Radiation Biology III:
Biological optimization of radiation therapy

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56th Annual Meeting of the AAPM

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

Yale SCHOOL OF MEDICINE

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

Background and Motivation

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

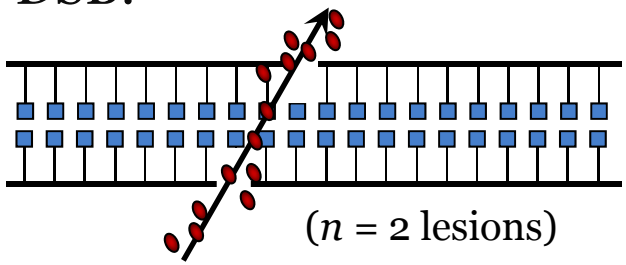
- **Dose-Based TP → *Physical objective functions***
  - Minimize dose gradients across tumor (uniformity), deliver prescribed isodose contours to target, minimize max. dose to critical structures, etc.
  - Uniform dose may not be most desirable

- **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)

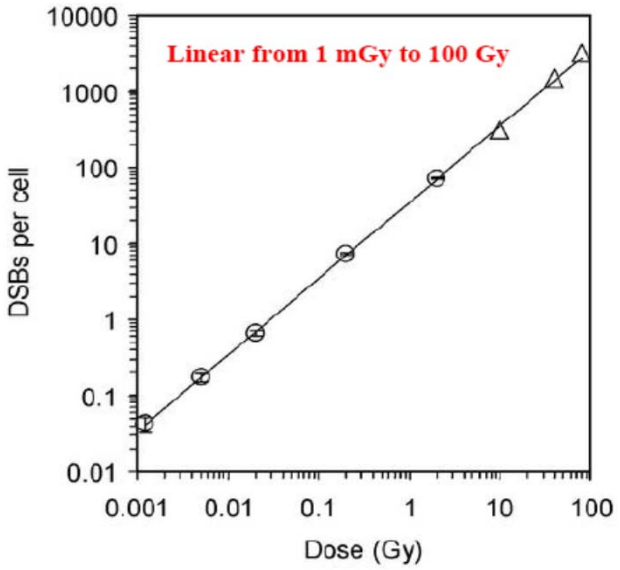
- A DSB is formed when two breaks in the sugar-phosphate backbone occur on opposite sides of DNA helix within **~10 base pairs**

- 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

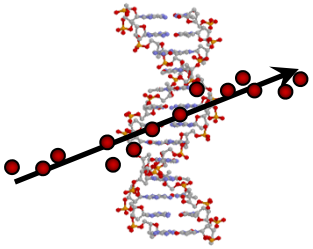


DSB induction in human fibroblasts (MRC-5) irradiated by 90 kVp x-rays (Rothkamm and Lobrich 2003)

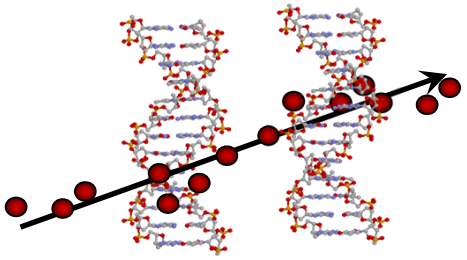
One- and two-track radiation damage

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

1 track damage
($\propto D$)

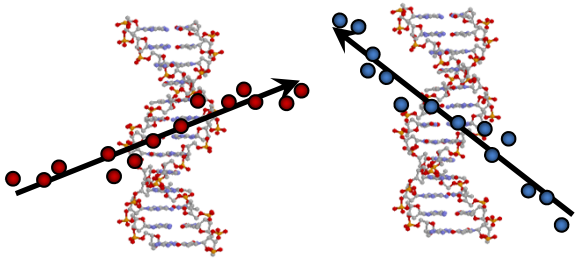


Lethal DSB misrepair, unrepairable damage



Pairwise interaction of two DSBs

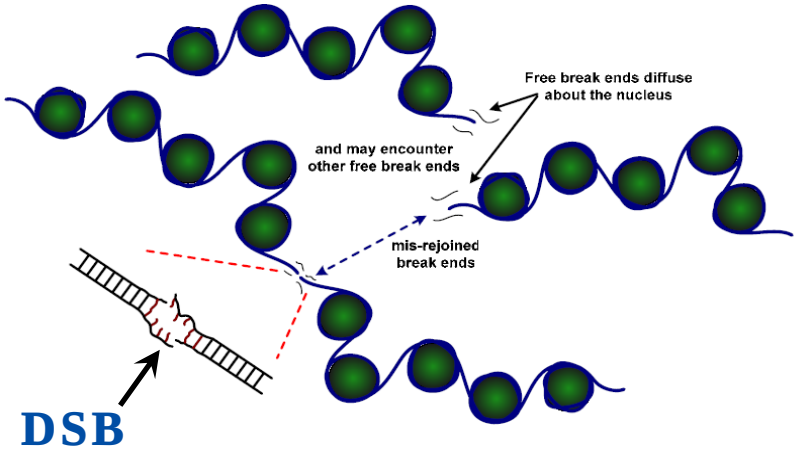
2 track damage
($\propto D^2$)



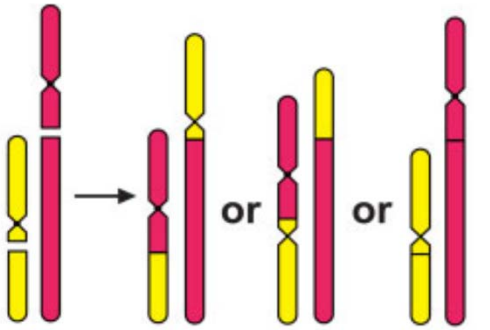
Pairwise interaction of two DSBs

Exchange-type aberrations

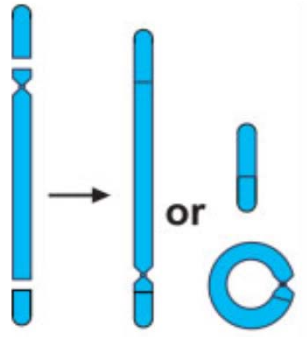
Pairwise damage interaction (binary misrepair)



2 chromosomes:



1 chromosome:



Linear-quadratic (LQ) cell survival model

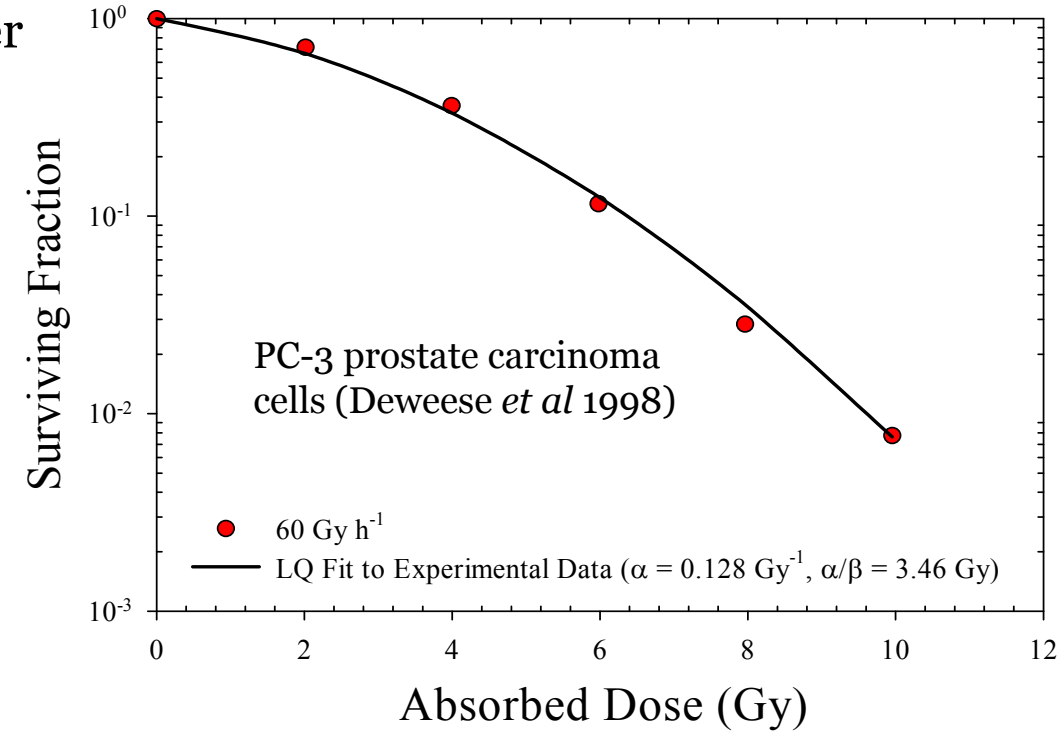
$$S(D) = \exp\left[-\left(\alpha D + \beta D^2\right)\right]$$

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

α = one-track lethal damage [Gy^{-1}]

β = two-track lethal damage [Gy^{-2}]

α/β [Gy] is clinically used descriptor of intrinsic radiosensitivity



Repair-misrepair-fixation (RMF) Model

Surviving fraction is related to yield of fatal lesions

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

1. Unrejoinable and lethal damage

3. Intra-track DSB interactions

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

2. Lethal misrepair and fixation

4. Inter-track DSB interactions

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

$f_R \equiv$ fraction of potentially rejoinable DSB
$\lambda \equiv$ rate of DSB repair (~10^{-1}–100 h^{-1})
$\eta \equiv$ rate of binary misrepair (~10^{-5}–10^{-4} h^{-1})
$\varepsilon \equiv z_E f_R \Sigma \equiv$ # of DSB per track per cell

$\Sigma \equiv$ expected # of DSB (Gy^{-1} $cell^{-1}$)
$\theta \equiv$ prob. DSB lethally misrepaired/fixed
$\gamma \equiv$ prob. exchange-type aberration lethal

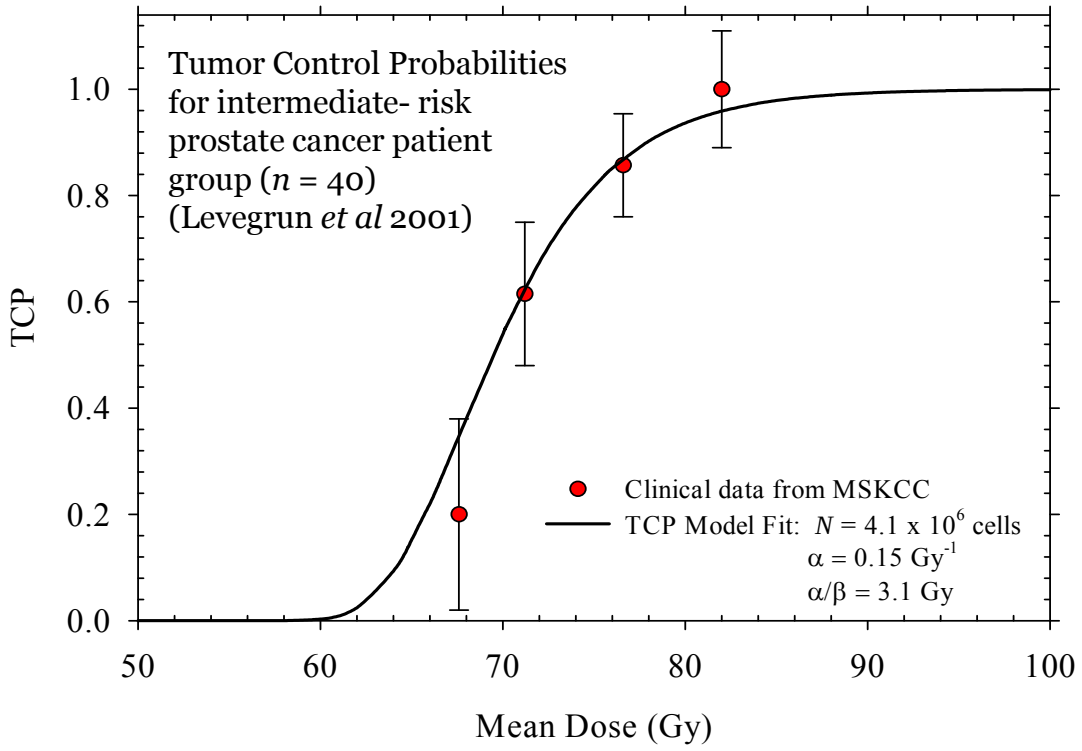
Carlson DJ, Stewart RD, Semenenko VA, Sandison GA. Combined use of Monte Carlo DNA damage simulations and deterministic repair models to examine putative mechanisms of cell killing. *Radiat. Res.* 2008; 169: 447–459.

