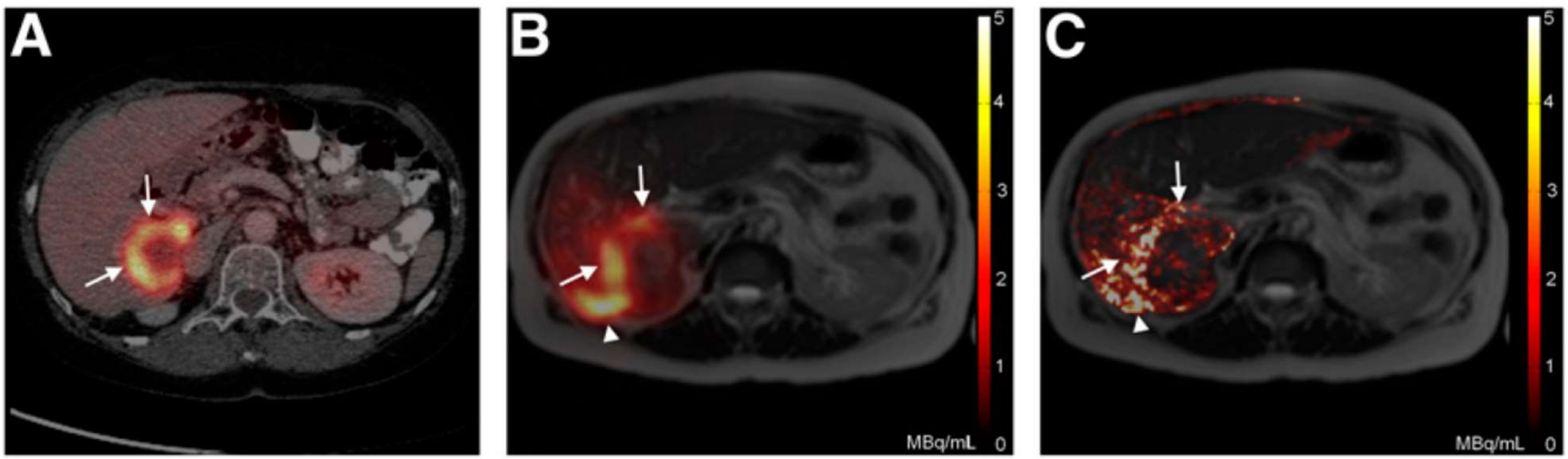
- Therapy imaging with ^{90}Y-bremsstrahlung SPECT/CT, or
  ^{90}Y-PET/CT

$$D(voxel) = \frac{\tilde{A}(vx) \cdot E_{90Y}}{M(vx)}$$

Courtesy of Dr. Carlo Chiesa, Instituto Tumori, Milan

^{166}Ho-microspheres in the liver

- Scout dose of ^{166}Ho-microspheres and SPECT prior to therapy administration
- Paramagnetic particles allow for MR imaging, in addition to SPECT/CT



Baseline 18FDG PET   166Ho SPECT on MR   166Ho MR

Smits et al, J Nucl Med 2013; 54:2093–2100

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^{177}Lu-DOTATATE peptide receptor radiotherapy

Half-life	6.65 d
Decay	b^{-}
Max beta energy	498 keV
Gamma Energy (yield)	113 keV (6%)
	208 keV (10%)

- Systemically administered ^{177}Lu- labelled somatostatin analogues
- Somatostain receptors highly expressed on neuroendocrine tumor cells
- Approved by EMA, Lutathera (AAA)

Sundlöv et al. EJNMMI Physics 2018 5:12
Sundlöv et al. EJNMMI. 2017;44:1480-9

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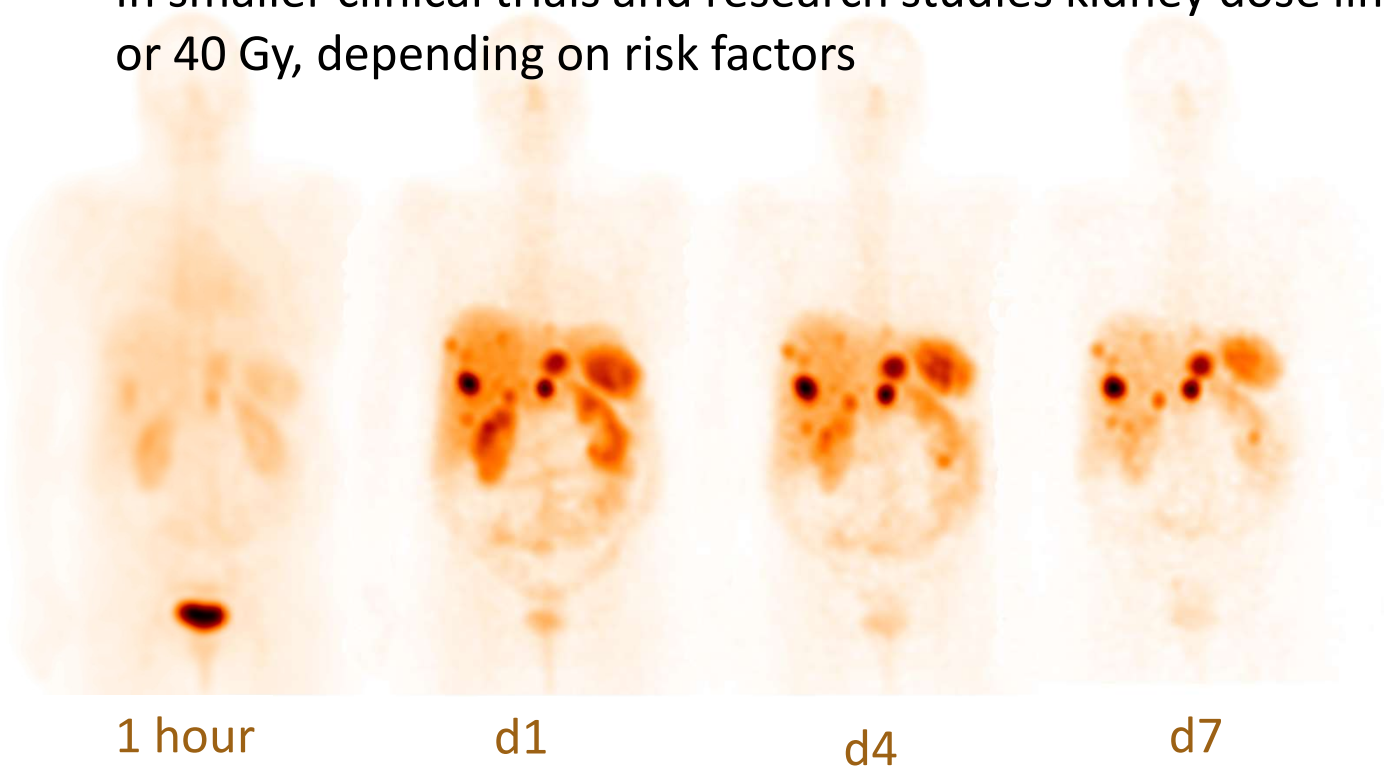
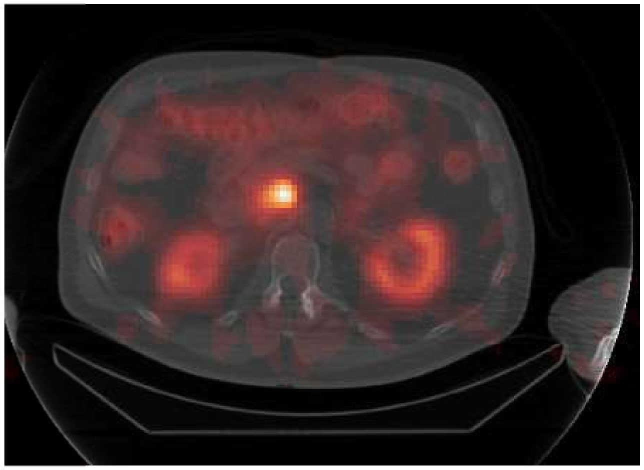
^{177}Lu-DOTATATE peptide receptor radiotherapy

