PET/CT and SPECT/CT for Lung and Liver Radiation Therapy Response Assessment of Tumor and Normal Tissue

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Hallmarks of Molecular Imaging for Assessing Response

- **Sensitivity**
  - Efficient detection of differential molecular image signal prior to, during, after therapy
- **Specificity**
  - Imaging marker changes associated with specific therapeutic response
  - Metabolism, proliferation, hypoxia, angiogenesis, apoptosis, perfusion
- **Quantification**
  - Accurate and reproducible estimate of molecular image intensity
- **Spatial resolution**
  - Resolve spatial heterogeneity in response of imaging biomarker
- **Clinical utility**
  - Imaging biomarkers of response associated with clinical outcome

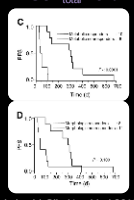
Sample RT Response Applications

1. FDG PET/CT for lung cancer response assessment
2. Perfusion & ventilation SPECT/CT for lung tissue response assessment
3. Sulfur colloid SPECT/CT for liver tissue response assessment
4. Radiotherapy Planning to Account for Tumor / Normal Tissue Response Variation

PET/CT for Lung Cancer Response to RT

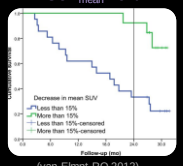
Clinical Utility of FDG PET Response for Lung Cancer Patient Survival Prediction

1 month post FDG PET
ΔSUV_{total} 25%



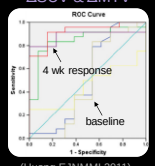
(Takahashi Clin Nuc Med 2012)

2 week mid FDG PET
ΔSUV_{mean} 15%



(van Elmpt RO 2012)

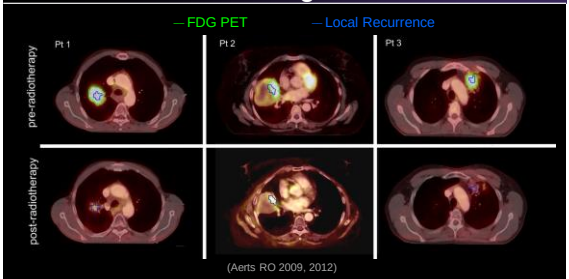
4 week mid FDG PET
ΔSUV & ΔMTV



(Huang EJNMMI 2011)

- Outcome prediction improves with FDG PET response measures relative to baseline FDG PET alone or CT response measures
- Combination of magnitude (SUV) and volume (MTV)

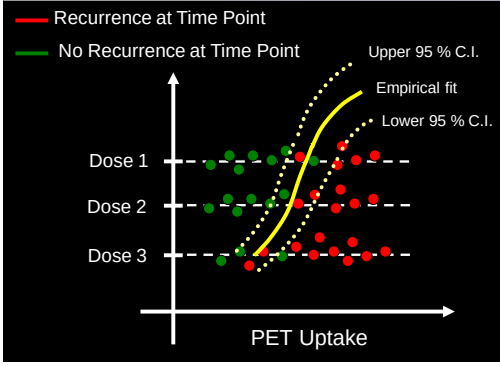
FDG PET Spatial Correlation with Lung Cancer Recurrence/Progression



(Aerts RO 2009, 2012)

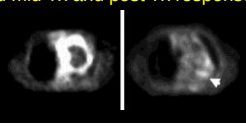
- FDG PET as spatial map of local failure risk distribution

Regional Dose-response Curve



Challenges in Regional Lung Tumor Response

- Spatial and temporal stability → test / retest
- Tumor volume regression and deformation → validated deformable image registration
- Attenuation correction artifacts at lung-tissue interfaces → motion-corrected PET & CT
- FDG PET inflammatory signal at lung-tumor boundary → optimized mid Tx and post Tx response time points

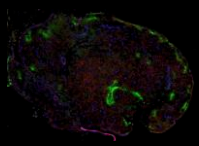


(Feng IJROBP 2009)

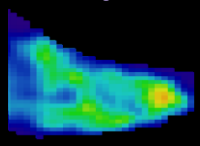
Multiscale Cancer Biology → From Global to Regional Response

- Tumor biology assessed at micron scale reveals high heterogeneity within PET millimeter voxels
- How does this affect response assessment?

