Quantitative Molecular Imaging Using PET/CT to Assess Response to Therapy

Paul Kinahan, PhD
Director of PET/CT Physics
Imaging Research Laboratory, Department of Radiology
University of Washington, Seattle, WA

Presented by: Joshua Scheuermann

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PET/CT Applications and Challenges

Primarily for Cancer Imaging -- works very well
• Diagnosis and staging

Expanding Areas -- with significant challenges
• Radiation treatment planning using PET and CT
• Neurological imaging
• Cardiac imaging
• Assessment of therapeutic response
Do Numbers Matter in PET Images?

Elevated uptake of FDG (somehow related to metabolism)

- The answer to the question “Is quantitation necessary for clinical oncological PET studies interpreted by physicians with experience in interpreting PET images?” is “no.”
- Image quantitation will become increasingly important in determining the effect of therapy in many malignancies.

Imaging FDG uptake (PET) with anatomical localization (CT) and CT-based attenuation correction
Response to therapy of liver met gastric GIST

- No morphological change in the metastasis

![Comparison of CT and PET/CT images before and after imatinib therapy.](image)

CT

PET/CT

Pre therapy

1 wk imatinib therapy

PET SUV 5 -> 1.8

Castell and Cook, British Journal of Cancer (2008)
Times to Relapse after Neoadjuvant Chemoradiotherapy compared to PET/CT for NSCLC

Time to extracerebral progression
Partition ratio: \( \frac{\text{SUV}_{\text{max,corr}}(t_2)}{\text{SUV}_{\text{max,corr}}(t_0)} \leq 0.5 \)

\[ P < 0.05 \]
What do PET scans Measure?
How it works: Positron Emission

Radioactive decay
- unstable atomic nuclei due to too many protons relative to the number of neutrons
- decays to stable form by converting a proton to a neutron
- ejects a 'positron' to conserve electric charge
- positron annihilates with an electron, releasing two anti-collinear high-energy photons

\[ E = mc^2 \]

\[ = 511 \text{ keV} \]

\[ \beta^+ \]

\[ e^- \]

\[ \approx 2 \text{ mm} \]

\[ \approx 180 \text{ deg} \]
How it works: Timing coincidence

- Timing coincidence is based on the detection of positron decay events.
- Positrons and electrons annihilate to produce two gamma rays that travel in opposite directions.
- The coincidence is determined by the timing of the detection of these gamma rays by two detectors, A and B.
- If the time difference $\Delta t$ between the detections is less than 10 ns, the event is recorded.
- The recorded events are used to reconstruct an image of SUV values.
PET Scans Measure Activity Concentration

- If everything goes well, the role of the PET scanner is to measure the radioactivity per unit volume.
- Typically measured as kBq/ml or µCi/ml.

10 mCi = 370 MBq

70 kg water = 70 L

concentration = 370,000 kBq / 70,000 ml
= 5.3 kBq/ml

Suppose there is a very small object that takes up 5x the local concentration, so its concentration = 26.5 kBq/ml.
What if there are different activities or distribution volumes?

- Injecting different amounts or changing the volume will change the concentration.

10 mCi = 370 MBq

- Concentration: 5.3 kBq/ml

5 mCi = 185 MBq

- Concentration: 2.8 kBq/ml

10 mCi = 370 MBq (35 kg = 35 L)

- Concentration: 10.6 kBq/ml

The hot spot has different uptake values in kBq/ml even though it has the same relative uptake compared to background.
Standardized uptake values (SUVs)

- Normalize by amounts injected per volume (i.e. weight) to get the same relative distribution with SUV = 1.0 for a uniform distribution.

10 mCi = 370 MBq

SUV = 5.3 kBq/ml / (370 MBq/70 Kg) = 1.0 gm/ml

5 mCi = 185 MBq

SUV = 1.0 gm/ml

10 mCi = 370 MBq

SUV = 1.0 gm/ml

35 kg = 35 L

SUV = 1.0 gm/ml

The hot spot now has the same SUV uptake values independent in activity injected or volume of distribution (i.e. patient size).
Measuring uptake: kBq/ml vs SUV

Same scale in units of kBq/ml

Liver values look more uniform between patients

Same scale in units of SUV [g/ml]
Sources of Error in SUV Values

\[
\text{SUV} = \frac{\text{PET}_{\text{ROI}}}{D'_{\text{INJ}} / V'}
\]

PET = measured PET activity concentration
\(D'\) = decay-corrected injected dose
\(V'\) = surrogate for volume of distribution

It is important to minimize SUV errors for \textit{serial} studies (excluding artifacts)

Some potential sources of error are:

- Determining that blood glucose levels are within range
- Changing dose uptake time
- Scanner calibration and cross calibration with dose calibrator
- Dose assay for each patient, which uses several pieces of information, all of which have to be correct:
  - Correct clock settings for scanners, injection times, and assay times for correct calculations of radioactive decay and dose uptake periods
  - Changing reconstruction or other processing protocols
  - Changing analysis methods: How ROIs are determined and whether max or mean SUV values are reported
- Weight is typically used as a surrogate for volume of distribution, but can also be further normalized for lean body mass or body surface area, which have to be estimated
Biological Effects
Effect of blood [Glu] on SUVs of liver mets from colorectal carcinoma