Organ at risk: kidneys

In smaller clinical trials and research studies kidney dose limits of 23 Gy / 27 Gy or 40 Gy, depending on risk factors



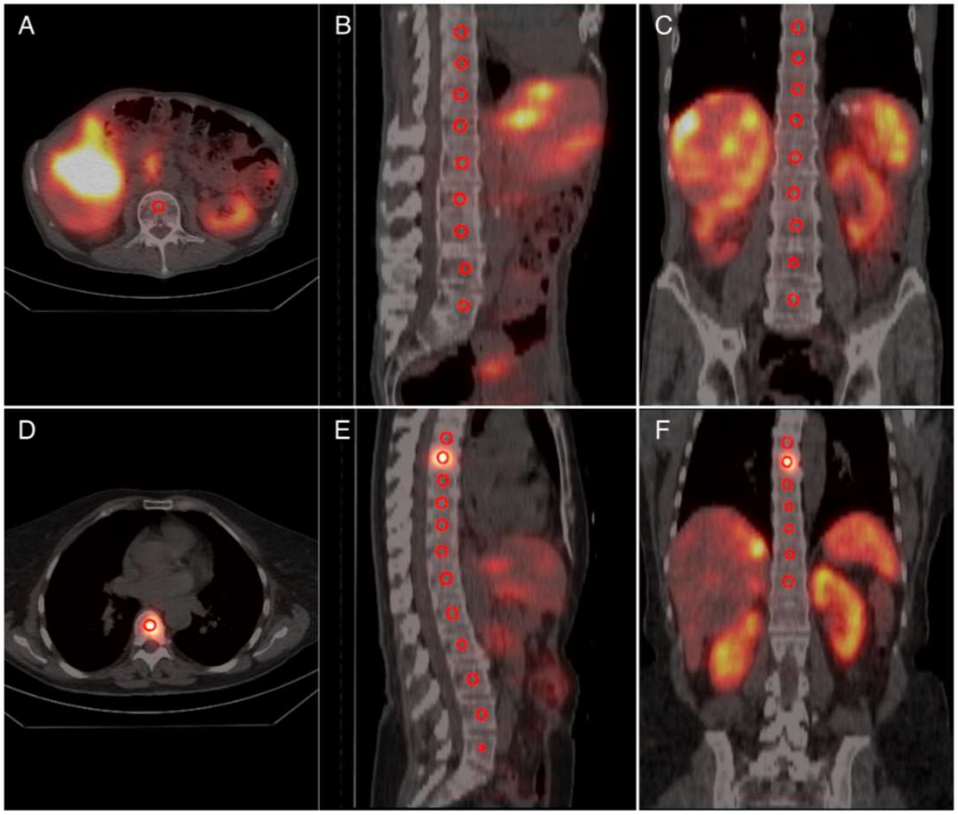


Bodei et al, EJNMMI, 2008
Sandström et al, JNM 2013
Bergsma et al, EJNMMI 2016
Sundlöv et al, EJNMMI, 2017

^{177}Lu-DOTATATE peptide receptor radiotherapy

- Organ at risk: bone marrow

- Image-based bone marrow dosimetry, due to possible metastases in the spine



Hagmarker et al, JNM, 2019, online first

Conclusions, thus far

- In many kinds of radionuclide therapy it is feasible to determine the absorbed doses given to individual patients.

- The choice of measurement technique for a particular kind of radionuclide therapy largely depends on
  - the emission spectrum of the radionuclide,
  - which tissue is considered to be at risk and for which dosimetry is needed,
  - the practical possibilities of undertaking repeated measurements after administration.

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Survey on the range of practice of radionuclide therapy procedures in 2015

– The EANM 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 Access

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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]

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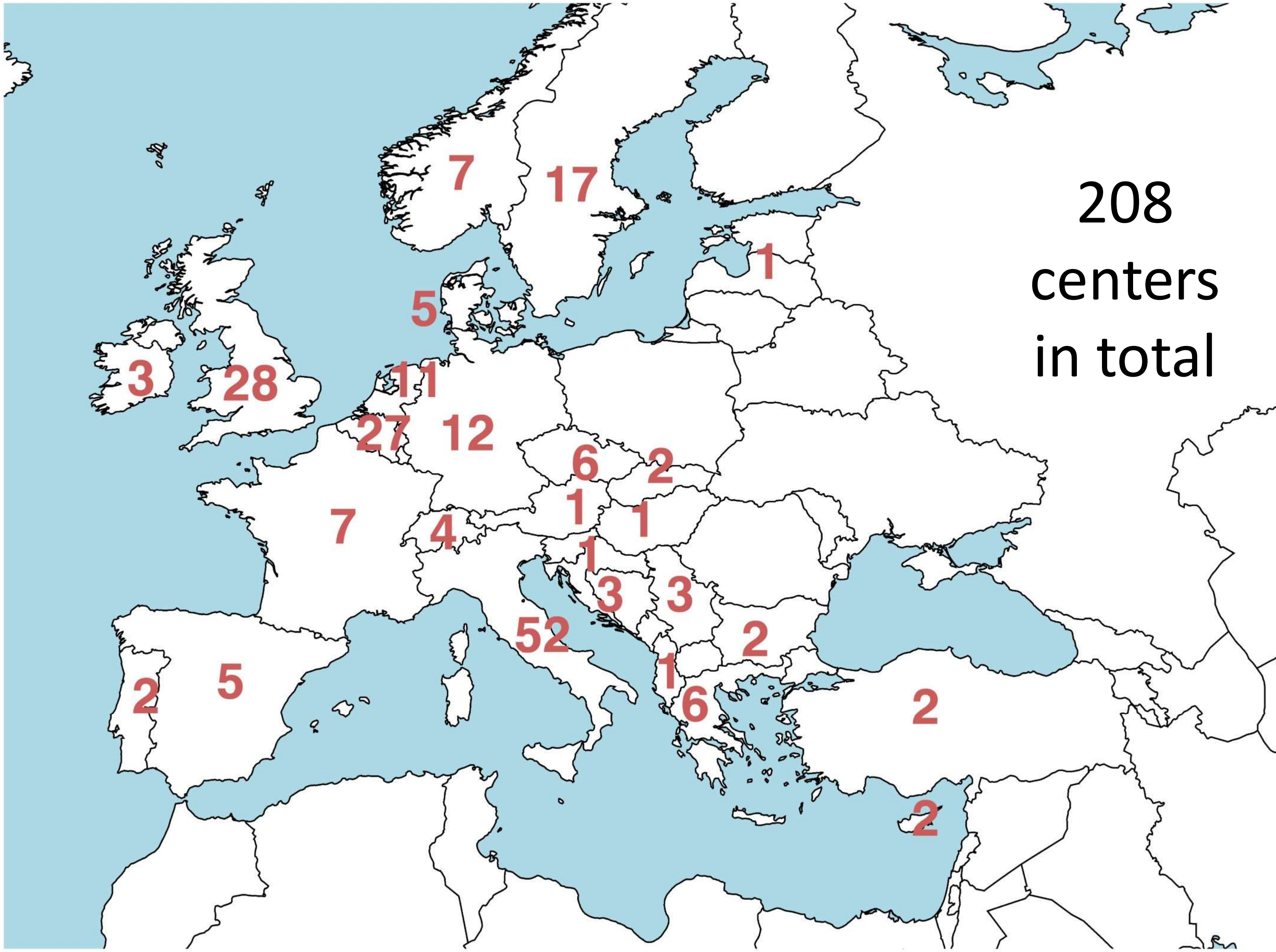
Responders:
208 centers across 26 countries