IHC Slide



PET Image

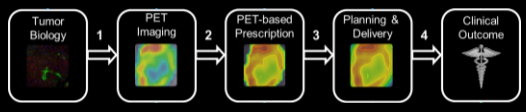


(courtesy of van der Kogel and Jeraj)

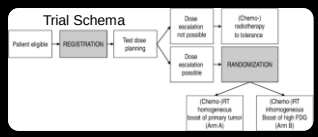
October 18, 2011
Email: srbowen@uw.edu

Accounting for Inter- and Intra-patient Variability in Tumor Response to RT

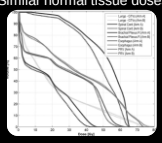
- Subvolume boosting
  - Biological target volumes (BTV) for uniform dose escalation
    (Ling 2000, Tome 2003, Madani 2009)
- Dose painting by numbers accounts for intratumoral variations in response to therapy
  (Brahme 2003, Bentzen 2005, Le 2007, Stewart 2007)



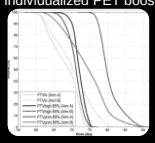
FDG PET Subvolume Boost Trial (Maastricht + NKI)



Similar normal tissue doses

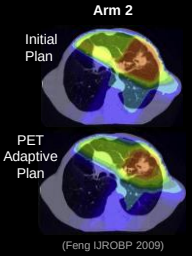


Individualized PET boost



- Average dose increase to PET avid areas up to 85+ Gy in 24 fractions
  (van Elmpt RO 2012)

FDG PET Adaptive Boost Trial (RTOG 1106)



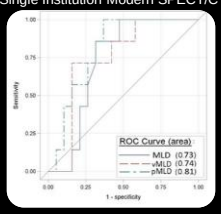
(Feng IJROBP 2009)

- Magnitude of dose escalation directly adapted based on mid Tx FDG PET (up to 80.4 Gy in 30 fractions)

SPECT/CT for Lung Tissue Response to RT

Clinical Utility of Lung Perfusion MAA SPECT for Pneumonitis Prediction

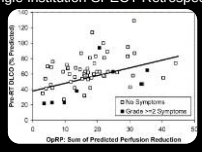
Single Institution Modern SPECT/CT



(Hoover JMIRO 2014)

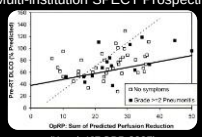
- Standardization of imaging technique and definition of response endpoint essential

Single Institution SPECT Retrospective



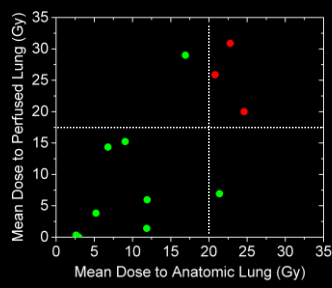
(Kocak IJROBP 2007)

Multi-institution SPECT Prospective



(Kocak IJROBP 2007)

Lung Perfusion Imaging Biomarker of Pneumonitis Risk



G2+ PNM Negative

G2+ PNM Positive

- Best combined predictors of pneumonitis (AUC > 0.92)
  - Mean lung dose
  - Mean perfused lung dose

(Bowen, Zeng World Lung 2015)

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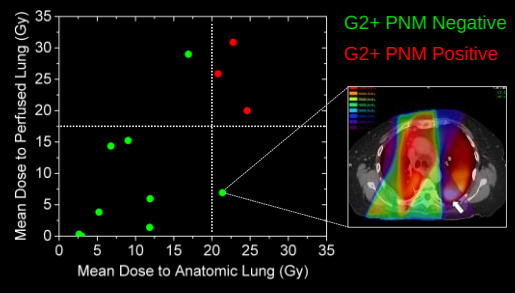
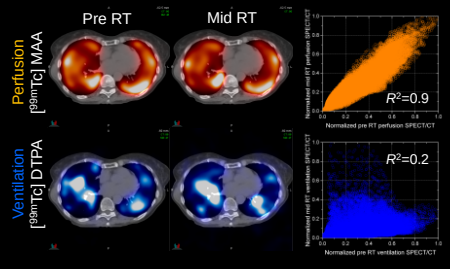
Lung Perfusion Imaging Biomarker of Pneumonitis Risk



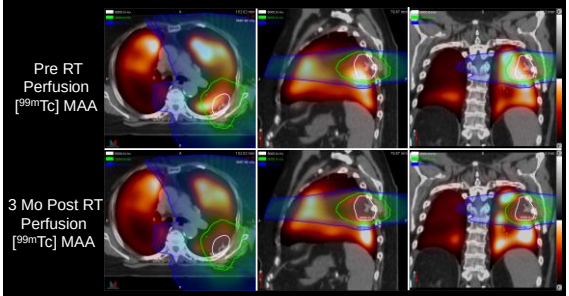
(Bowen, Zeng World Lung 2015)

