Clinical Outcomes Modeling and Molecular Imaging for Hypofractionated Radiotherapy

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Conflict of Interest: *None*

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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
- Optimize treatment conditions based on ***biological objectives***

What are the Big Questions for hypofractionated RT?

- **To what extent does classical radiobiology apply at high doses?**
- **Fundamental difference in biology between conventional and SBRT?**
  - Primary mechanism of cell death in fractionated RT is mitotic cell death related to biological processing of DSBs (standard view until ~2000)
  - Could the relevant biological mechanisms differ at high doses
- **Are conventional models valid at high doses per fraction?**
- **Is there an optimal time course for SBRT?**

The utilization of SBRT is rising

Primary early-stage NSCLC patients treated with SBRT (U.S. National Cancer Data Base, published in Corso et al. *Am. J. Clin. Oncol.* 2014)

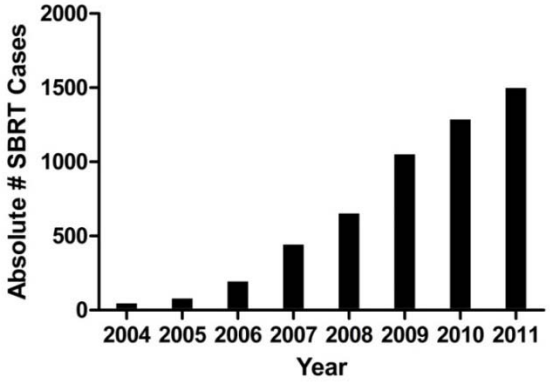


Table 1 – Selected published series of stereotactic body radiotherapy for early stage NSCLC. Retrospective and phase I–II studies.

Author	Patients	Study	Doses	Local control	Toxicity
Onishi 2004[21]	245	Multicentric retrospective	18–75 Gy/1–22 fx	5 years 84%	7.6% grade ≥ 3
Baumann 2006[20]	138	Multicentric retrospective	30–48 Gy/3 fx	33 months 88%	10% grade ≥ 3
McGarry 2005[22]	47	Phase I	60–66 Gy/3 fx	15 months 79%	15% grade ≥ 3
Timmerman 2006[23,24]	70	Phase II	60–66 Gy/3 fx	2 years 95%	20% grade ≥ 3
Zimmerman 2005[18]	68	Retrospective	24–40 Gy/3–5 fx	3 years 88%	9% grade ≥ 3
Nyman 2006[19]	57	Phase II	15 Gy/3 fx	3 years 92%	26% grade ≥ 3
Lagerwaard 2008[26]	206	Multicentric retrospective	60 Gy (3 × 20 Gy/5 × 12 Gy/8 × 7.5 Gy)	3 years 93%	6% grade ≥ 3

Rubio *et al.*, 2013 Reports of Practical Oncology and Radiotherapy; 18: 387–396

Why are clinical outcomes so good for SBRT?

Unique biological mechanisms have been suggested:

Tumor vasculature damage at high doses

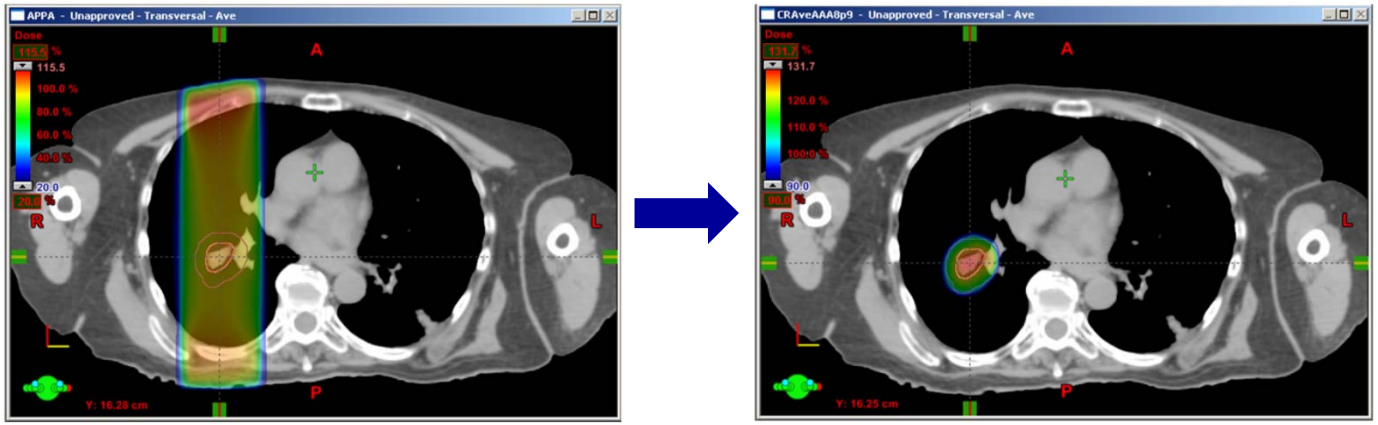
- Rapid tumor vascular shutdown due to endothelial cell apoptosis increases tumor hypoxia and reduces repair of radiation damage to tumor cells
  (Fuks and Kolesnick, MSKCC)
- Vascular damage at high doses produces secondary cell killing *(Song, UM)*

Enhanced antitumor immunity at high doses

A detailed analysis of evidence for and against these mechanisms is in
Brown JM, Carlson DJ, Brenner DJ. *Int. J. Radiat. Oncol. Biol. Phys.* 88: 254–262 (2014).

