Memorial Sloan Kettering Cancer Center

The radiobiology of (imaged) tumor response to radiotherapy

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Disclosure:

- Our work is supported by:
  - US NIH (R01 to J. Deasy)
  - US NIH Cancer Center support grant to MSK
  - The Breast Cancer Research Foundation
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  - Varian
  - Philips
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- I am a founder and shareholder in a computational pathology company, PAIGE.AI.

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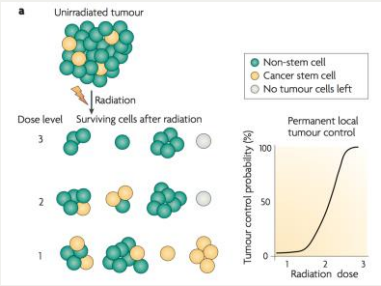
- Jan-Jakob Sonke
- Jung Hun Oh, PhD
- Allen Tannenbaum, PhD
- John Humm, PhD
- Amita Shukla-Dave, PhD

Key topics

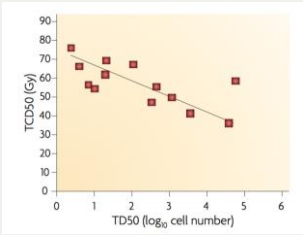
- Basic radiobiological processes that impact tumor response,
- Variability of tumor regression and relationship to growth fraction
- Local control following radiotherapy and impact of hypoxia.
- Relationship of SUVmax with local control.
- Modeling of tumor response

The importance of cancer stem cells



(Baumann et al., Nat Rev Ca 2008)

The proportion of stem cells affects radiocurability



(Baumann et al., Nat Rev Ca 2008)

Cells need for successful transplant

Hypoxia reduces DNA damage

(Desouky et al., J of Radiat Res Appl Sci, 2015)

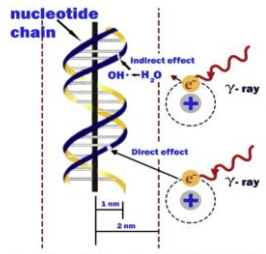


Fig. 1 – Direct and indirect actions of radiation (modified from Hall & Giaccia, 2011).

HNSCC outcomes depend on persistent hypoxia

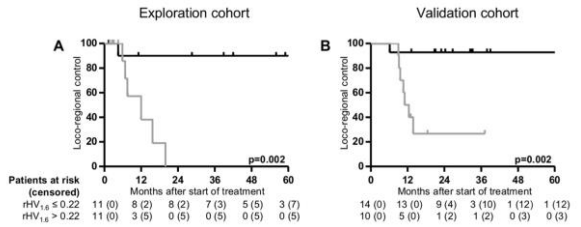
Prospective clinical trial

Residual tumour hypoxia in head-and-neck cancer patients undergoing primary radiochemotherapy, final results of a prospective trial on repeat FMISO-PET imaging

Steffen Löck [a,b,c,d,1], Rosalind Perrin [a,e,1], Annekatrin Seidlitz [a,c], Anna Bandurska-Luque [a,c], Sebastian Zschaeck [a,c,3], Klaus Zöphel [f,g], Mechthild Krause [a,c,d,g,h,i], Jörg Steinbach [g,j], Jörg Kotzerke [f,g], Daniel Zips [k,l], Esther G.C. Troost [a,c,d,g,h,e,2], Michael Baumann [a,c,d,g,f,i,2]

(Rad Onc 2017)

HNSCC outcomes depend on persistent hypoxia



$rHV_{1.6}$ = residual hypoxia volume w/ cutoff 1.6.

Is classical cell kill dominant in SBRT/SRS?

Radiobiological basis of SBRT and SRS

Chang W. Song · Mi-Sook Kim · L. Chinsoo Cho · Kathryn Dusenbery · Paul W. Sperduto

Int J Clin Oncol (2014) 19:570–578

"…, little is known about the effect of high dose hypo-fractionated radiation on human tumor vasculatures."

"…irradiation of experimental tumors with high-dose hypo-fractionated irradiation, i.e. [10–15 Gy/fraction], causes profound vascular damage in various experimental tumors"

Critical Review

The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?