Tumor Control Probability (TCP) Model

TCP → relates tumor size and radiation dose to the prob. 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* = 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

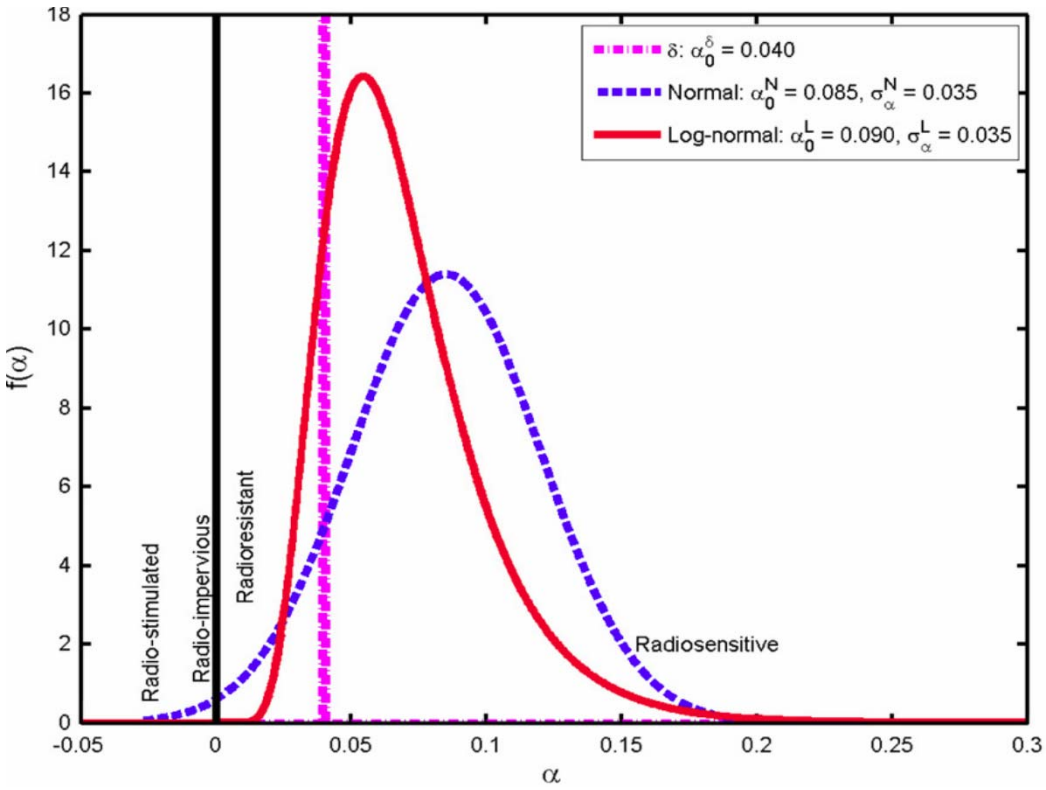
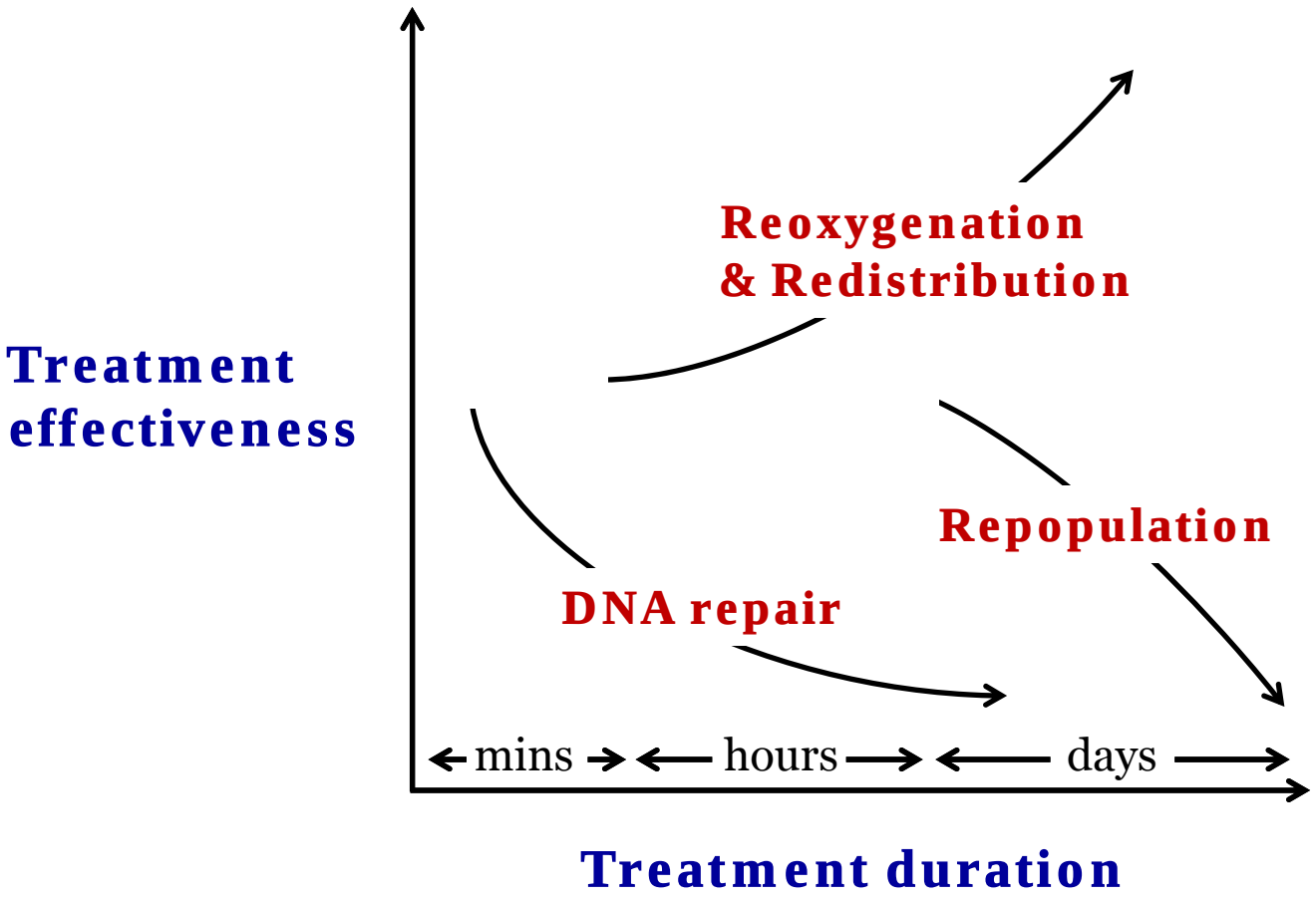


Figure from: Keall PJ, Webb S. Optimum parameters in a model for tumour control probability, including interpatient heterogeneity: evaluation of the log-normal distribution. *Phys. Med. Biol.* 2007; 52: 291–302.

Factors that alter treatment effectiveness

4 R's of Radiobiology give rise to "dose rate" effects:



Factors that alter treatment effectiveness

Divide a tumor into voxels with radiosensitivity α_i and β_i. Correct SF for dose heterogeneity, inter- and intra-tumor variability in radiosensitivity and the R's of radiobiology:

$$\mathrm{TCP} = \prod_i \mathrm{TCP}_i$$

$$\mathrm{TCP}_i = \exp\left\{-N_0 f_i \exp\left[-D\left(\alpha_i + \beta_i G_i D_i\right) + \gamma_i T\right]\right\}$$

Oxygen and LET effects (α and β)

Repair effects (μ or τ)

$N_0 f_i$ is initial # of cells in the *i*th tissue region

Repopulation rate in *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

α = one-track lethal damage coefficient [Gy^{-1}]

β = two-track lethal damage coefficient [Gy^{-2}]

G[μ,t] is the Lea-Catcheside dose protraction factor

$\mu = \ln 2/\tau$ = rate of DSB rejoining [h^{-1}]

Limiting cases:

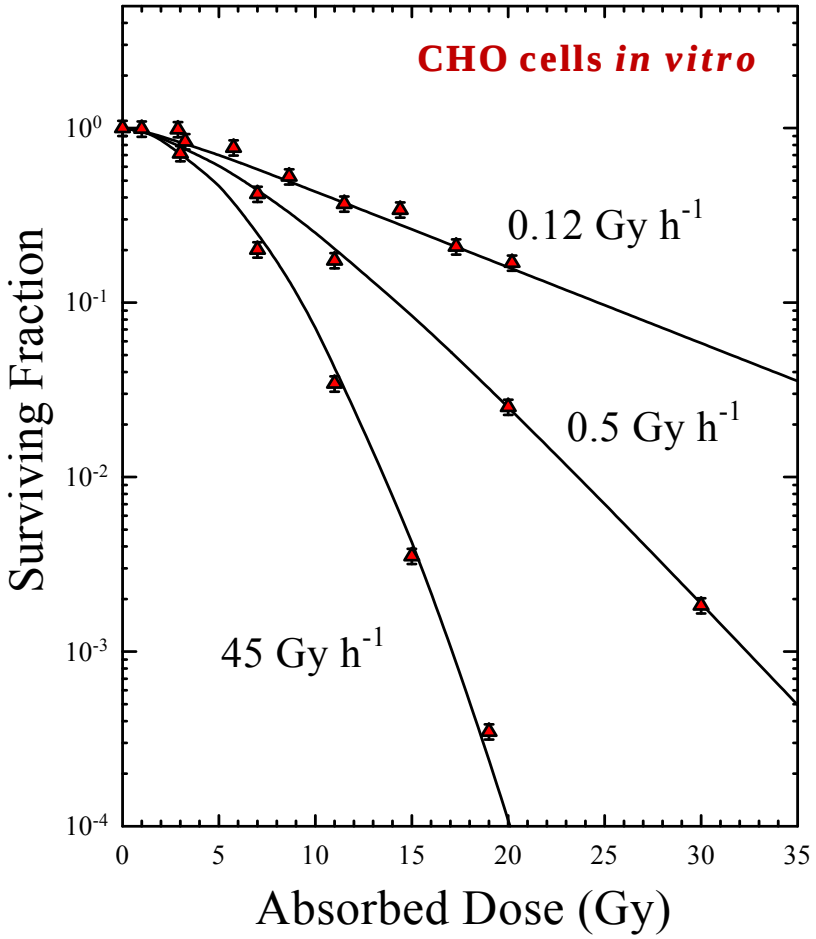
$\lim_{t\to 0} G = 1$ ← **Instantaneous dose delivery**

$\lim_{t\to \infty} G = 0$ ← **Infinitely protracted dose**

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

Sachs RK, Hahnfeld P, Brenner DJ. The link between low-LET dose-response relations and the underlying kinetics of damage production/repair/misrepair. *Int. J. Radiat. Biol.* 72(4): 351–74 (1997).

