Functional Image-guided Thoracic and Hepatic Radiation Therapy: synergies between nuclear medicine and radiation oncology

Stephen R. Bowen, PhD, DABR
Associate Professor, Radiation Oncology & Radiology (joint)
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UW Medicine

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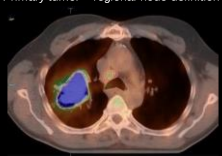
Synergy: Nuc Med Imaging for Precision Rad Onc

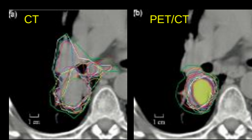
- Key premise is that therapeutic ratio (efficacy / toxicity) can be individually optimized
- Nuc med imaging as a biomarker to risk stratify rad onc patients
  - Select therapies, dosing, fractionation
  - Define target / organs-at-risk volumes + dose objectives
- Nuc med imaging as a biomarker to evaluate individual RT response
  - Adapt therapies, dosing, fractionation
  - Adapt target / organs-at-risk volumes + dose objectives
- Nuc med imaging to spatially optimize RT dose distribution
- Applications of nuc med imaging to radiation therapy for thoracic / hepatic cancers

FDG PET/CT for RT Target Definition

Primary tumor + regional node definition



De Ruysscher 2012

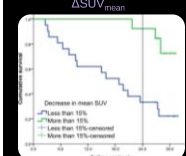


	CT	PET/CT
SD	1 cm	0.4 cm
Disagreement	45%	18%
Delineation time	16 min	12 min

Steenbakkers RJ et al. IJROBP 64: 435-448, 2006

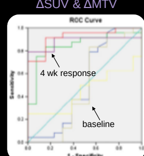
Mid-RT PET Response Outcome Stratification

2 week mid FDG PET
ΔSUV_{mean}



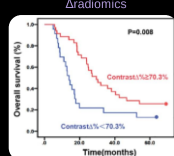
van Elmpt JNM 2012

4 week mid FDG PET
ΔSUV & ΔMTV



Huang EJNMMI 2011

4 week mid FDG PET
Δradiomics

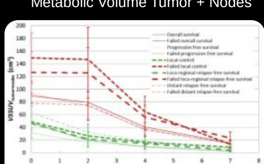


Dong PLoS One 2016

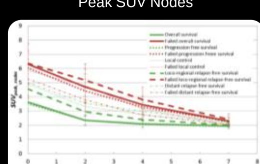
- Outcome prediction improves with FDG PET mid-RT response measures relative to baseline FDG PET

Timing of PET Response Assessment during RT

Metabolic Volume Tumor + Nodes



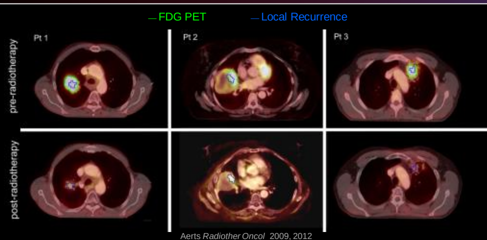
Peak SUV Nodes



Bissonette *et al. Radiother Oncol* 2018

- Improved risk stratification on mid-PET within 4 weeks of RT start

FDG PET Predicts RT Failure Patterns



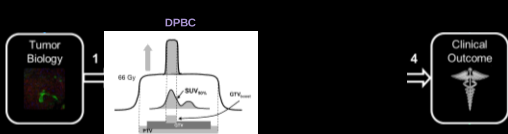
Aerts *Radiother Oncol* 2009, 2012

- FDG PET as spatial map of local treatment failure risk distribution

Jouglar *Radiother Oncol* 2018

NM Imaging to Optimize RT Spatial Dose Distribution

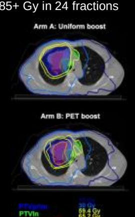
- Dose painting by contours / Subvolume boosting
  - Biological target volumes (BTV) for uniform dose escalation (Ling 2000, Tome 2003, Madani 2009)
- Dose painting by numbers accounts for intratumoral variations in response to therapy (Brahme 2003, Bentzen 2005, Le 2007, Stewart 2007)



Meijer et al. 2011 Radiother Oncol

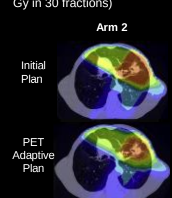
FDG PET-guided Lung Dose Painting Clinical Trials

- NKI+Maastricht: average dose increase to PET avid areas up to 85+ Gy in 24 fractions



van Elmpt *Radiother Oncol* 2012

- RTOG 1106: dose escalation based on mid Tx PET (up to 80.4 Gy in 30 fractions)