Spatial Stability of Normal Tissue Response Assessment

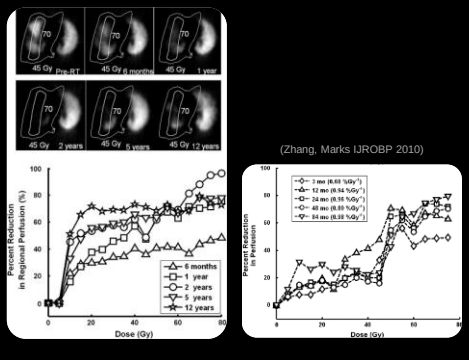


- MAA SPECT perfusion: median Pearson *R* = 0.95 (IQR 0.83-0.96)
- DTPA SPECT ventilation: median Pearson *R* = 0.63 (IQR 0.42-0.86)

MAA SPECT/CT Regional Perfusion Response at 3 Months Post RT

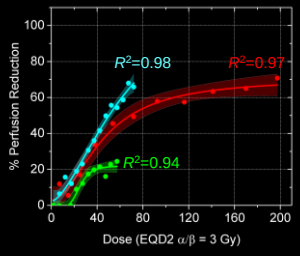


MAA SPECT Lung Perfusion Response at 3 months – 7 years Post RT



(Zhang, Marks IJROBP 2010)

MAA SPECT/CT Lung Perfusion Dose Response Curve Sensitivity



Baseline perfusion defect (VQ mismatch)

SBRT Regimen

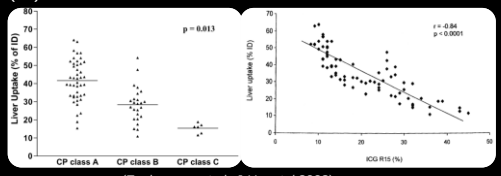
Baseline lung function normal

- Perfusion reduction normalized to lung regions < 5 Gy EQD2
- Shape of individual dose-response curves sensitive to baseline lung function and treatment regimen

SPECT/CT for Liver Tissue Response to RT

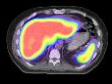
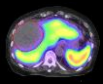
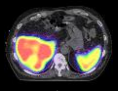
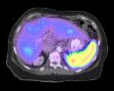
Clinical Utility of Colloid SPECT as Biomarker of Liver Function

- [^{99m}Tc] phytate colloid SPECT imaging
- Liver uptake = % injected dose (ID) normalized to volume (cc) of liver



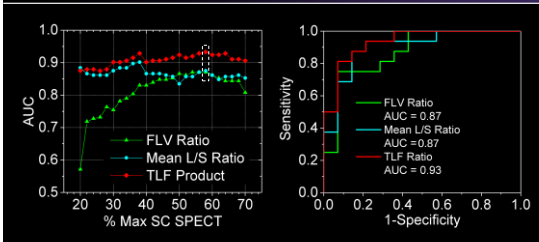
(Zuckerman et al. *J Hepatol* 2003)

Patterns of [^{99m}Tc] Sulfur Colloid (SC) SPECT Uptake

	High Global Uptake	**Low Global** Uptake
Homogeneous Regional Uptake	 Untreated CP-A6	 Untreated CP-B7
Heterogeneous Regional Uptake	 Treated CP-A5 Chemoembolization	 Untreated CP-B7

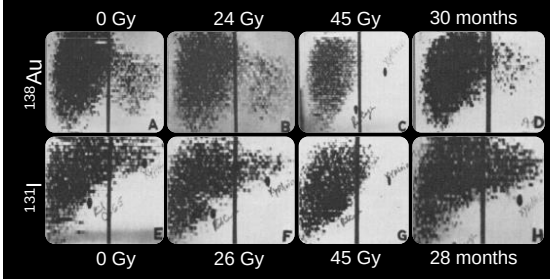
(Bowen, Apisarnthanarax SNMMI 2014)

Correlation of Global SC SPECT to Clinical Liver Function (Child-Pugh score)



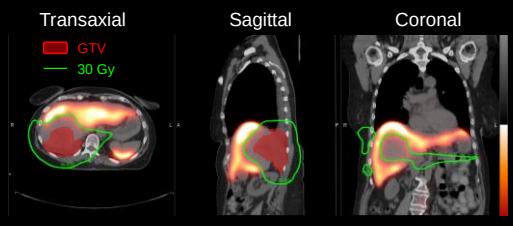
- Quantitative imaging biomarkers of liver function magnitude (liver-to-spleen ratio) and volume can be tracked during and post RT to assess response