Estimated to represent ~20% of European centers administering radionuclide therapy



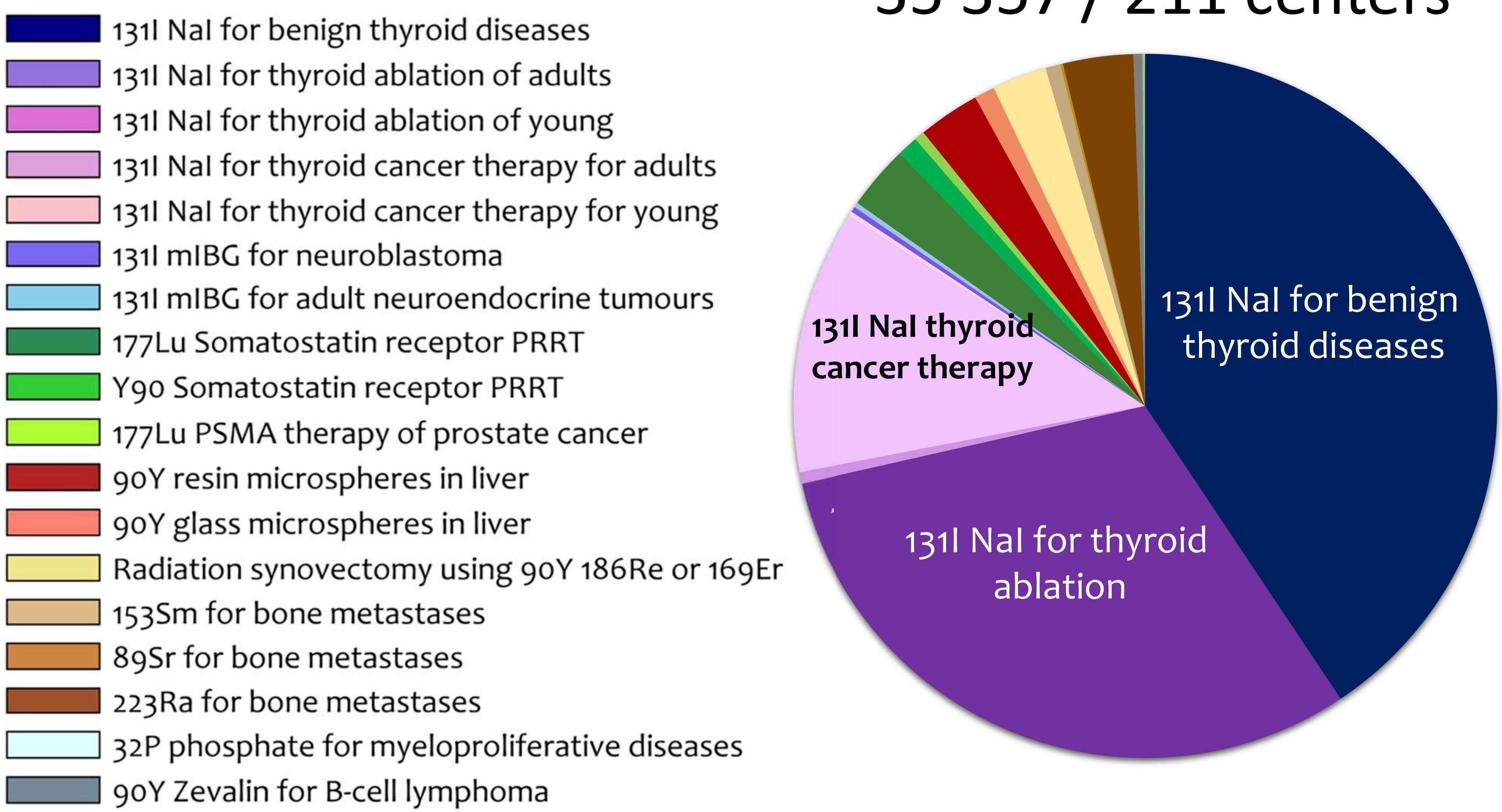
208 centers in total

Number of patients
treated in the year 2015 ?

Treated patients in 2015

18 explicitly considered radionuclide therapies

35 357 / 211 centers

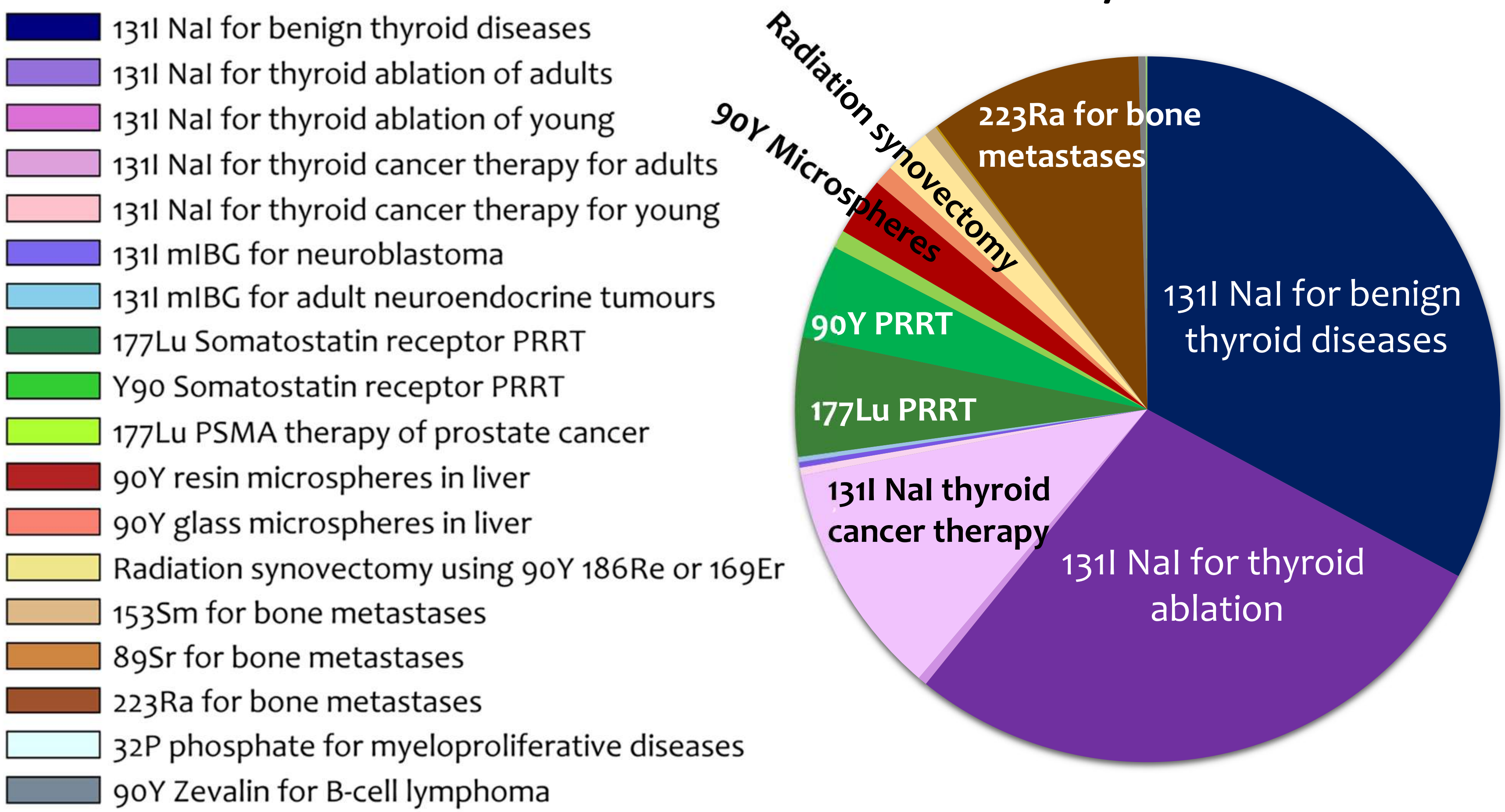


Number of treatments performed in 2015 ?

