# Quantitative imaging for dosimetry studies: potential and limitations

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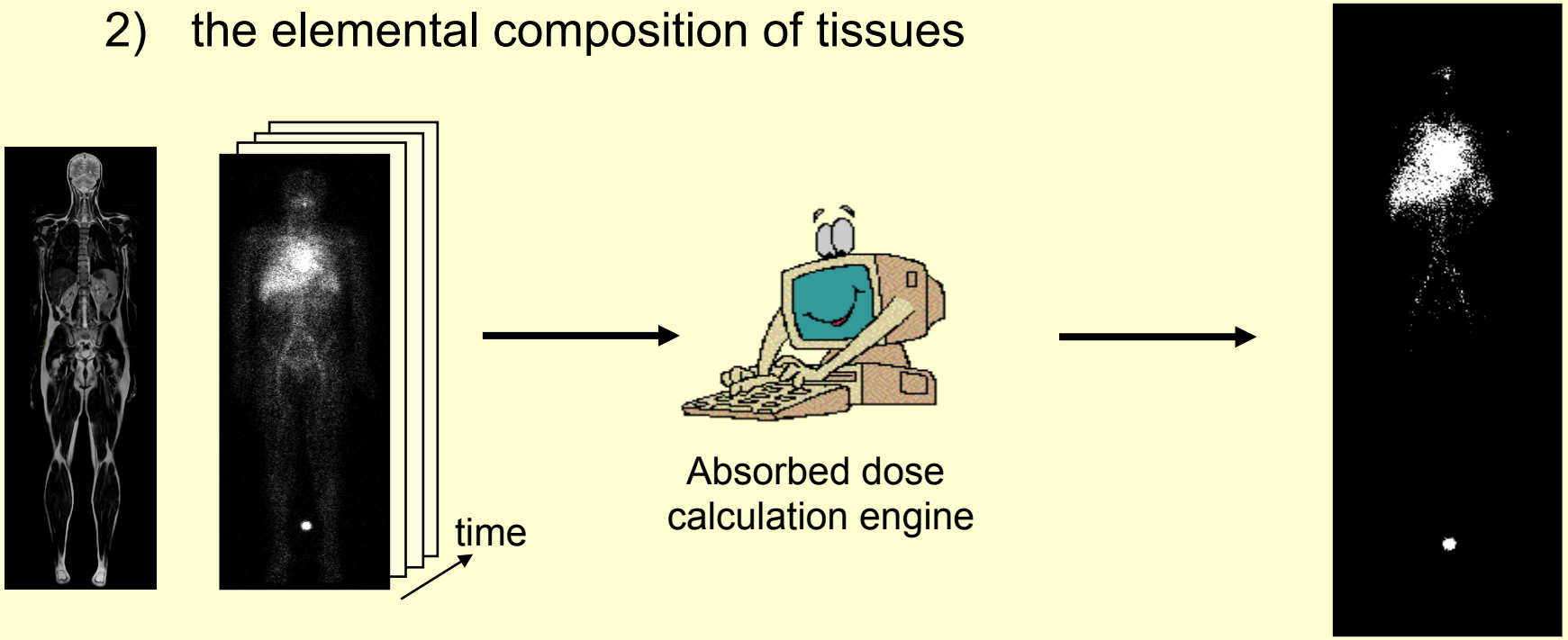
# Context

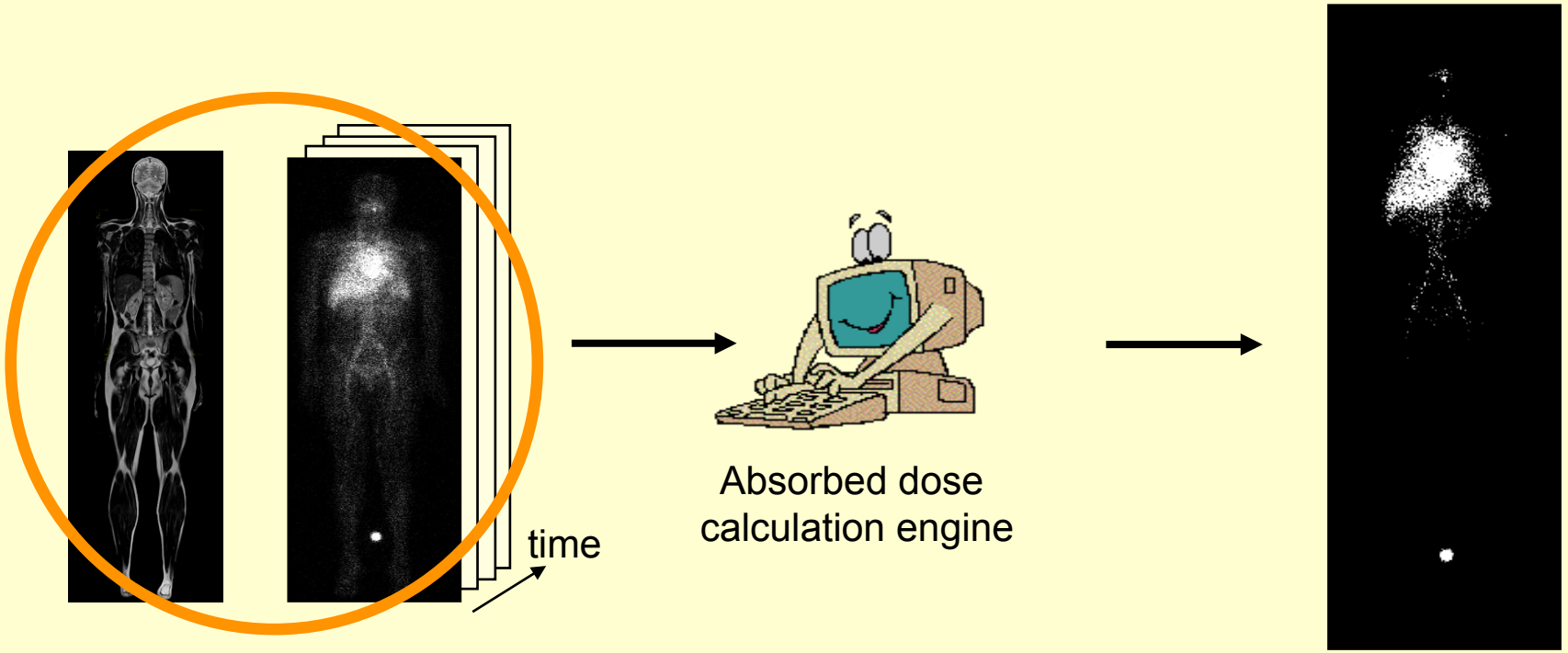
• Using patient-specific data obtained from imaging towards personalized dosimetry

• Goal: get an accurate estimate of spatial distribution of the absorbed dose at the required scale

• Prerequisite: get an accurate estimate of
  1) the cumulated activity distribution
  2) the elemental composition of tissues



