Biological Dose Escalation and Outcomes Modeling in the Era of Stereotactic Radiotherapy

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PENN RADIATION ONCOLOGY
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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 stereotactic RT?

- To what extent does classical radiobiology apply at high doses?
- Fundamental difference in biology between conventional and SBRT?
- Are conventional models valid at high doses per fraction?

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)

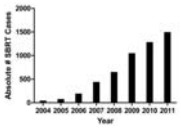


Table 1 - Selected published series of stereotactic body radiotherapy for early stage NSCLC. Retrospective and phase I-II studies.

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[25]	57	Phase II	15 Gy/1 fx	3 years 92%	26% grade ≥ 3
Lagerward 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

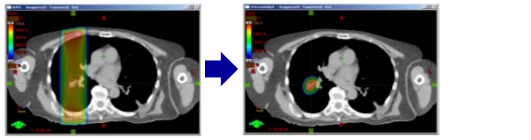
- **Rapid tumor vascular shutdown due to endothelial cell apoptosis increases tumor hypoxia and reduces repair of radiation damage to tumor cells *(Fuks and Kolesnick, MSKCC)***
- **Vascular damage at high doses produces secondary cell killing *(Song, UM)***

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 limited tissue volume, containing gross tumor + margin, with very high doses and hotspots within the target → facilitated by advancement in technology of IMRT/IGRT/VMAT**
  2. **Minimize volume of normal tissue receiving high doses → sharp dose gradients**

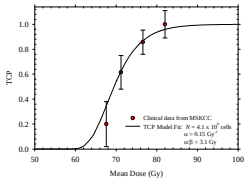


Tumor Control Probability (TCP) Model

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 well known
- 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 unrealistically steep dose-response curve

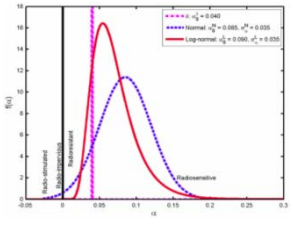


Figure from: Keall PJ, Webb S. Optimum parameters in a model for tumour control probability, including interpatient heterogeneity: evaluation of the log-normal distribution. *Phys. Med. Biol.* 2007; 52: 291–302.

How do we move towards hypofractionation?

Isoeffect BED Example for Prostate

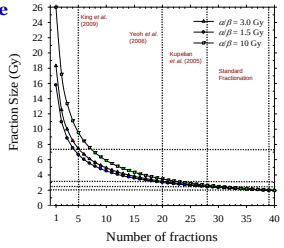
- Conventional: 39 fractions of 2 Gy ($\alpha/\beta = 3$ Gy):

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

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

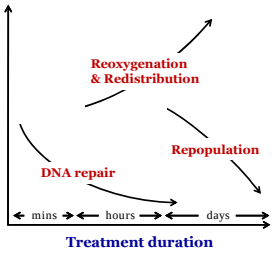
- Rearrange simplified BED equation:

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



Factors that alter treatment effectiveness

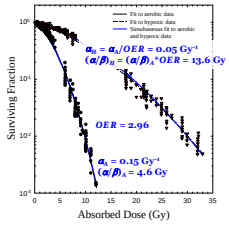
4 R's of Radiobiology give rise to "dose rate" effects:



Treatment effectiveness

5th R: Intrinsic **Radiosensitivity**

What about tumor hypoxia at high doses?



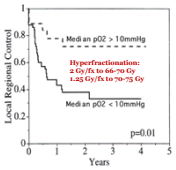
V79 379A Chinese hamster cell survival data from Watts *et al.* (1986)

- *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, $OER_\alpha \sim OER_{\sqrt{\beta}}$
  - 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: 3105–315 (2006).

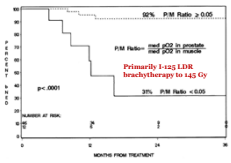
Clinical significance of tumor hypoxia

Head and neck cancer



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

Prostate cancer



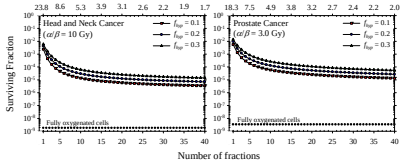
B. Movsas *et al., Urology*, 2002

~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?