Number of treatments in 2015

18 explicitly considered radionuclide therapies

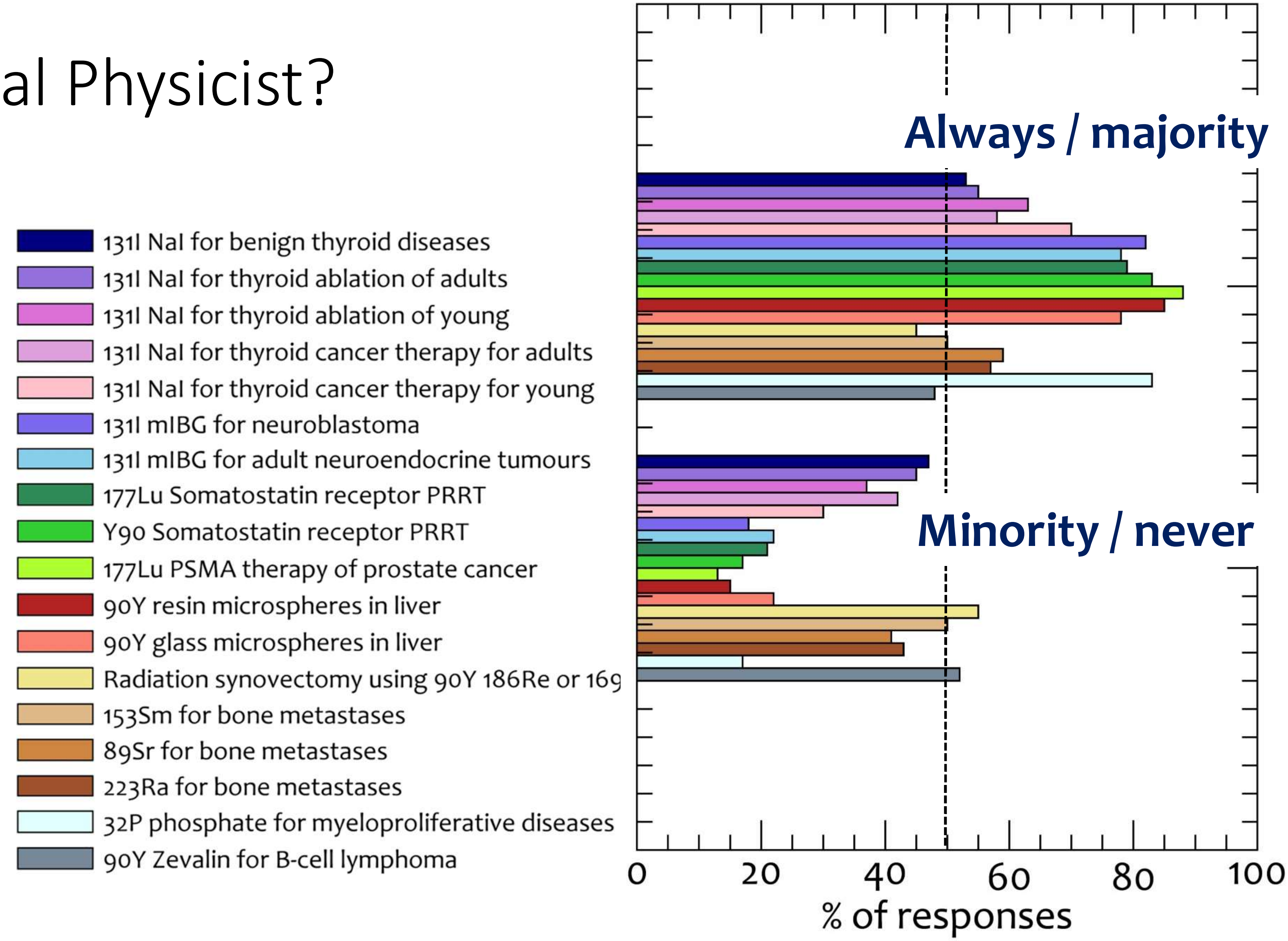
44 483 / 211 centers



Is a medical physicist involved in each treatment?

- Always
- Majority
- Minority
- Never

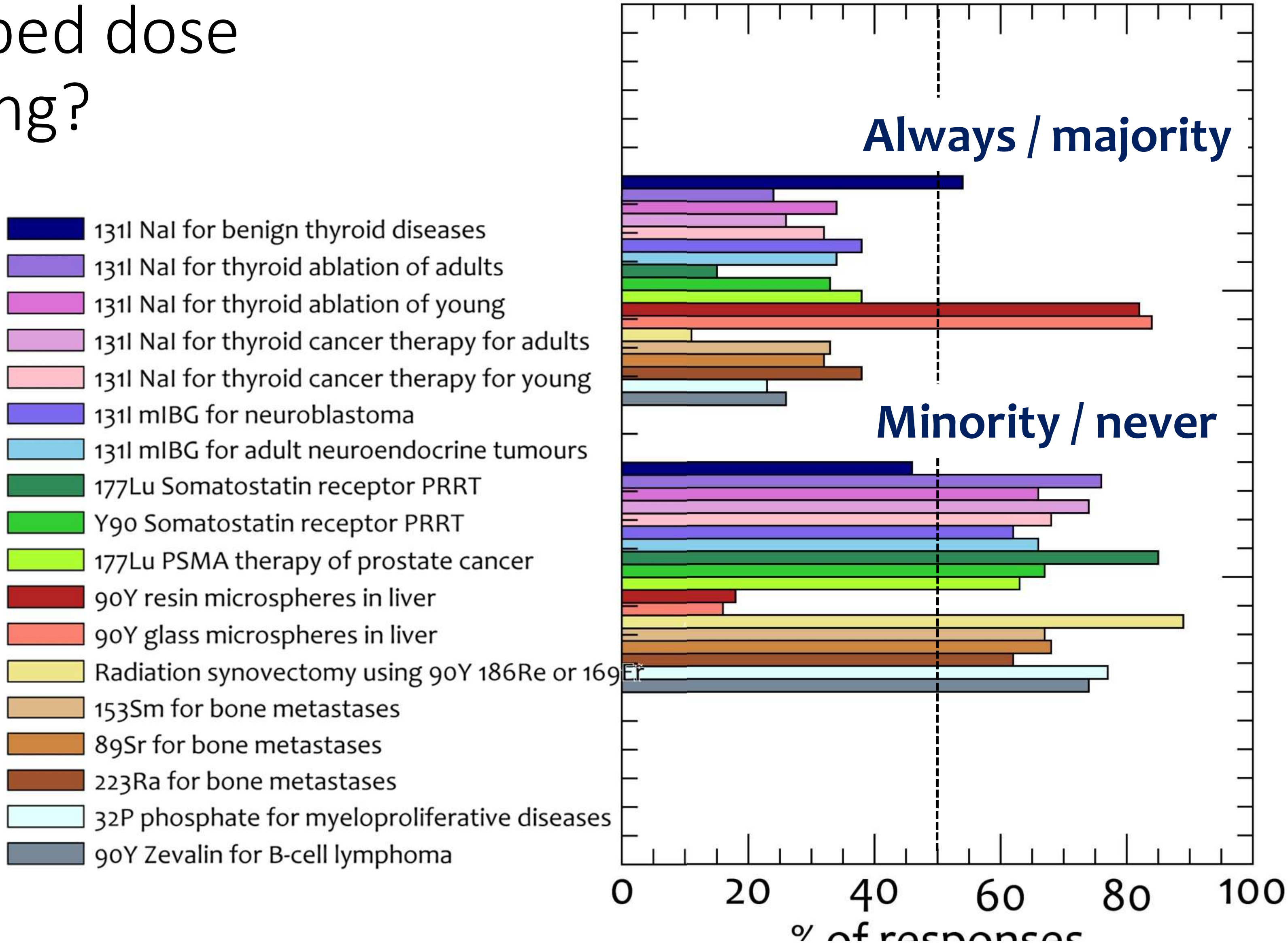
Medical Physicist?



