Radiation Biology III: Biological optimization of radiation therapy

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**Date and Time:** July 24, 2014 from 7:30-9:30 AM
**Location:** Austin Convention Center, Austin, TX
Learning Objectives

1. Review commonly used radiobiological models in radiation oncology (and underlying mechanistic basis)
   – Can be incorporated into treatment planning as biological objective functions

2. Understand factors that alter radiation response
   – DNA damage repair, hypoxia & reoxygenation, radiation quality

3. Learn how to apply concepts of biological effective dose (BED) and RBE-weighted dose (RWD)
   – Implementation and implications for fractionation and particle therapy

4. Discuss clinical strategies to increase therapeutic ratio
   – Spatial and temporal optimization of dose delivery (# of $n$ and dose per $n$)
   – Concurrent therapeutics, e.g., hypoxic cell radiosensitizers or cytotoxins

5. Appreciate model limitations and sources of uncertainty

Conflict of interest: Nothing to disclose
Biologically Guided Radiation Therapy (BGRT)

- Systematic method to derive prescription doses that integrate patient-specific information about tumor and normal tissue biology
- **Problem:** derived prescriptions may have large uncertainties
  - Uncertainties in physical and biological factors (experimental and clinical) that influence tumor and normal-tissue radiation response
  - Incomplete understanding of molecular and cellular mechanisms

**Background and Motivation**

- **Dose-Based TP → Physical objective functions**
  - Minimize dose gradients across tumor (uniformity), deliver prescribed isodose contours to target, minimize max. dose to critical structures, etc.
  - Uniform dose may not be most desirable

- **BGRT → Biological objective functions**
  - More direct approach to optimization instead of relying on dose-based surrogates
    - Maximize tumor cell killing (LQ) and tumor control probability (TCP)
    - Minimize normal tissue complication probability (NTCP)
The double strand break (DSB)

- A DSB is formed when two breaks in the sugar-phosphate backbone occur on opposite sides of DNA helix within $\sim 10$ base pairs

- Simple DSB:

- Many experiments for all types of DNA damage, including DSB, show that damage formation is proportional to absorbed dose up to hundreds of Gy

**DSBs are formed through one-track mechanisms**

DSB induction in human fibroblasts (MRC-5) irradiated by 90 kVp x-rays (Rothkamm and Lobrich 2003)
One- and two-track radiation damage

Lethal lesions are created by the actions of one or two radiation tracks

1 track damage
(\(\propto D\))

- Lethal DSB misrepair, unrepairable damage
- Pairwise interaction of two DSBs

2 track damage
(\(\propto D^2\))

- Pairwise interaction of two DSBs
Exchange-type aberrations

Pairwise damage interaction (binary misrepair)

2 chromosomes:
- Stable
- Lethal
- Stable

1 chromosome:
- Stable
- Lethal
Linear-quadratic (LQ) cell survival model

\[ S(D) = \exp \left[ - \left( \alpha D + \beta D^2 \right) \right] \]

\((\alpha D + \beta D^2)\) = expected number of lethal lesions per cell

\[ \alpha = \text{one-track lethal damage [Gy}^{-1}\text{]} \]
\[ \beta = \text{two-track lethal damage [Gy}^{-2}\text{]} \]

\[ \frac{\alpha}{\beta} \text{[Gy]} \] is clinically used descriptor of intrinsic radiosensitivity

PC-3 prostate carcinoma cells (Deweese et al 1998)

60 Gy h\(^{-1}\)

LQ Fit to Experimental Data (\(\alpha = 0.128 \text{ Gy}^{-1}\), \(\alpha/\beta = 3.46 \text{ Gy}\))

Absorbed Dose (Gy)

Surviving Fraction

Yale SCHOOL OF MEDICINE
Repair-misrepair-fixation (RMF) Model

Surviving fraction is related to yield of fatal lesions

\[ S(D) = \exp[-F(\infty)] = \exp\left[-\left(\alpha D + \beta GD^2\right)\right] \]