Dose rate effects and DNA damage repair



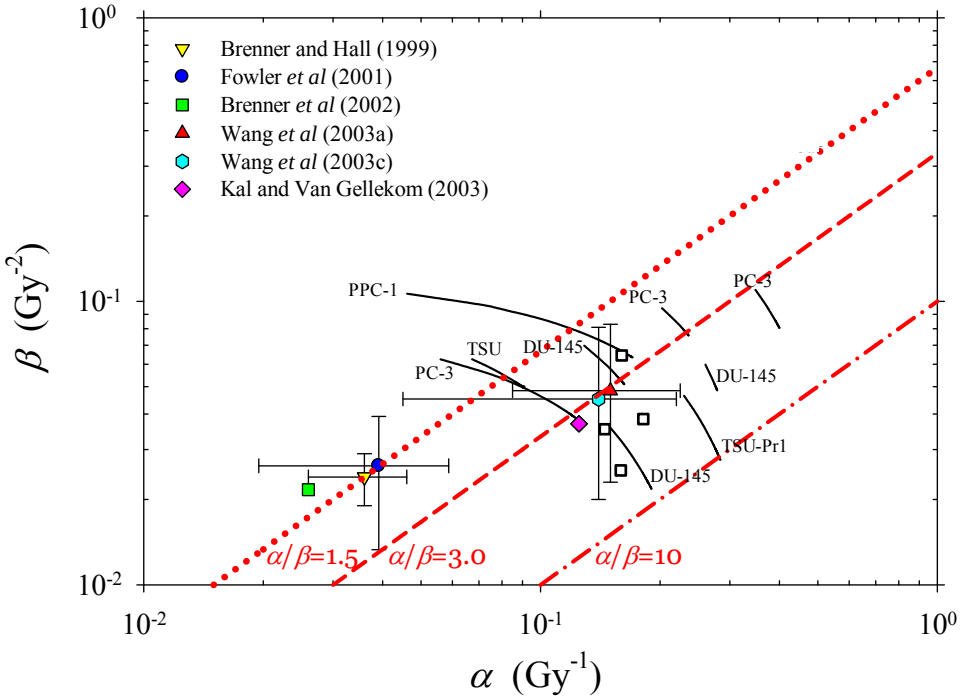
- Cell killing decreases with decreasing dose rate
- If $G(\mu,t)$ included, unique set of parameters can predict the data:

  $\alpha = 0.04$ Gy^{-1} , $\beta = 0.02$ Gy^{-2}, $\tau = 6.4$ h
- Repair of DNA damage occurs between fractions *and* during treatment delivery
- Effect increases with increase in delivery time

→ **More important for SBRT, SRS, and brachytherapy**

Measured data from Stackhouse M.A. and Bedford J.S. *Radiat. Res.* **136**, 250-254 (1993) and Wells R.L. and Bedford J.S. *Radiat. Res.* **94**(1), 105-134 (1983).

Prostate Cancer: review of *in vitro* and *in vivo* data



***In vitro* estimates:**

- α = 0.09–0.4 Gy^{-1}
- α/β = 1.1–6.3 Gy

***In vivo* estimates:**

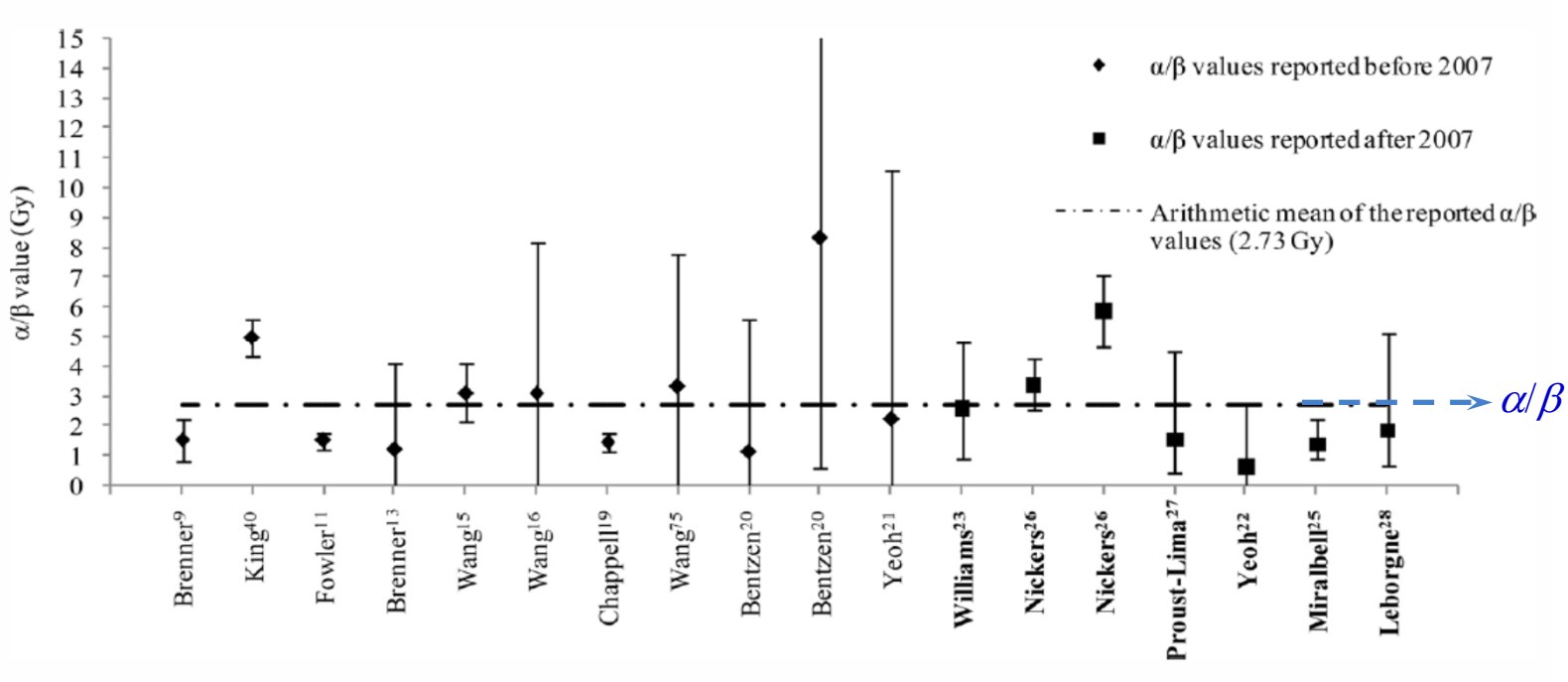
- α = 0.036–0.15 Gy^{-1}
- α/β = 1.5–3.1 Gy

***In vitro* and *in vivo* data support a low α/β for prostate cancer**

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

Carlson DJ, Stewart RD, Li XA, Jennings K, Wang JZ, Guerrero M. Comparison of in vitro and in vivo α/β ratios for prostate cancer. Phys. Med. Biol. 49, 4477-4491 (2004).

Review of studies deriving prostate α/β



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"

Oliveira SM, Teixeira NJ, Fernandes L. What do we know about the α/β for prostate cancer? *Med. Phys*. 2012; 39: 3189-3201.

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

Take the negative logarithm of *S* and divide by α:

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

Physical dose

Relative effectiveness

"Lost" dose due to repopulation effect

Isoeffect Example for Prostate Cancer

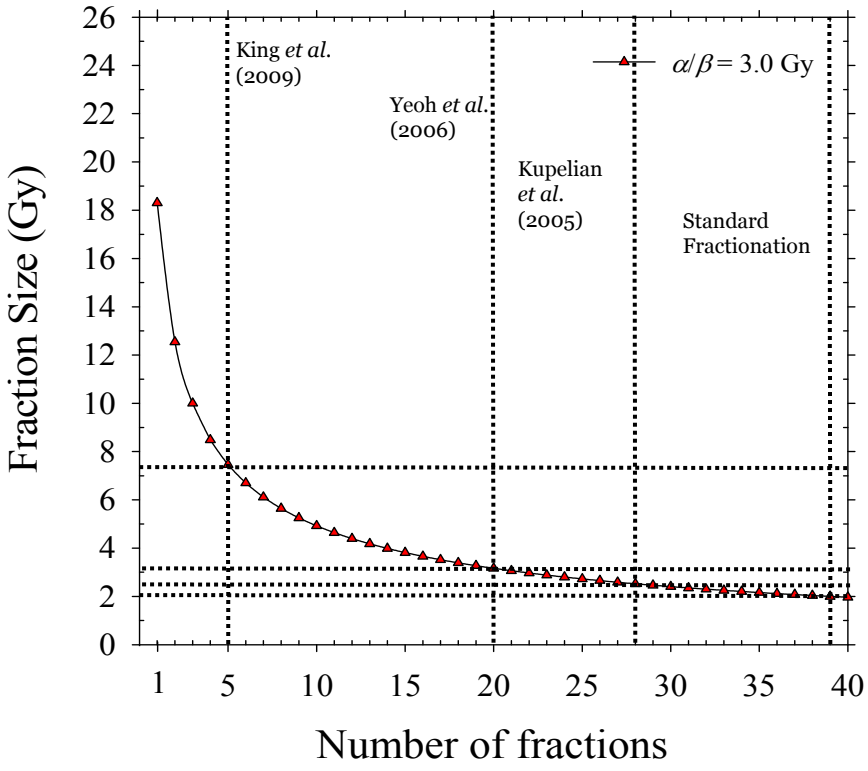
- Assume $\alpha/\beta = 3$ Gy, for a standard EBRT fractionation of 39 fractions of 2 Gy:

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

- Rearrange simplified BED equation:

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

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



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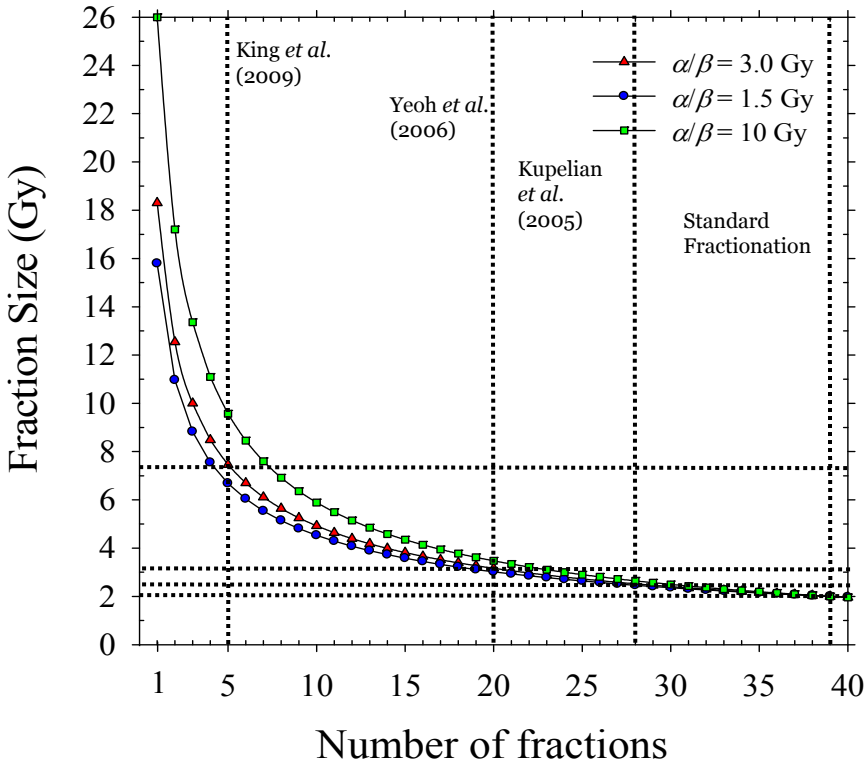

Radiobiology and the AAPM

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[a)]

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Li XA, Alber M, Deasy JO, *et al*. 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. *Med. Phys*. 2012; 39: 1386–1409.

Hypofractionation and Tumor Hypoxia

Tumor hypoxia is an important mechanism of radioresistance in hypofractionated radiotherapy and must be considered in the treatment planning process

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Colin G. Orton, Ph.D., Moderator

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OVERVIEW

With the increased use of normal tissue sparing highly conformal therapy it has become possible to treat patients with fewer treatments at high dose/fraction. Fewer fractions, however, mean fewer opportunities for radioresistant hypoxic cells to reoxygenate during the course of treatment and this might reduce tumor control. It has been suggested that tumor hypoxia is an important consideration for such hypofractionated regimes, and, as such, it should be considered in treatment planning. This is the concern debated in this month's Point/Counterpoint debate.

Arguing for the Proposition is David J. Carlson, Ph.D. Dr. Carlson obtained his Ph.D. in Medical Physics from Purdue University and then completed a Radiation Oncology Physics Residency at Stanford University. He then moved to his current appointment as Assistant Professor at the Yale Univer-

Arguing against the Proposition is Kamil M. Yenice, Ph.D. Dr. Yenice obtained his Ph.D. in Physics from the University of Toledo, Ohio and, subsequently, completed an M.S. in Radiological Physics at Wayne State University, Detroit. He worked as a faculty physicist at Memorial Sloan Kettering Cancer Center from 1999 to 2005. In 2005 he moved to University of Chicago, where he became the Chief of Clinical Physics in 2007. He is certified by the American Board of Medical Physics in Radiation Oncology Physics. He has served on several AAPM committees including the AAPM Task Group 101 (SBRT).

