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

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1. "Clinical" use of PET

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Newly diagnosed T3B N2 rectal cancer
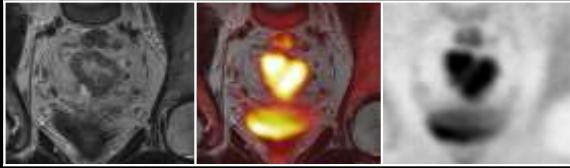
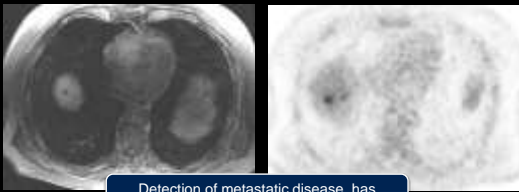## Newly diagnosed T3B N2 rectal cancer

Detection of metastatic disease, has dramatic impact on patient management

Recurrence in bladder wall

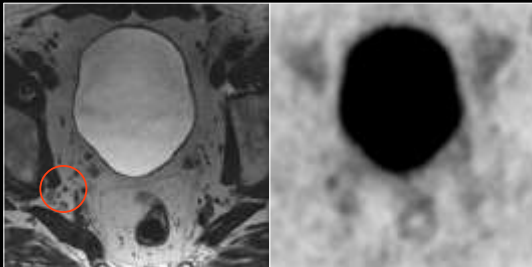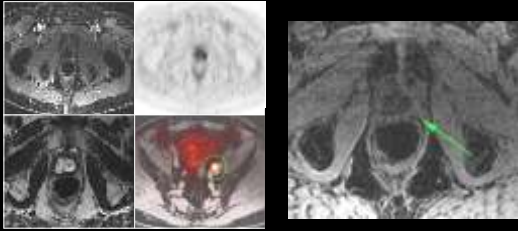68 year old with lymphoma

Deauville Criteria

Negative on post-treatment PET

Positive on post-treatment PET
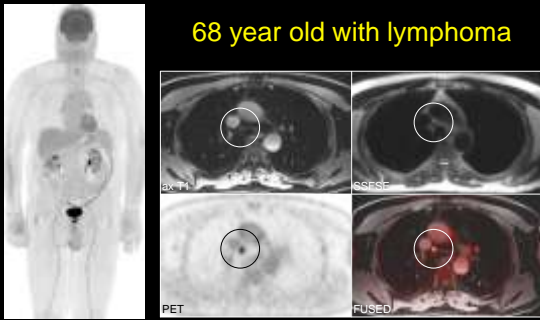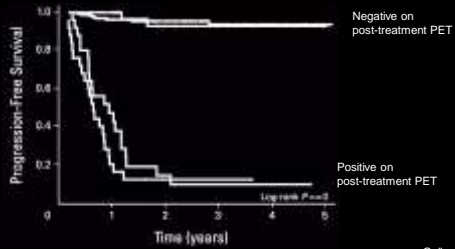
Gallamini 2009 JCO

50 year old woman with progressive NET

4 cycles of ^{177}Lu-DOTATATE
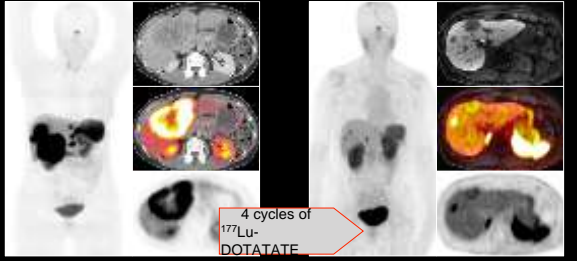
Detection vs Characterization

Detection	Characterization
· Typically based on qualitative interpretation · Quantitative accuracy of limited value · Majority of what we do in clinical interpretation (ie are there metastases)	· 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

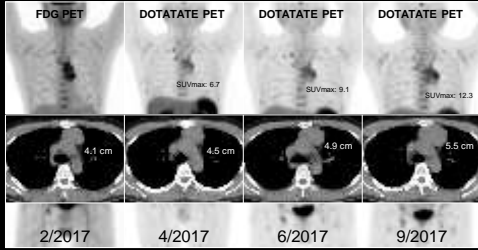|	RECIST		PERCIST
CR	Disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10 mm.	CMR	Complete resolution of 18F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.	PMR	Reduction of minimum of 30% in target measurable tumor 18F-FDG SUL peak. Absolute drop in SUL must be at least 0.8 SUL units
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.	SMD	Not CMR, PMR, or PMD. SUL peak in metabolic target lesion should be recorded
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum 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.	PMD	> 30% increase in 18F-FDG SUL peak, with .0.8 SUL unit, increase in tumor SUV peak from baseline scan in pattern typical of tumor and not of infection/treatment effect.