- 8 patients w/ 20 liver metastases by CT (size 10-75 mm, mean 32 mm)
- Fasting FDG-PET scan followed 2 days later by glucose-loaded scan (i.v. glucose infusion (4 mg/kg/min for 2 hr)

<table>
<thead>
<tr>
<th></th>
<th>Fasting scan</th>
<th>Glucose loaded</th>
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</thead>
<tbody>
<tr>
<td>[Glu] (mg/100 ml)</td>
<td>92.4 ± 10.2</td>
<td>158 ± 13.8</td>
</tr>
<tr>
<td>SUV (all lesions)</td>
<td>9.4 ± 5.7</td>
<td>4.3 ± 8.3</td>
</tr>
<tr>
<td>known lesions seen</td>
<td>20/20</td>
<td>14/20</td>
</tr>
</tbody>
</table>

*Crippa F. et al. Tumori, 1997*
The same study at different post-injection times will give different SUVs.
This problem is worse when two different studies are compared looking for an increase or decrease in SUVs between exams.

Beaulieu JNM 2003
Quantitative Corrections
Quantitative errors in measurement

- no LOR
- incorrectly determined LORs

- Lost (attenuated) event
- Scattered coincidence event
- Random coincidence event
Effects of Attenuation: Patient Study

- Reduced mediastinal uptake
- 'Hot' lungs
- Non-uniform liver
- Enhanced skin uptake

PET: without attenuation correction
PET: with attenuation correction (accurate)
CT image (accurate)
Scanner Calibration
Effect of ACF calibration error

- Can not visually see ACF (scanner activity calibration factor) error

Incorrect ACF
Max SUV = 23.6

Corrected ACF
Max SUV = 19.7

Note: Both images scaled to max value
Activity Correction Factor Variation in Time

Scanner 1

Standard Deviation

- $^{68}\text{Ge} = 3.2\%$
- $^{18}\text{F} = 6.1\%$

Outliers Removed

- $^{18}\text{F} = 4.1\%$

Scanner 2

Standard Deviation

- $^{68}\text{Ge} = 3.1\%$
- $^{18}\text{F} = 11.0\%$

Outliers Removed

- $^{18}\text{F} = 7.0\%$

Lockhart SNM 2009
Resolution Effects
Size-Dependent Resolution Losses

- Hot sphere diameters of 10, 13, 17, 22, 28, and 37-mm
- Target/background ratio 4:1

Modified NEMA NU-2 IQ Phantom
SNM Phantom: Key results of SUV measurements

Variations are introduced by the scanner type, acquisition protocol, calibration differences, processing (e.g. image reconstruction method or smoothing) and ROI definition method.

Plots of recovery coefficient (RC) = measured in ROI/true

averaged coefficients of variation
mean SUV: 8.6%, max SUV: 11.1%

Kinahan et al 2009 SNM
Effect of changing post-reconstruction smoothing

SNM Chest phantom, 2 iterations, 28 subsets - True SUV (average) is 4.0

SUVmax for 1 cm spheres

- 4 mm smoothing: 3.4
- 7 mm smoothing: 2.1
- 10 mm smoothing: 1.6

- 3 cm

2.9

3.2
Artifacts
Regional Errors (Artifacts)

PET-based errors
- Calibration problems (localized)
- Detector failures
- Resolution and partial volume effects

Errors from CT-based attenuation correction in PET/CT
- CT artifacts
- non-biological objects in patients
- patient motion
- truncation
Data flow for CT based attenuation correction

- X-ray acquisition
- PET Emission Acquisition
- Smooth to PET Resolution
- Attenuation Correct PET Emission Data
- Translate CT to PET Energy (511 keV)
- Functional (PET) Reconstruction
- Display of PET and CT DICOM image stacks

CT Image
PET Image
Metal Clip

CT PET with CTAC

Artifact

CT

PET with CTAC

Courtesy O Mawlawi
MDACC
Patient and/or bed shifting

- Large change in attenuation at lung boundaries, so very susceptible to errors
Breathing Artifacts: Propagation of CT breathing artifacts via CT-based attenuation correction

Attenuation artifacts can dominate true tracer uptake values
Summary of Factors that Influence PET/CT Accuracy and Precision

- Biological effects: both true uptake (what we want) and biological noise
- Patient preparation: fasting, glucose levels, uptake period
- Quantitative corrections: Attenuation, scatter, randoms, detector efficiency normalization
- Resolution loss: aka partial volume errors
- Reconstruction method (smoothing and iterations)
- Analysis method: ROI definition method and SUV mean vs max
- Artifacts
  - patient motion: respiratory and other
  - incorrect SUV scaling
  - Attenuation correction with CT: truncation, motion, incorrect scaling, general CT artifacts
- Care should be used if serial studies rely only on lesion SUV values, e.g. monitoring progression of disease
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