Imaging in Clinical Trials
Choosing the right imaging application for therapy response assessment
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Acknowledgements:
Thomas F. Hany, MD
Disclaimer and comment

1. Imaging is a large field: My views are obviously limited by my own experience: mainly MR, CT, PET and SPECT

2. I have limited US experience

3. I am trying to be fair to all imaging modalities, but this is not easy

4. Imaging world is organized into imaging „parties“
   => technological organization in imaging departments
   => fortunately integrated imaging is changing this
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1. Setting the stage
2. Quantifying medical images – which images?
3. Standardizing image acquisition
4. Imaging in clinical trials
   - therapy response
   - data pooling
5. Conclusions
Rationales for imaging in clinical trials
more effective identification of therapeutic success

1. Fewer study patients needed for statistical significance
   - e. g. cardiac ejection fraction vs treadmill testing
   - e. g. change on images vs. lab value changes

2. Faster (surrogate) study end-points
   - tumor size or metab. activity assessment vs. survival
   - e. g. AD plaque imaging burden vs. mental testing
Surrogate end point: lymphoma

short term follow up series: prognostic role

Signif. difference in PPV for PET vs CT regarding PFS and OS

Issues concerning imaging in clinical trials

Key issues

Cost issues
- con: imaging is expensive => use lab tests
- pro: fewer patients less expensive => use imaging

Imaging specific issues
- which imaging modality to use => e. g. PET vs US
- discrimination of relevant vs irrelevant
- lab value 1 D data, imaging set 3 – 5 D data
- standardization of imaging difficult at various levels

We will only discuss issues in imaging
### Sensitivity: Nucs is the only clinical MI

*only nuclear imaging has „the touch“*

<table>
<thead>
<tr>
<th>Imaging-method</th>
<th>„contrast agent“-concentration (mol/kg kg)</th>
<th>spatial/temporal resolution (mm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sono</td>
<td>$10^{-3}$</td>
<td>$1 / 0.01$</td>
</tr>
<tr>
<td>CT</td>
<td>$10^{-3}$</td>
<td>$0.6 / 0.1$</td>
</tr>
<tr>
<td><strong>Conventional NM</strong></td>
<td><strong>$10^{-9}$ - $10^{-12}$</strong></td>
<td><strong>$10 / 1$</strong></td>
</tr>
<tr>
<td><strong>PET</strong></td>
<td><strong>$10^{-9}$ - $10^{-12}$</strong></td>
<td><strong>$5 / 5$</strong></td>
</tr>
<tr>
<td>MRI</td>
<td>$10^{-5}$</td>
<td><strong>$0.1 - 1 / 0.05 - 0.2$</strong></td>
</tr>
<tr>
<td>MRS</td>
<td>$10^{-5}$</td>
<td><strong>$10 / 100$</strong></td>
</tr>
</tbody>
</table>
Issues concerning imaging in clinical trials

*Standardisation at various levels*

1. **Single imaging system study**
   - intra-patient imaging comparability
   - inter-patient imaging comparability
   - variability in study protocol adherence

2. **Single imaging site study**
   - comparability of like imaging systems: same vendor
   - comparability of like imaging systems: different vendors

3. **Multicenter study**
   - comparability of patient handling
   - comparability of imaging systems

=> **STANDARDISATION**
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2. Which imaging modality to use?
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   - data pooling
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Imaging modalities used

1. Osteodensitometry (easy to standardize)
2. Ultrasound
3. CT
4. MRI / MRS
5. PET and SPECT
Ultrasonography (US)

Pros - relatively cheap
- no radiation to patient
- linear dimensions are standardizable

Cons - system stability and interobserver variability
- not generally applicable (brain, chest)
- functional US, e.g. microbubbles (acceptability?)

Measures (non-inclusive)
- dimensions
- ejection fraction (but this is also dimensional)
- flow velocity
- tissue perfusion and receptor function
X-ray computed tomography (CT)

Pros
- Anatomic dimensions and HU well defined
- high system stability
- cost (much less expensive than MRI, PET)
- imaging speed

Cons
- cost (more expensive than US !?)
- radiation exposure, contrast media
- anatomic changes frequently late findings
- standardising functional imaging (e. g. perfusion)

Measures (non-inclusive)
- dimensions 1D, 3D
- contrast media enhancement
- perfusion measures (but better than US)
Magnetic resonance imaging: MRI

Pros
- no radiation to patient (repeatability, volunteers)
- soft tissue contrast (important in „all or none“ response)

Cons
- cost
- system stability
- cost and length of procedure
- anatomic changes late findings
- standardising functional imaging (e. g. perfusion)