FOR THE PROPOSITION: David J. Carlson, Ph.D.

Opening Statement

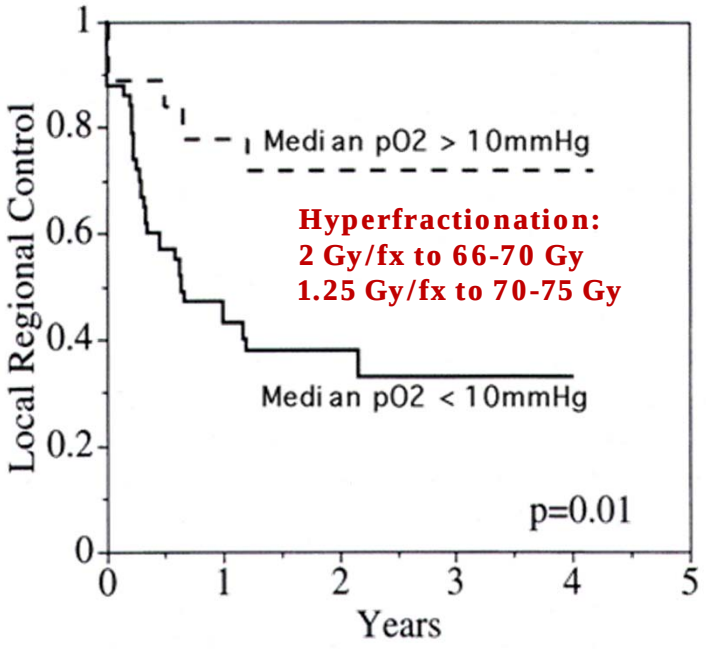
Tumor hypoxia is a well-established and accepted mechanism of radioresistance and correlates with treatment failure in

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).

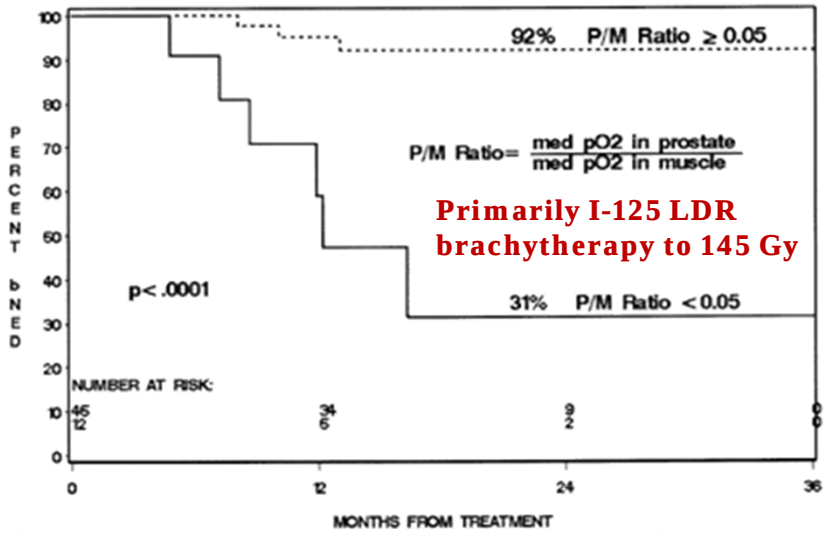
Clinical significance of tumor hypoxia

Head and neck cancer



D.M. Brizel *et al.*, *Radiother. Oncol.*, 1999

Prostate cancer

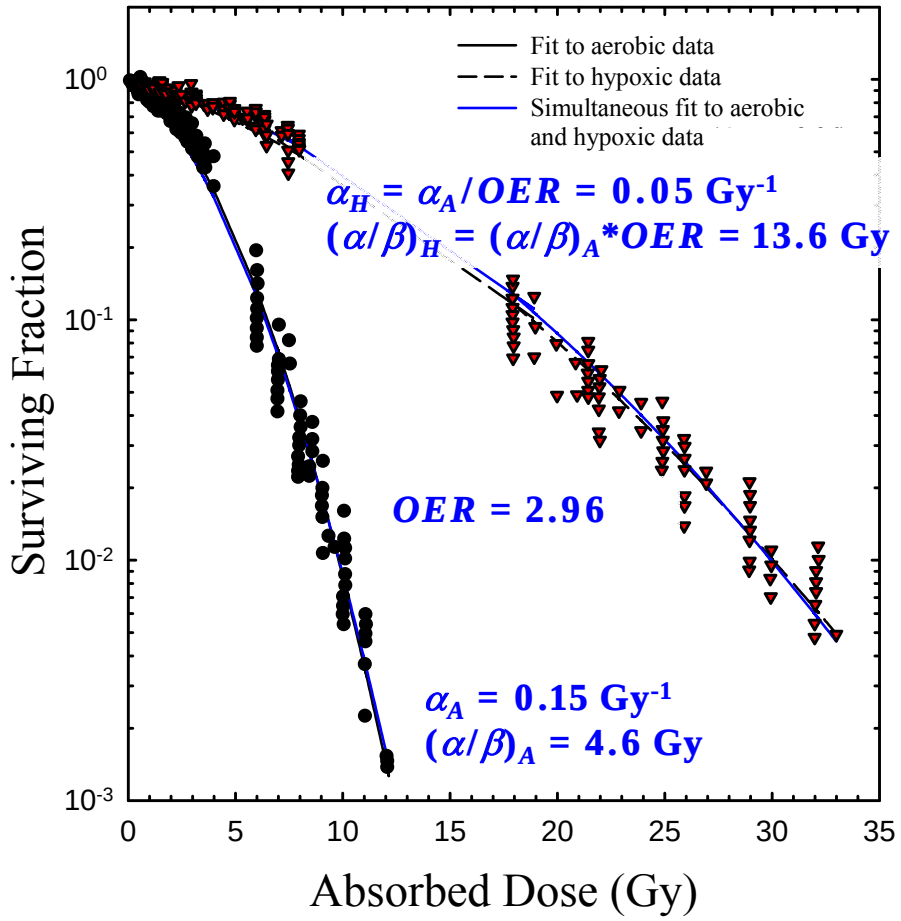


B. Movsas *et al.*, *Urology*, 2002

~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?

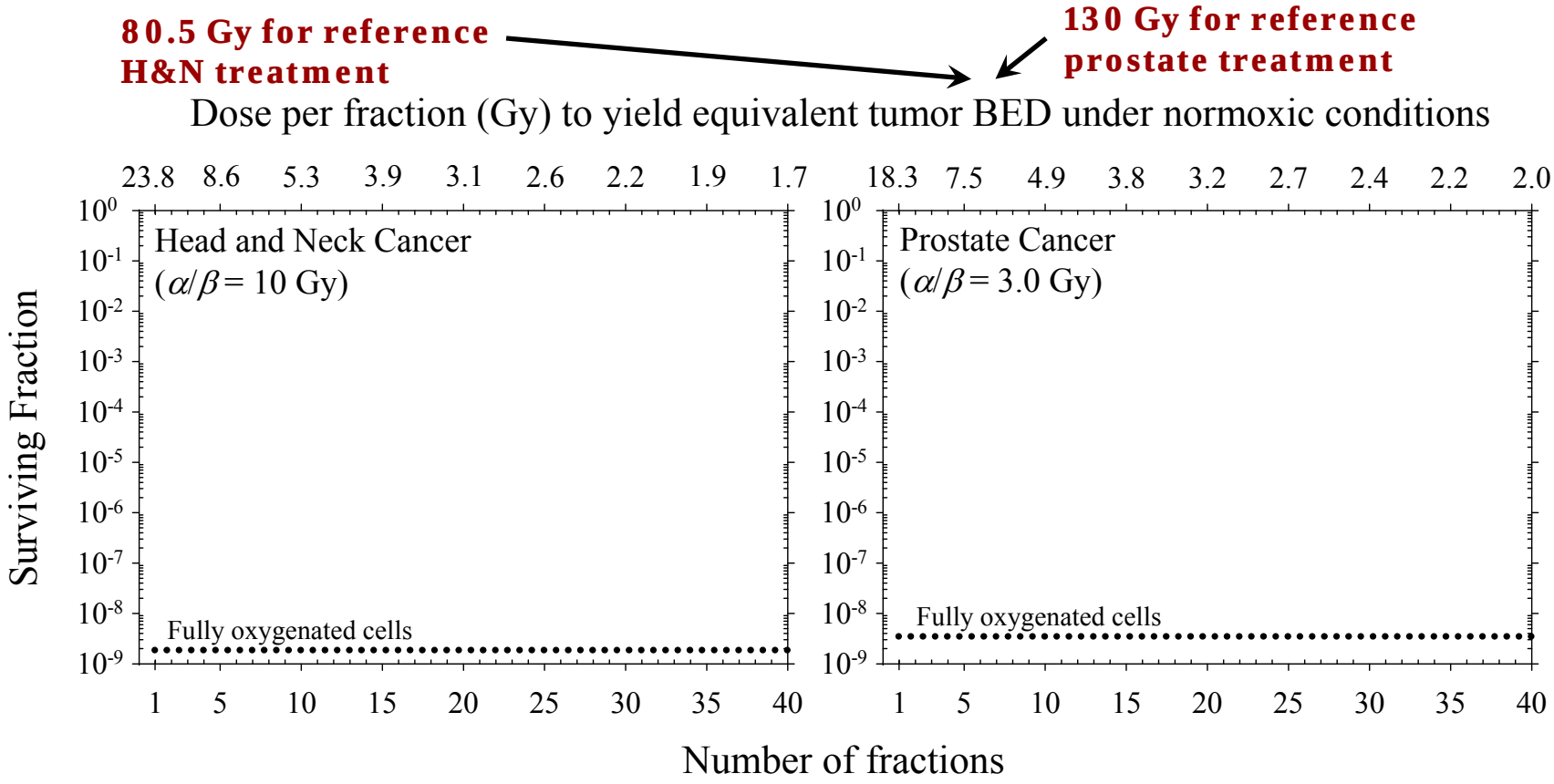
V79 379A Chinese hamster cell survival data from Watts *et al.* (1986)



- *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)

Carlson DJ, Stewart RD, Semenenko VA. Effects of oxygen on intrinsic radiation sensitivity - a test of the relationship between aerobic and hypoxic linear-quadratic (LQ) model parameters. *Med Phys*; 33: 3105–3115 (2006).