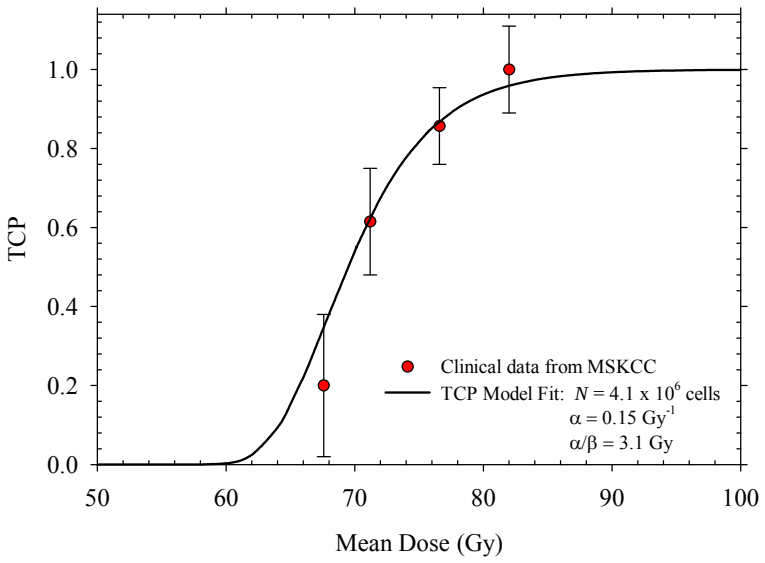
Treatment Planning and Delivery

- Objective in **conventional RT** to deliver uniform Rx dose to target volume
- Paradigm shift for prescribing dose for SBRT
  1. Target a limited tissue volume, containing gross tumor and margin, with very high doses and **hotspots within the target are acceptable** → facilitated by advancement in technology of IMRT/IGRT/VMAT
  2. Minimize volume of normal tissue receiving high doses → **sharp dose gradients**



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

Data from: Levegrun *et al. IJROBP* 2001; 51 (4): 1064–1080

Inter-patient variability in radiosensitivity

- Heterogeneity of human tumour radiation response is well known
- Can account for variation in inter- (and intra-) patient radiosensitivity by assuming that parameter values are normally distributed across the population
- If interpatient heterogeneity is ignored, TCP model generally results in an unrealistically steep dose-response curve

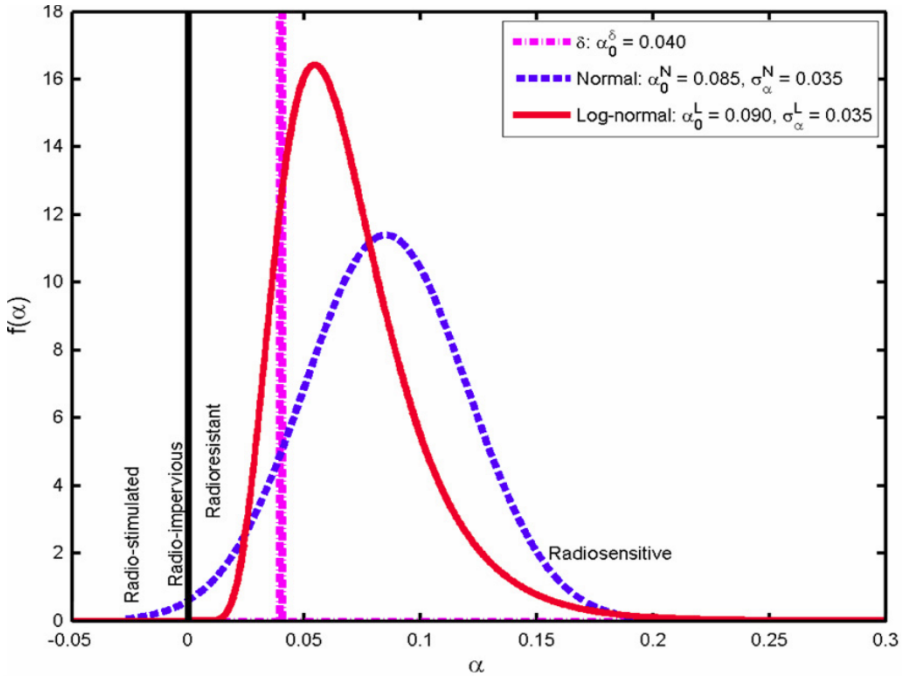


Figure from: Keall PJ, Webb S. Optimum parameters in a model for tumour control probability, including interpatient heterogeneity: evaluation of the log-normal distribution. *Phys. Med. Biol.* 2007; 52: 291–302.

How do we move towards hypofractionation?

Isoeffect BED Example for Prostate

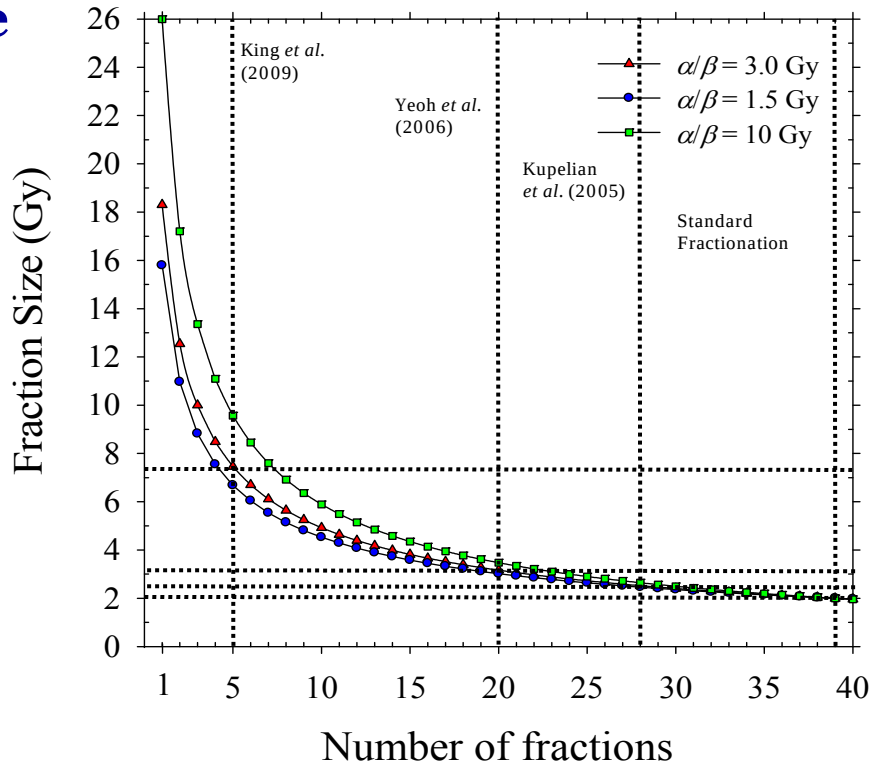
- Conventional: 39 fractions of 2 Gy (α/β = 3 Gy):