1. Unrejoinable and lethal damage

\[ \alpha = (1 - f_R)\Sigma + \theta f_R \Sigma + \left[\eta / \lambda\right][\gamma - \theta]\varepsilon f_R \Sigma \]

2. Lethal misrepair and fixation

\[ \beta = \left[\eta / (2\lambda)\right][\gamma - \theta](f_R \Sigma)^2 \]

3. Intra-track DSB interactions

4. Inter-track DSB interactions

\[ f_R \equiv \text{fraction of potentially rejoinable DSB} \]
\[ \lambda \equiv \text{rate of DSB repair (} \sim 10^{-1} - 100 \text{ } \text{h}^{-1}) \]
\[ \eta \equiv \text{rate of binary misrepair (} \sim 10^{-5} - 10^{-4} \text{ } \text{h}^{-1}) \]
\[ \varepsilon \equiv z f_R \Sigma \equiv \text{# of DSB per track per cell} \]
\[ \Sigma \equiv \text{expected # of DSB (Gy}^{-1} \text{ cell}^{-1}) \]
\[ \theta \equiv \text{prob. DSB lethally misrepaired/fixed} \]
\[ \gamma \equiv \text{prob. exchange-type aberration lethal} \]

Tumor Control Probability (TCP) Model

TCP → relates tumor size and radiation dose to the probability of tumor control (i.e., no tumor cells survive)

\[
TCP = \exp\left[-N \cdot S(D)\right] = \exp\left[-N \cdot \left(e^{-\alpha D - \beta D^2}\right)\right]
\]

\(N = \text{initial \# of tumor clonogens}\)
Inter-patient variability in radiosensitivity

- Heterogeneity of human tumour radiation response is well known.

- Many groups have accounted for variations in interpatient tumour heterogeneity by assuming that radiosensitivity values are normally distributed across the population.

- If interpatient heterogeneity is ignored, TCP model generally results in an unrealistically steep dose-response curve.

Factors that alter treatment effectiveness

4 R’s of Radiobiology give rise to “dose rate” effects:

- DNA repair
- Repopulation
- Reoxygenation & Redistribution

Treatment duration

Treatment effectiveness

<table>
<thead>
<tr>
<th>mins</th>
<th>hours</th>
<th>days</th>
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Divide a tumor into voxels with radiosensitivity $\alpha_i$ and $\beta_i$. Correct SF for dose heterogeneity, inter- and intra-tumor variability in radiosensitivity and the R’s of radiobiology:

$$TCP = \prod_{i} TCP_i$$

$$TCP_i = \exp\left\{-N_0f_i \exp\left[-D \left(\alpha_i + \beta_iG_iD_i\right) + \gamma_iT\right]\right\}$$

- **Oxygen and LET effects ($\alpha$ and $\beta$)**
- **Repair effects ($\mu$ or $\tau$)**
- **Repopulation rate in $i$th tissue region**

$N_0f_i$ is initial # of cells in the $i$th tissue region
DNA damage repair in the LQ model

\[ S(D) = \exp \left[ -\left( \alpha D + \beta G[\mu, t]D^2 \right) \right] \]

\((\alpha D + \beta G[\mu, t]D^2)\) = expected number of lethal lesions per cell
\(\alpha = \) one-track lethal damage coefficient\([\text{Gy}^{-1}]\)
\(\beta = \) two-track lethal damage coefficient\([\text{Gy}^{-2}]\)

**G[\mu, t] is the Lea-Catcheside dose protraction factor**
\(\mu = \ln 2 / \tau = \) rate of DSB rejoining\([\text{h}^{-1}]\)

**Limiting cases:**
- \(\lim_{t \to 0} G = 1 \quad \text{Instantaneous dose delivery}\)
- \(\lim_{t \to \infty} G = 0 \quad \text{Infinitely protracted dose}\)

**Dose protraction factor often neglected**
\((G = 1), \text{ only reasonable when irradiation time is short compared to DSB repair half-time}\)