Is the absorbed dose individually planned for each patient?

- Always
- Majority
- Minority
- Never

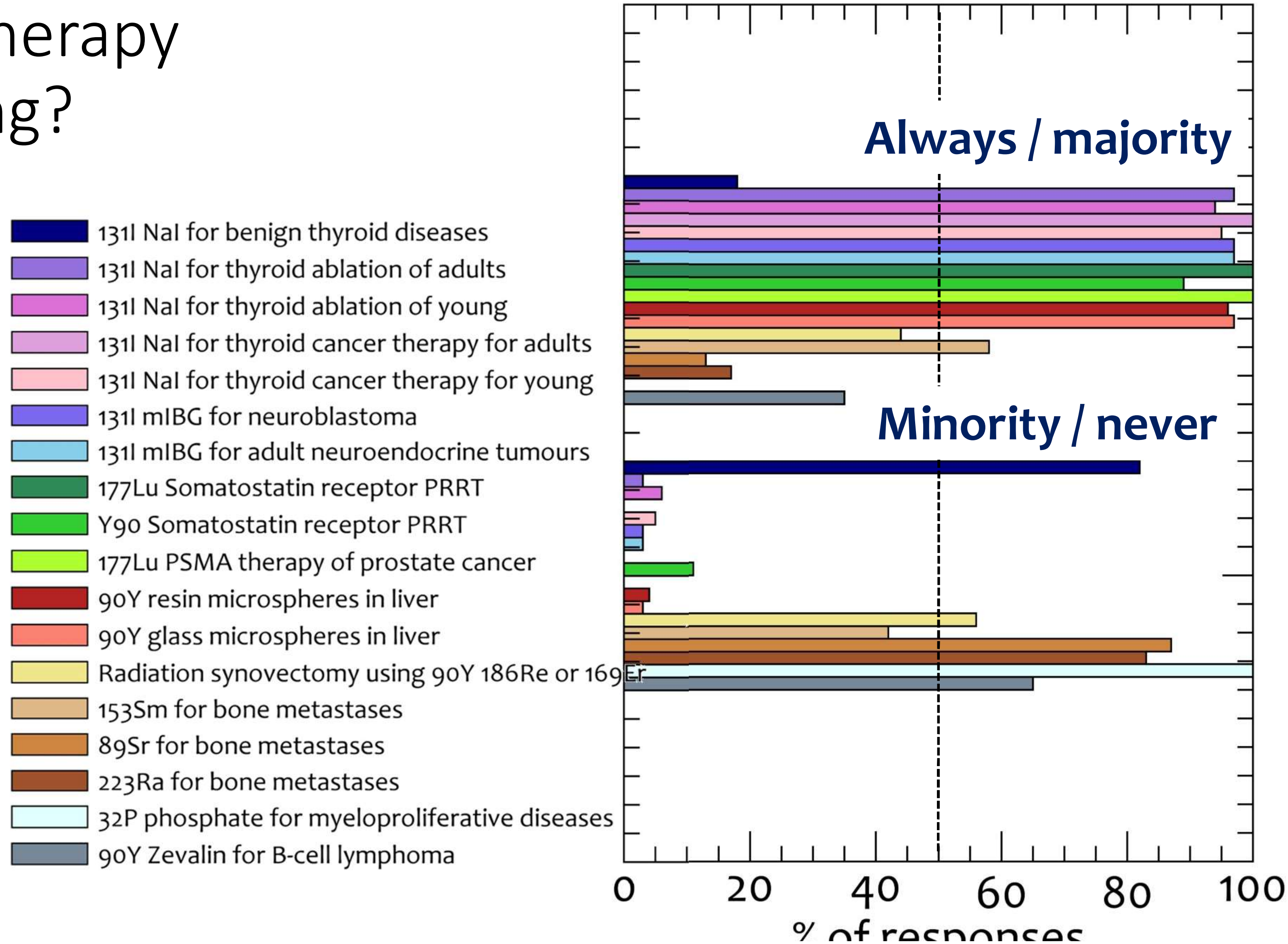
Absorbed dose planning?



Is post-therapy imaging performed?

- Always
- Majority
- Minority
- Never

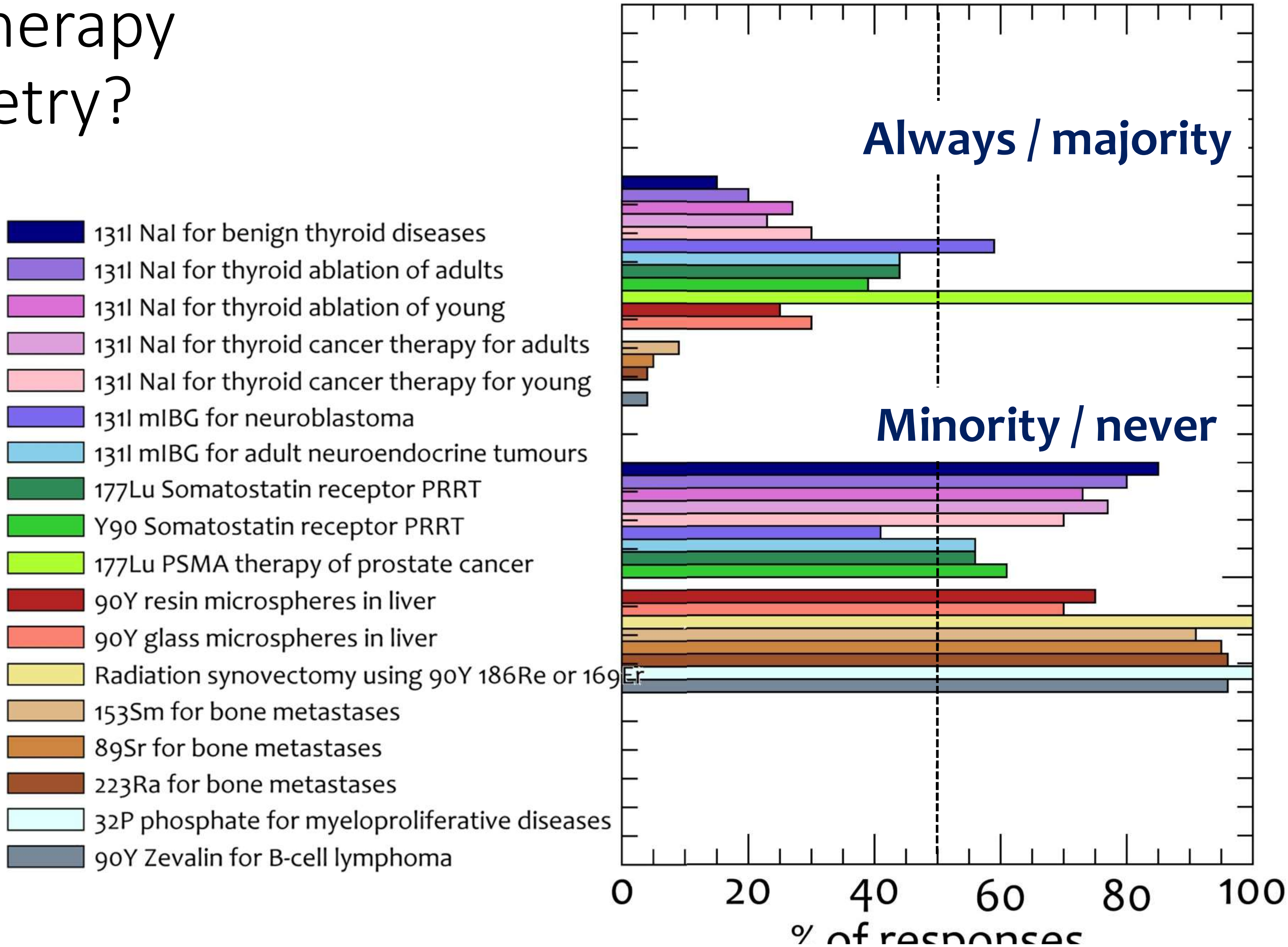
Post-therapy imaging?