Planar Scintigraphy for Functional Liver Radiation Dose Response and Recovery



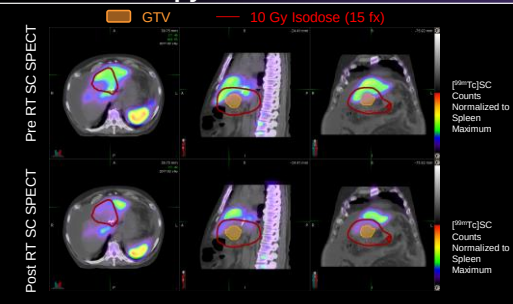
(Kurohara et al. *Radiology* 1967)

Functional Liver Imaging Response to Radiation Therapy



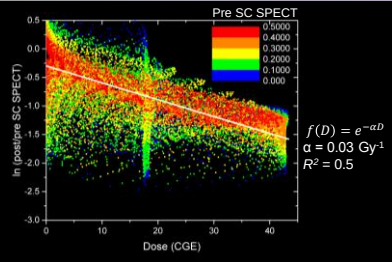
- 1 month post radiation therapy time point following functional liver response but prior to recovery

Functional Liver Imaging Response to Radiation Therapy in HCC



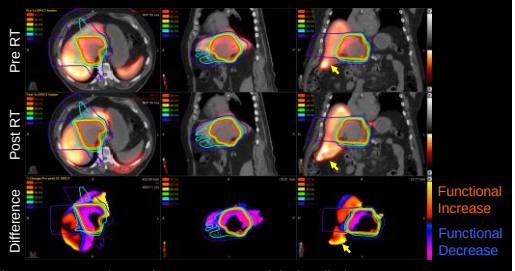
- Global response of cirrhotic liver: functional volume percentage of total liver volume reduced from 20% to 10%

Voxelwise Log-linear Dose Response



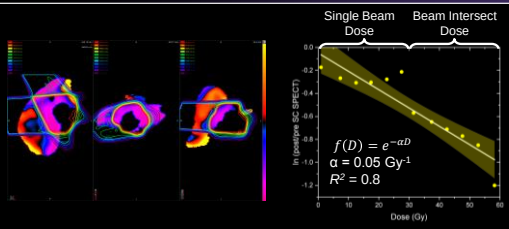
- Response models with/without covariance term for neighboring image voxels
- Statistical noise amplified in low dose / low baseline liver function areas

Impact of Liver Deformation and Tissue Recovery on Response



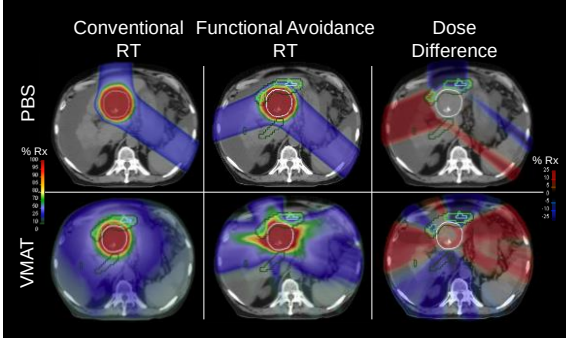
- Liver compensation reduces apparent global radiation response on imaging → functional liver volume decreased from 40% to 35%
- Deformable registration necessary for some cases

Binned Log-linear Dose Response



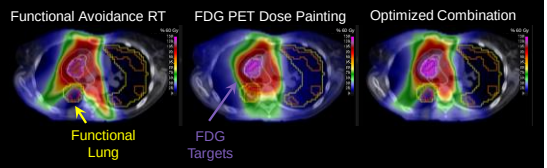
- Statistical averaging over bins of radiation dose mitigates uncertainties in image voxel alignment
- High dynamic range of doses provides more statistical power than discrete beams of homogeneous dose

Dose Painting to Avoid Functional Liver



(Bowen et al. *RO* 2015)

Dose Painting to Avoid Functional Lung and Escalate Tumor Dose



- Functional lung avoidance to reduce pneumonitis risk
  - Mean perfused lung dose reduced below 10 Gy
- Tumor dose escalation to reduce local failure risk
  - PTV covered by base dose of 60 Gy
  - FDG avid regions redistributed to 90+ Gy

Summary

- Imaging biomarker response assessment comes in different flavors
  - Tumor response (global / regional)
  - Normal tissue response (global / regional)
- Dose painting based on imaging biomarkers accounts for heterogeneity in response
  - Tumor: PET Boost Trial, RTOG 1106, H&N PET adaptive
  - Normal tissue: functional lung, functional liver, proliferative bone marrow avoidance
- Future opportunities
  - Integrating imaging and tissue biomarkers into response assessment of combination therapy (e.g. RT + immunotherapy)
  - Maximizing therapeutic ratio through molecular image-guided RT dose painting of tumor and normal tissue

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- Dosi, Sim, RT staff
- (and many more)

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