Quantitative Imaging for Treatment Response Assessment

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Memorial Sloan Kettering Cancer Center

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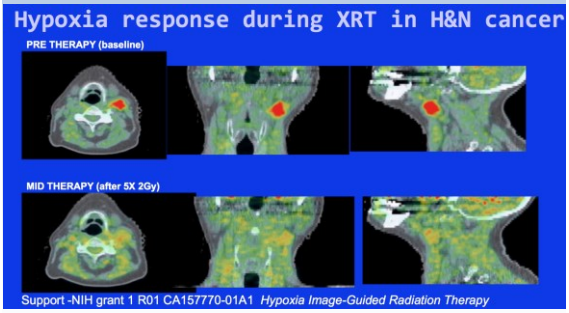
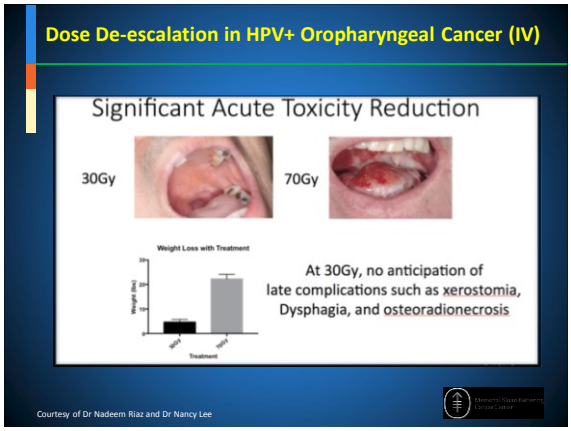
Predicting response to RT or chemo can be based on:

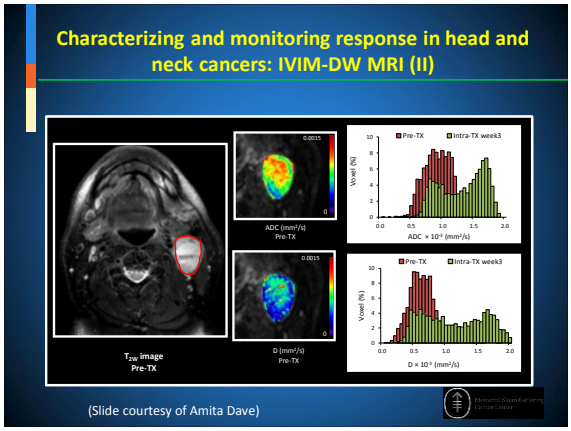
- Volumetrics
- Radiomics
- Imaging relevant to drug bioavailability
- Imaging relevant to tumor microenvironment (e.g., hypoxia)
- Models of TCP that include imaging variables
- …using PET, MRI, CT.

To dose or not to dose…

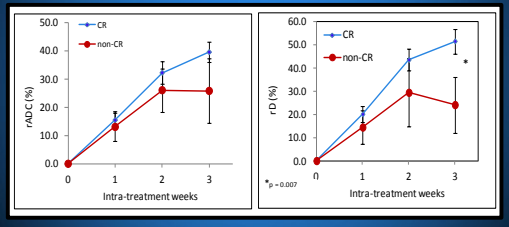


If hypoxia is resolved on F-MISO scan in two weeks…de-escalate to 30 Gy!





Responders vs. non-responders

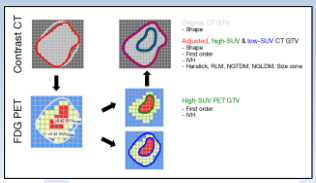


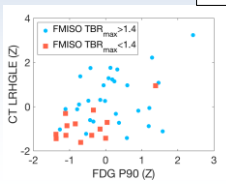
$rADC\ (\%) = (ADC_{irek} - ADC_{Dwk0})/ADC_{Dwk0} * 100\ ;\ i = 1, 2, 3\ ;\quad rD\ (\%) = (D_{irek} - D_{Dwk0})/D_{Dwk0} * 100\ ;\ i = 1, 2, 3$

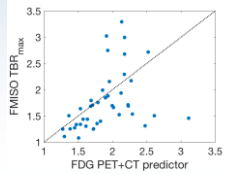
(Image courtesy Amita Dave)

Combined PET and CT radiomics features predict maximum FMISO uptake in head and neck cancer (Crispin-Ortuzar et al.)