Dose rate effects and DNA damage repair

- Cell killing decreases with decreasing dose rate
- If $G(\mu,t)$ included, unique set of parameters can predict the data: $\alpha = 0.04 \text{ Gy}^{-1}$, $\beta = 0.02 \text{ Gy}^{-2}$, $\tau = 6.4 \text{ h}$
- Repair of DNA damage occurs between fractions and during treatment delivery
- Effect increases with increase in delivery time

$\rightarrow$ More important for SBRT, SRS, and brachytherapy

Prostate Cancer: review of in vitro and in vivo data

**In vitro estimates:**
- $\alpha = 0.09 - 0.4$ Gy$^{-1}$
- $\alpha/\beta = 1.1 - 6.3$ Gy

**In vivo estimates:**
- $\alpha = 0.036 - 0.15$ Gy$^{-1}$
- $\alpha/\beta = 1.5 - 3.1$ Gy

**In vitro and in vivo data support a low $\alpha/\beta$ for prostate cancer**

1) Corrections for intrafraction DNA damage repair have significant impact on $\alpha/\beta$
2) Observed variability demonstrates uncertainty associated w/ parameter estimation
3) Radiobiology of prostate cancer suggests hypofractionation may ↑ therapeutic ratio

Review of studies deriving prostate $\alpha/\beta$ 

At least 24 studies since Brenner & Hall’s 1999 paper:
- EB-LDR
- EB-HDR
- EB alone
- in vitro

Modeling: RBE, repair, repopulation, dose heterogeneity, hypoxia

"Clinical practice of hypofractionation in the treatment of prostate cancer seems not to increase late complication and shows a biochemical outcome superior or equivalent to conventional schedules"

Biologically Effective Dose (BED)

- BED is an LQ based estimate of the effective biological dose that accounts for delivered total dose, the dose fractionation, and the radiosensitivity of tissue.
- Commonly used for isoeffect calculations.

Recall: \[ S(D) = \exp\left[-\alpha D - \beta GD^2 + \gamma T\right] \]

Take the negative logarithm of \( S \) and divide by \( \alpha \):

\[ \text{BED} \equiv \frac{-\ln S(D)}{\alpha} = D \left[ 1 + \frac{GD}{\alpha / \beta} \right] - \frac{\gamma T}{\alpha} \]

- Physical dose
- Relative effectiveness
- “Lost” dose due to repopulation effect
Isoeffect Example for Prostate Cancer

- Assume $\alpha/\beta = 3$ Gy, for a standard EBRT fractionation of 39 fractions of 2 Gy:

$$\text{BED} = 78 \text{ Gy} \left[ 1 + \frac{2 \text{ Gy}}{3 \text{ Gy}} \right] = 130 \text{ Gy}$$

- Rearrange simplified BED equation:

$$d = \frac{\alpha / \beta}{2n} \left( -n + \sqrt{n^2 + \frac{4n\text{BED}}{\alpha / \beta}} \right)$$

$$= \frac{3 \text{ Gy}}{2n} \left( -n + \sqrt{n^2 + \frac{4n \times 130 \text{ Gy}}{3 \text{ Gy}}} \right)$$
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Radiobiology and the AAPM

The use and QA of biologically related models for treatment planning: Short report of the TG-166 of the therapy physics committee of the AAPM

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Hypofractionation and Tumor Hypoxia

Point/Counterpoint debate in December 2011 issue of Medical Physics

Carlson DJ, Yenice KM, Orton CG. Point/Counterpoint: Tumor hypoxia is an important mechanism of radioresistance in hypofractionated radiotherapy and must be considered in the treatment planning process. Med. Phys. 38: 6347–6350 (2011).
Clinical significance of tumor hypoxia

Head and neck cancer

Prostate cancer

~90% of solid tumors have median values below normal (40-60 mmHg), half have median values <10 mmHg, and a third contain subvolumes with concentrations <2.5 mmHg (Vaupel and Hockel, in Tumour Oxygenation, 1995 and Brown JM, Mol. Med. Today, 2000)
What about tumor hypoxia?

