The radiobiology of (imaged) tumor response to radiotherapy

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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
- Proportion of stem cells affects radiocurability.

The proportion of stem cells affects radiocurability
- Cells need for successful transplant.
Hypoxia reduces DNA damage

(Hypoxia reduces DNA damage)


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 Lack, Roseline Perria, Arnekaarin Setelha, Anna Randurka-Luppe, Sebastian Zehnle, Klaus Zscheiler, Mechthild Krause, Jürg Steinbach, Jörg Kutzerke, Daniel Zipp, Esther G. Toett, Michael Baumans. (Rad Onc 2017)

HNSCC outcomes depend on persistent hypoxia

(rHV1.6 = residual hypoxia volume w/ cutoff 1.6.)
Is classical cell kill dominant in SBRT/SRS?

**Radiobiological basis of SBRT and SRS**

Chang W. Song · M-Sook Kim · L. Chimee Cho · Kathryn Duneshory · Paul W. Scribner


"...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"

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**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 Radiobiological Research, Columbia University Medical Center, New York, New York

(JROBP, 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"  

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**Preclinical determinants of radiocurability**

**MULTIVARIATE DETERMINANTS OF RADIOCURABILITY 1: PREDICTION OF SINGLE FRACTION TUMOR CONTROL DOSES**

Leo E. Gerwick, 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

(JROBP, 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 radio-curability.

Modelling the interplay between hypoxia and proliferation in radiotherapy tumour response

J Jeong\(^1\), K I Shohji\(^2\) and J O Dearn\(^1\)

\(^1\) Memorial Sloan-Kettering Cancer Center, New York, NY, USA
\(^2\) Washington University in St. Louis, St. Louis, MO, USA


**Simulation model: the basics**

- We introduce a 'constant-resource' tumor response model
- Chemical supply is assumed constant over the course of RT

(Feong et al. PMB (2013) 58:4897)
Assume re-compartmentalization: this leads to reoxygenation

After an (exaggerated) time step:

- 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

Impact of hypoxia: Carlson et al.

\[ \alpha_k = \alpha_{fr}/OER_k \quad \text{and} \quad \beta_k = \beta_{fr}/OER_k \]
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 EQD_{6})

Treatment duration = 23 days
TD_{50} = 62 Gy (in EQD_{6})

Dose response across different fractionation regimes:
Three additional cohorts (including WUSTL, NKI) (N=512)
Validation data – reported after training data
Reproduces ‘kickoff’

Withers' repopulation plot for H&N Ca

The model reproduces the clinical trend

- The slope of the repopulation is dependent on the normalization
- Normalized in EQD2 as the original Withers' plot, the slopes become 0.59 (simulation) vs. 0.62 (clinical) Gy/day.
- Linear correlation: slope of 0.92 (R²=0.83) & r²=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

John Jeong and Joseph O. Deasy
Memorial Sloan-Kettering Cancer Center, New York, NY

(To be presented at ASTRO 2019)

$\alpha = 1.38$, $\alpha/\beta$ ratio $= 17.5$, OERI $= 1.1$

Dose-response of oligometas

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
John Jong*, Jeremy S. Settles*, Nancy Y. Lee*, Jung Hua Oh*, Joseph O. Deasy*
*Department of Medical Physics and *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.)

- PET + contrast-enhanced CT
- Maximum intensity projection (MIP) 
- LASSO + 10x10-fold CV
- Selected predictors:
  - Long run high grey level emphasis in low FDG subregion
  - Validation AUC = 0.83 (2017, Phys Med Biol)

Methods to include image heterogeneity
A radiobiological model of radiotherapy response and its correlation with prognostic imaging variables

Mário Chopin-Ortiz, João Jasson, Andreia N Fontanella and Joseph G Deasy

**Imaging variables**

- Change in max FDG SUV
- Percentiles of perfusion histograms
- "Malignancy"

**Including heterogeneity & cell migration**

- Neighbouring cells have different chemical migration
- Radiotherapy enhances migrating tumour cells
- Starving tumour cells
- Proliferative
H&N hypoxia histogram evolution during RT

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

What about dynamic contrast imaging?

Semi-quantitative Parameters

(Slide courtesy Neelam Tyagi and Sang Ho Lee)
Better fluid transport approaches to DCE

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

Rena Elkin | Saud Nadeem | Eve LoCastro | Ramesh Pandyal
Valos Hatzoglou | Nancy Y. Lea | Anita Shukla-Dave | Joseph O. Drancy
Allen Tannenbaum

Meds Reson Med. 2019;00:1–12.

\[ \dot{\rho} + \nabla \cdot (\rho \mathbf{u}) = \nabla \cdot (D \nabla \rho), \]

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!