Measures (non-inclusive)
- dimensions
- contrast media enhancement
- perfusion, diffusion (standardization?)
Positron Emission-CT imaging: PET-CT
(includes conventional NN with SPECT-CT)

Pros
- high system stability
- anatomic information and functional information
- high lesion to background contrast
- rel. good standardization of functional information

Cons
- cost
- radiation exposure
- lesion size not easily assessed
- standardisation of anatomic measures difficult

Measures (non-inclusive)
- ejection fraction (dimensional)
- activity (radioactive uptake), SUV
- perfusion (quantitative), blood pool
## Assessment of FDG uptake

**How quantitative do we need to be?**

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual interpretation:</td>
<td>No blood sampling</td>
<td>Non-quantitative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uptake-time</td>
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<tr>
<td></td>
<td></td>
<td>Glucose level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial volume</td>
</tr>
<tr>
<td>Semi-quantitative: (SUV)</td>
<td>No blood sampling</td>
<td>Uptake-time</td>
</tr>
<tr>
<td></td>
<td>Easy computation</td>
<td>Glucose level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial volume</td>
</tr>
<tr>
<td>Kinetic modelling:</td>
<td>Dynamic data quantitative</td>
<td>Arterial blood sampling</td>
</tr>
</tbody>
</table>
Kinetic modeling

*quantitative, but very involved*

needs arterial input function!
Cerebral perfusion in Alzheimer’s disease
quantitative PET perfusion imaging

young

age matched

Alzheimer
Standardized uptake value SUV normalized to lean body mass (lbm)

SUV\textsubscript{lbm} avoids overestimation of FDG uptake in obese patients
Which imaging modality to use?

**Summary**

Information content with high reproducibility

- PET-CT > SPECT-CT > CT > MRI ≥ US

Cost of examination

- US ≤ CT < MRI ≤ SPECT-CT < PET-CT

Linear dimensions ok, but

- => late and insensitive response criteria

Functional parameters not easy to standardize

- => most promising and possibly reproducible: PET
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   why is PET so interesting?
5. Conclusions
General remarks on standardisation

1. Using serial assessment of same patient

2. Using ratio measurements within images (i.e. grey to white matter) is easier on standardisation conditions, then

3. Cohort studies, i.e. comparing activity in certain areas in a cohort of Alzheimers vs normals

=> Systematic deviations are „normalized“ away, but not random deviations!
Standardizing US image acquisition

1. difficult to standardize between manufacturers echogenicity useless measure
2. Difficult to standardize between systems
3. Difficult to standardize from day to day
4. Difficult to standardize between examinations
   ⇒ static and dynamic linear dimension assessment
   ⇒ patients as self-controls (therapy control)
Standardizing CT image acquisition

1. Scanners are rel. Comparable; H. U. well defined
2. Possible to standardize between scanners
3. Systems stable over long periods of time
4. Examinations useful in self-reference studies

=> Low interobserver variability for 1D measures
clear definition of target vs non-target lesions

RECIST
Standardizing MR image acquisition

1. Difficult to standardize between scanners pulse sequences difficult to standardize between manufacturers => S.I. useless as value

2. Difficult to standardize from day to day

3. Difficult to standardize between examinations on same patient, particularly with surface coils

⇒ ok interobserver variabilities for dimensional meas. Functional meas. available, but still under validation
Standardizing PET-CT image acquisition

1. Good anatomic and best available functional imaging tool
2. PET scanners have differing characteristics (intra- and inter-company variability)
   - spatial resolution
   - sensitivity (crystals)
   - data reconstruction
3. Possible to standardize over longer periods
4. Standardization for intra-patient measurements possible from system point of view but take care of potentially changing glucose metabolism
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PET(-CT) imaging in clinical trials

*PET-CT best imaging modality in many ways*

1. CT RECIST criteria (linear dimension measurements) only currently accepted tumor response criteria

2. All medical therapies: molecular
   => best to use molecular info to assess success
   => distance measurements inadequate and insufficient

3. Early response parameters sought
   => because of costly therapy (early stop in failure)
   => surrogate endpoints (death as endpoint too late)

4. Ideal imaging technology: PET-CT
   it has „old“ CT advantages and new PET advantages

5. FDG-PET data strongly correlate with survival
Lymphoma

Follow-up of residual mass

after radiation treatment
residual mass, but negative in PET
Esophageal carcinoma: neoadjuvant scheme

metabolic inactivity (decreased) surrogate endpoint?

Initial pres.  100 days after CRT  18 mos. post-op

How to place ROI?
Rectal cancer

*PET response predicts course of disease (Kalff et al., JNM 2006)*

**FIGURE 2.** Kaplan–Meier survival curves illustrate highly significant effect of PET-determined metabolic response to chemoradiation on overall survival in the 30 T3/4 Nx M0 patients who underwent radical surgery. (X) = number of patients in each group.