- FDG PET + contrast-enhanced CT to predict maximum FMISO TBR
- 79 training, 42 hold-out validation
- LASSO + 10x10-fold CV
- Selected predictors:
  - *P90 FDG SUV*
  - *Long run high grey level emphasis in low-FDG subregion*
- Validation AUC = 0.83





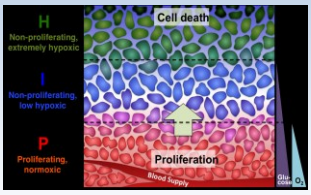


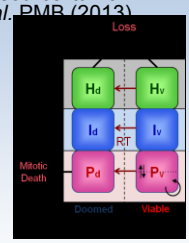
Cellular State Simulations to Predict Response to Radiation Therapy

Jeho Jeong, Mireia Crispin-Ortuzar, Andrew Fontanella, and Joe Deasy

Simulation model: the basics

- We introduce a 'constant-resource' tumor response model (Jeong *et al.* PMB (2013) 58:4897)



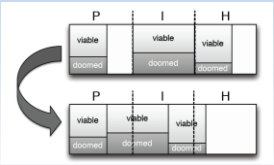


- Chemical supply is assumed constant over the course of RT

Assume re-compartmentalization: *this leads to reoxygenation*

- Assume oxygen and glucose can 'feed' a constant number of cells
- Then re-distribution constantly occurs that assumes P is the preferred state, then I, then H.
- This implies a 'reoxygenation' process

After an (exaggerated) time step:



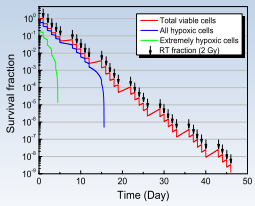
Lung tumor cohort dose-response

- Dose response across different fractionation regimes: Mehta et al. (Pract. Radiat. Oncol. (2012) 2:288-295) (N=2189)
- Three additional cohorts (including WUSTL, NKI) (N=512)

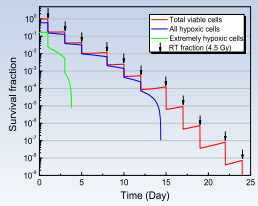
(Jeong et al., Clinical Cancer Res, In press)

Use the model at 2 Gy/day as a reference

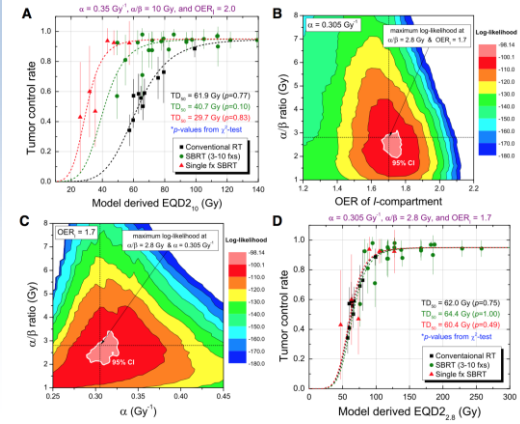
- 2 Gy/fx (5 fx/wk)
- 4.5 Gy/fx (3 fx/wk)

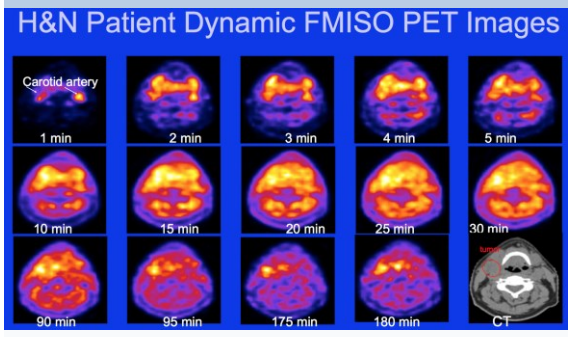


Treatment duration = **45.4 days**
TD_{50} = **66.8 Gy** (in $EQD2_6$)