Thymic NET, no interval treatment (Ki67 15)

FDG PET	DOTATATE PET	DOTATATE PET	DOTATATE PET
	SUVmax: 6.7	SUVmax: 9.1	SUVmax: 12.3
4.1 cm	4.5 cm	4.9 cm	5.5 cm
2/2017	4/2017	6/2017	9/2017

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

SPARTAN Trial

M0 CRPC
CT and bone
scan negative

Smith, NEJM 2018

There is no such thing as M0 CRPC!
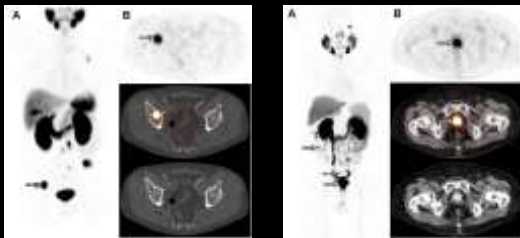
Courtesy of Wolfgang Fendler

The majority of clinical uses for PET does not depend on quantitative accuracy

| 1. "Clinical" use of PET |
| 2. Potential roles for PET |
| 3. Harmonization |
| 4. Approaches in PET/MRI |

Potential for combination
MRI+PET biomarkers

Complete Response after Neoadjuvant Therapy in Rectal Cancer: To Operate or Not to Operate?

Georgia Dedemadi   Steven D. Wexner

Cleveland Clinic Florida, Weston, Fla., USA

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
  - in 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
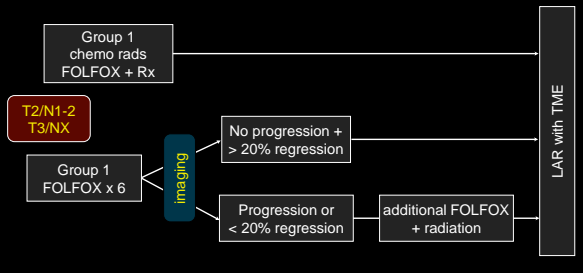
The key is an accurate biomarker of response

PROPSECT trial (N1048 protocol)

```
Group 1
chemo rads
FOLFOX + Rx ──────────────────────────┐
                                       │
T2/N1-2                                │
T3/NX                                  │
           ┌─> No progression +        │── LAR with TME
           │   > 20% regression        │
Group 1    │                           │
FOLFOX x 6 ─imaging                    │
           │                           │
           └─> Progression or ─> additional FOLFOX
               < 20% regression       + radiation
```

OPRA trial

T3-4/N0
TX/N1

FOLFOX/CapeOX
then radiation

radiation then
FOLFOX/CapeOX

imaging

Residual tumor

No EO disease

Based on MRI
(both T2 and DWI)

LAR with TME

NOM

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
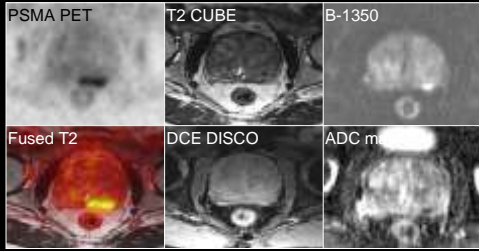
PSMA SUV$_{max}$ vs Gleason score
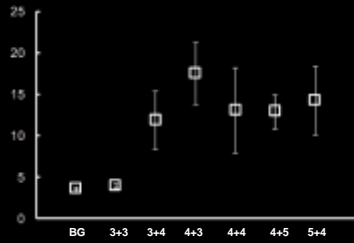
Changing prostatectomy population
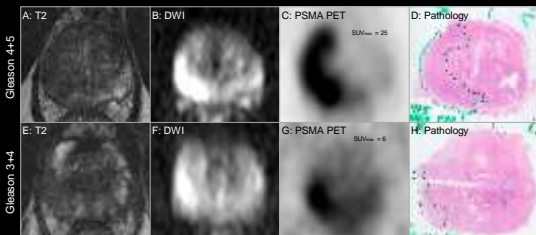
In PET/MRI, where the combination of PET and MRI biomarkers are being proposed, quantitative accuracy will be critical

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PET "*Harmonization*"

- Harmonzation 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

- <u>Biological</u>: blood glucose level, uptake time, patient motion (breathing or else)
- <u>Technical</u>: scanner absolute calibration, cross calibration of PET scanner to local dose calibrator, clock synchronization,…
- <u>Physical</u>: 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
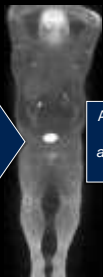
PET reconstruction

List mode acquired PET data

PET reconstruction *scatter correction, FBP / OSEM…*

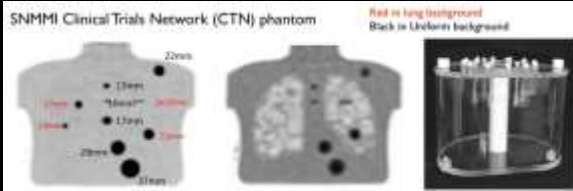Attenuation correction *compensates for attenuation of photons within tissue*