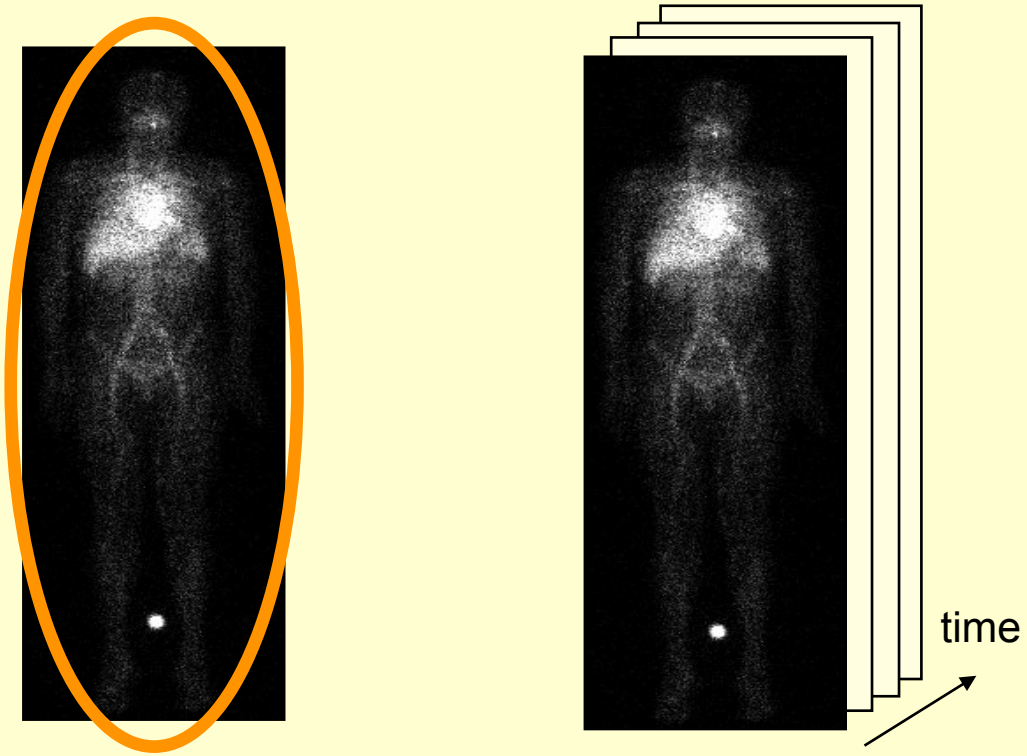
# Topics covered by the talk




- How accurate can the input images be?
- In which conditions?
- Specificities of activity quantitation in molecular radiotherapy applications.
- How to move forward?

# What do we need from images?

- Accurate activity distribution at each relevant time point, given the radiopharmaceutical kinetics
- Cumulated activity from these activity distributions
- Tissue elemental composition co-registered with the cumulated activity values



# First step: accurate activity distribution at each time point

• Accuracy of the estimated activity distribution **highly depends on the radioisotope associated with the β- emitter used for therapy**

• In diagnostic imaging, PET accuracy tends to be equal to or better than SPECT accuracy thanks to higher sensitivity (x10), better spatial resolution (~ 5 mm against ~ 8 mm) and easy attenuation correction. Yet, **this is only true for "clean" emitters** (eg, F18, Tc99m)

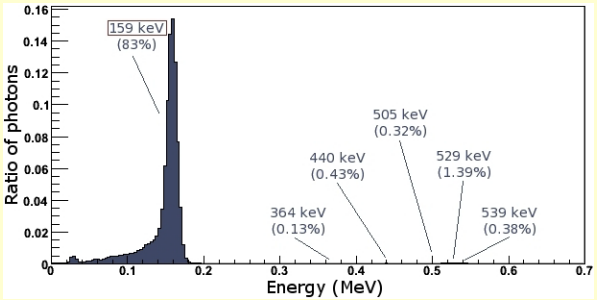
• When it comes to "dirty" isotopes or isotopes with a complicated decay scheme (In111, I124, I131, Y90, etc) :

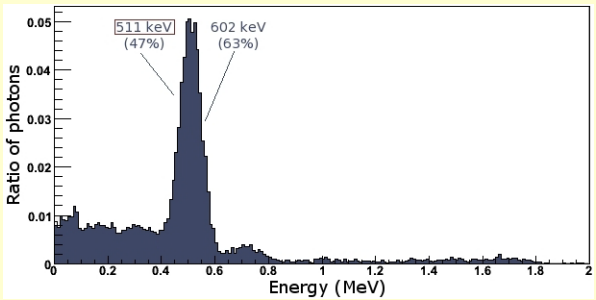
- Conventional imaging protocols are usually sub-optimal.
- The best imaging strategy to get accurate activity estimates (PET vs SPECT) has to be carefully investigated when a choice is possible.
- The accuracy and precision have to be characterized for each imaging protocol.

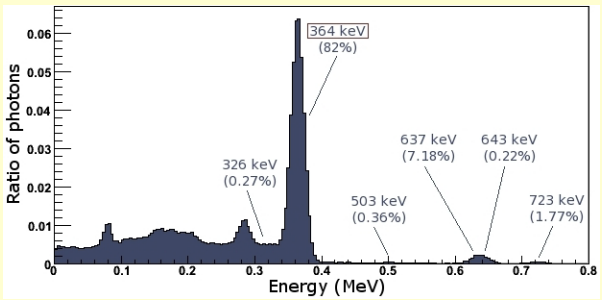
# Example

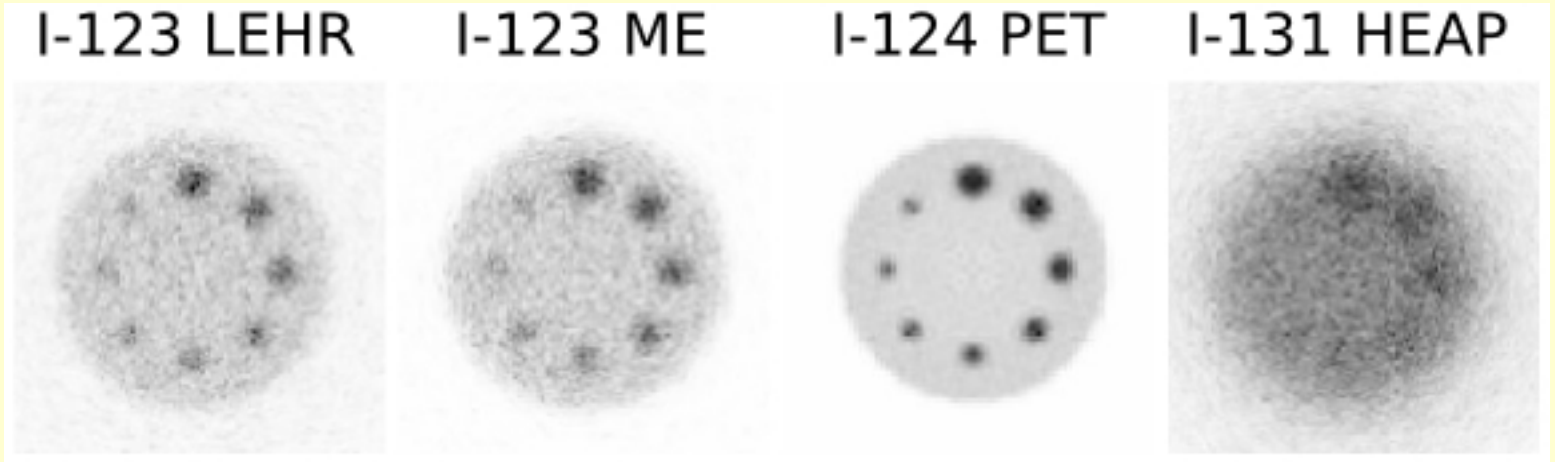
- From Rault et al, Cancer Biotherapy 2007