Effects of Hypoxia and Fractionation on Cell Survival

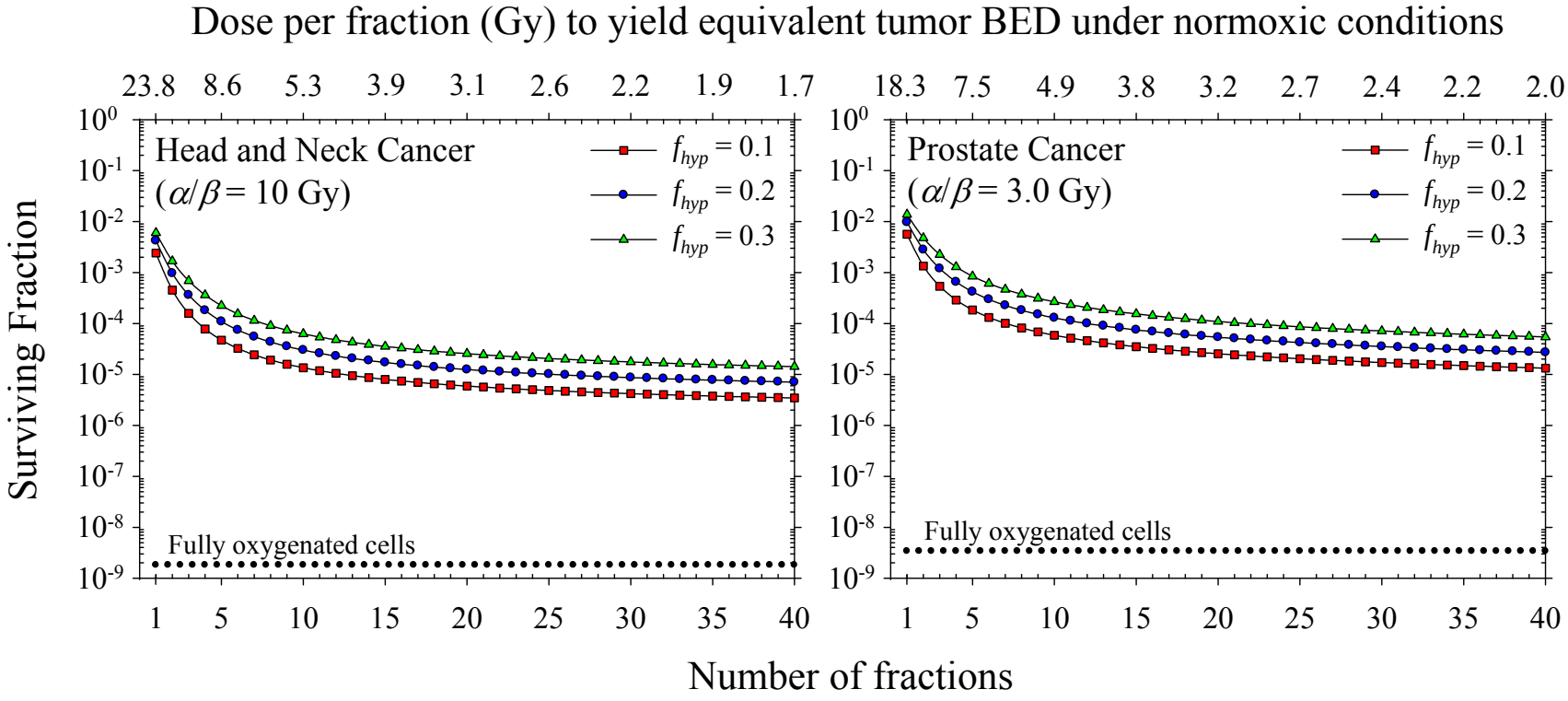


$$S_{overall} = S(d)^n = \left[\exp\left(-\alpha_A d - \beta_A d^2\right)\right]^n$$

Carlson DJ, Keall PJ, Loo BW, Chen ZJ, Brown JM. Hypofractionation results in reduced tumor cell kill compared to conventional fractionation for tumors with regions of hypoxia. *Int. J. Radiat. Oncol. Biol. Phys.* 79: 1188-1195 (2011).

Effects of Hypoxia and Fractionation on Cell Survival

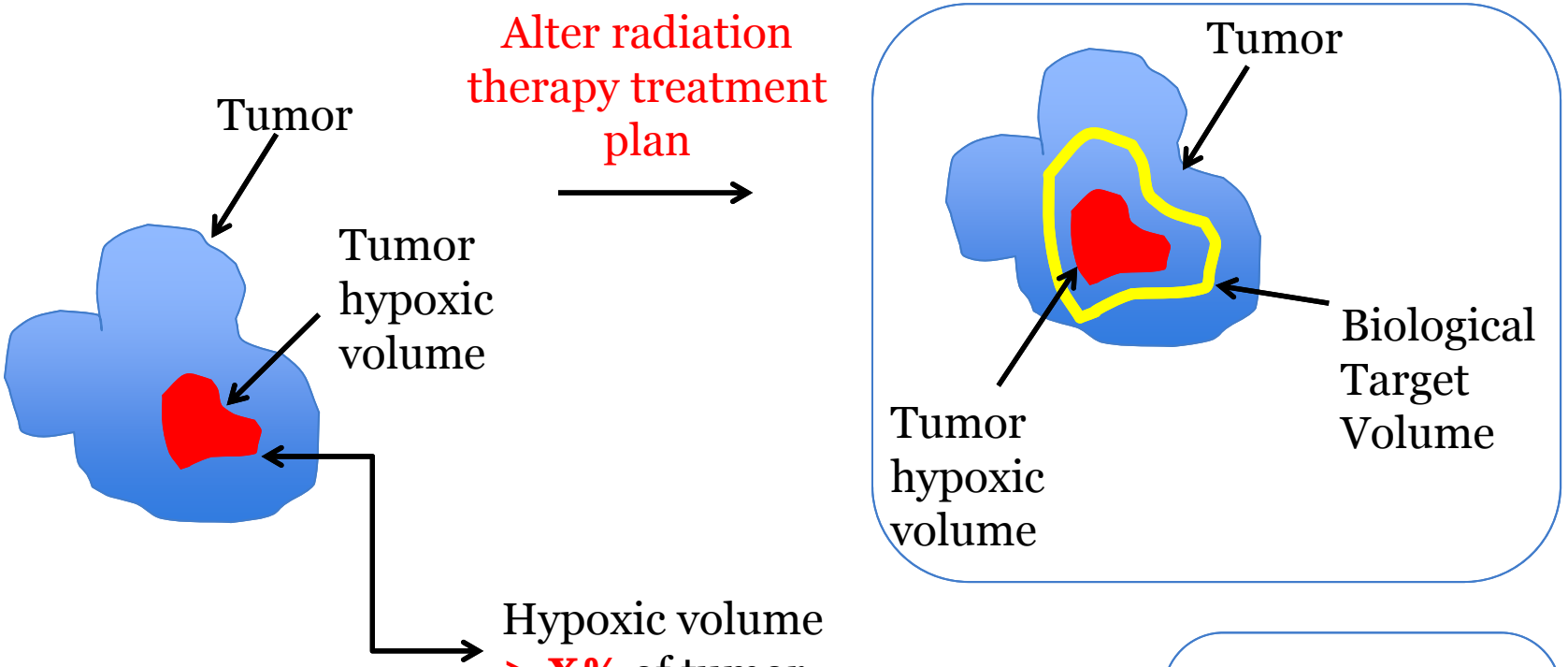
What happens to total cell killing if we include hypoxia?



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

Carlson DJ, Keall PJ, Loo BW, Chen ZJ, Brown JM. Hypofractionation results in reduced tumor cell kill compared to conventional fractionation for tumors with regions of hypoxia. *Int. J. Radiat. Oncol. Biol. Phys.* 79: 1188-1195 (2011).

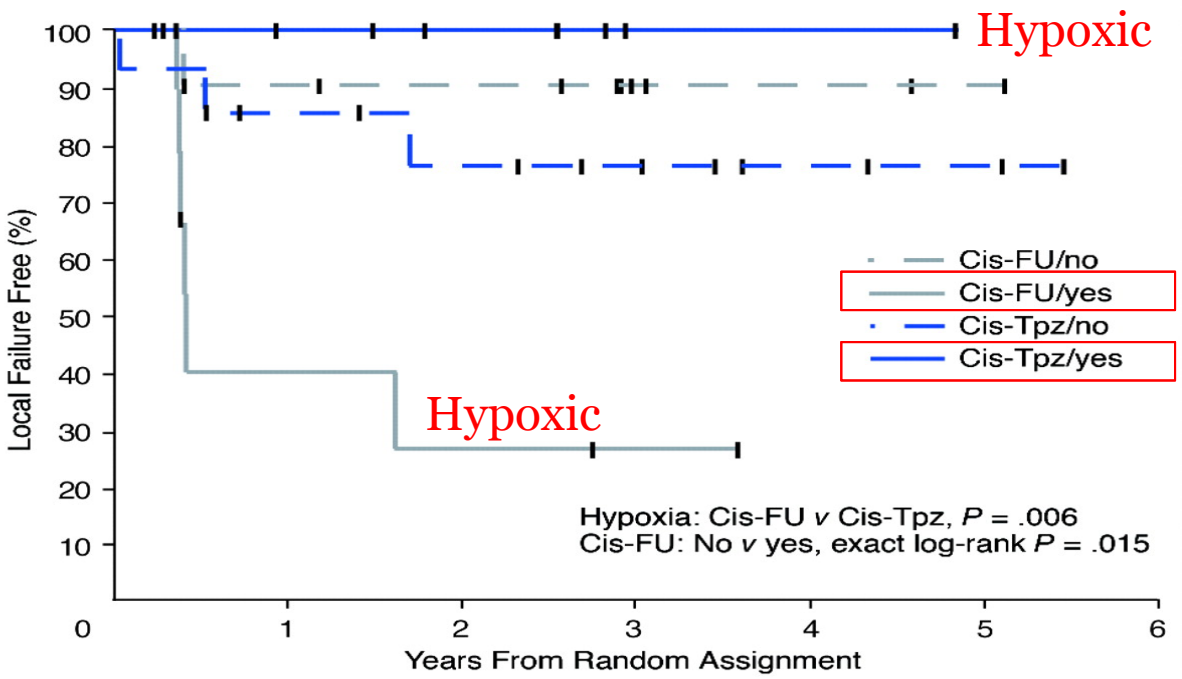
Strategies to overcome tumor hypoxia?



Kelada, O.J. and Carlson, D.J. Molecular Imaging of Tumor hypoxia with Positron Emission Tomography. *Radiat. Res.* 2014; 181: 335-349.

^{18}F-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 ^{18}F-FMISO PET performed



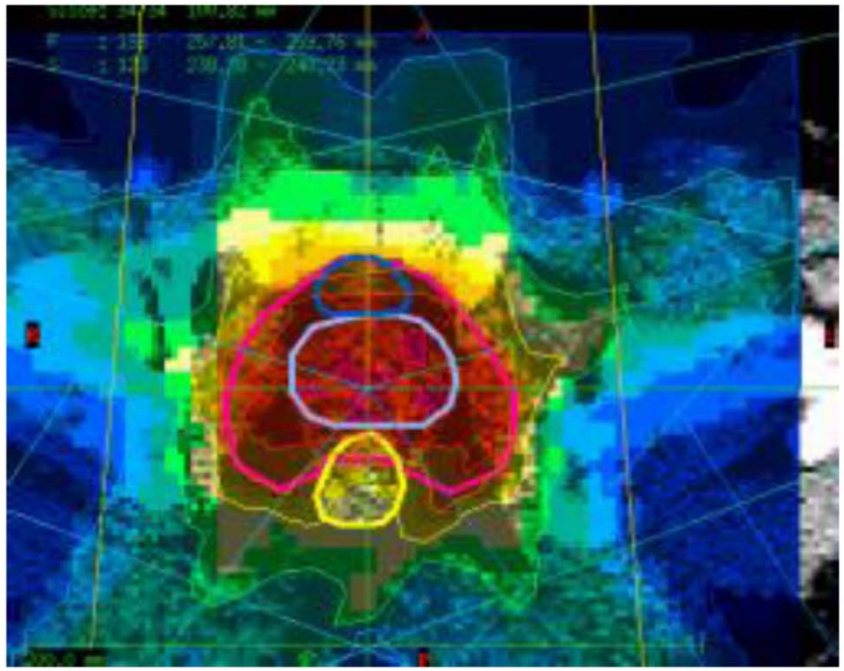
- **In patients with hypoxic tumors, 0 of 8 treated with Cis-TPZ had local failure compared with 6 of 9 treated with Cis-FU**
- **First clinical evidence to support tirapazamine specifically targets hypoxic tumor cells**

Rischin, D., R. J. Hicks, et al. (2006). "Prognostic significance of [18F]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer" J Clin Oncol **24**(13): 2098-2104.