Is post-therapy dosimetry performed?

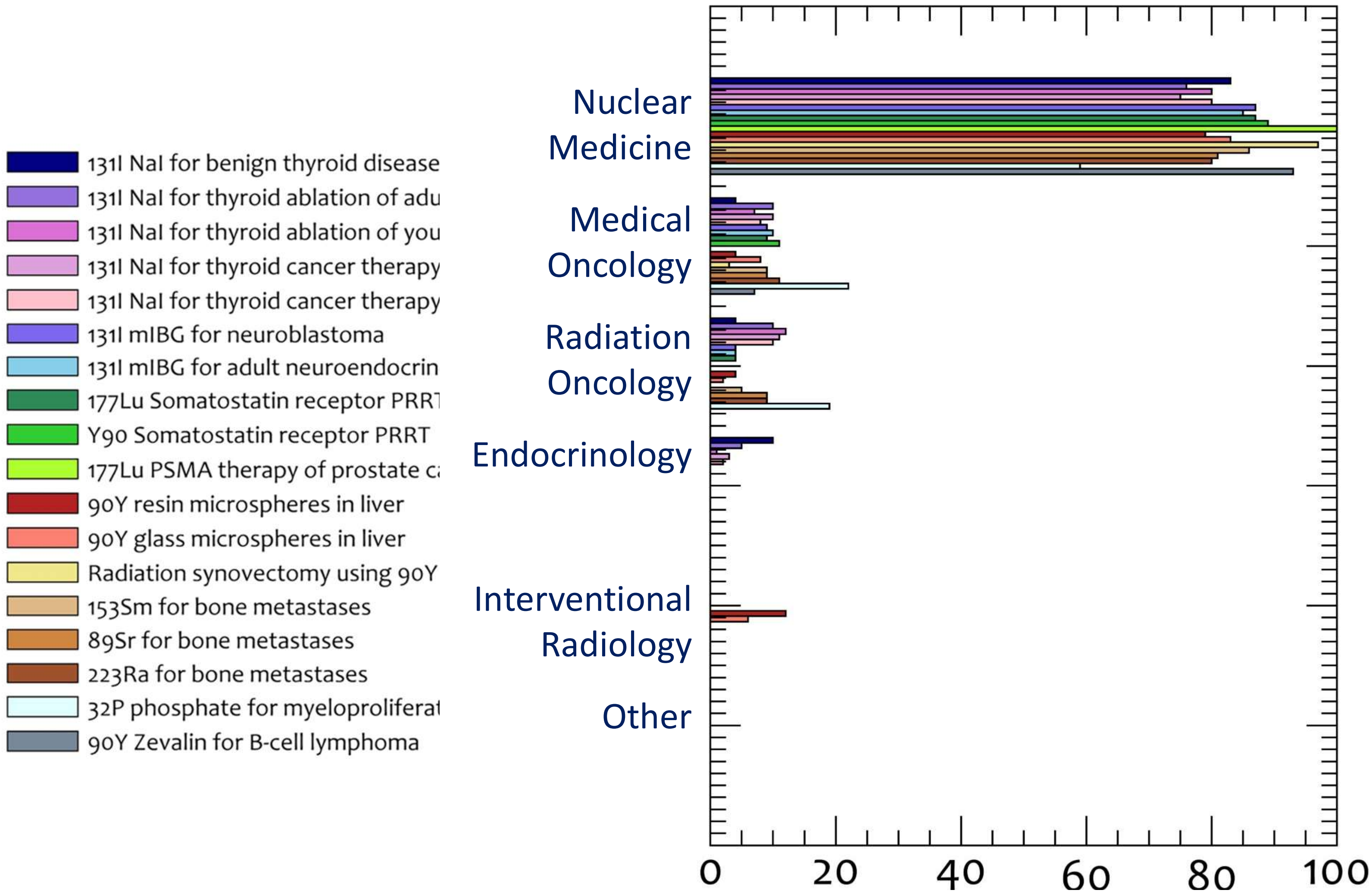
- Always
- Majority
- Minority
- Never

Post-therapy dosimetry?