V79 379A Chinese hamster cell survival data from Watts et al. (1986)

- **OER** values for cell death are relatively constant over a large dose range
  - May actually increase slightly with dose (Wouters and Brown 1997, Nahum et al. 2003)

- Statistically, $OER_\alpha \sim OER_\beta$
  - Reasonable assumption for large number of *in vitro* data sets (Carlson et al. 2006)

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Effects of Hypoxia and Fractionation on Cell Survival

80.5 Gy for reference H&N treatment

Dose per fraction (Gy) to yield equivalent tumor BED under normoxic conditions

130 Gy for reference prostate treatment

Number of fractions

Surviving Fraction

$S_{overall} = S(d)^n = \left[ \exp\left(-\alpha_A d - \beta_A d^2\right) \right]^n$

Effects of Hypoxia and Fractionation on Cell Survival

What happens to total cell killing if we include hypoxia?

Dose per fraction (Gy) to yield equivalent tumor BED under normoxic conditions

\[
S_{\text{overall}} = \left[ f_{\text{hyp}} \cdot S_{\text{hyp}} + (1 - f_{\text{hyp}}) \cdot \int_{a}^{R_{\text{hyp}}} f(r) \exp\left(-[\alpha_A / HRF(r)]d -[\beta_A / HRF(r)^2]d^2\right)dr \right]^n
\]

Strategies to overcome tumor hypoxia?

Tumor hypoxic volume

Hypoxic volume > X% of tumor or Hypoxic volume < X% of tumor

Alter radiation therapy treatment plan

Tumor hypoxic volume

Give patient drug ‘Y’

Drug clinical trial

Do not give patient drug ‘Y’

18F-FMISO PET: Can select patients for drug trials

- 45 patients with stage III or IV squamous cell carcinoma of H&N
- Randomly assigned to RT (70 Gy in 35 fx) plus cisplatin + tirapazamine (TPZ) or cisplatin + fluorouracil
- Pretreatment and midtreatment 18F-FMISO PET performed

- In patients with hypoxic tumors, 0 of 8 treated with Cis-TPZ had local failure compared with 6 of 9 treated with Cis-FU
- First clinical evidence to support tirapazamine specifically targets hypoxic tumor cells

Photon versus proton dosimetry

- Protons allow a reduction of integral dose and lower doses outside target

**Photons**

**Protons**

Image courtesy of Uwe Oelfke (ICR, London)
Proton versus carbon ion dosimetry

- Carbon ions provide a steeper gradient at target edge, but contribute a higher integral dose (distal tail)

**Protons**

**Carbon ions**

Image courtesy of Uwe Oelfke (ICR, London)
Physical and Biological Aspects of Particle Therapy

Image courtesy of Uwe Oelfke (ICR, London)
Biological effects of radiation quality

Predicting trends in radiosensitivity

Cell-specific model constants calculated based on low-LET reference parameters for 200 kVp X-rays:

\[ \kappa = \frac{2\beta_x}{\Sigma_x^2} \quad \theta = \frac{\alpha_x}{\Sigma_x} \left[ 1 - \frac{2\Sigma_x}{(\alpha / \beta)_x} \right] \]

Radiosensitivity parameters for V79 cells irradiated in vitro. Symbols: estimates of \(\alpha\) and \(\beta\) reported by Furusawa et al. (2000) for He-3 (blue circles), C-12 (green triangles) and Ne-20 (red squares). Lines: RMF-predicted parameters.