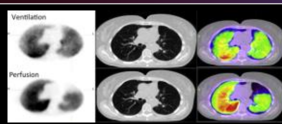


Kong et al. NRG

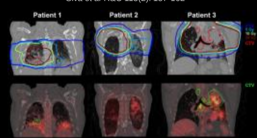
Email: srbowen@uw.edu

Nuc Med Lung Functional Imaging

- Perfusion
  - ^{99m}Tc-MAA SPECT/CT
  - ^{68}Ga-MAA PET/CT
- Ventilation
  - ^{99m}Tc-DTPA SPECT/CT
  - ^{99m}Tc-Technegas SPECT/CT
  - ^{68}Ga-Galligas PET/CT
- Inflammation
  - FDG PET/CT

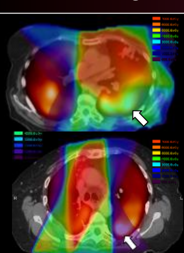


Siva *et al* R&O 115(2): 157-162



Petit, DeRuysscher IJROBP 2011

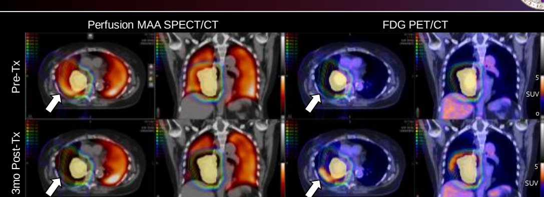
Functional Lung Dosimetry for Toxicity Prediction



Dahmi et al. *Strahlenther Onkol* 2017
Lee et al. *IJROBP* 2018

- Patients with similar clinical characteristics & anatomic dosimetry (MLD)
  - Upper lobe primary tumors
  - Conventionally fractionated chemoRT
  - Anatomic mean lung dose 16.6 Gy (top) vs. 16.4 Gy (bottom)
- Different functional lung dosimetry (pMLD)
  - Top (pneumonitis): perfused mean lung dose 24.2 Gy
  - Bottom (no pneumonitis): perfused mean lung dose 8.6 Gy
- Combined MLD and pMLD best predict for Grade 2+ pneumonitis in initial (AUC = 0.92) and expanded patient cohorts (AUC = 0.94)

Functional Lung RT Dose-response Modeling



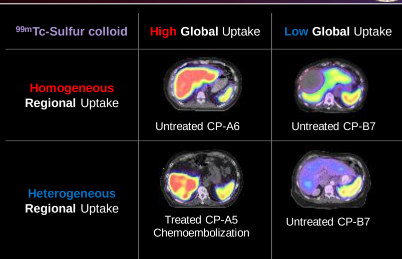
- Perfusion decline spatially correlates with increased inflammation in high dose regions
- Baseline high perfusion regions have steeper (more sensitive) dose-response curves

Thomas et al. *BJR* (under review)

Owen et al. *IJROBP* 2018

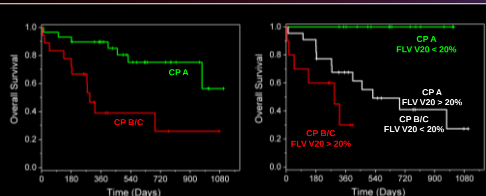
Nuc Med Liver Functional Imaging

- PET/CT
  - FDG
  - FDGalactose
- SPECT/CT
  - GSA
  - HIDA
  - Sulfur colloid



Bowen et al. *EJNMMI Res* 2016

Functional Liver Dosimetry for Outcome Stratification

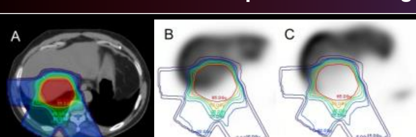


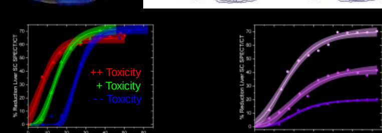
Group	Median OS (days)	1 year OS	Log rank p
CP A	-	90%	0.002
CP B/C	292	39%	

Schaub et al. *IJROBP* 2018

Group	Median OS (days)	1 year OS	Log rank p
Low Risk	-	100%	
Intermediate Risk	525	68%	0.0002
High Risk	292	30%	

Functional Liver RT Dose-response Modeling

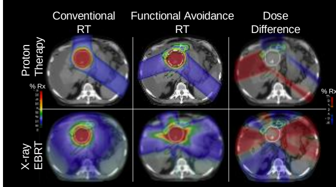




Price *et al. IJROBP* 2018

Functional Liver Avoidance Clinical Trials

Differential Hepatic Avoidance Radiation Therapy (DHART) Planning (U Wash)



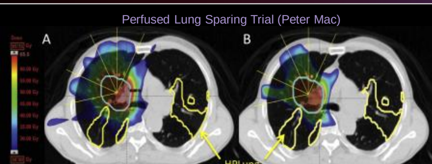
Bowen et al. *Radiother Oncol* 2015

Functional liver image-guided hepatic therapy (FLIGHT) trial (Indiana)