Photon versus proton dosimetry

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

Photons



Protons

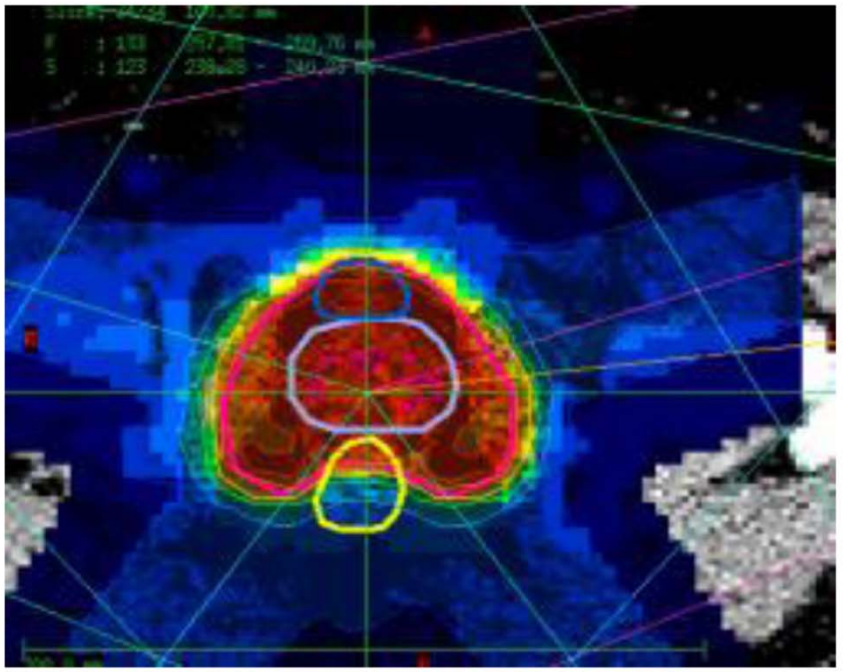
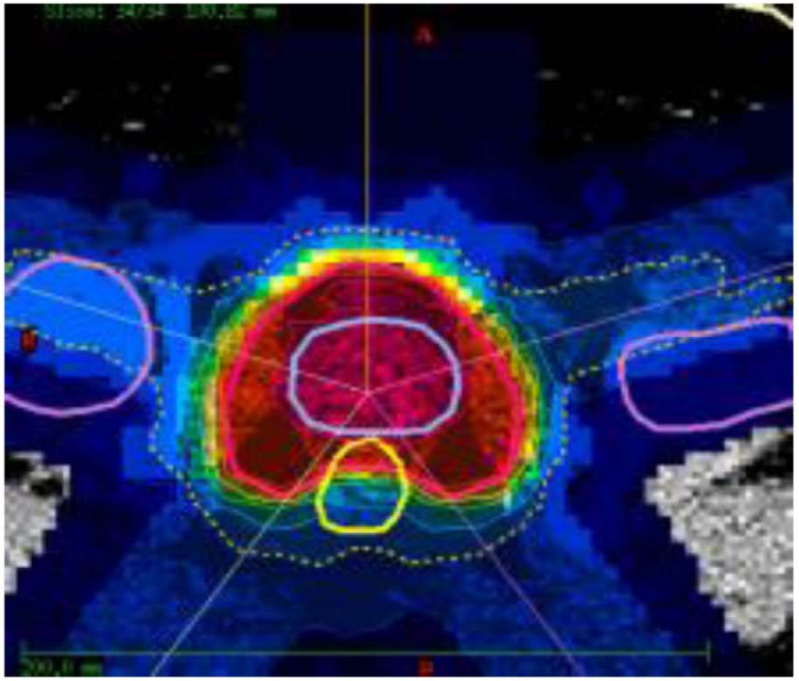


Image courtesy of Uwe Oelfke (ICR, London)

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

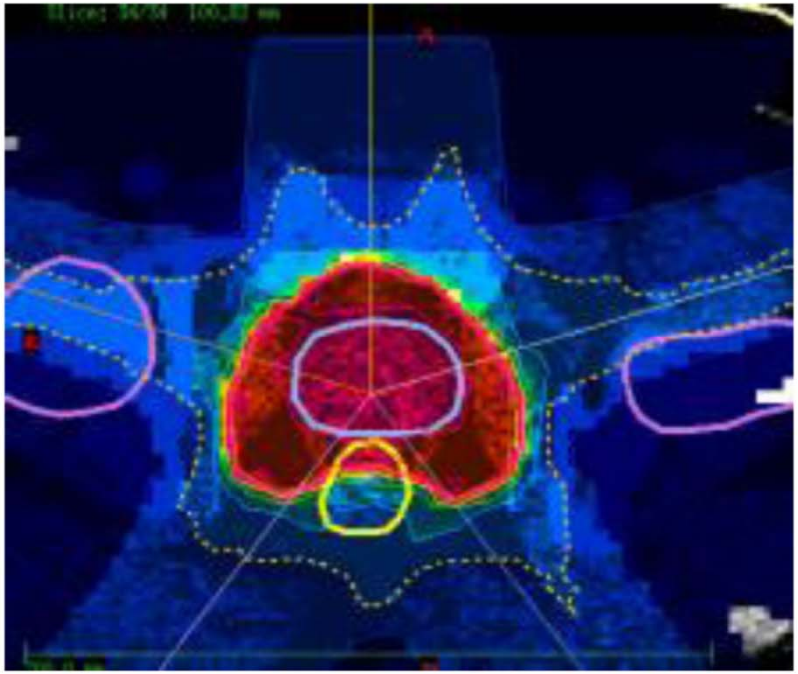


Image courtesy of Uwe Oelfke (ICR, London)

Physical and Biological Aspects of Particle Theray

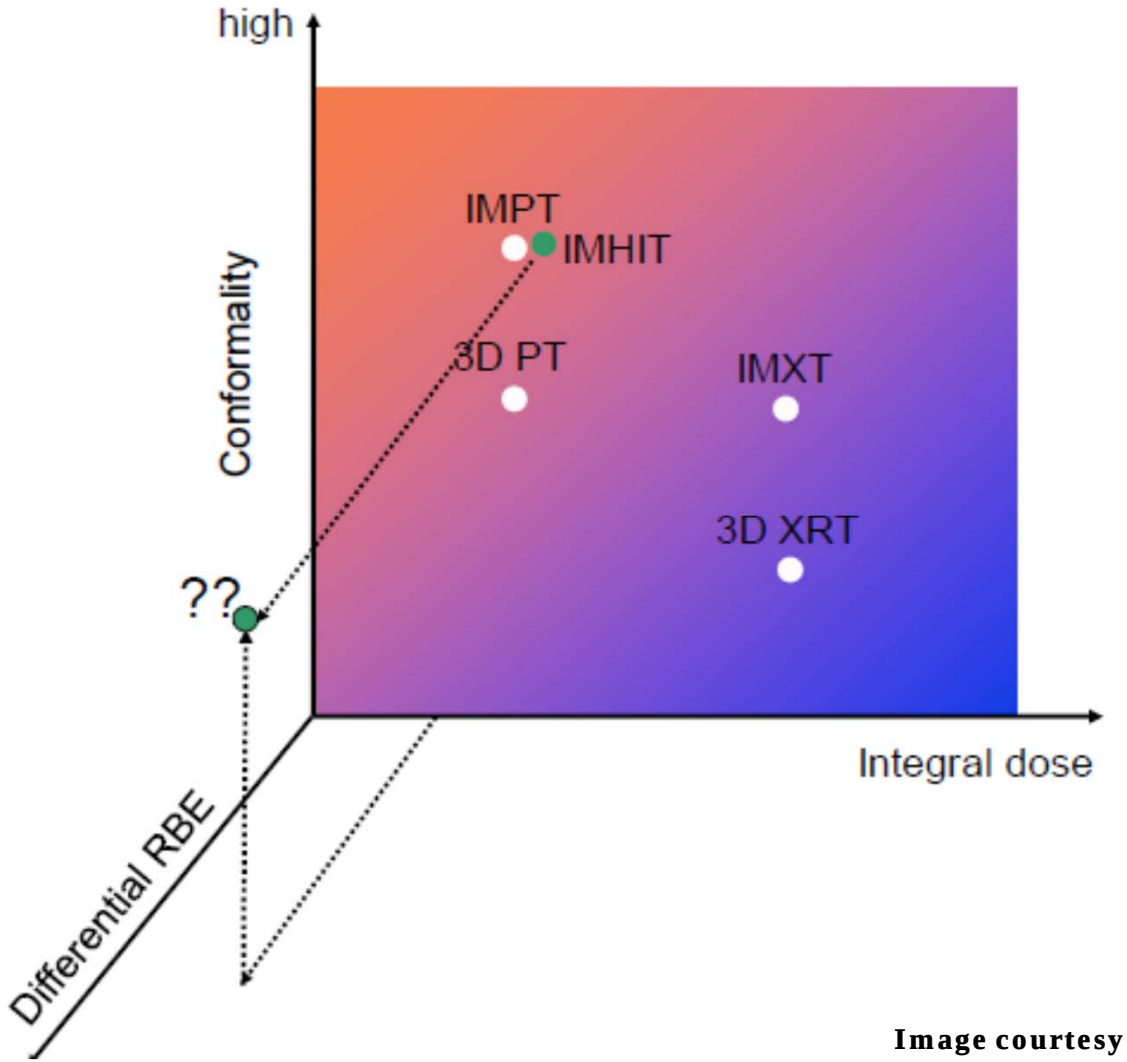
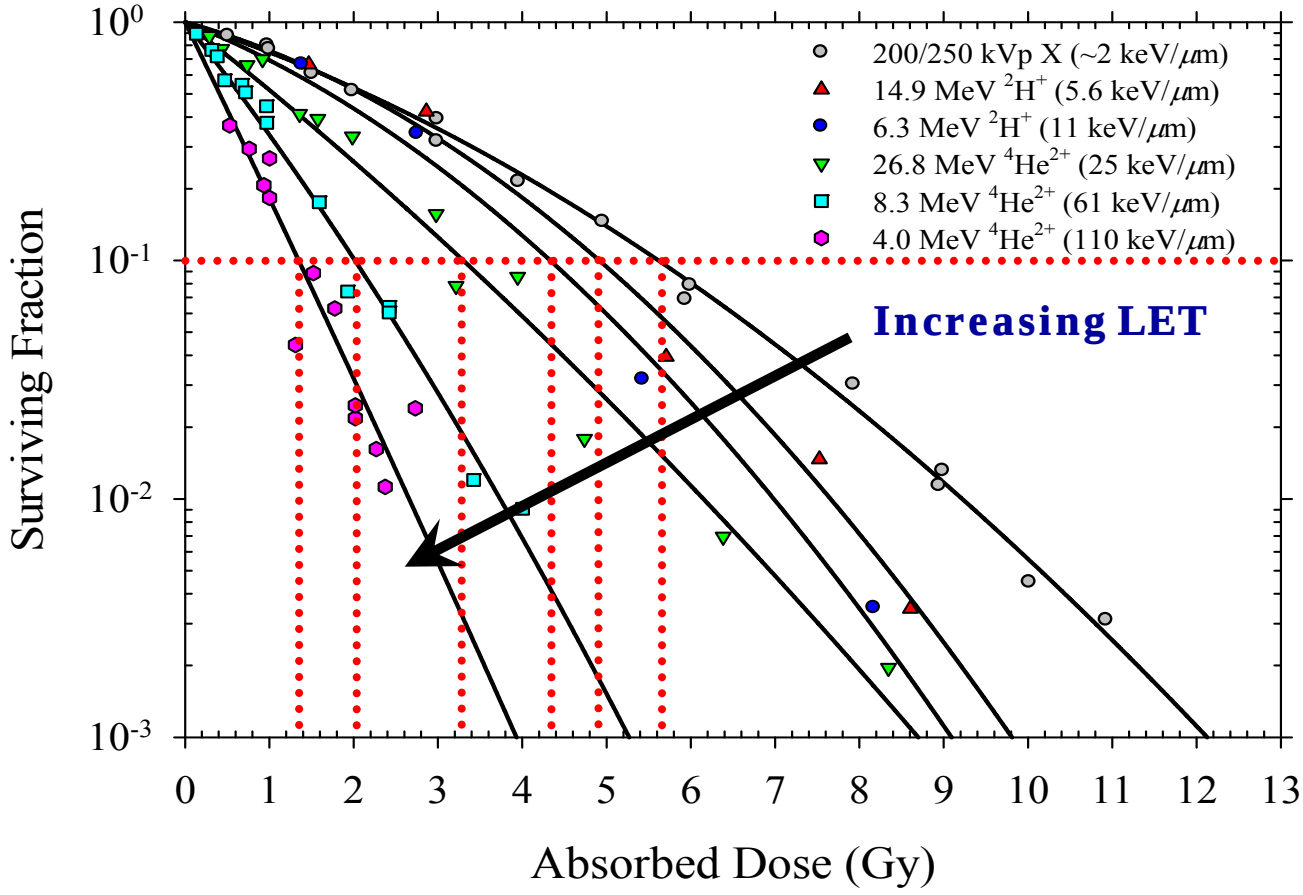