Clinically-relevant pristine Bragg peaks

Physical and biological properties of proton and carbon ion pristine Bragg peaks:

- Dose & LET calculated using analytical approximations (Bortfeld 1997, Wilkens and Oelfke 2003)
- DSB yields simulated with MCDS
- \(\alpha\) and \(\beta\) calculated assuming chordoma reference parameters
- All calculations include Gaussian particle spectrum

RBE for cell killing in Proton SOBP

**Conditions:**
1. Normoxic chordoma cells: $\alpha_x = 0.1$ Gy$^{-1}$, $(\alpha/\beta)_x = 2.0$ Gy
2. Proximal edge of SOBP: 10 cm
3. Distal edge of SOBP: 15 cm
4. Distance between Bragg peaks: 0.3 cm
5. # of Bragg peaks: 17

**Results:**
1. Entrance RBE ~1.0
2. RBE ranges from 1.03 to 1.34 from proximal to distal edge of the SOBP
3. Mean RBE across SOBP is ~1.11

Dose, energy, and LET calculated using analytical approximation proposed by Bortfeld (1997) and Wilkens and Oelfke (2003)

Potential for biological hot and cold spots within proton SOBP
RBE for cell killing in Carbon Ion SOBP

**Conditions:**
1. Normoxic chordoma cells: $\alpha_x = 0.1 \text{ Gy}^{-1}$, $(\alpha/\beta)_x = 2.0 \text{ Gy}$
2. Proximal edge of SOBP: 10 cm
3. Distal edge of SOBP: 15 cm
4. Distance between Bragg peaks: 0.3 cm
5. # of Bragg peaks: 17

**Results:**
1. Entrance RBE $\sim 1.3$
2. RBE ranges from 1.8 to 5.4 from proximal to distal edge of the SOBP
3. Mean RBE across SOBP is $\sim 2.8$

Dose, energy, and LET calculated using analytical approximation proposed by Bortfeld (1997) and Wilkens and Oelfke (2003)
Dependence on tissue radiosensitivity

Physical (solid line) and RBE-weighted (RWD) dose for a representative clinical spread-out Bragg peaks in proton and carbon ion radiotherapy. Dashed, dash-dotted, and dotted lines represent RWD for chordoma, prostate, and head and neck cancer, respectively.

Physical dose optimization

Clinical objective is to deliver a uniform biological effect (RWD)

Spread out Bragg peaks consisting of pristine Bragg peaks whose fluences were optimized to yield a constant RBE-weighted absorbed dose of 3 Gy (RBE) using method of Wilkens and Oelfke (2006)

AAPM Task Group #256

- Task Group on “Proton Relative Biological Effectiveness (RBE)” formed in December 2013 by Harald Paganetti
Model assumptions and limitations

• **Limitations of the LQ model**
  – Does not explicitly capture many important biological factors, e.g., low dose hyper-radiosensitivity, bystander effects, possibility of other biological targets (e.g., endothelial cell apoptosis in vasculature)
  – High dose controversy (approximation for low dose rates and low doses, predictive up to ~10 Gy or higher?)

• **Uncertainties in radiosensitivity parameters**
  – Assumed values not meant to be interpreted as only biologically plausible parameters (inter- and intra-patient variability in radiosensitivity)
  – Lack of adequate data for many tumor sites and normal tissue

• **Best to practice evidence-based medicine**
  – Clinical data is the gold standard → must be skeptical of simplified models and understand limitations
  – Value of models highest in absence of good data → guide treatment decisions instead of relying on trial and error
Conclusions

- **BGRT** has potential to improve outcomes through optimization based on biological objective functions instead of dose-based surrogates
  - Goal to develop systematic methods to derive prescription doses that integrate patient-specific information about tumor and normal tissue radiobiology

- **Biologically optimal treatments** must balance gains associated with reducing tumor repopulation against potential for a loss of treatment efficacy associated with tumor hypoxia and DNA repair
  - **Hypoxia imaging** can provide prognostic information for cancer patients undergoing radiotherapy
  - Potential to overcome radioresistance identified by pre-treatment imaging by optimizing dose fractionations and distributions or drug delivery

- **Biologically-motivated mechanistic models can be used for optimization in particle therapy**
  - Determination of RBE values for cell killing that can be practically used in proton and carbon ion radiotherapy
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