- HIDA SPECT/CT
- Maximize functional liver volume receiving < 15 Gy
- Inter-patient variability in benefit

Functional Lung Avoidance Clinical Trials

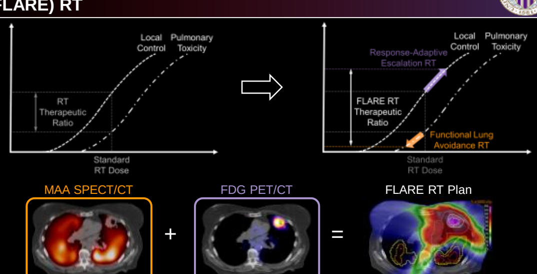
Perfused Lung Sparing Trial (Peter Mac)



Siva *et al* R&O 115(2): 157-162

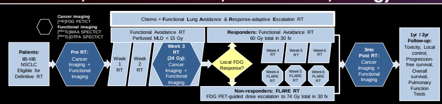
- IMRT plans adapted to avoid perfused lung on 4D MAA PET/CT
- Ongoing functional lung avoidance trials using NM imaging
  - 4D MAA PET/CT (Peter MacCallum)
  - MAA SPECT/CT (U. Washington, U. Michigan)

Functional Lung Avoidance & Response-adaptive Escalation (FLARE) RT



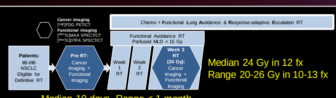
Lee et al. *Med Phys* 2017

FLARE-RT Phase II Trial (NCT02773238, R01CA204301, PI: Bowen, Zeng)



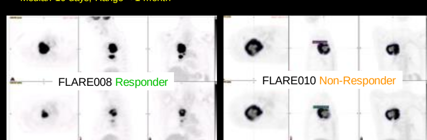
- All patients get functional lung avoidance RT: potential quality of life benefit
- Only high local failure risk patients get FDG PET-guided dose escalation: potential survival benefit
- 1° endpoint: 2 yr overall survival vs. RTOG 0617 60 Gy arm
- 2° endpoints: 1 yr local control, grade 2+ pneumonitis incidence vs historical rates

FLARE-RT Mid-Tx PET Response Assessment



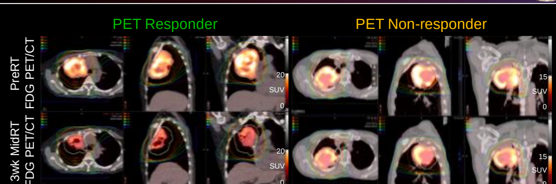
Median 24 Gy in 12 fx
Range 20-26 Gy in 10-13 fx

Median 10 days, Range < 1 month

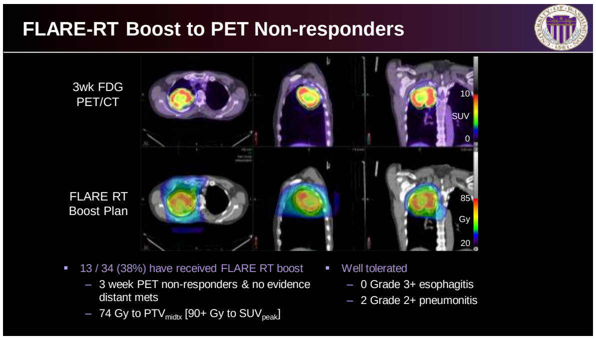


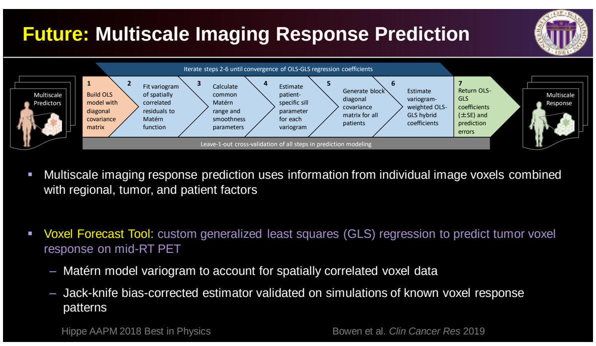
- PET Responders: ΔSUV_{peak} decrease 40% (32-48%), ΔMTV decrease 40% (32-62%)
- PET Non-responders: ΔSUV_{peak} decrease 13% (8-23%), ΔMTV decrease 9% ([-5]-21%)