  Simulated data



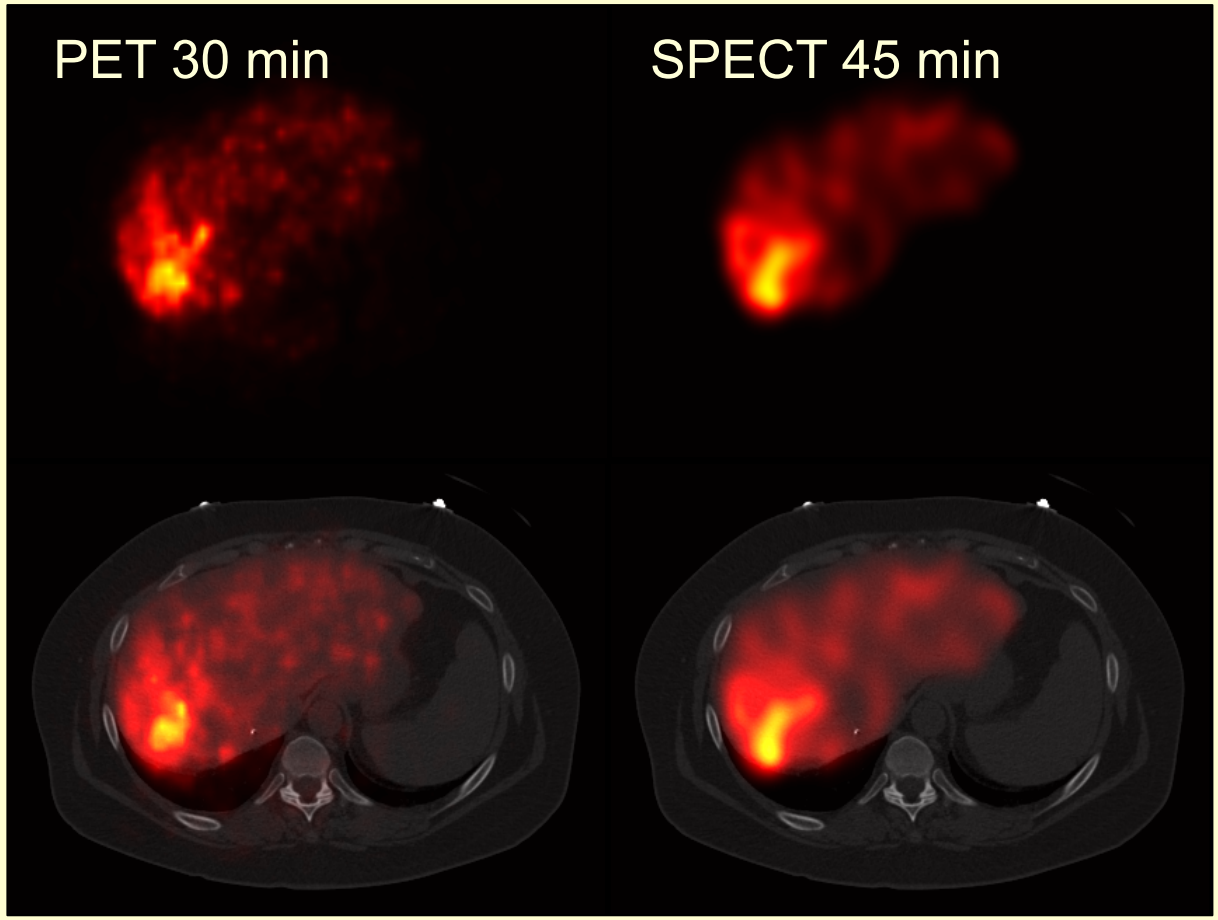



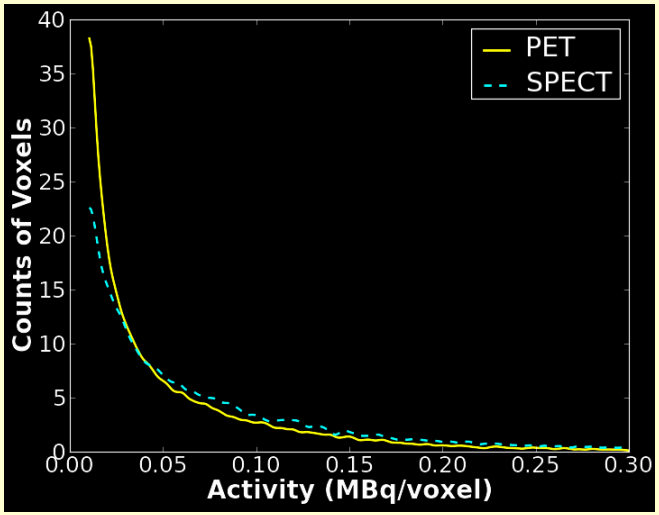



# Example

- From Yue et al, IEEE Medical Imaging Conference 2013

Y90 SPECT versus Y90 PET in patients with liver radioembolization




Activity volume histogram

# First take-home message

In image-based dosimetry, the advantages/drawbacks of PET versus SPECT imaging approaches have to be very carefully investigated, as **the isotopes associated with the β- emitters have specific features**. Quantitative performance obtained with clinical PET and SPECT protocols involving F18 or Tc99-labelled agents are thus not necessary representative of what to expect in molecular radiotherapy.

There is **no easy answer regarding which accuracy can be obtained**. It all depends on the isotope of interest and imaging protocol.

# Ingredients for accurate activity quantitation in ET in general

**Ideally:**

- 3D imaging (versus 2D imaging) as soon as more than whole body dosimetry is needed
- Attenuation compensation
- Scatter compensation
- Compensation for the detector response (to reduce blur and distortions)
- Positron range correction (in PET)
- Motion correction
- Partial volume effect correction
- Tissue fraction effect correction
- Dead time correction

# Ingredients for accurate activity quantitation in ET in general

**State of the art ("clean" isotopes)**

• 3D imaging (versus 2D imaging) as soon as more than whole body dosimetry is needed: **SPECT(/CT) and PET/CT are widely available**.