CTN PET phantom

SNMMI Clinical Trials Network (CTN) phantom

Red in lung background
Black in Uniform background

Sunderland, 2015, JNM

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PET reconstruction

List mode
acquired PET data

PET reconstruction
*scatter correction,
FBP / OSEM…*

Step 1

Attenuation correction
*compensates for
attenuation of photons
within tissue*
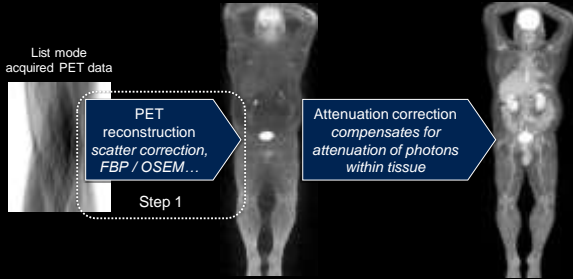
NEMA-IQ phantom imaging (*Siemens*)

Contrast Recovery Coefficients

SUV mean   SUV max   SUV peak
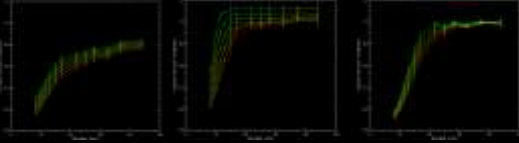
• Siemens mMR - 3 iterations, 21 subsets
• Red – 3D-OSEM
• Green – 3D-OSEM+PSF

Richard Laforest

NEMA-IQ phantom imaging (*GE*)

Contrast Recovery Coefficients

SUV mean   SUV max   SUV peak
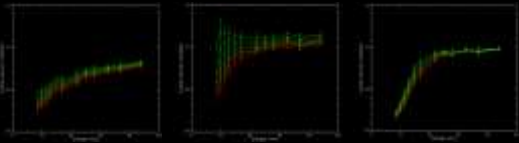
• GE Signa - 4 iterations, 16 subsets
• Red – 3D-OSEM+TOF
• Green – 3D-OSEM+TOF + Sharp IR

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NEMA-IQ phantom imaging (*BEST MATCH*)

Contrast Recovery Coefficients

SUV mean   SUV max   SUV peak

mMR: 4it – 5mm   mMR: 4it – 5mm   mMR: 4it – 3mm
Signa: 2it+IR – 7mm Signa: 2it – 5mm   Signa: 2it+IR – 5mm
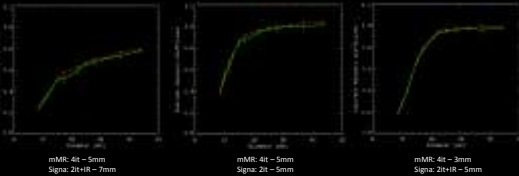
Richard Laforest

Harmonization is possible between the two available PET/MRI scanners

but…

PET reconstruction

List mode acquired PET data

PET reconstruction
scatter correction, FBP / OSEM…

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

3.3%

3.9%

7.8%

11.0%

Leynes, Med Phys 2017

ZTE based MRAC for florbetapir
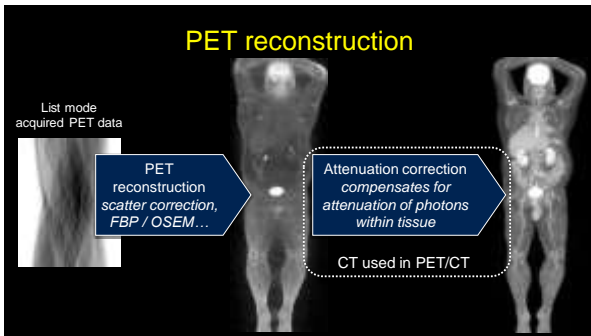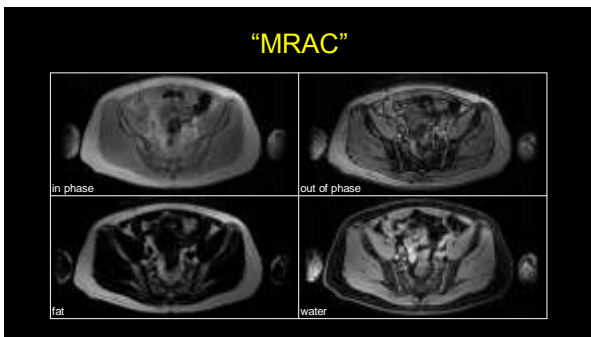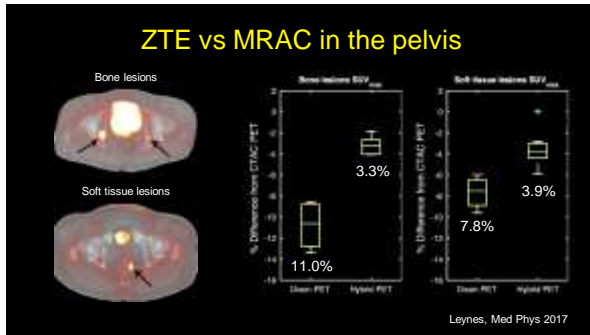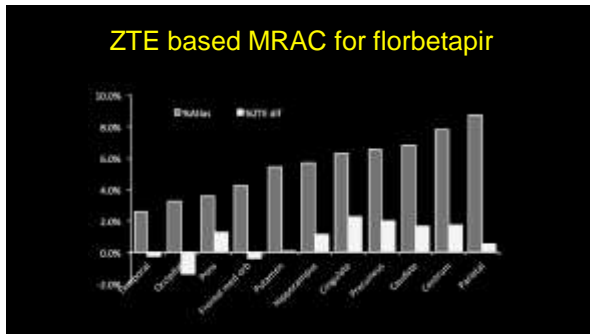
PET quantification errors in PET/MRI are spatially dependent