Treatment duration = **23 days**
TD_{50} = **62 Gy** (in $EQD2_6$)





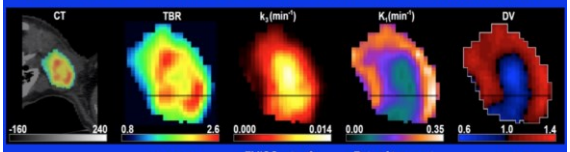
(Images courtesy John Humm)

Spatial and Temporal Effects

Use kinetic models that govern the radiopharmaceutical transport

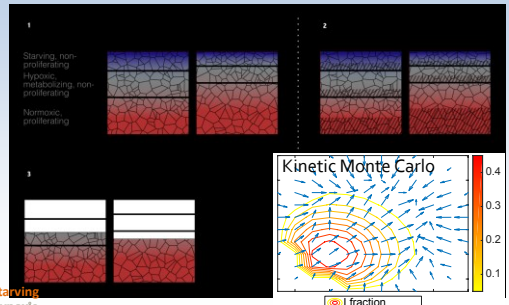
Determine the rate constants that measure the desired parameters

Grkovski M, Schöder H, Lee N, Carlin SD, Beattie BJ, Riaz N, Leeman JE, O'Donoghue JA, Humm JL. Multiparametric imaging of tumor hypoxia and perfusion with ^{18}F-FMISO dynamic PET in head and neck cancer. J Nucl Med. 2017 Feb 9.



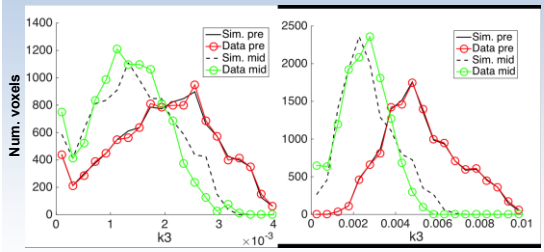
FMISO distribution at 3hr | FMISO rate of irreversible trapping | Rate of transport blood to extravascular space | FMISO distribution volume

Including heterogeneity & cell migration



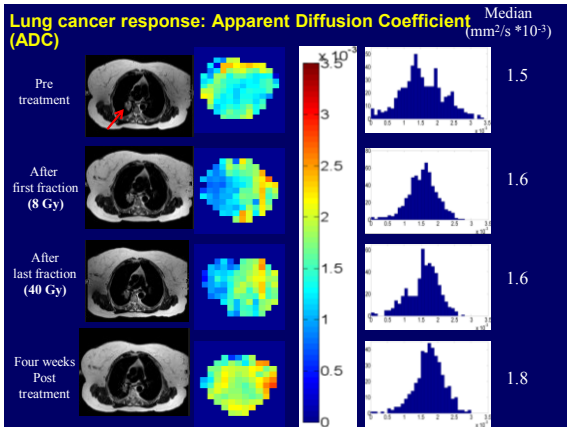
Starving
Hypoxic
Proliferative

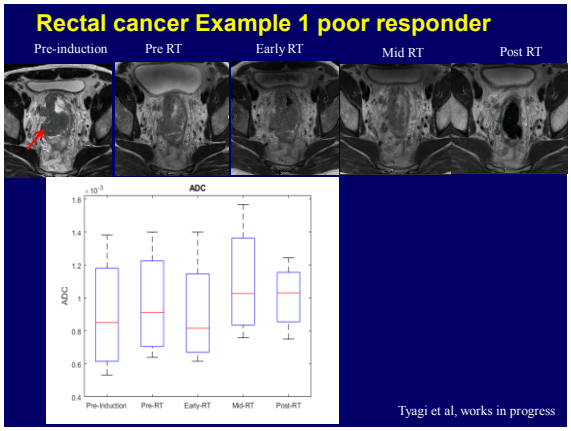
The model can make predictions of H&N hypoxia histogram evolution during RT

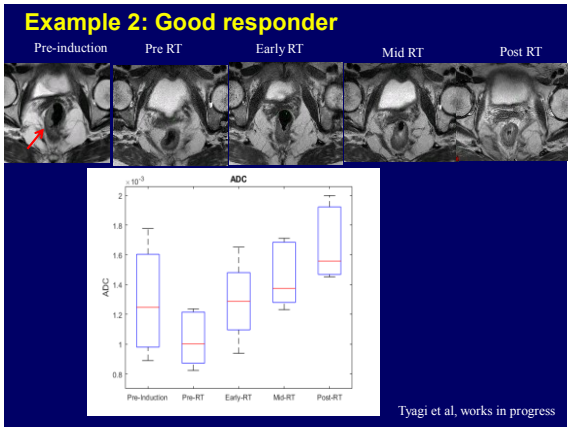


Works well for about 60% of tumors studied thus far.