$$\mathrm{BED} = D\left[1+\frac{d}{\alpha/\beta}\right]$$

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

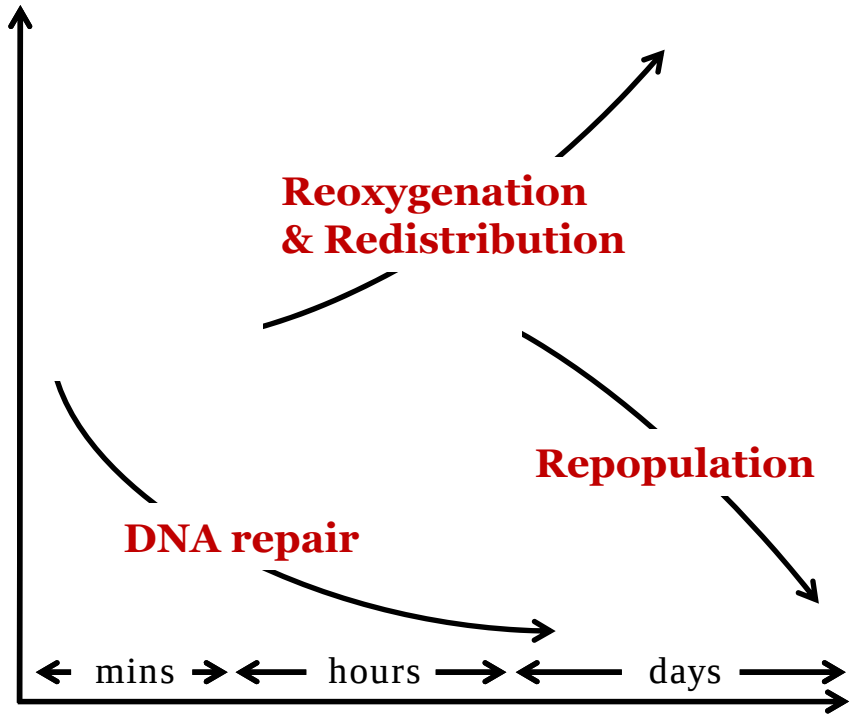
- Rearrange simplified BED equation:

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



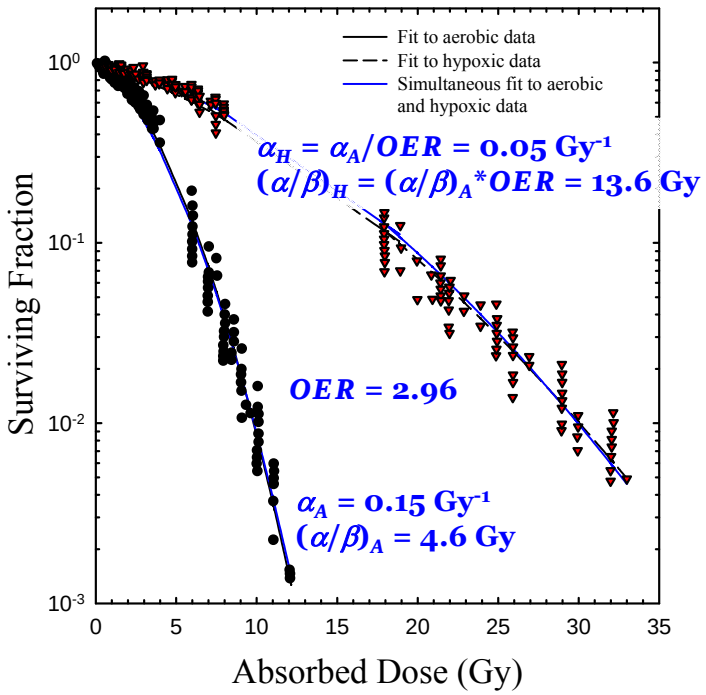
Factors that alter treatment effectiveness

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



5th R: Intrinsic **Radiosensitivity**

What about tumor hypoxia at high doses?



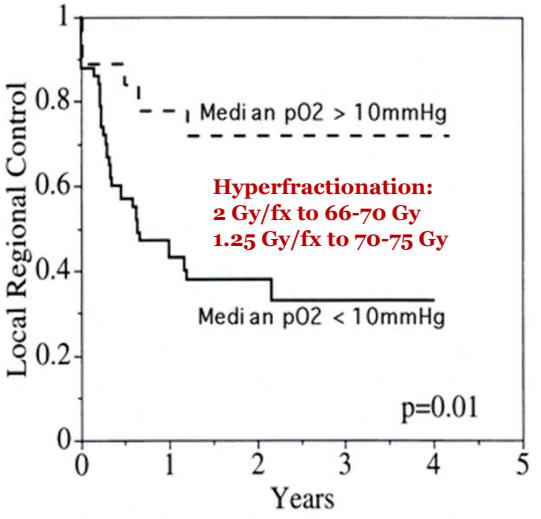
V79 379A Chinese hamster cell survival data from Watts *et al.* (1986)

- *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).