• Attenuation compensation: **accurate on SPECT/CT and PET/CT scanners** by modelling attenuation within the reconstruction procedure based on CT-derived attenuation coefficients.

• Scatter compensation: **effective on SPECT(/CT) and PET/CT scanners** using vendor solutions for Tc99m and F18.

• Compensation for the detector response (to reduce blur and distortions): **accurate in SPECT(/CT)**, **effective in PET/CT**. Yet, resulting images remain blurred.

• Positron range correction (in PET): useless in F18-PET, **not available in commercial PET/CT scanners**.

# Ingredients for accurate activity quantitation in ET in general

**State of the art (clean isotopes)**

- Motion correction: **not available in SPECT(/CT)**, **in progress in PET/CT**
- Partial volume effect correction: **not available in SPECT(/CT)**, **nor in PET/CT**
- Tissue fraction effect correction: **not available in SPECT(/CT)**, **nor in PET/CT**
- Dead time correction: not needed in diagnostic imaging

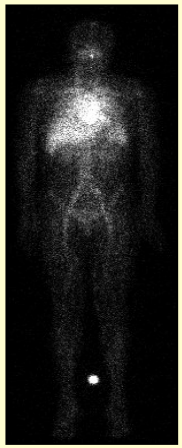
# Activity quantitation in ET for dose calculation purpose

• 3D imaging (versus 2D imaging) as soon as more than whole body dosimetry is needed: **SPECT(/CT) and PET/CT are widely available and should be used whenever possible**.

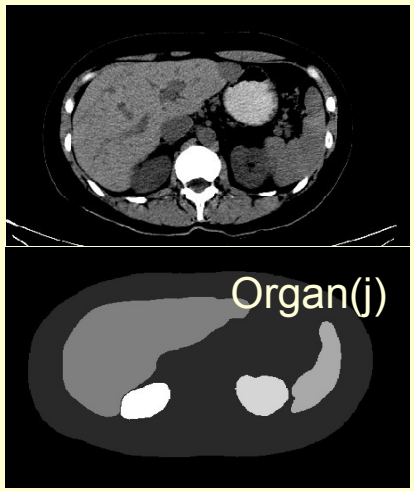
Activity estimates at the voxel level is impossible without 3D imaging.

An alternative: **2.5D imaging** = combining planar imaging with CT.

Planar(i)



Planar scintigraphy




CT
for organ delineation and calculation of the R(i,j)

Iterative inversion of $[Planar(j)]_j = [R(i,j)]_{i,j}.[Organ(j)]_j$ to retrieve $[Organ(j)]_j$ given $[Planar(i)]_i$

**Need for an accurate model of the camera response**

**Price to pay: organ based activity estimates (no dose volume histograms)**

# Example

- From He et al, Phys Med Biol 2006

  In111 imaging, Monte Carlo simulated data

| Method\organs | Heart (%) | Lungs (%) | Liver (%) | Kidneys (%) | Spleen (%) | Marrow (%) | Blood vessels (%) |
|---|---|---|---|---|---|---|---|
| CPlanar (realistic) | 14.76 ± 0.53 | 9.40 ± 0.29 | −8.35 ± 0.27 | 13.90 ± 2.08 | 45.59 ± 1.72 | −47.62 ± 0.65 | 5.77 ± 0.32 |
| QSPECT | −0.46 ± 0.68 | −1.84 ± 0.94 | −1.34 ± 0.35 | −3.42 ± 1.54 | −0.39 ± 1.20 | 2.14 ± 0.74 | 1.36 ± 0.84 |
| QPlanar | −1.76 ± 0.31 | 13.36 ± 0.34 | −0.20 ± 0.16 | −4.03 ± 0.86 | −1.39 ± 0.71 | 3.35 ± 0.52 | 1.59 ± 0.81 |
| QPlanar (short scan) | −1.81 ± 1.20 | 13.82 ± 1.18 | −0.21 ± 0.68 | −3.55 ± 4.27 | −1.30 ± 3.06 | 3.14 ± 1.84 | 1.44 ± 2.50 |

[a] Calculated by (estimate − true)/true × 100%. Negative signs indicate underestimation compared to the true.

2D

3D

2.5D

Best is 3D imaging, but 2.5D is definitely better than planar.

**3D is the way to go.**

# Activity quantitation in ET for dose calculation purpose

• Attenuation compensation: **accurate modelling in SPECT/CT and PET/CT scanners** within the reconstruction procedure based on CT-derived attenuation coefficients.

$$p = R_{\mu} \cdot f$$

• But increased complexity for “dirty” gamma emitting isotopes and bremmsstrahlung imaging: $\mu$ depends on energy. Hence $R_{\mu}$ should be energy dependent.

$$p = R_{\mu} \cdot f \quad \Rightarrow \quad p = R_{\mu}(E) \cdot f$$

Attenuation compensation will not be accurate because E has to be coarsely sampled (eg every hundred keV or more in bremmsstrahlung).

# Example

- From Rong et al, Med Phys 2012 (and see Michael's talk)

Y90 bremmsstrahlung SPECT, Monte Carlo simulated data

Percent errors in organ activity estimates[a] for data w/o added noise.

| $R_\mu(E)$ | Lung (%) | Spleen (%) | Kidneys (%) | Liver (%) | Heart (%) |
|---|---|---|---|---|---|
| MER 100–500 keV | 11.9 | −5.9 | −3.2 | −1.6 | −2.4 |
| SER 100–500 keV | −27.0 | −11.3 | −29.6 | −15.3 | −8.8 |
| SER 105–195 keV | −21.1 | −9.1 | −25.5 | −12.8 | −7.1 |

Note that $R_\mu(E)$ also included scatter modelling

[a]After 200 iterations of 16 subsets per iteration.

Accounting for the energy dependence of $R_\mu$ is essential

**Attenuation correction becomes approximate but remains effective**

# Activity quantitation in ET for dose calculation purpose

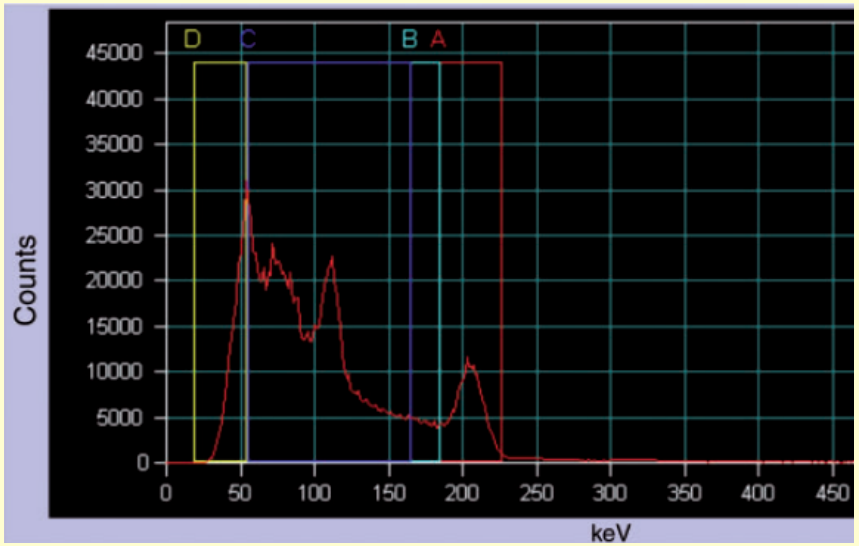
• Scatter compensation: **effective (and various) methods available in SPECT/CT and PET/CT scanners** either using multiple energy windows (SPECT) or a model of scatter spatial response within R (SPECT and PET)

• But increased complexity for “dirty” isotopes emitting high energy photons that produce downscatter.