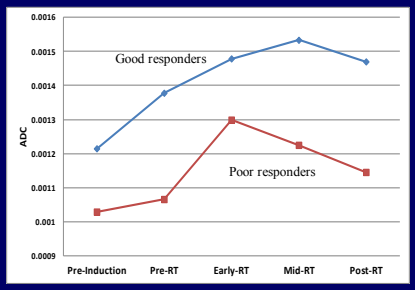
M. Crispin-Ortuzar, M. Grkovski, B. Beattie, J. Humm, N. Lee, N. Riaz.


Lung cancer response: Apparent Diffusion Coefficient (ADC)
Median (mm^2/s $*10^{-3}$)
Pre treatment
After first fraction (8 Gy)
After last fraction (40 Gy)
Four weeks Post treatment
x 10^-3
3.5
3
2.5
2
1.5
1
0.5
0
1.5
1.6
1.6
1.8


Rectal cancer Example 1 poor responder
Pre-induction
Pre RT
Early RT
Mid RT
Post RT
ADC
Pre-Induction
Pre-RT
Early-RT
Mid-RT
Post-RT
Tyagi et al, works in progress


Example 2: Good responder
Pre-induction
Pre RT
Early RT
Mid RT
Post RT
ADC
Pre-Induction
Pre-RT
Early-RT
Mid-RT
Post-RT
Tyagi et al, works in progress

ADC as a marker of therapy response for rectal cancer

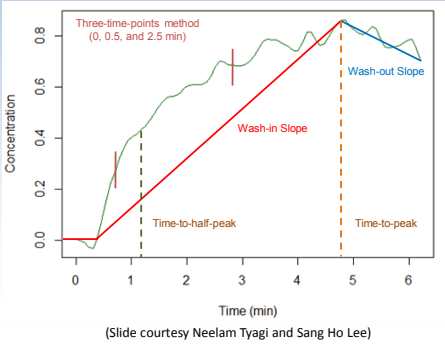


Tyagi et al, works in progress

Semi-quantitative Parametric Analysis in DCE-MRI: Preliminary Application to Mesothelioma & Non-small Cell Lung Cancer

Neelam Tyagi, Sang Ho Lee, Andreas Rimner, et al.

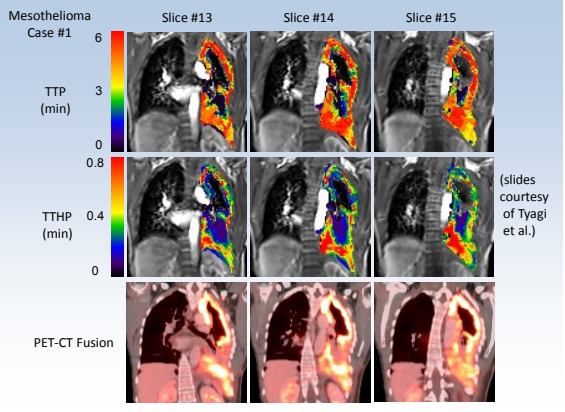
Semi-quantitative Parameters



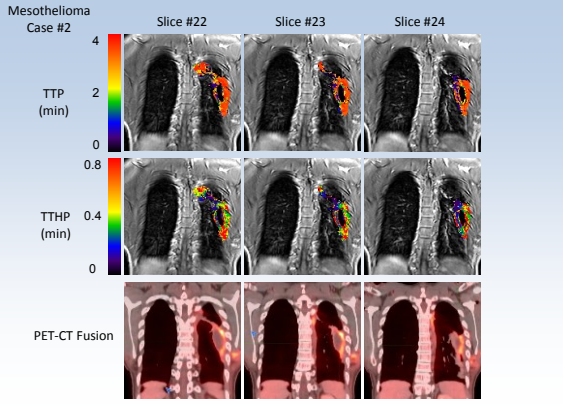
(Slide courtesy Neelam Tyagi and Sang Ho Lee)