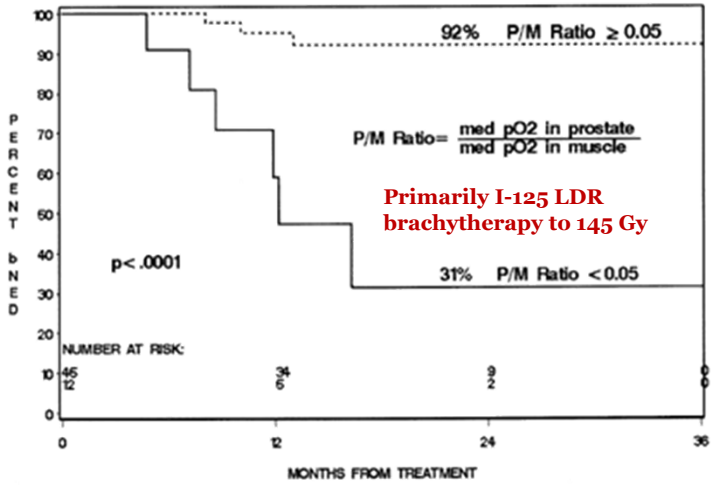
Clinical significance of tumor hypoxia

Head and neck cancer



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

Prostate cancer

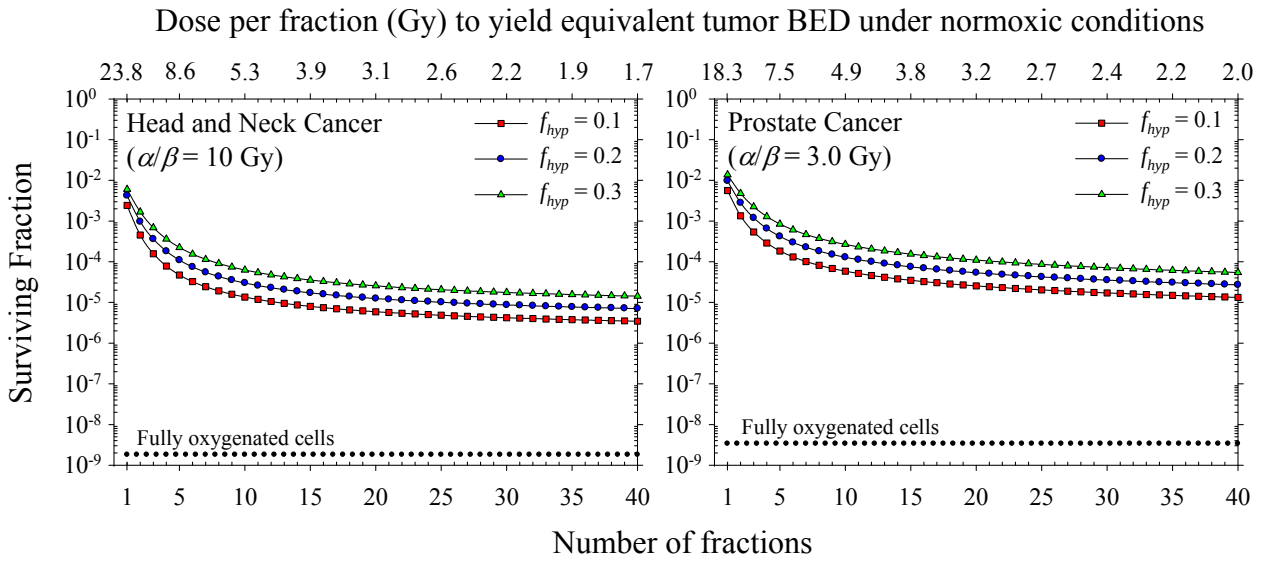


B. Movsas *et al.*, *Urology*, 2002

~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)

Effects of Hypoxia and Fractionation on Cell Survival

What happens to total cell killing if we include hypoxia?