Image courtesy of Uwe Oelfke (ICR, London)

Biological effects of radiation quality

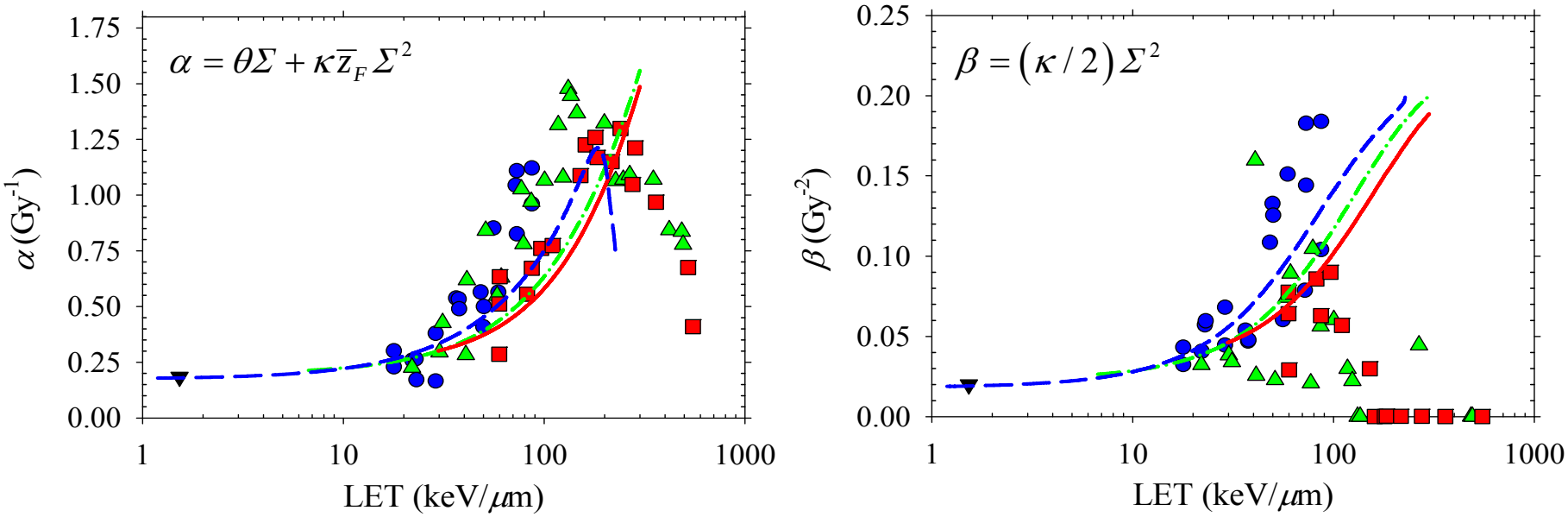


Barendsen *et al.* (1960, 1963, 1964, 1966): *In vitro* cell survival data for human kidney T-1 cells

Predicting trends in radiosensitivity

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

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



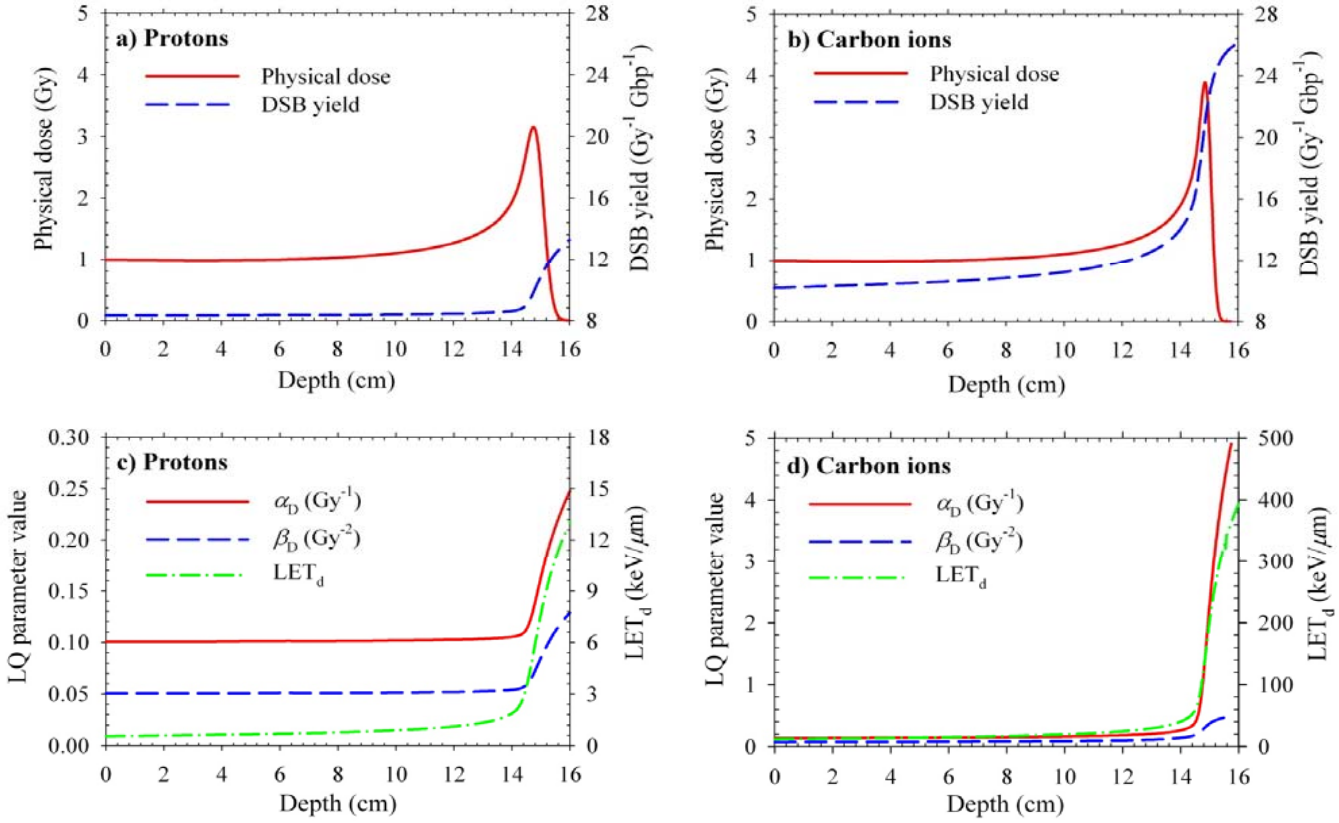
Radiosensitivity parameters for V79 cells irradiated *in vitro*. **Symbols:** estimates of α and β reported by **Furusawa *et al.* (2000)** for He-3 (**blue circles**), C-12 (**green triangles**) and Ne-20 (**red squares**). **Lines:** RMF-predicted parameters.

Frese MC, Yu VK, Stewart RD, **Carlson DJ**. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2012; 83: 442–450.

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
- α and β calculated assuming chordoma reference parameters
- All calculations include Gaussian particle spectrum



Frese MC, Yu VK, Stewart RD, **Carlson DJ**. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2012; 83: 442–450.

RBE for cell killing in Proton SOBP

Conditions:

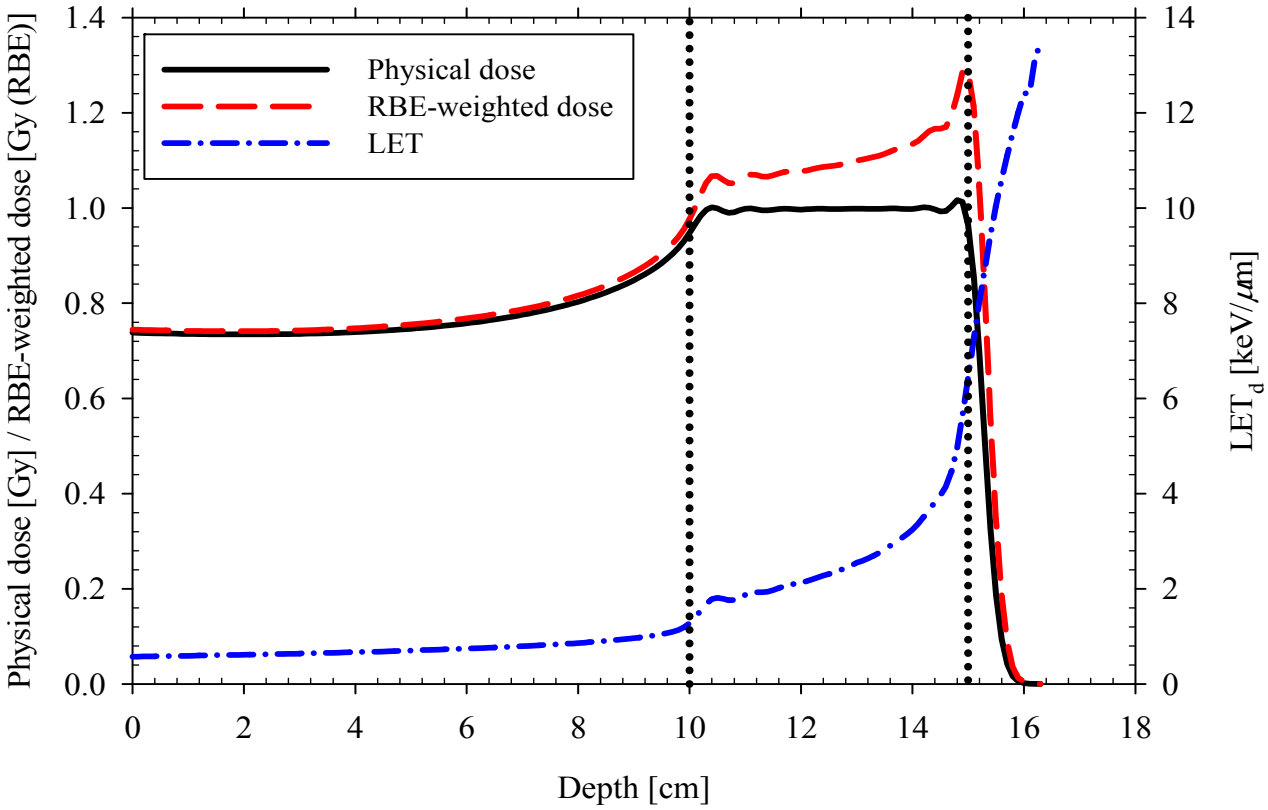
1. Normoxic chordoma cells: α_x= 0.1 Gy^{-1}, $(\alpha/\beta)_x$=2.0 Gy
2. Proximal edge of SOBP: 10 cm
3. Distal edge of SOBP: 15 cm
4. Distance between Bragg peaks: 0.3 cm
5. # of Bragg peaks: 17