J. Martin Brown, PhD,* David J. Carlson, PhD,† and David J. Brenner, PhD‡

*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California; †Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut, and ‡Center for Radiological Research, Columbia University Medical Center, New York, New York

(IJROBP, 2013)

"…for most tumors, the standard radiobiology concepts of the 5 Rs are sufficient to explain the clinical data, and the excellent results obtained from clinical studies are the result of the much larger biologically effective doses that are delivered with SRS and SBRT."

Preclinical determinants of radiocurability

MULTIVARIATE DETERMINANTS OF RADIOCURABILITY I: PREDICTION OF SINGLE FRACTION TUMOR CONTROL DOSES

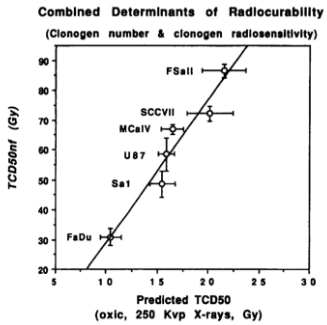
LEO E. GERWECK, PH.D., SYED T. ZAIDI, M.S. AND ANTHONY ZIETMAN, M.D.

Department of Radiation Oncology, Edwin L. Steele Laboratory of Cellular Radiation Biology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114

(IJROBP, 1994)

Stem cell fraction and slope of cell kill curve (i.e., radiosensitivity.)

Combining estimate of stem cell fraction with radiosensitivity allows prediction of tumor radiocurability



Modelling the interplay between hypoxia and proliferation in radiotherapy tumour response

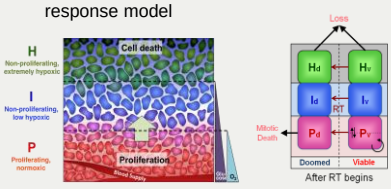
J Jeong[1], K I Shoghi[2] and J O Deasy[1]

[1] Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[2] Washington University in St. Louis, St. Louis, MO, USA

Phys. Med. Biol. **58** (2013) 4897–4919

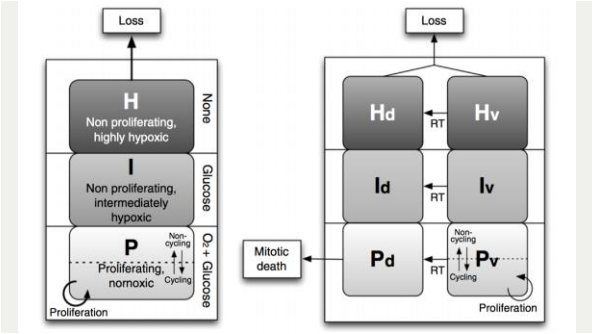
Simulation model: the basics

- We introduce a 'constant-resource' tumor response model



- Chemical supply is assumed constant over the course of RT

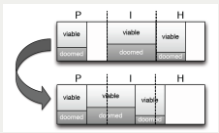
(Jeong *et al.* PMB (2013) 58:4897)



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:

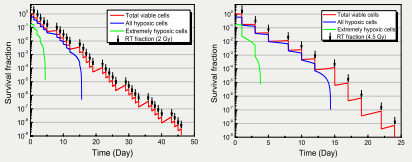


Impact of hypoxia: Carlson et al.

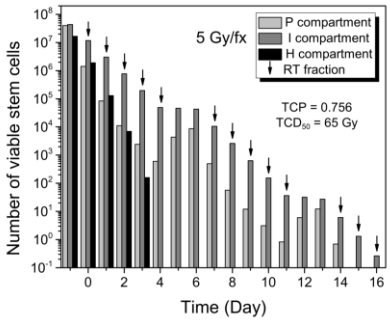
$$\alpha_X = \alpha_P/\mathrm{OER}_X \quad \text{and} \quad \beta_X = \beta_P/\mathrm{OER}_X^2$$

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**	Treatment duration = **23 days**
TD_{50} = **66.8 Gy** (in $EQD2_6$)	TD_{50} = **62 Gy** (in $EQD2_6$)