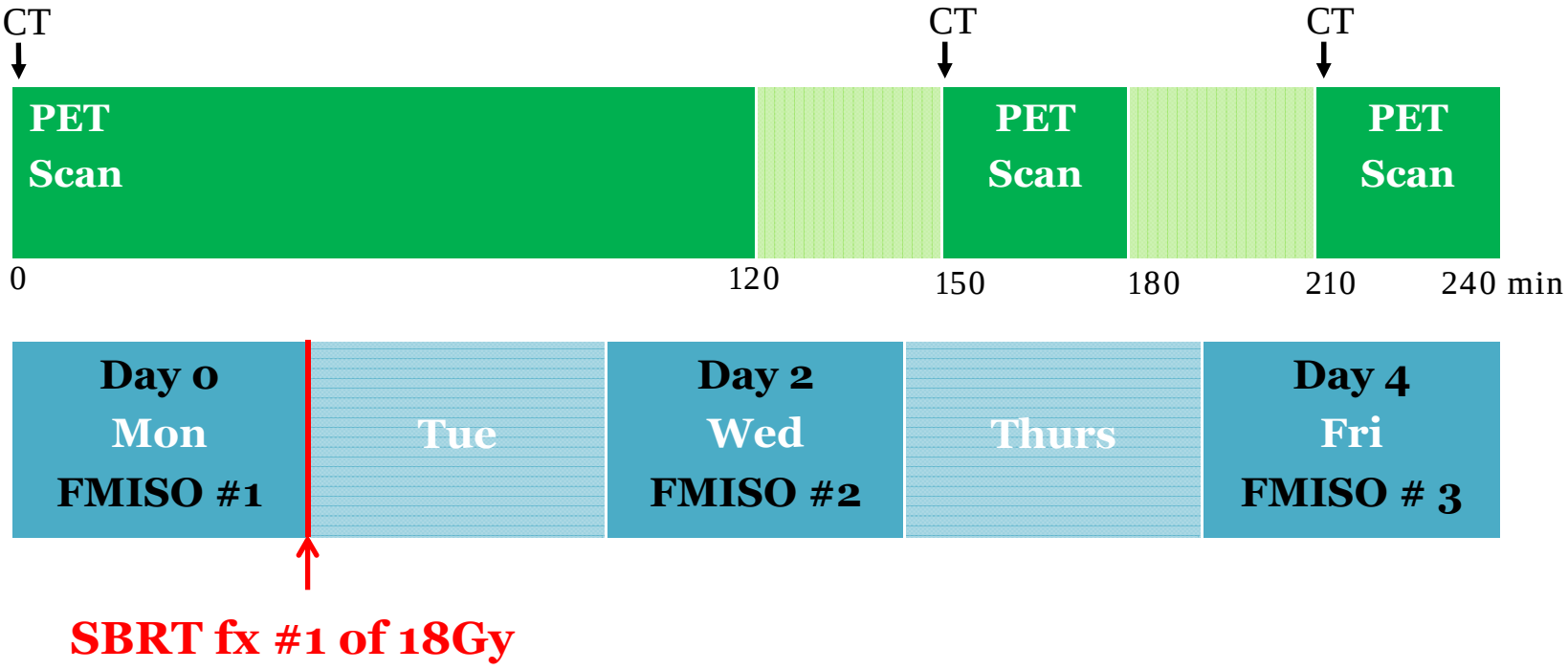


$$S_{overall} = \left[f_{hyp} \cdot S_{hyp} + (1 - f_{hyp}) \cdot \int_{a}^{R_{hyp}} S(r) \exp\left[-\left(\alpha_A + \alpha_A / \beta_A \cdot HRF(r) \right) d \right] - \left[\beta_A / HRF(r)^2 \right] d^2 \right) dr \Bigg]^n$$

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).

Hypoxia Imaging Clinical Trial at Yale: Methods

- IRB-approved protocol to perform serial ^{18}F-fluoromisonidazole (FMISO) PET imaging in early-stage NSCLC cancer patients undergoing SBRT



Hypoxia Imaging at Yale: Patient characteristics

- IRB-approved protocol to perform serial ^{18}F-fluoromisonidazole (FMISO) PET imaging in early-stage NSCLC cancer patients undergoing SBRT

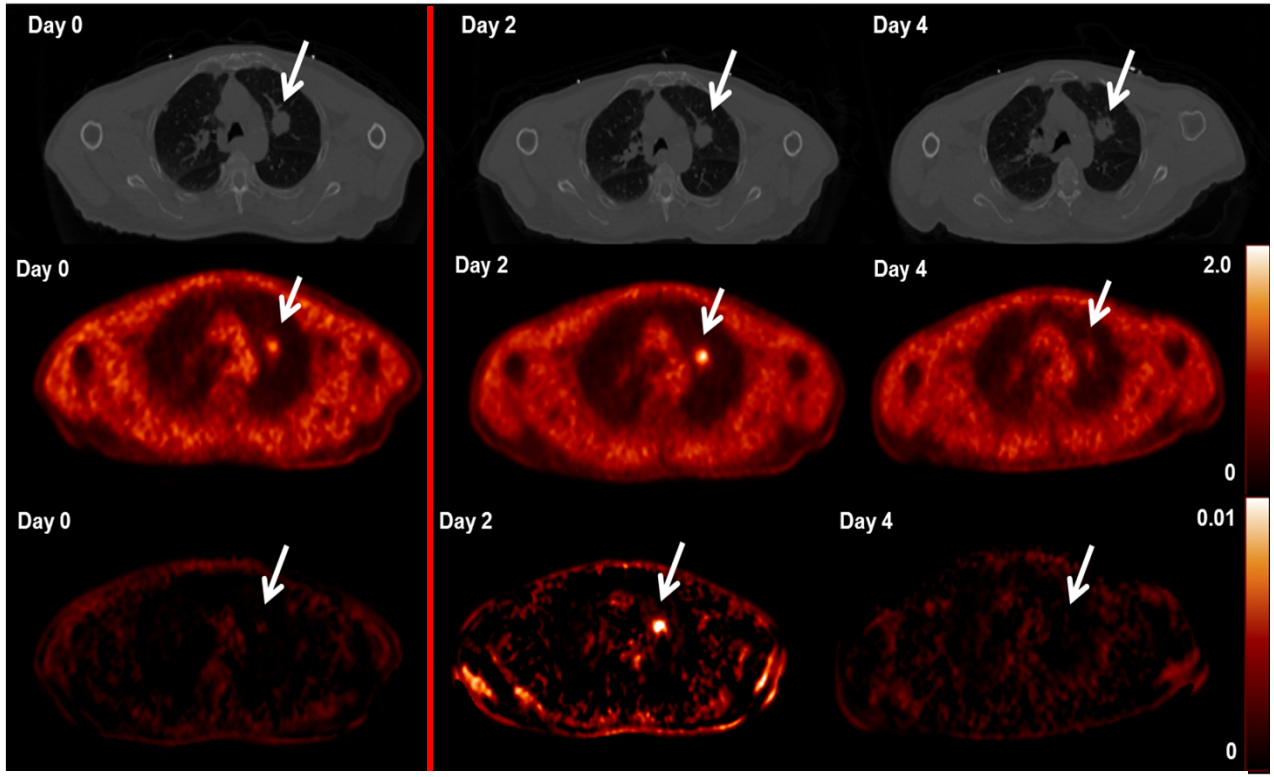
Pt	Age	Gender	Histologic diagnosis	Stage (TNM)	Tumor diameter (cm)	Tumor location	Max motion (mm)	Dose	FMISO PET
1	78	M	adenocarcinoma	stage IIA, cT2bN0M0	4.1	right upper lobe	8.8	18 Gy x 3	Incomplete
2	68	M	squamous cell carcinoma	stage IA, cT1bN0M0	2.2	left upper lobe	4.8	18 Gy x 3	Complete
3	75	M	adenocarcinoma	stage IA, pT1aN0	1.6	left lower lobe	12.4	18 Gy x 3	Complete
4	65	F	non-biopsied (ground glass based on CT)	stage IA, pT1bN0	2.5	right upper lobe	4.4	18 Gy x 3	Complete
5	66	M	non-biopsied	stage IA, pT1aN0	1.3	right upper lobe	2.6	18 Gy x 3	Complete
6	69	M	squamous cell carcinoma	stage IIB, T3N0	5.3	right lower lobe	14.6	10 Gy x 5	Complete