**FIGURE 3.** Very significant effect of PET metabolic response to chemoradiation on time-to-disease progression is demonstrated in Kaplan–Meier plot. (X) = number of patients in each group.
### Definition of tumor response with FDG

**EORTC criteria**

<table>
<thead>
<tr>
<th>Status</th>
<th>SUV</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive metabolic disease</td>
<td>&gt;25%↑</td>
<td>Visual increase of extent, new locations</td>
</tr>
<tr>
<td>Stable metabolic disease</td>
<td>&lt;25%↑, &lt;15%↓</td>
<td>No visible increase</td>
</tr>
<tr>
<td>Partial metabolic response</td>
<td>&gt;15%↓</td>
<td>one cycle CT</td>
</tr>
<tr>
<td></td>
<td>&gt;25%↓</td>
<td>several cycles CT</td>
</tr>
<tr>
<td>Complete metabolic response</td>
<td></td>
<td>FDG uptake resolved</td>
</tr>
</tbody>
</table>

Young H et al., European Organization for Research and Treatment of Cancer (EORTC)  

Issues concerning imaging in clinical trials

Standardisation at various levels: critical issues

1. Single imaging system study
   - adequate imaging protocols
   - adequate SUV measurements

2. Single imaging site study
   - comparability of like imaging systems: same vendor
   - comparability of like imaging systems: different vendors

3. Multicenter study
   - standardise both 1 and 2
Issues concerning imaging in clinical trials

1. single imaging system study - FDG

1. System stability (daily – weekly system QC measurements)

2. Defined patient examination parameters
   - delay between injection and scanning (site and sponsor)
   - blood glucose control (site and sponsor)
   - defined interval between studies (sponsor)

3. Defined data acquisition protocols (sponsor)

4. Defined data analysis protocols (sponsor)
   single lesion: SUV max vs CT and PET based volume average SUV (guidelines) → define cut-off
Issues concerning imaging in clinical trials

2. Single imaging site study

1. All rules of single imaging study – FDG

2. Studies on single patient on same scanner or at least same scanner type (longitudinal studies)

3. Cross-check scanners with phantoms
Issues concerning imaging in clinical trials

3. Multicenter studies

1. All rules of single imaging study – FDG
2. All rules of single imaging site study – FDG
3. Scan same patient at same site on same scanner
4. Cross-check scanners with phantoms
5. Use similar reconstruction algorithms
   (different algorithms result in highly different SUV values, especially SUV max)
6. Use core-lab for central overread of imaging results
Standardizing PET scanning

**Issues in standardisation**

- Intra-patient variability => problem
- Inter-patient variability => purpose of trials, sequ. studies
- Intra-observer variability => core labs, central reading
- Intra-system variability => daily/weekly system QC
- Inter-system variability => big issue
- Inter-site variability => big issue
Standardized acquisition of PET scans

joint effort by SNM clinical trial network and CRO’s / Core labs specializing in medical imaging

To achieve standardisation in multi-center trials

1. labels qualifying sites
   - such as SNM clinical trial network, ACRIN

2. General Standards, Templates for clinical trials
   - in collaboration with PhRMA and imaging CRO’s
   - Uniform Protocols for Imaging in Clinical Trials (UPICT) and Image Response Assessment Teams (IRATs) etc.

3. Standardisation of data acquisition and data analysis between sites for specific trials
   - need standardisation efforts by bodies like SNM
   - CRO’s who are specialists in imaging (e. g. Timaq)
Other radiopharmaceuticals (and specific contrast media in US, MR)

Issues

1. Availability
   - setting up new synthesis so far very expensive
   => solution: cassette systems, but also various vendors

2. Clinical value
   - evidence of correlation with survival?

3. Applications likely to be limited in the foreseeable future
   - proof of concept studies
   - early drug testing
   - in-vivo pharmacokinetics of new drugs
Other radiopharmaceuticals

How to evaluate

1. Relations of ROI values in intra-study comparisons (consistency of imaging systems required !)

2. Relations of ROI values in longitudinal studies

3. Assessment of „all or none“ changes in same lesion

4. Change in number of lesions
Conclusions

1. Imaging in clinical trials can be very useful

2. Major issues are
   - choice of imaging modality
   - patients vs cost vs length of trial vs feasibility

3. When morphologic info is needed, mainly CT

4. When molecular info relevant, the mid-term future belongs to FDG-PET-CT, role of US, MR?

5. Standardisation is not simple
   - efforts by societies such as SNM to provide standards
   - efforts by CROs and core labs specialized in imaging