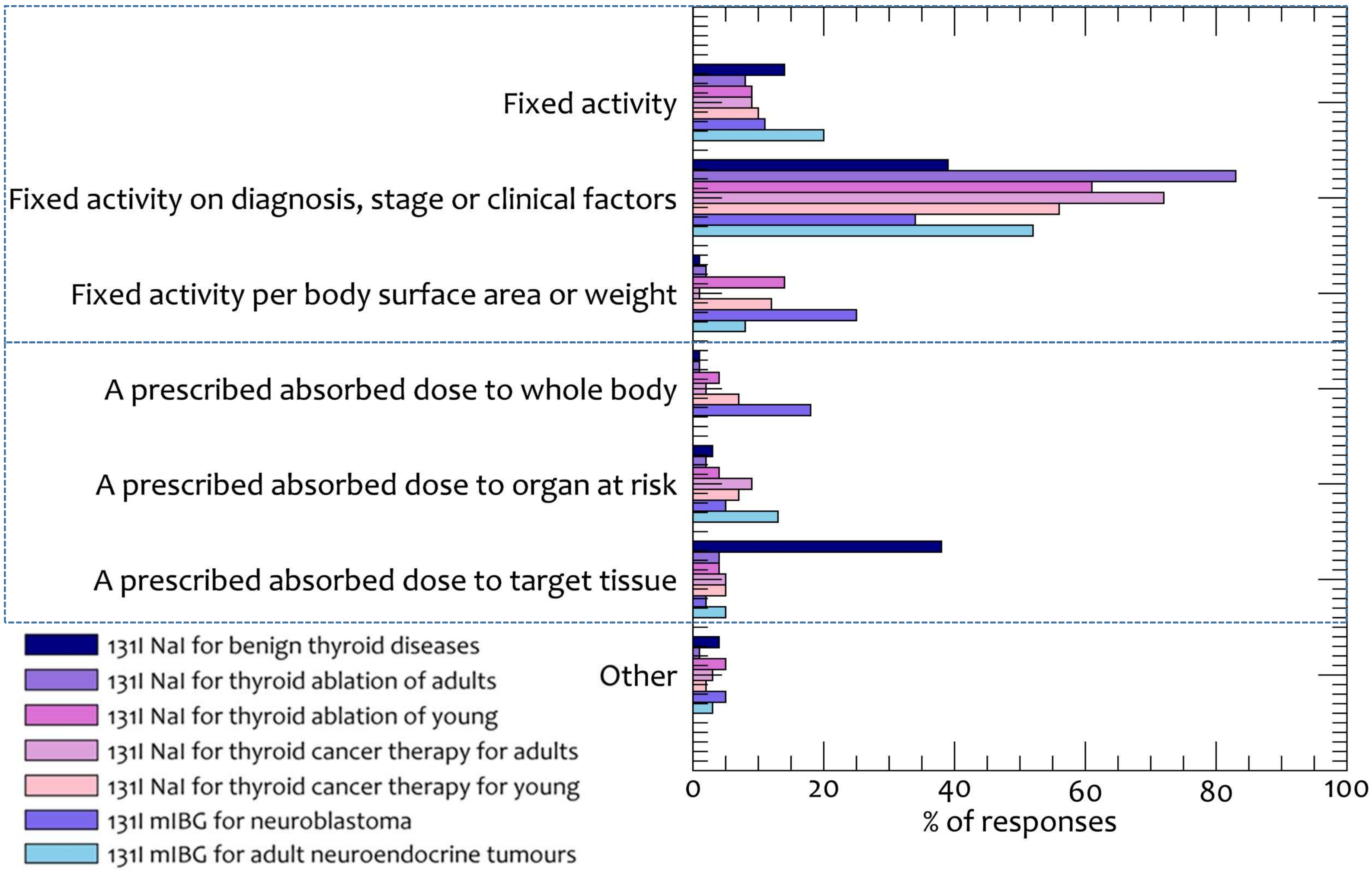
Which medical specialty owns the license to administer treatment?

Medical specialty?

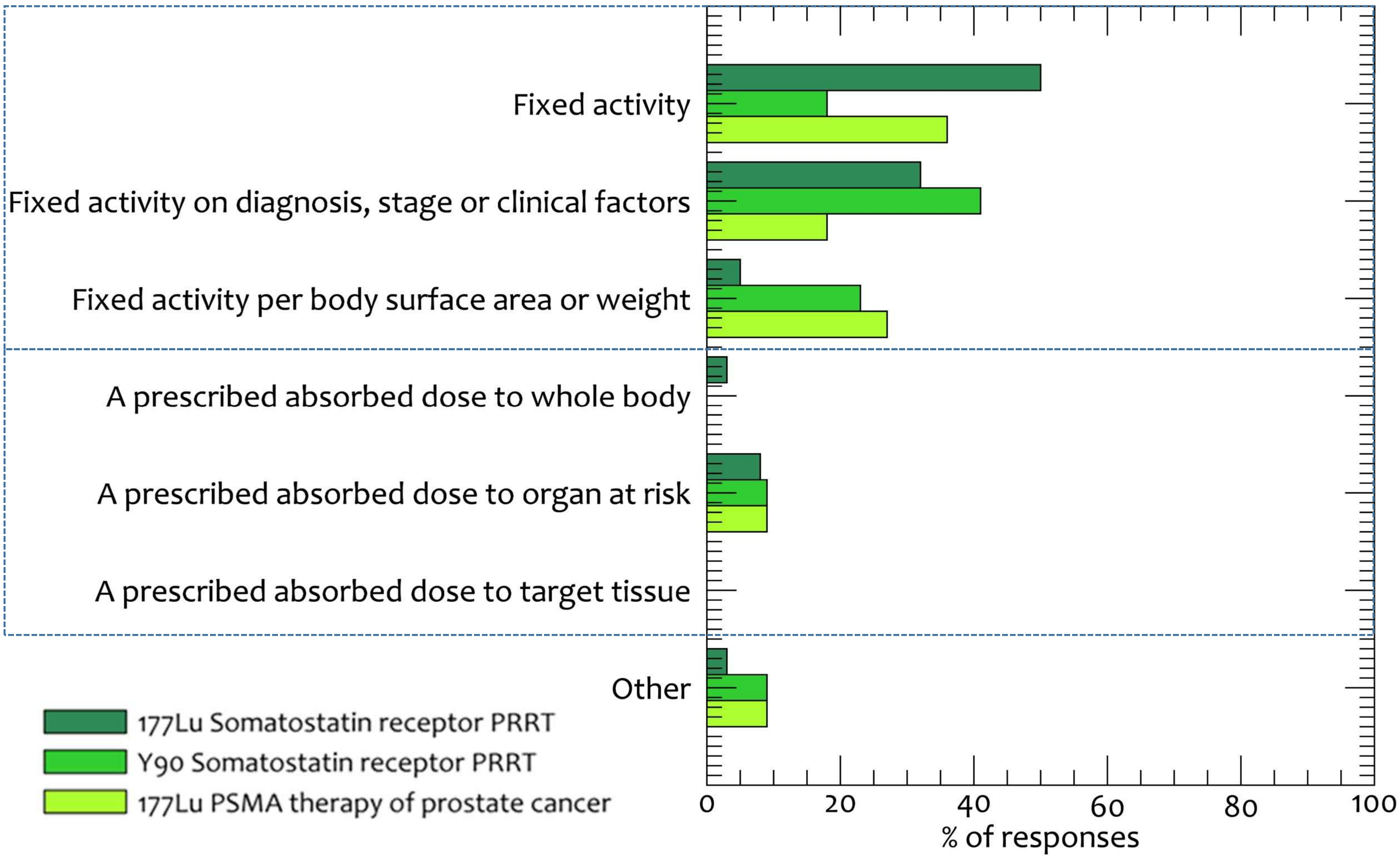


What basis of therapy prescription do you typically use?