Personalized Medicine and Imaging

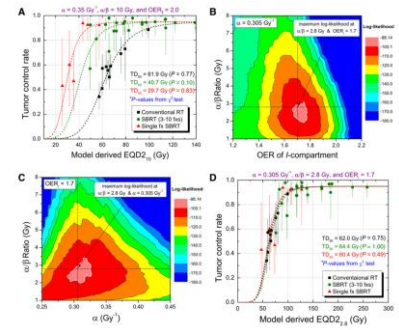
Clinical Cancer Research

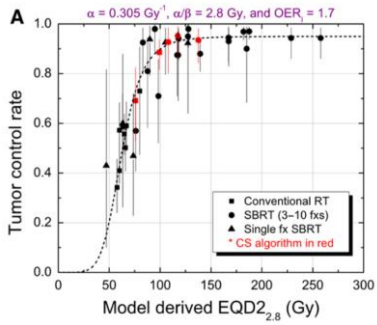
Modeling the Cellular Response of Lung Cancer to Radiation Therapy for a Broad Range of Fractionation Schedules

Jeho Jeong[1], Jung Hun Oh[1], Jan-Jakob Sonke[2], Jose Belderbos[2], Jeffrey D. Bradley[3], Andrew N. Fontanella[1], Shyam S. Rao[4], and Joseph O. Deasy[1]

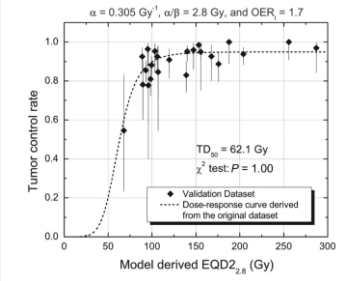
(2017)

- 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)

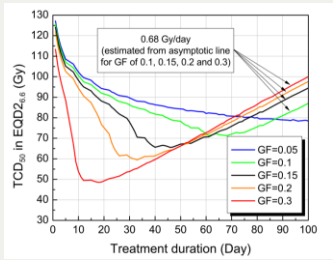




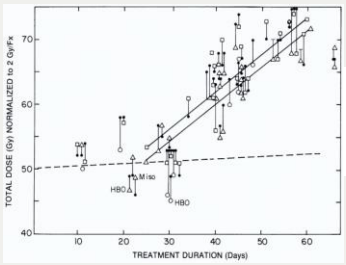
Validation data – reported after training data



Reproduces 'kickoff'



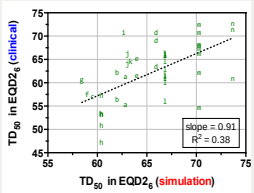
Withers' repopulation plot for H&N Ca



Withers et al., Acta Oncol (1988)

The model reproduces the clinical trend

- The slope of the repopulation is dependent on the normalization
- Normalized in $EQD2_{25}$ (as the original Withers' plot), the slopes become 0.59 (simulated) vs. 0.62 (clinical) Gy/day.
- linear correlation: slope of 0.92 (R^2=0.63) & r_S= 0.74 (p<0.001)

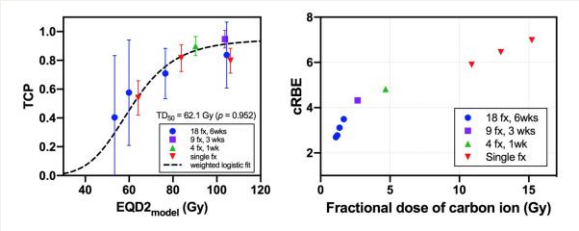


Estimation of clinical relative biological effect (cRBE) of carbon ion radiation therapy (CIRT) for early stage lung cancer based on mechanistic tumor response modeling

Jeho Jeong and Joseph O. Deasy

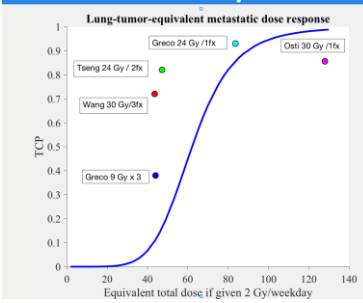
Memorial Sloan-Kettering Cancer Center, New York, NY

(To be presented at ASTRO 2019)



