Quantitative Inaccuracy in PET/MRI: Is It Real and When Does it Matter

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1. “Clinical” use of PET
2. Potential roles for PET
3. Harmonization
4. Approaches in PET/MRI
Newly diagnosed T3B N2 rectal cancer

Detection of metastatic disease has dramatic impact on patient management
Recurrence in bladder wall

68 year old with lymphoma

Deauville Criteria

Gallamini 2009 JCO
50 year old woman with progressive NET

Detection vs Characterization

**Detection**
- Typically based on qualitative interpretation
- Quantitative accuracy of limited value
- Majority of what we do in clinical interpretation (i.e., are there metastases)

**Characterization**
- Can be broken down into two parts: characterizing response and current state of disease
- Often times does not depend on quantitative accuracy (are the tumors receptor positive)
- Response does depend on quantitative accuracy

### Response criteria

<table>
<thead>
<tr>
<th>RECIST</th>
<th>PERCIST</th>
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<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Complete resolution of 18F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels.</td>
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<tr>
<td><strong>PR</strong></td>
<td>At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters while on study.</td>
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<tr>
<td><strong>SD</strong></td>
<td>Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest measurable diameters while on study.</td>
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<tr>
<td><strong>PD</strong></td>
<td>At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum diameters on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must demonstrate an increase of at least 5 mm.</td>
</tr>
<tr>
<td><strong>CMR</strong></td>
<td>Complete resolution of 18F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels.</td>
</tr>
<tr>
<td><strong>PMD</strong></td>
<td>Not CMR, PR, or SD. SUL peak in metabolic target lesion should be recorded. &gt;30% increase in 18F-FDG SUL peak, with 0.6 SUL unit, increase in tumor SUV peak from baseline scan in pattern typical of tumor and not of infection/treatment effect.</td>
</tr>
</tbody>
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Thymic NET, no interval treatment (Ki67 15)

SUVmax: 6.7
SUVmax: 9.1
SUVmax: 12.3

FDG PET
DOTATATE PET
DOTATATE PET
DOTATATE PET

Imaging biomarkers play a critical role in the approval of therapeutic agents

SPARTAN Trial
M0 CRPC
CT and bone scan negative

There is no such thing as M0 CRPC!

There is no such thing as M0 CRPC!
The majority of clinical uses for PET does not depend on quantitative accuracy

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Potential for combination MRI+PET biomarkers
Why is it important to predict therapy response?

- Both radiation therapy and total mesorectal exenteration are associated with significant side effects.
- In South America, there are large series of patients with "cCR" or a complete clinical response after chemoradiation—this cohort patients have demonstrated good five-year disease-free survival and overall survival.
- cCR was based on endoscopic evaluation.
- If we can predict response, we can withhold surgery or therapy.

The key is an accurate biomarker of response.

PROPSECT trial (N1048 protocol)

- Group 1: chemo rads FOLFOX + Rx
- Group 1: FOLFOX x 6
  - T2/N1:2 T3/NX
  - No progression + >20% regression
  - Progression or <20% regression additional FOLFOX + radiation
  - LAR with TME
OPRA trial

T3-4N0
TX/N1

FOLFOX/CapeOX then radiation

imaging

Based on MRI (both T2 and DWI)

Residual tumor

radiation then FOLFOX/CapeOX

LAR with TME

NOM

No EO disease

Therapy response: 58 year old with rectal cancer

pre-therapy

post-therapy

SUVmax = 25

SUVmax = 5
68M with a PSA of 19 and 4+3 disease

PSMA PET
T2 CUBE
B-1350
Fused T2
DCE DISCO
ADC m

PSMA SUV$_{\text{max}}$ vs Gleason score

Changing prostatectomy population
In PET/MRI, where the combination of PET and MRI biomarkers are being proposed, quantitative accuracy will be critical.

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**PET “Harmonization”**

- Harmonization refers to adjusting reconstruction parameters on PET scanners in order to obtain the same quantitative result when imaging a known quantity.
- Standardization refers to uniform processes and procedures.
- SUV: standardized uptake value, typically represents a percent uptake of the injected radiotracer in an quantity of tissue adjusted by the patient’s body weight.