Hypoxia Imaging Clinical Trial at Yale: Results

CT

^{18}F-FMISO PET (TBR)

^{18}F-FMISO PET (Ki)



#1 SBRT 18Gy

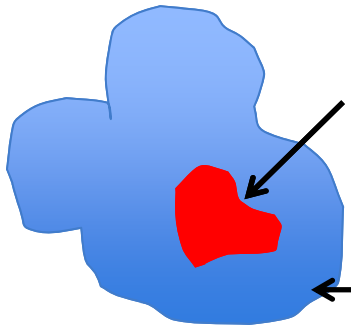
Hypoxia Imaging at Yale: All analyzed patients to date

Imaging Day	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
	Tumor Vol. = 23 cm^3	Tumor Vol. = 8 cm^3	Tumor Vol. = 3 cm^3	Tumor Vol. = 5 cm^3	Tumor Vol. = 2 cm^3	Tumor Vol. = 94 cm^3
	HV (%) calculated on late summed 4D images (TBR >1.2)					
Mon	69.1	23.5	0.0	0.0	16.6	37.4
Wed	–	40.4	0.0	0.0	45.2	56.0
Fri	–	23.1	0.0	0.0	41.9	74.9

#1

- **Potential for large variation in hypoxic fractions post-SBRT**
- **Heterogeneity between baseline levels of hypoxia is significant**
  → Opportunity for therapeutic intervention

Therapeutic Intervention



Alter radiation therapy treatment plan

SBRT delivery schedule:

- All in one week – M,W,F
- Once a week
- 2 fractions Week 1 (M, F) and a 3rd fraction in Week 2

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

Drug clinical trial

Targeted therapeutic trials:

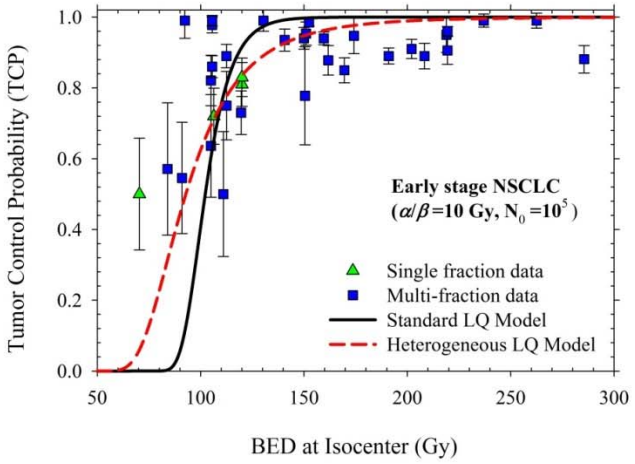
- Hypoxic radiosensitizers (more effective for SBRT?)
- Hypoxic cytotoxins

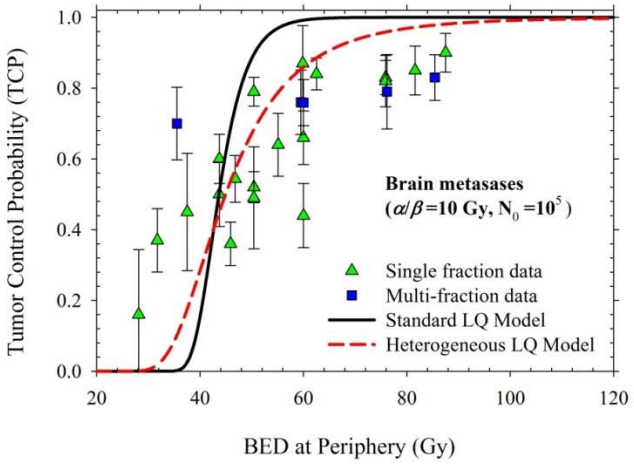
Kelada, O.J. and **Carlson, D.J.** Molecular Imaging of Tumor hypoxia with Positron Emission Tomography. *Radiat. Res.* 2014 Apr; 181(4):335-49

Local Control for Early-Stage NSCLC and Brain Mets

Data from literature over past 15 years reporting TCP at ≥1 year, fx #, and dose

- 33 studies (19 NSCLC, 14 brain mets) with 2,965 patients (2,028 NSLC, 937 brain mets)
- 59 dose regimens: 31% single fraction (median # of fractions is 3, max. # of fractions is 15)