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

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

Potential for biological hot and cold spots within proton SOBP



RBE for cell killing in Carbon Ion SOBP

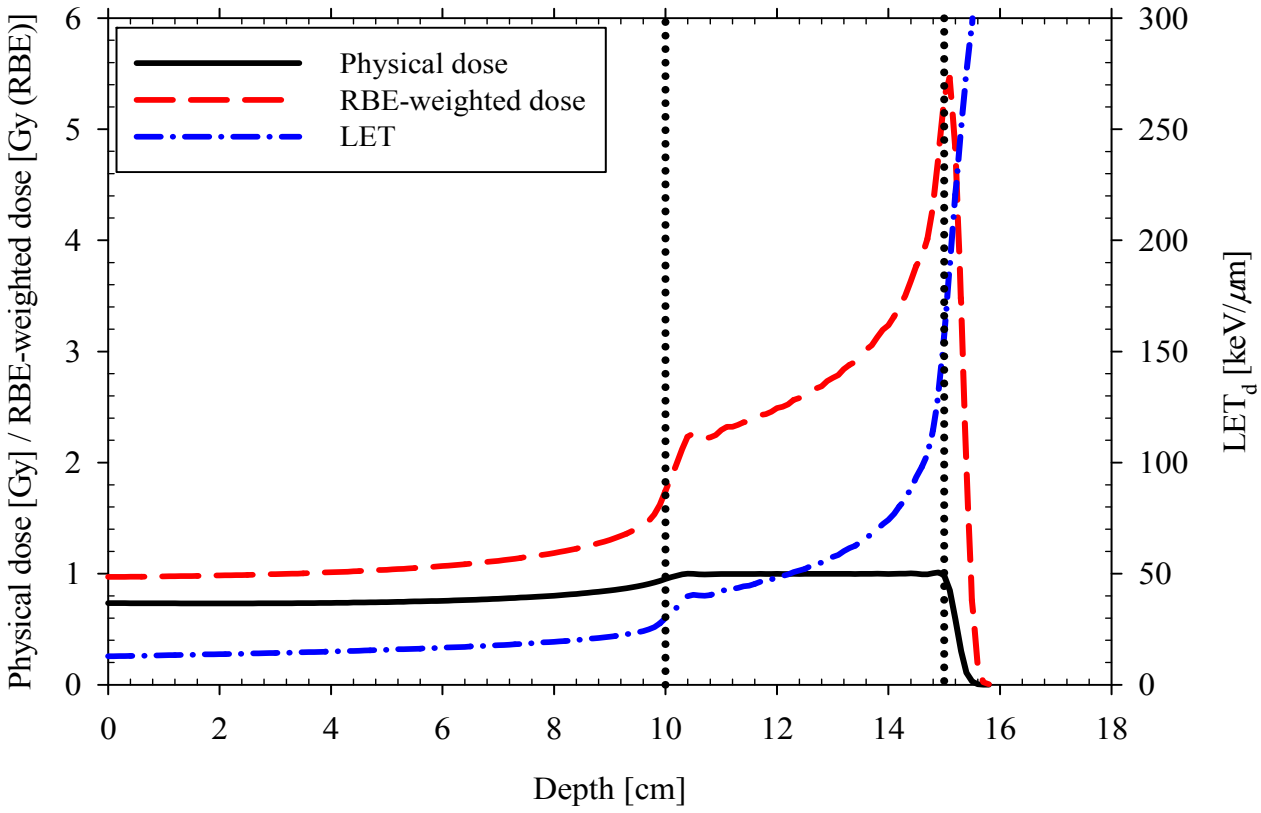
Conditions:

1. Normoxic chordoma cells: α_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

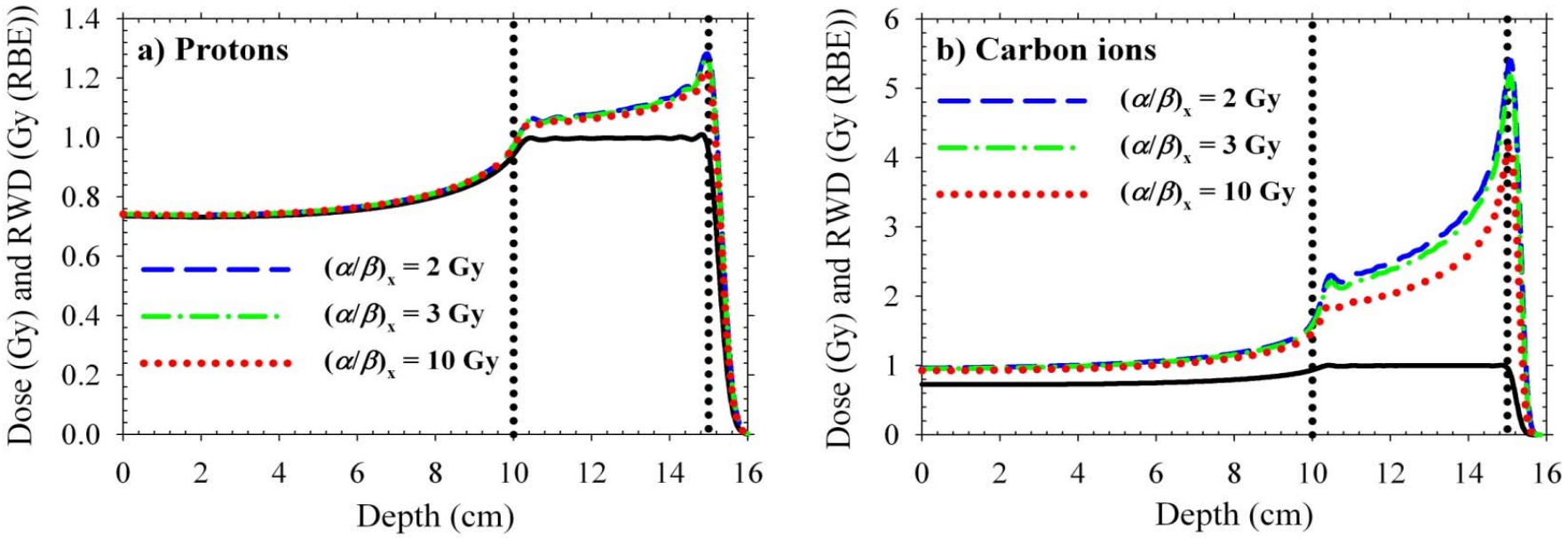
Results:

1. Entrance RBE ~1.3
2. RBE ranges from 1.8 to 5.4 from proximal to distal edge of the SOBP
3. Mean RBE across SOBP is ~2.8

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



Dependence on tissue radiosensitivity

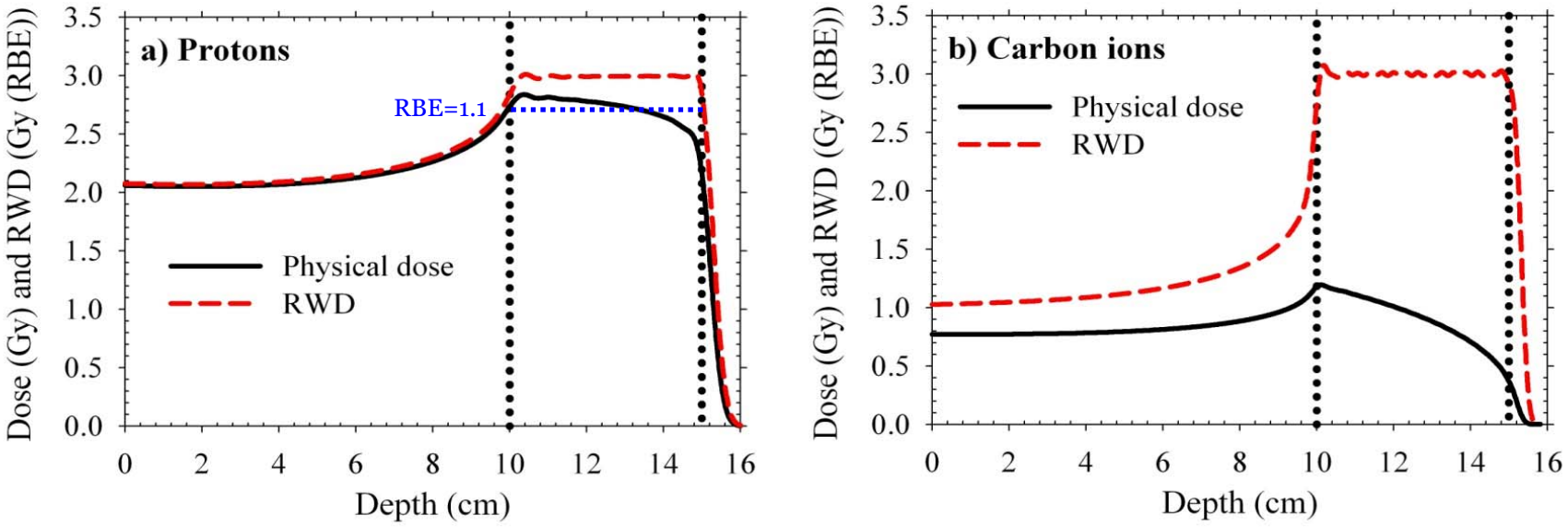


Physical (solid line) and RBE-weighted (RWD) dose for a representative clinical spread-out Bragg peaks in proton and carbon ion radiotherapy. Dashed, dash-dotted, and dotted lines represent RWD for chordoma, prostate, and head and neck cancer, respectively.

Frese MC, Yu VK, Stewart RD, **Carlson DJ**. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2012; 83: 442–450.

Physical dose optimization

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

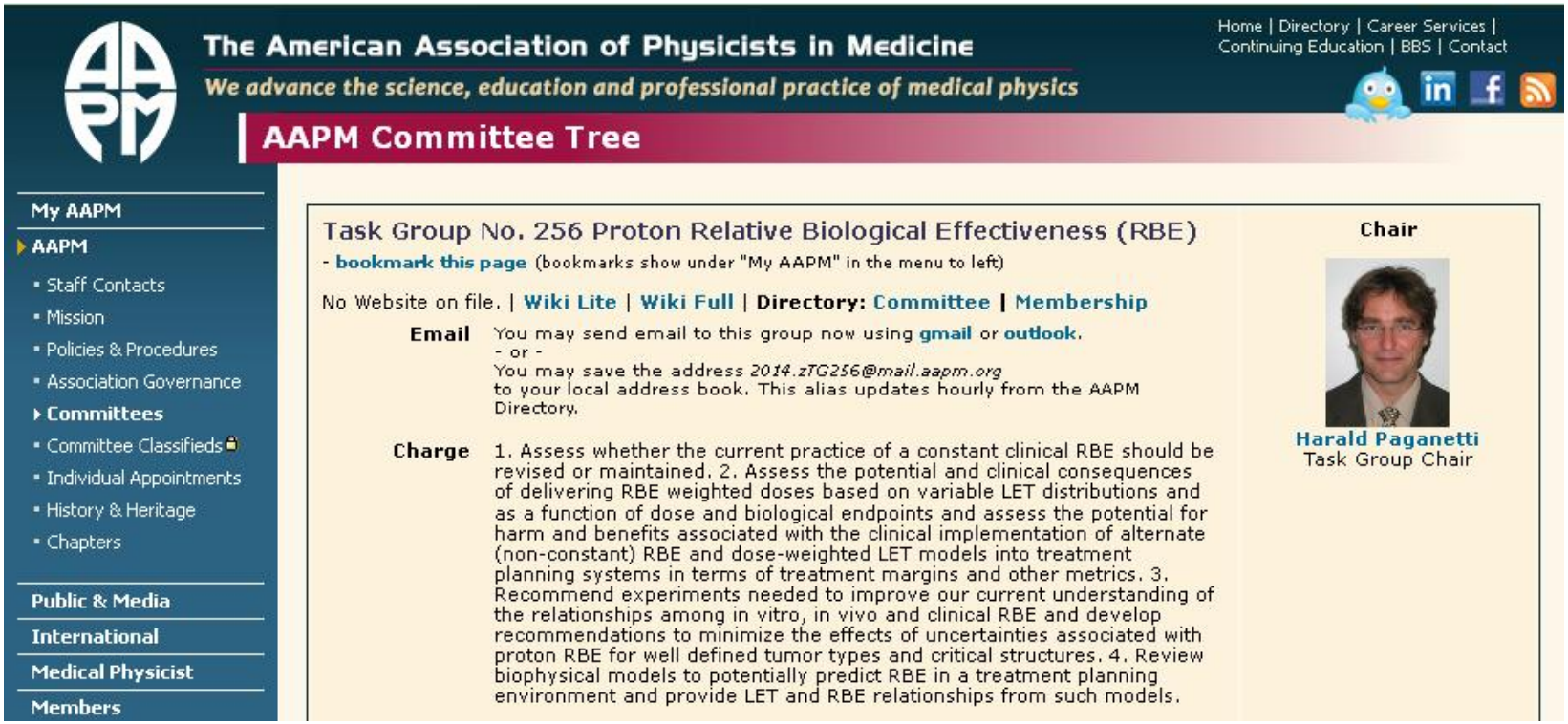


Spread out Bragg peaks consisting of pristine Bragg peaks whose fluences were optimized to yield a constant RBE-weighted absorbed dose of 3 Gy (RBE) using method of Wilkens and Oelfke (2006)

Frese MC, Yu VK, Stewart RD, **Carlson DJ**. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys*. 2012; 83: 442–450.

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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