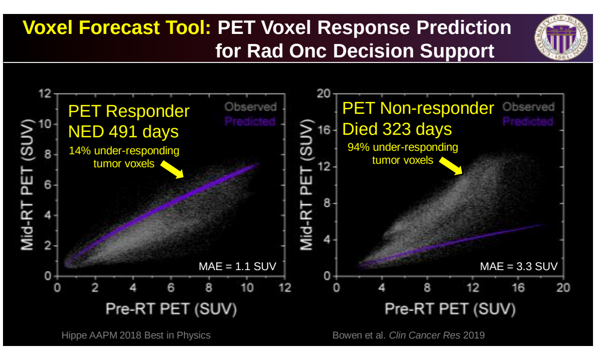
FLARE-RT Plan Adaptation Decisions



- PET Responder: required anatomic adaptation to 60 Gy in 30 fx
- PET Non-responder: required functional adaptation to 74 Gy in 30 fx

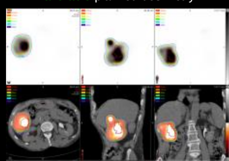

FLARE-RT Boost to PET Non-responders
3wk FDG PET/CT
10
SUV
0
FLARE RT Boost Plan
85
Gy
20
13 / 34 (38%) have received FLARE RT boost
– 3 week PET non-responders & no evidence distant mets
– 74 Gy to PTVmidtx [90+ Gy to SUVpeak]
Well tolerated
– 0 Grade 3+ esophagitis
– 2 Grade 2+ pneumonitis


Future: Multiscale Imaging Response Prediction
Iterate steps 2-6 until convergence of OLS-GLS regression coefficients
Multiscale Predictors
1 Build OLS model with diagonal covariance matrix
2 Fit variogram of spatially correlated residuals to Matérn function
3 Calculate common Matérn range and smoothness parameters
4 Estimate patient-specific sill parameter for each variogram
5 Generate block diagonal covariance matrix for all patients
6 Estimate variogram-weighted OLS-GLS hybrid coefficients
7 Return OLS-GLS coefficients (±SE) and prediction errors
Multiscale Response
Leave-1-out cross-validation of all steps in prediction modeling
Multiscale imaging response prediction uses information from individual image voxels combined with regional, tumor, and patient factors
Voxel Forecast Tool: custom generalized least squares (GLS) regression to predict tumor voxel response on mid-RT PET
– Matérn model variogram to account for spatially correlated voxel data
– Jack-knife bias-corrected estimator validated on simulations of known voxel response patterns
Hippe AAPM 2018 Best in Physics
Bowen et al. Clin Cancer Res 2019

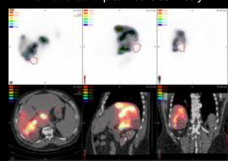

Voxel Forecast Tool: PET Voxel Response Prediction for Rad Onc Decision Support
PET Responder
NED 491 days
14% under-responding tumor voxels
Observed
Predicted
MAE = 1.1 SUV
PET Non-responder
Died 323 days
94% under-responding tumor voxels
Observed
Predicted
MAE = 3.3 SUV
Mid-RT PET (SUV)
Pre-RT PET (SUV)
Hippe AAPM 2018 Best in Physics
Bowen et al. Clin Cancer Res 2019

Future: Personalizing NM+RO for HCC management

Favorable planned dosimetry



Unfavorable planned dosimetry



- Favorable planned dosimetry: personalize ^{90}Y-microsphere prescriptions to achieve isotoxicity in liver → verify on ^{90}Y-SPECT/PET dosimetry
- Unfavorable planned dosimetry: modify ^{90}Y-microsophere injection site → boost any remaining cold ^{90}Y-SPECT/PET dosimetry regions with SBRT

Summary: Synergies between Nuc Med and Rad Onc

- Nuc Med imaging to personalize Rad Onc
  - Risk stratify patients
  - Define targets and functional normal tissues
  - Optimize prescriptions and planned radiation dose distributions
  - Assess early response for adaptive therapy
- Future: combined NM image-guided RT with NM therapies
  - RT + targeted radionuclide therapy (TRT) + immunotherapy (IO)
  - NM imaging for targeting / avoidance / dosimetry / verification / response
  - Radiomics / machine learning of NM imaging to personalize NM + RO Tx

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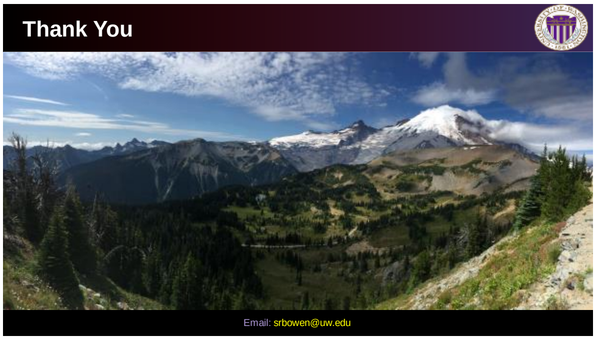
Thank You
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