**Scatter is highly isotope-specific**.
In SPECT, energy windows and associated weighting schemes must be optimized differently for each isotope.
In SPECT and PET, scatter spatial response functions to be used in reconstruction must be optimized differently for each isotope.

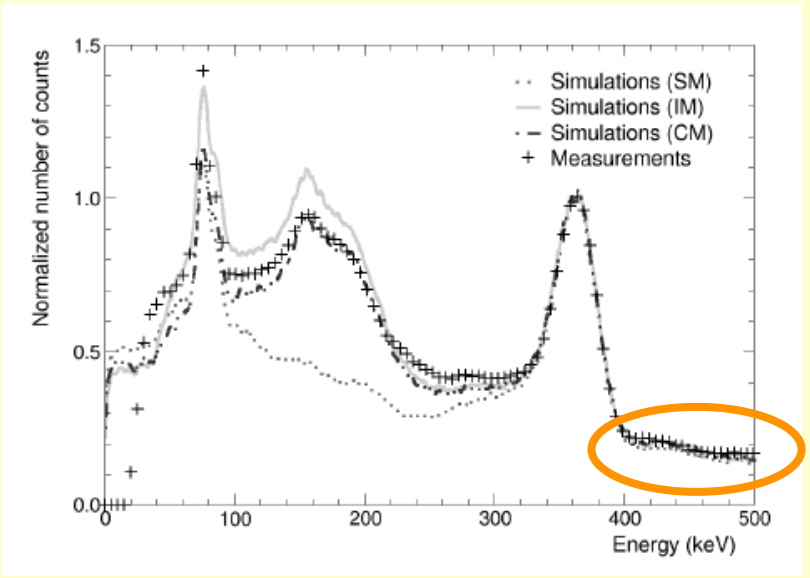
**Monte Carlo modelling is the reference approach to derive and optimize a scatter correction model and parameters**.

# Examples




Easy case: Lu177: no high energy contaminant:
Spectral windows can be sufficient for effective scatter correction (Beauregard et al, Cancer Imaging 2011)

364.5 keV (81.8%, 150 keV),
637.0 keV (7.2%, 182 keV),
722.9 keV (1.8%, 189 keV)




Complex case: I131: Monte Carlo simulations are needed to derive a scatter model to be used in reconstruction

# Activity quantitation in ET for dose calculation purpose

• Compensation for the detector response (to reduce blur and distortions): **now available, accurate in conventional SPECT(/CT)**, **effective in PET/CT**.

$$p = R_{DRF} \cdot f$$

• Increased complexity for “dirty” isotopes emitting high energy photons that lead to septal penetration.

$$p = R_{DRF} \cdot f \Rightarrow p = R_{DRF}(E) \cdot f$$

See Michael’s example with Multiple Energy Range approach.

# Activity quantitation in ET for dose calculation purpose

• Positron range correction (in PET): useless in F18-PET given current detector spatial resolution, **not available in commercial PET/CT scanners**.

**Feasible** for longer range positron emitters, eg I124.

$$p = R_{\beta+\ \text{range}} \cdot f$$

**Both analytical and Monte Carlo models have been described.**

Impact in molecular radiotherapy applications has not been reported, but work in progress with I124, for instance.

**Should definitely be kept in mind for PET-based dosimetry at the voxel level**

# Ingredients for accurate activity quantitation in ET in general

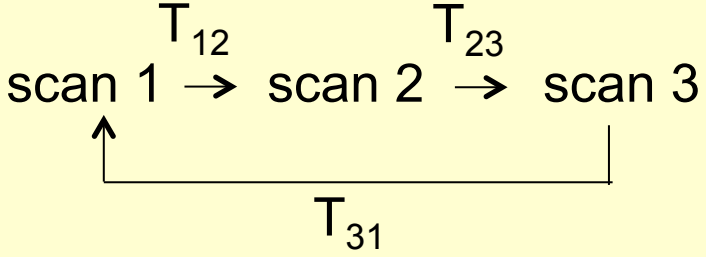
- Motion correction: **not available in SPECT/CT**, **in progress in PET/CT**

At the moment, **second order problem** in most dosimetry applications.

Motion is mostly of concern for registering serial scans to calculate cumulated activity distribution **at the voxel level**.

**Locally, registration within a voxel (~ 4-5 mm) is feasible. In whole-body scans, registration is poorer.**

Accurate registration along serial scans in clinical studies can be checked using consistency measurements *(Holden et al, IEEE Trans Med Imaging 2000)*.

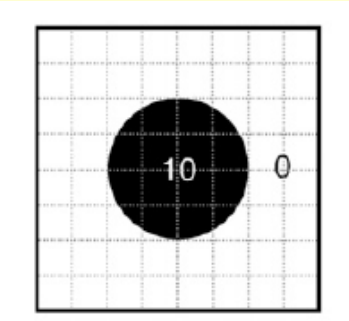



$$E = I - T_{31}T_{23}T_{12}$$

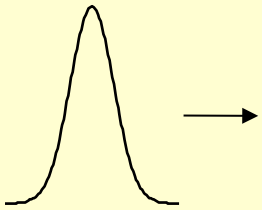
# Ingredients for accurate activity quantitation in ET in general

• Partial volume effect correction: **not available in SPECT/CT, nor in PET/CT, research in progress**

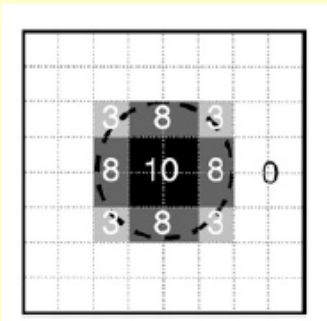
SPECT and PET images are always blurred, leading to partial volume effect, which:
- spreads the activity volume histogram (hence the dose volume histogram)
- yields to activity underestimation in structure < ~ 3 FWHM and activity overestimation in cold regions surrounded by hot regions.