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Issues with existing phantoms

Tropp J. J Magn Reson. 2004;167:12–24.
Ziegler S, et al. J Nucl Med. 2013;54:1464–1471.

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
(T2*/R2*)

Day 1

Day 14

Larson and Chandramohan
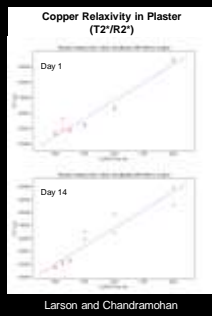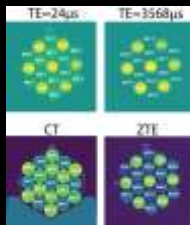
Summary

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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PSMA PET

ax PSMA

Fused

T1

Acknowledgements

NIH NATIONAL CANCER INSTITUTE

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Squamous cell carcinoma of the lip: restaging
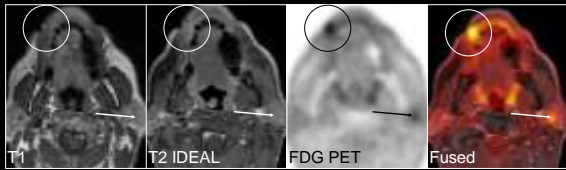
UCSF PET/MRI case load
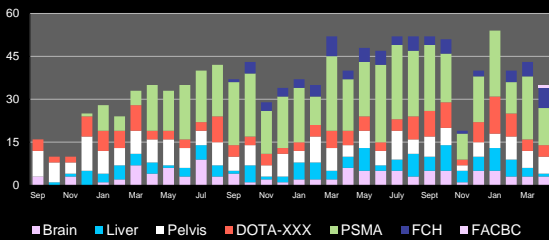
41 year old female with seizures

T2   Fused   PET
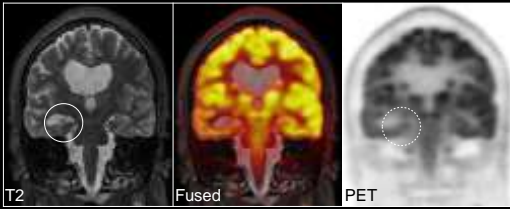
37 year old man with NET status post TI resection - follow-up staging

PET   T1

fused - T1   DWI (b=600)   physiologic activity
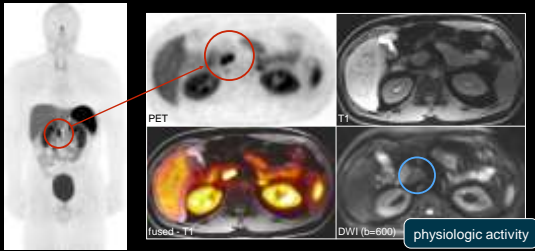
40 year old man with neuroendocrine tumor with known hepatic metastases

DOTA-TOC PET   T1

Fused   DWI (b-600)   true positive disease
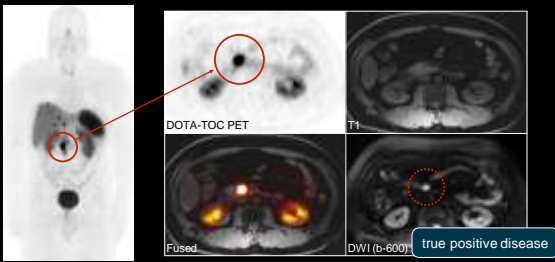
PET/MRI: Evaluation of hepatic metastasis

Eovist, hepatobiliary phase   15 minute dedicated liver acquisition