Courtesy of Richard Laforest
Causes for variability in PET/MRI

- **Biological**: blood glucose level, uptake time, patient motion (breathing or else)
- **Technical**: scanner absolute calibration, cross calibration of PET scanner to local dose calibrator, clock synchronization,…
- **Physical**: Scanner geometry, image reconstruction parameters, data acquisition and data correction (attenuation, scatter), data analysis methodology

Courtesy of Richard Laforest

QIBA FDG PET profile

- Addresses “acquisition, reconstruction and post-processing, analysis and interpretation as steps in a pipeline that transforms data to information to knowledge”
  - Goal is to have a within subject coefficient of variation of less than 12%
  - Increase in SUVmax of 39% or more, or a decrease of -28% or more, indicates that a true change has occurred with 95% confidence
- Defines protocols for patient preparation, injection, scan acquisition, PET reconstruction, image analysis etc.
- There is also similar EANM/EARL protocols

Aide EJNMMI 2017; qibawiki.rsna.org

PET reconstruction

- List mode acquired PET data
- PET reconstruction scatter correction, FBP / OSEM…
- Attenuation correction compensates for attenuation of photons within tissue
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NEMA-IQ phantom imaging (Siemens)

Contrast Recovery Coefficients

- Siemens mMR: 3 iterations, 21 subsets
- Red – 3D-OSEM
- Green – 3D-OSEM+PSF

NEMA-IQ phantom imaging (GE)

Contrast Recovery Coefficients

- GE Signa: 4 iterations, 16 subsets
- Red – 3D-OSEM+TOF
- Green – 3D-OSEM+TOF+Sharp IR

NEMA-IQ phantom imaging (BEST MATCH)

Contrast Recovery Coefficients

- mMR: 4 iterations – 5mm
- Signa: 2 iterations + IR – 7mm
- mMR: 4 iterations – 3mm
- Signa: 2 iterations + IR – 5mm

Richard Lafontest
Harmonization is possible between the two available PET/MRI scanners

but…

PET reconstruction

List mode acquired PET data

Attenuation correction compensates for attenuation of photons within tissue

CT used in PET/CT

"MRAC"

in phase

out of phase

fat

water
ZTE vs MRAC in the pelvis

Bone lesions
Soft tissue lesions

11.0%
3.3%
7.8%

3.9%

Leynes, Med Phys 2017

ZTE based MRAC for florbetapir

PET quantification errors in PET/MRI are spatially dependent
Issues with existing phantoms

PET/MRI phantom

• Requirements:
  – Needs to have density and T1/T2/T2* values that mimic human tissue
  – Preferably anthropomorphic in the era of machine learning
  – Needs to be stable over time

• Questions:
  – Does it need to have hot spheres?
  – Can we split evaluation between two phantoms?
  – Are MRAC issues generalizable across scanners?
    • Can a lesion insertion tool answer this question?

Making PET/MRI phantoms

Copper Relaxivity in Plaster

Larson and Chandramohan
Summary

1. Clinical use of PET imaging, frequently does not depend on quantitative accuracy
2. Due to attenuation correction issues, PET/MRI has spatial quantitative biases (it is real!)
3. Approaches to harmonizing and qualifying PET/MRI scanners do not exist limiting roles in clinical trials

Thank you!
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Acknowledgements

- UCSF
  - Thomas Hope
  - Dharshan Chandramohan
  - Peder Larson
  - Vahid Ravanfar
- Washington University
  - Richard Laforest
  - Hongyu An
  - Kathy Fowler
- University of Washington
  - Paul Kinahan
  - Darren Byrd
- University of Iowa
  - John Sunderland
- GE Healthcare
  - Tim Deller
  - Mandi Kissel
- Siemens
  - David Faul
  - Mike Casey
  - Maurizio Corli

FUNDING:
NCI R01CA212148
Squamous cell carcinoma of the lip: restaging

UCSF PET/MRI case load
41 year old female with seizures

37 year old man with NET status post TI resection - follow-up staging

40 year old man with neuroendocrine tumor with known hepatic metastases
PET/MRI: Evaluation of hepatic metastasis

Eovist, hepatobiliary phase  15 minute dedicated liver acquisition