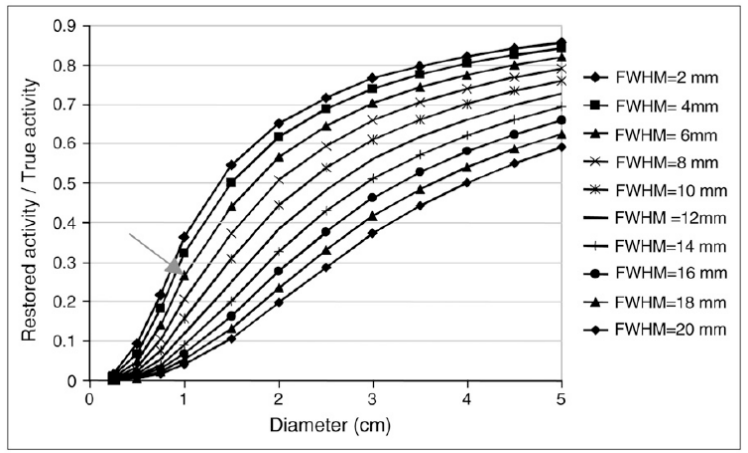

True activity distribution



⊗ DRF




Measured blurred image



# Ingredients for accurate activity quantitation in ET in general

- Partial volume effect :

**Improvement of spatial resolution through detector response function compensation reduces PVE** and is useful for dosimetry applications

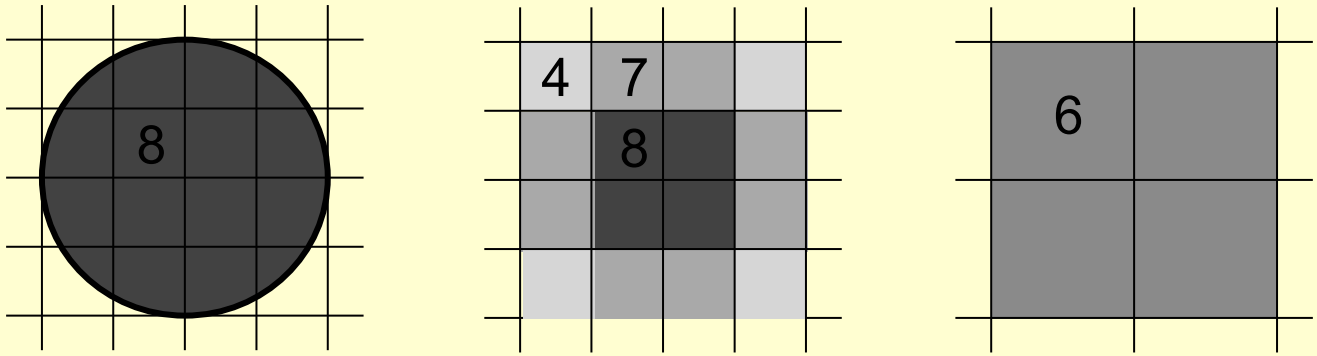
**PVE questions the relevance of voxel-based dosimetry** and should be kept in mind when interpreting such results

Small structures are severely affected by PVE, so **dose calculation in small structures** (< 3 FWHM) **should be interpreted with caution**.

**Regional corrections are available in research labs allowing for improved dose estimates at the organ level**

# Ingredients for accurate activity quantitation in ET in general

- Tissue fraction effect correction: **not available in SPECT/CT, nor in PET/CT**

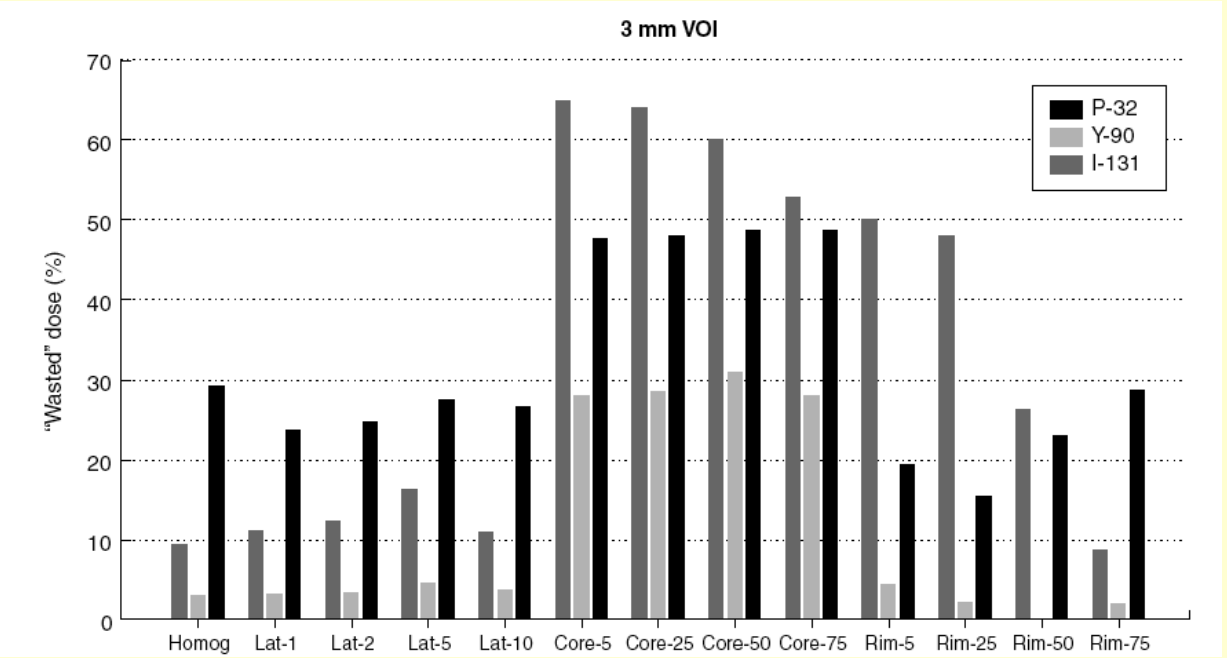



SPECT and PET images are always sampled, leading to tissue fraction effect, which:
- yields an average activity value over a voxel
- spreads (and possibly shifts) the activity volume histogram
- introduces biases in dose calculation

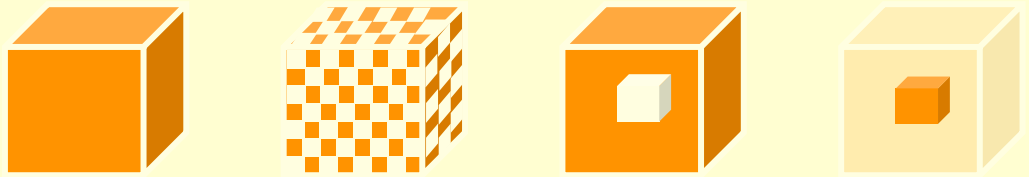
# Example

- From Calogioanni et al, Cancer Biother Radiopharm 2007

% diff between effective uniform dose and biologically effective dose




Various types of heterogeneity within a voxel



For a given activity value in a voxel (corresponding to an average of sub-voxel activity values), biological effect differ: ET imaging input alone will never be able to predict biological effect. **Additional modeling is needed**.

# Ingredients for accurate activity quantitation in ET in general

• Dead time correction: absolute activity estimate is needed for dosimetry purpose, so **calibration is a key step**.

Several calibration methods accounting for deadtime have been described.