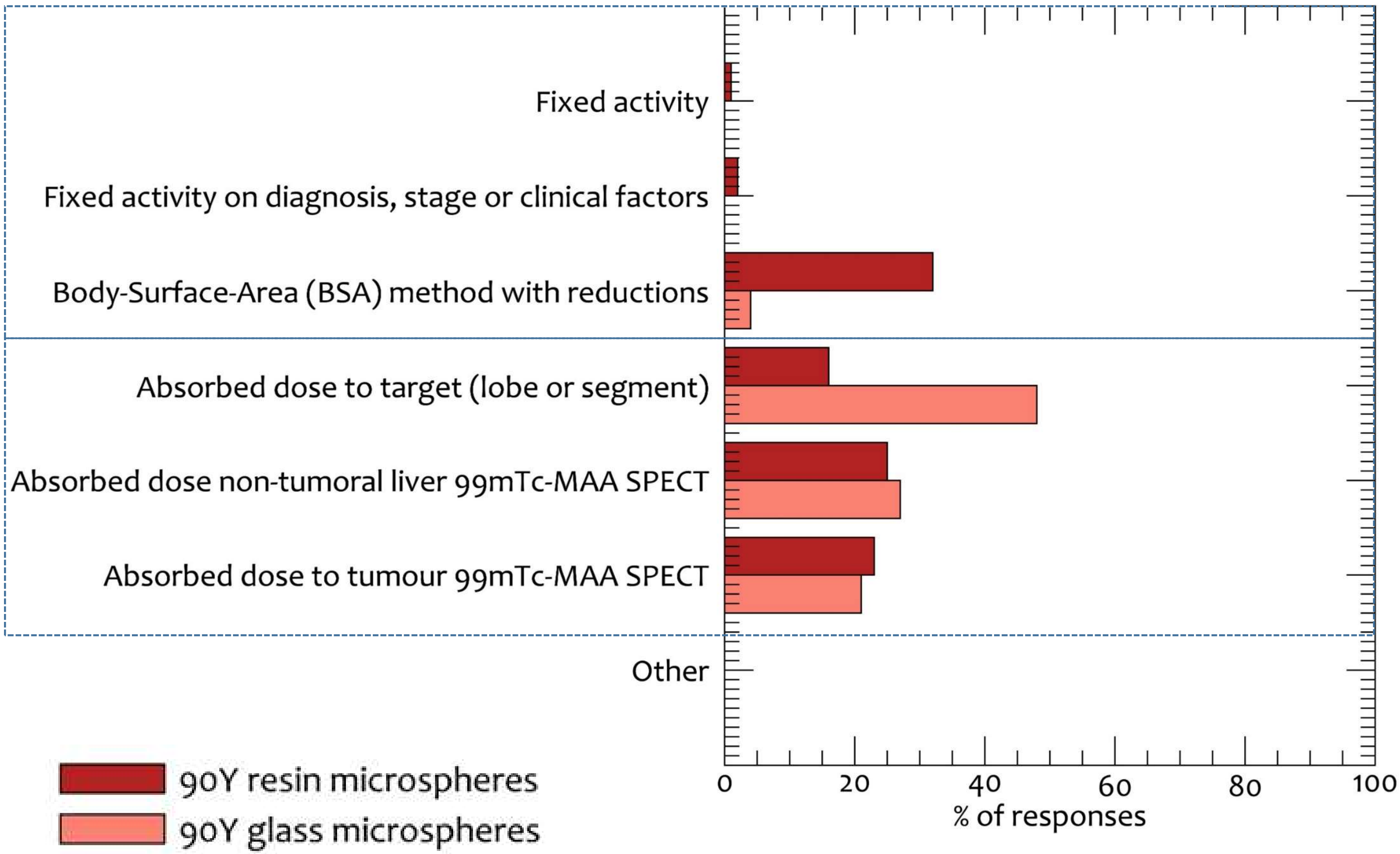
Basis of prescription - therapies using ^{131}I



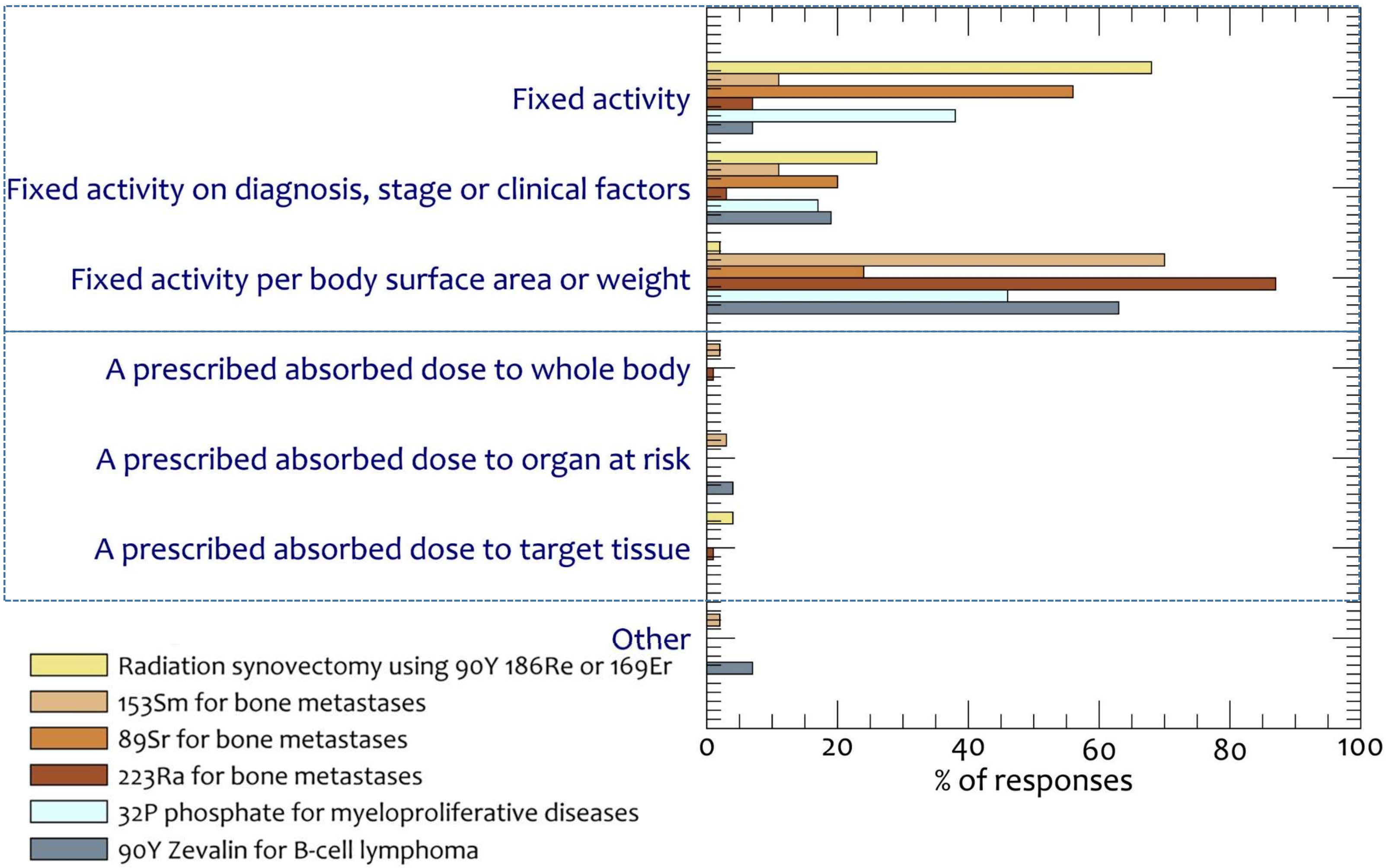
Basis of prescription – ^{177}Lu or ^{90}Y peptides



Basis of prescription – ^{90}Y microspheres



Basis of prescription – other therapies



Conclusions from the survey

- The involvement of a medical physicist was reported to **minority/never in 32%** of the therapies (average over all therapies).
- The absorbed dose was **not individually calculated (minority/never) for 64%** of treatments.
  - Exceptions; ^{90}Y microspheres (83%), ^{131}I-mIBG for neuroblastoma (59%), and ^{131}I-NaI for benign thyroid diseases (54%).
- Most protocols used fixed activity prescriptions
  - Exception; ^{90}Y microspheres (75%)

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Conclusions overall

- Dosimetry is indeed feasible for many kinds of radionuclide therapy.
- Yet, the implementation of dosimetry is low.
- Medical physicists need to be involved, this is key for the understanding of what an absorbed dose is, and the value of dosimetry.
- The activity meter is used as a reference instrument – Traceable activity measurements for therapeutic radionuclides needs to be assured – this is where everything starts.

Thank you for your attention!

- Acknowledgements;
  - Members of Internal dosimetry task force, Dosimetry and Radiation protection committees of the EANM
  - All my colleagues in Lund, Michael Ljungberg, Johan Gustafsson, Anna Sundlöv, and many more.

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