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



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

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

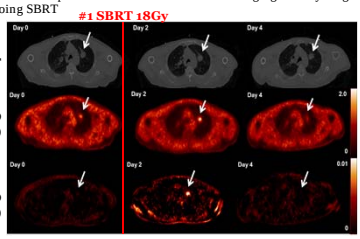
- IRB-approved protocol to perform serial ^{18}F-FMISO PET imaging in early-stage NSCLC cancer patients undergoing SBRT

#1 SBRT 18Gy

CT

^{18}F-FMISO PET (TBR)

^{18}F-FMISO PET (Ki)



Kelada OJ, Decker RH, ..., Carson RE, Oelfke U, **Carlson DJ**. High single doses of radiation may induce elevated levels of hypoxia in early-stage non-small cell lung cancer tumors. *Int. J. Radiat. Oncol. Biol. Phys.* 102: 174–183 (2018).

Hypoxia Imaging at Yale: All analyzed patients to date

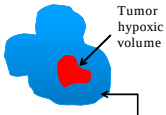
Imaging Day	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
	Tumor Vol. = 23 cm^3	Tumor Vol. = 8 cm^3	Tumor Vol. = 3 cm^3	Tumor Vol. = 5 cm^3	Tumor Vol. = 2 cm^3	Tumor Vol. = 94 cm^3
	HV (%) calculated on late summed 4D images (TBR >1.2)					
Mon	69.1	23.5	0.0	0.0	16.6	21.7
Wed	-	40.4	0.0	0.0	45.2	32.7
Fri	-	23.1	0.0	0.0	41.9	18.1

#1

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

Kelada OJ, Decker RH, ..., Carson RE, Oelfke U, **Carlson DJ**. High single doses of radiation may induce elevated levels of hypoxia in early-stage non-small cell lung cancer tumors. *Int. J. Radiat. Oncol. Biol. Phys.* 102: 174–183 (2018).

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:

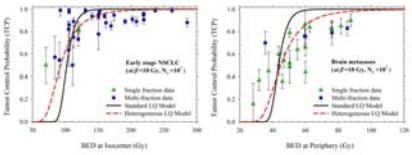
- Hypoxic radiosensitizers (more effective for SBRT?)
- Hypoxic cytotoxins

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)

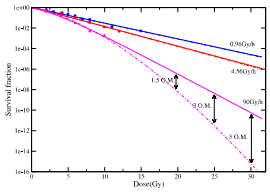


- **Monotonic increase in TCP with BED provides little evidence for significant differences in biological mechanisms at high dose per fx**
- **Success of SRT may be due to new technologies that allow clinician to prescribe very high tumor BEDs, simply not practical with conventional techniques**

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?

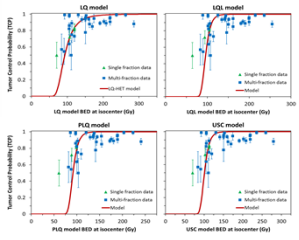
- **LQ is an approximation to more sophisticated kinetic reaction-rate models**



- 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.

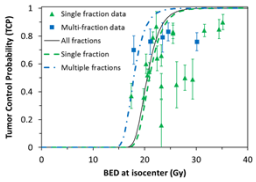
What about alternate "high-dose" models?



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

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?

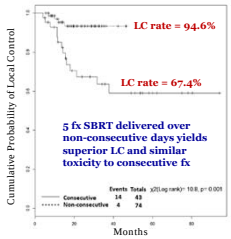


- **For brain metastases the analysis suggest that multiple fractions have higher effectiveness than single fractions**
- **No evidence that single fractions are more effective than multiple fractions**

- **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; 121: 9-14.

Conclusions

1. Available clinical data for early-stage NSCLC and brain mets provide no clear evidence that "new biology" is needed to explain clinical outcomes from SBRT

- Need for better, i.e., more homogeneous, clinical data to continue to test hypothesis

2. Caution should still be taken with extreme hypofractionation due to effects of hypoxia

- High single doses may have the potential to induce hypoxia → clinical impact is unclear

3. LQ appears to provide reasonable approximation at SRT doses

4. Must practice evidence-based medicine

- Clinical data is gold standard → must be skeptical of simplified models, understand limitations

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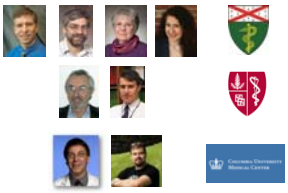
- Columbia University
  - David J. Brenner, Ph.D.
  - Igor Shuryak, M.D., Ph.D.



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