Example: Lu177 SPECT

| No. | Calibrated activity (MBq) | | | | QSPECT activity (MBq)[a] | | | | Deviation (%)[a] | | | | Dead-time count loss (%) | Total deviation no DTC (%)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | Total | A | B | C | Total | A | B | C | Total | | |
| 1 | 22.6 | 0 | 0 | 22.6 | 20.5 | – | – | 20.5 | −9.5 | – | – | −9.5 | 0.0 | −9.5 |
| 2 | 78.7 | 0 | 0 | 78.7 | 82.1 | – | – | 82.1 | 4.3 | – | – | 4.3 | −0.2 | 4.1 |
| 3 | 75.3 | 0 | 314 | 390 | 71.6 | – | 302 | 373 | −5.0 | – | −4.0 | −4.2 | −0.9 | −5.0 |
| 4 | 75.2 | 146 | 314 | 535 | 65.9 | 131 | 315 | 512 | −12.4 | −10.2 | 0.4 | −4.3 | −1.3 | −5.6 |
| 5 | 75.0 | 146 | 940 | 1160 | 63.9 | 131 | 903 | 1100 | −14.9 | −10.2 | −3.9 | −5.4 | −2.9 | −8.2 |
| 6 | 650 | 145 | 938 | 1730 | 616 | 139 | 891 | 1650 | −5.2 | −4.3 | −5.0 | −5.0 | −4.4 | −9.1 |
| 7 | 373 | 83.4 | 538 | 994 | 360 | 73.4 | 498 | 932 | −3.4 | −12.0 | −7.4 | −6.3 | −2.5 | −8.6 |

A and B, cylindrical insert compartments (175 $cm^3$); C, large cylinder compartment (2,500 $cm^3$).
[a]QSPECT data with dead-time correction (DTC).
[b]SPECT data corrected for attenuation, scatter and sensitivity, but not for dead-time.