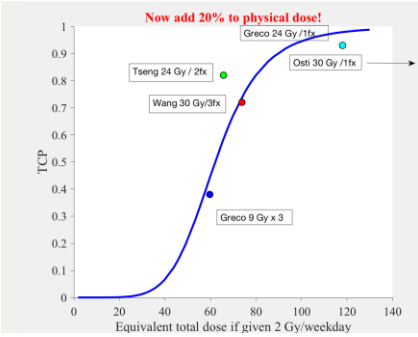
α = 1.28, α/β ratio = 17.5, OERI = 1.1

Dose-response of oligomets



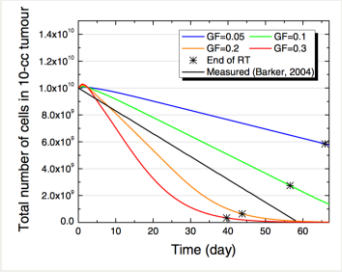
Only studies with > 100 lesions

Typical F/U 2 yrs.



Universal dose-response?

Reproduces regression rates



Caveat: many, possibly most cells in tumor may be host cells!

What do PET images imply about required dose?

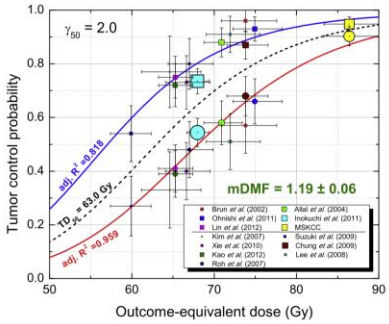
Review

Estimate of the impact of FDG-avidity on the dose required for head and neck radiotherapy local control

Jeho Jeong [a], Jeremy S. Setton [b], Nancy Y. Lee [b], Jung Hun Oh [a], Joseph O. Deasy [a,*]

[a] Department of Medical Physics; and [b] Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA

(Radio Oncol, 2013)



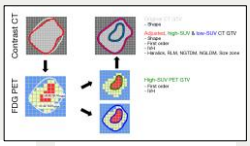
FDG may predict radiocurability so well because…

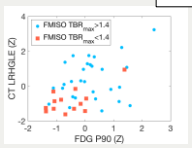
- It is correlated with hypoxia and OER
- It represents good/adequate blood flow
- It represents increased cell density
- It identifies stem cell niches
- All of the above?
- This is an open question

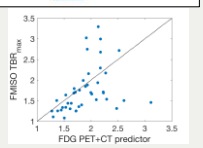
Can radiomics help in understanding tumor response?

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



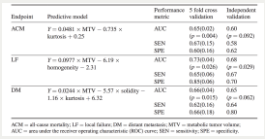




Predictive modeling of outcomes following definitive chemoradiotherapy for oropharyngeal cancer based on FDG-PET image characteristics

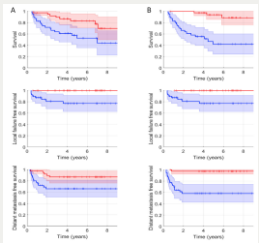
(2017, Phys Med Biol)

Michael R Folkert[1], Jeremy Setton[1], Aditya P Apte[1], Milan Grkovski[1], Robert J Young[1], Heiko Schöder[2], Wade L Thorstad[3], Nancy Y Lee[1], Joseph O Deasy[1] and Jung Hun Oh[1,3]



Endpoint	Predictive model	Performance metric	5 fold cross validation	Independent validation
ACM	$F = 0.0481 \times MTV - 0.735 \times kurtosis + 0.25$	AUC	0.650 (0.02) ($p = 0.004$)	0.60 ($p = 0.092$)
		SEN	0.67 (0.15)	0.58
		SPE	0.80 (0.16)	0.62
LF	$F = 0.0077 \times MTV - 6.19 \times homogeneity - 2.31$	AUC	0.73 (0.04) ($p = 0.026$)	0.68 ($p = 0.029$)
		SEN	0.65 (0.06)	0.67
		SPE	0.81 (0.06)	0.70
DM	$F = 0.0244 \times MTV - 5.57 \times solidity - 1.16 \times kurtosis + 6.32$	AUC	0.66 (0.04) ($p = 0.015$)	0.65 ($p = 0.062$)
		SEN	0.82 (0.16)	0.64
		SPE	0.66 (0.18)	0.80

ACM = all-cause mortality; LF = local failure; DM = distant metastasis; MTV = metabolic tumor volume; AUC = area under the receiver operating characteristic (ROC) curve; SEN = sensitivity; SPE = specificity.