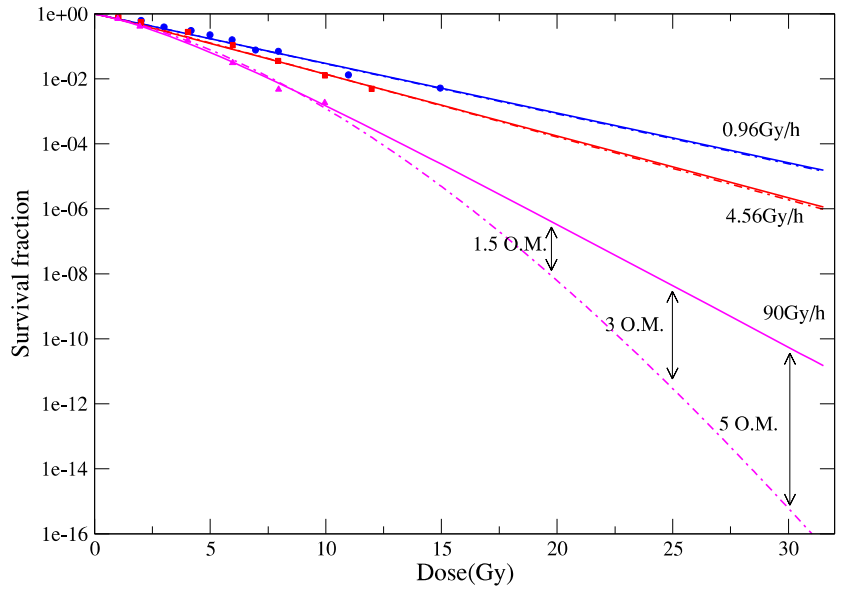


- **Monotonic increase in TCP with BED provides little evidence for significant differences in biological mechanisms at high dose per fx**
- **Success of SRT may be due to new technologies that allow clinician to prescribe very high tumor BEDs, simply not practical with conventional techniques**

Shuryak I, **Carlson DJ**, Brown JM, Brenner DJ. High-dose and fractionation effects in stereotactic radiation therapy: analysis of tumor control data from 2,965 patients. *Radiother. Oncol.*115: 327-334 (2015).

Are conventional models valid at high doses?

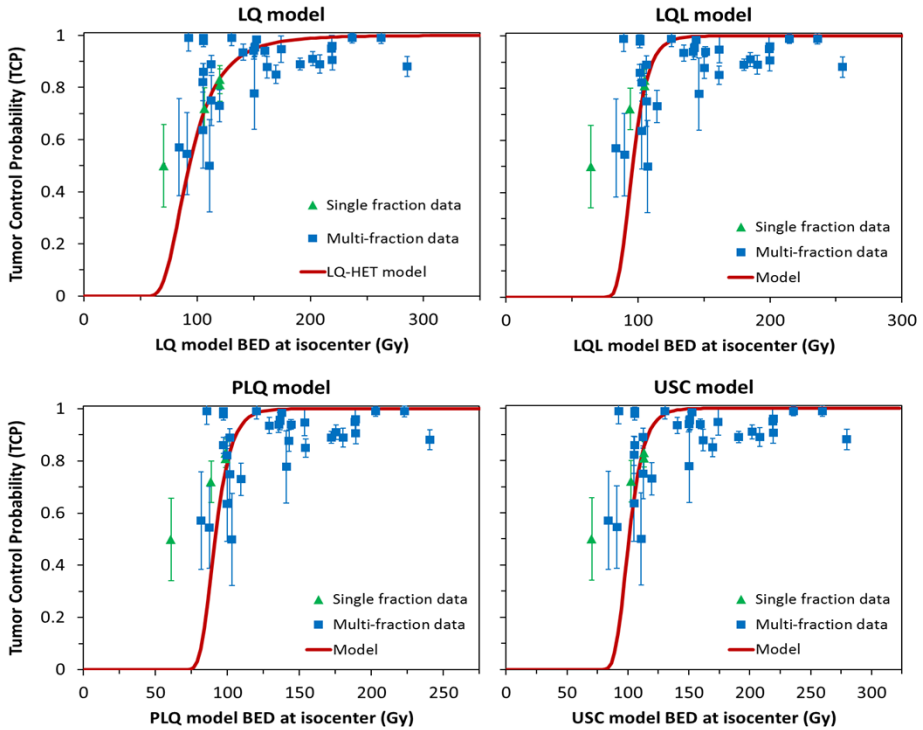
- **LQ is an approximation to more sophisticated kinetic reaction-rate models**



- LQ and LPL indistinguishable for low doses and low dose rates
- Predictions begin to deviate above ~5 Gy
- LQ predicts experimental survival data well up to ~10 Gy
- When extrapolating to doses >15 Gy, LQ can exhibit order of magnitude difference
- No consideration of potential "new biology" *in vivo*

Guerrero M, Li XA. Extending the linear–quadratic model for large fraction doses pertinent to stereotactic radiotherapy. *Phys. Med. Biol.* 2004; 49: 4825–4835.