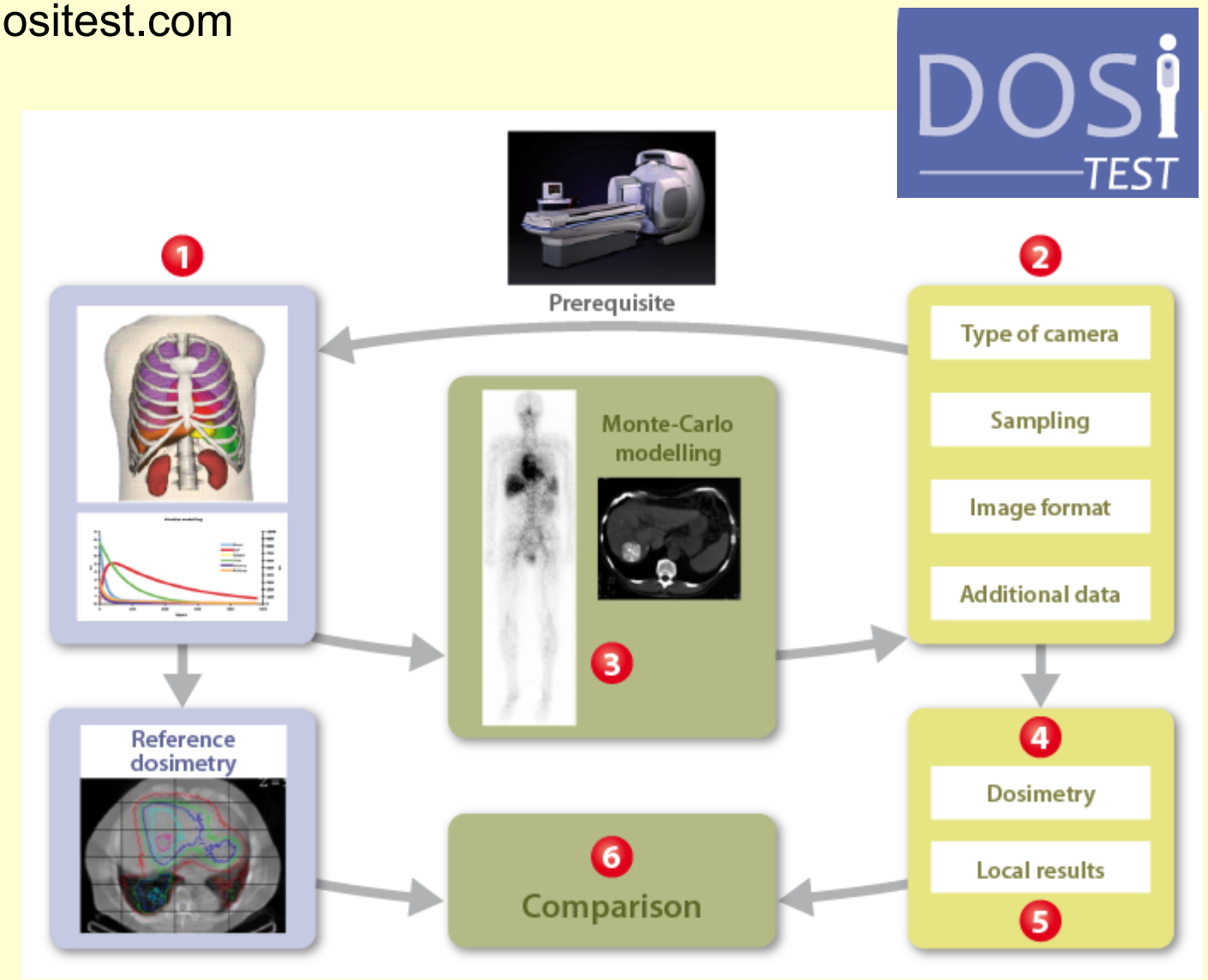
Beauregard et al Cancer Imaging 2011

# Discussion and conclusions

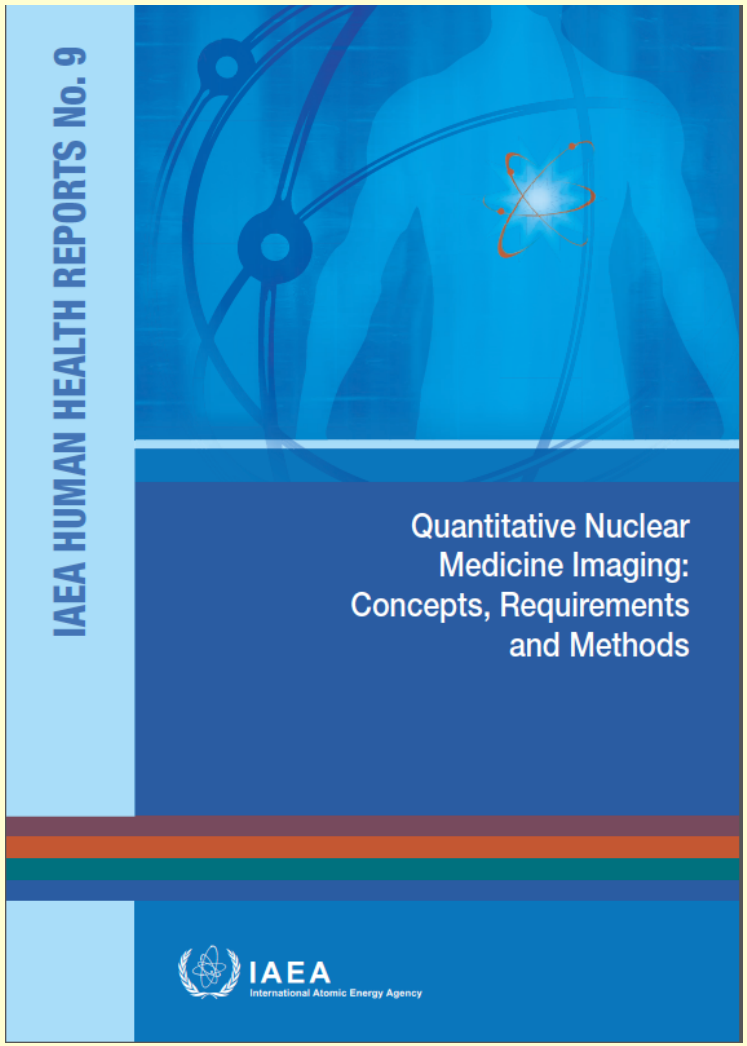
- **Accurate activity estimates** in ET for dose calculation in molecular radiotherapy is **more difficult than in conventional SPECT and PET**.
- **Accuracy is extremely isotope-dependent and protocol-dependent**.
- **The issues to address** for improving the accuracy in activity estimates **are well identified**, even if not all solved.
- **Solutions developed for conventional SPECT and PET can be adapted for improved quantification** in the dosimetry context. Examples of such adaptations now exist.
- **Given the room for improvement in activity estimate accuracy, it can be expected that such improvements will help demonstrate dose-effect relationships**.
- Images are an essential ingredient for dose calculation but at a **millimetric** scale at best. Other ingredients also play critical roles.
- As the **accuracy** of the imaging data directly impacts the accuracy of dose estimates, it **should be precisely characterized for sound dosimetric studies**. Work in that direction is in progress and is essential.

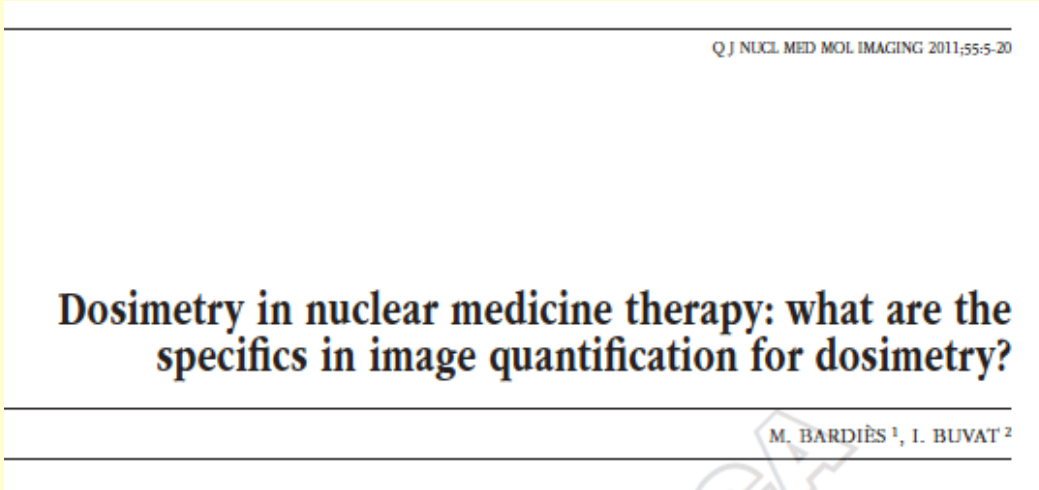
# Quality control: evaluating the accuracy of a dosimetry protocol

- www.dositest.com



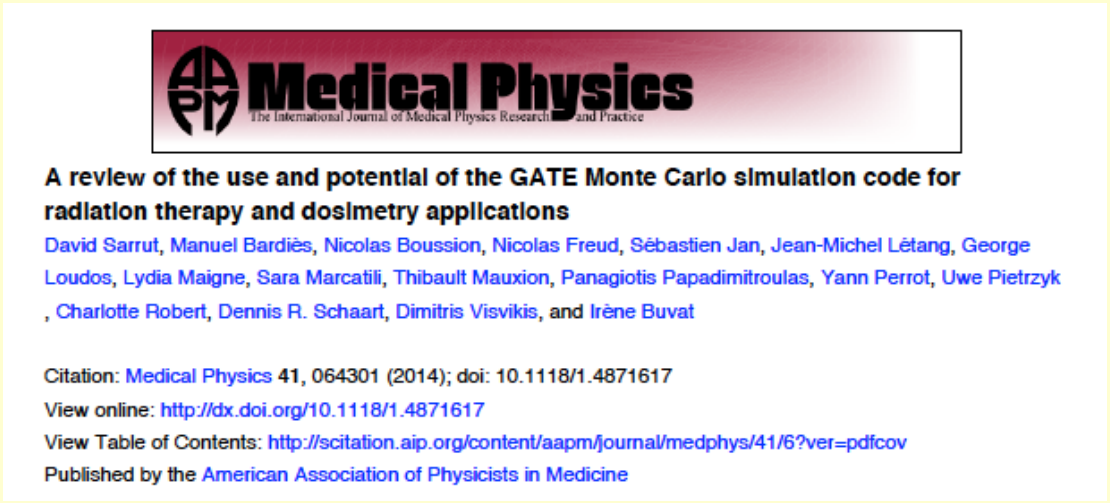
# Further reading





Q J NUCL MED MOL IMAGING 2011;55:5-20

**Dosimetry in nuclear medicine therapy: what are the specifics in image quantification for dosimetry?**

M. BARDIÈS [1], I. BUVAT [2]


Medical Physics
The International Journal of Medical Physics Research and Practice

**A review of the use and potential of the GATE Monte Carlo simulation code for radiation therapy and dosimetry applications**

David Sarrut, Manuel Bardiès, Nicolas Boussion, Nicolas Freud, Sébastien Jan, Jean-Michel Létang, George Loudos, Lydia Maigne, Sara Marcatili, Thibault Mauxion, Panagiotis Papadimitroulas, Yann Perrot, Uwe Pietrzyk , Charlotte Robert, Dennis R. Schaart, Dimitris Visvikis, and Irène Buvat

Citation: Medical Physics 41, 064301 (2014); doi: 10.1118/1.4871617
View online: http://dx.doi.org/10.1118/1.4871617
View Table of Contents: http://scitation.aip.org/content/aapm/journal/medphys/41/6?ver=pdfcov
Published by the American Association of Physicists in Medicine

The holy grail is probably too ambitious, we should look for improved accuracy, and most important clinical usefulness (even if not perfect accuracy)