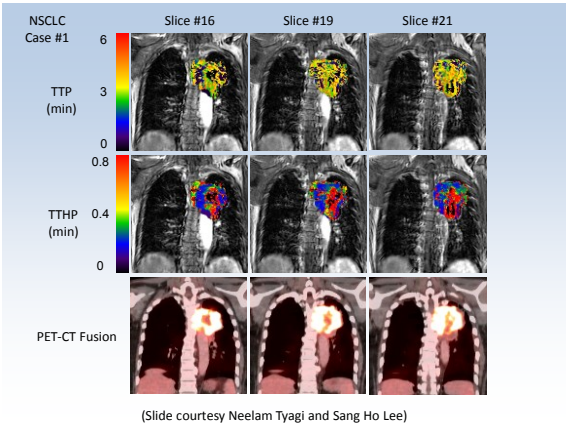
Why semi-quantitative parameters?

- Because Gd flows and is not trapped in cells…
- ...therefore kinetic models that do not include intervoxel diffusion **are unlikely to be realistic.**
- Empirical parameters such as TTHP are likely to be robust with respect to imaging parameters
- ....and relevant to drug delivery as well as radiobiological microenvironmental conditions
- Hypothesis: histograms of TTHP might be predictive of drug or radiotherapy response

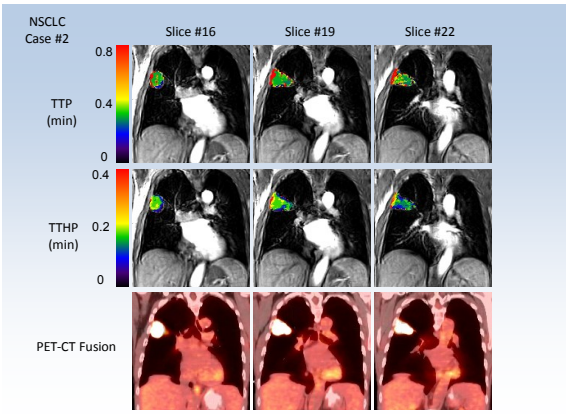


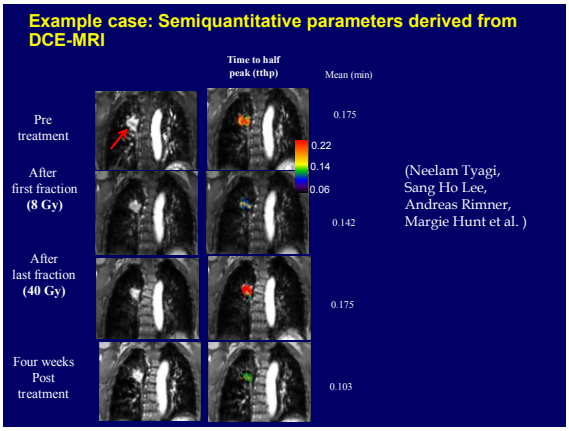
(slides courtesy of Tyagi et al.)





(Slice courtesy Neelam Tyagi and Sang Ho Lee)





Looking ahead [1/2]

- Need to organize and test relatively simple image biomarkers from
  - dynamic contrast measurements (e.g., TTHP)
  - ADC and related parameters
  - Caveat: diffusion parameter behavior during RT is site specific
- Such parameters ae probably relevant to both RT and cytotoxic drug response
- Could become a standard part of Phase I drug response analyses
- Could form a personalized ground for adaptation, as well as disease phenotype classification

Looking ahead [2/2]

- Many opportunities to not only better understand individual tumor physiology vs. response, but also many opportunities to monitor and adapt to variable response.
- The relatively empirical use of hypoxia imaging during RT to choose dose is already proving useful in H&N.
- There is the potential to use multi-modality imaging with tumor response modeling to predict tumor response and to identify radiobiological outliers