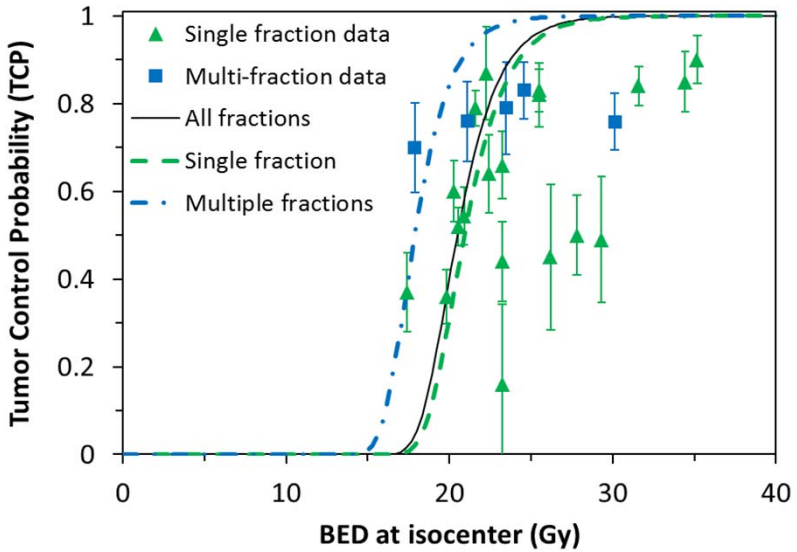
What about alternate “high-dose” models?



- **Clinical data most consistent with predictions of LQ model with heterogeneity in radiosensitivity over the whole dose/BED range**
- **Addition of extra high-dose terms to standard LQ did not improve agreement with clinical data compared to LQ with heterogeneity**

Shuryak I, **Carlson DJ**, Brown JM, Brenner DJ. High-dose and fractionation effects in stereotactic radiation therapy: analysis of tumor control data from 2,965 patients. *Radiother. Oncol.*115: 327-334 (2015).

What about single-fraction vs. multi-fraction?

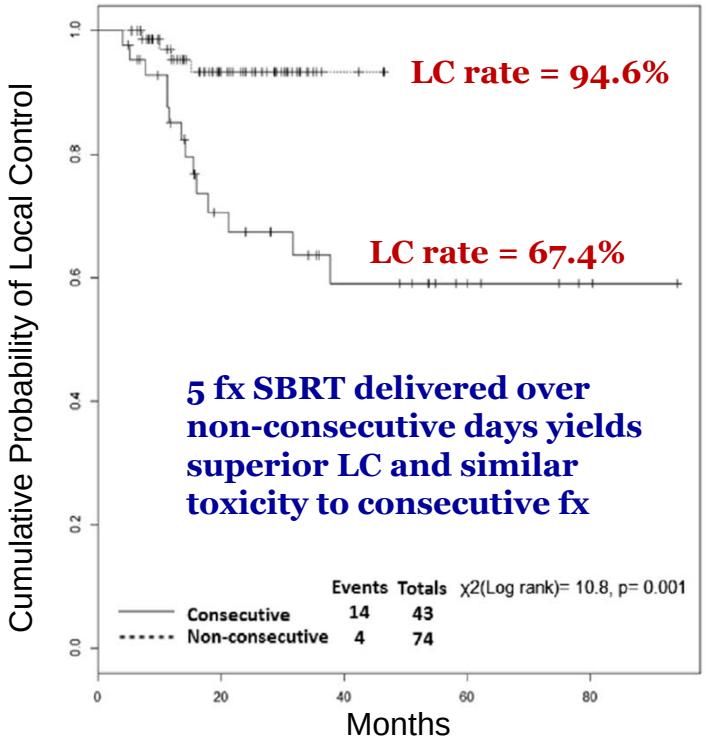


- **For brain metastases the analysis suggest that multiple fractions have higher effectiveness than single fractions**
- **No evidence that single fractions are more effective than multiple fractions**

- **Consistent with expectations in context of tumor hypoxia and reoxygenation as predicted by conventional models (*IJROBP* 2011; 79: 1188-1195)**
- **Pre-treatment imaging of hypoxia may provide a clearer picture**

Shuryak I, **Carlson DJ**, Brown JM, Brenner DJ. High-dose and fractionation effects in stereotactic radiation therapy: analysis of tumor control data from 2,965 patients. *Radiother. Oncol.*115: 327-334 (2015).

Is there an optimal time course for lung SBRT?



- *Hypothesis*: Nonconsecutive SBRT fraction delivery may be advantageous
- Loyola University Chicago
  - Retrospective analysis comparing local control (LC) in patients treated with consecutive daily fractions (M-F) vs. nonconsecutive days (2 fx/week)
  - 107 stage I-II NSCLC patients (117 tumors) treated with curative intent at Loyola between 2006-2014
  - LINAC-based SBRT to either 50 or 60 Gy in 5 fractions
  - Propensity score analysis performed to generate matched cohort on the following criteria: age, KPS, follow-up time, tumor pathology & stage, and dose

  (Courtesy Matthew Harkenrider, MD, Loyola)

Alite F, Stang K, Balasubramanian N, Adams W, Shaikh MP, Small C, Sethi A, Nagda S, Emami B, Harkenrider MM. Local control dependence on consecutive vs. nonconsecutive fractionation in lung stereotactic body radiation therapy. *Radiother. Oncol.* 2016: *In Press.*

Conclusions

- **Available clinical data for early-stage NSCLC and brain mets suggest success of SRT may simply be a result of new technologies that allow clinician to deliver very high tumor BEDs**
  - No clear clinical evidence that a different high-dose biology is necessary to explain excellent clinical outcomes from SBRT
    - Unique biological mechanisms may exist at high doses per fraction but do not appear to significantly affect local tumor control
    - Need for better, i.e., more homogeneous, clinical data to continue to test hypothesis
  - Caution should still be taken with extreme hypofractionation due to effects of hypoxia
    - High single doses may also have the potential to induce hypoxia → clinical impact is unclear
- **LQ model seems to provide a reasonable approximation at SRT doses**
  - Clinical data for NSCLC and brain mets most consistent with LQ model with heterogeneity
- **Best to practice evidence-based medicine**
  - Clinical data is gold standard → skeptical of simplified models and understand limitations
  - Value of models highest in absence of good data → guide treatment decisions instead of relying on trial & error

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