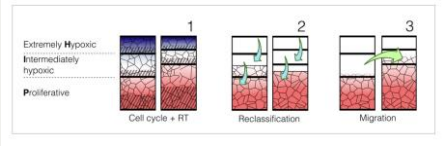


Methods to include image heterogeneity

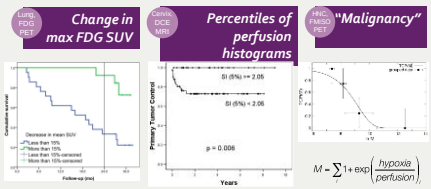
IOP Publishing | Institute of Physics and Engineering in Medicine
Physics in Medicine & Biology
Phys. Med. Biol. 62 (2017) 2658–2674
https://doi.org/10.1088/1361-6560/aa5042

A radiobiological model of radiotherapy response and its correlation with prognostic imaging variables

Mireia Crispin-Ortuzar[1], Jeho Jeong, Andrew N Fontanella and Joseph O Deasy



Imaging variables

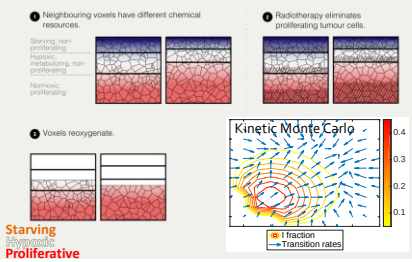


[Van Elmpt et al, J Nucl Med. 2012]

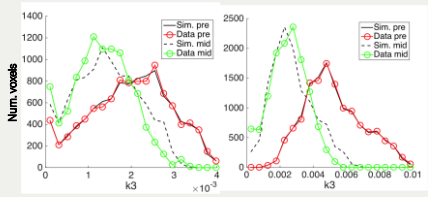
[Mayr et al, Invest Radiol. 2009]

[Thorwarth et al, Int J Radiat Oncol Biol Phys. 2007]

Including heterogeneity & cell migration



H&N hypoxia histogram evolution during RT

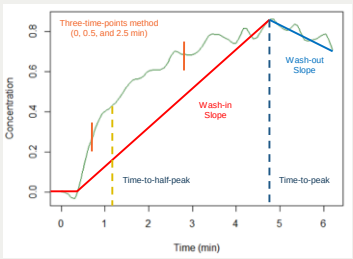


Works well for about 60% of tumors studied thus far.

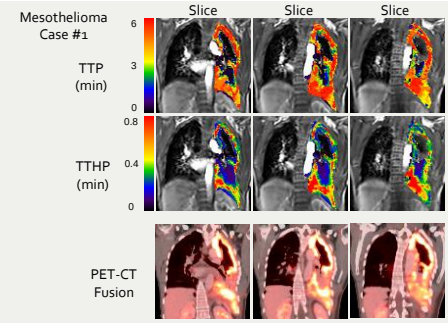
M. Crispin-Ortuzar, M. Grkovski, B. Beattie, J. Humm, N. Lee, N. Riaz, unpublished.

What about dynamic contrast imaging?

Semi-quantitative Parameters



(Slide courtesy Neelam Tyagi and Sang Ho Lee)



(slide courtesy of Neelam Tyagi)

Better fluid transport approaches to DCE

Optimal mass transport kinetic modeling for head and neck DCE-MRI: Initial analysis

Rena Elkin[1] | Saad Nadeem[2] | Eve LoCastro[2] | Ramesh Paudyal[2] | Vaios Hatzoglou[3] | Nancy Y. Lee[4] | Amita Shukla-Dave[2,3] | Joseph O. Deasy[2] | Allen Tannenbaum[5]

Magn Reson Med. 2019;00:1–12.

$$\partial_t \mu + \nabla \cdot (\mu v) = \nabla \cdot (D \nabla \mu),$$

Key summary points

- Imaging provides crucial insights into tumor biology
- Methods to understand tumor heterogeneity are only now being developed
- Imaging provides powerful tools to potentially understand outcomes variations
- Imaging and radiomics will increasingly be used to stratify patients in the future.
- **Imaging should be combined with modeling to form testable hypothesis and to maximize scientific insight!**