Why is stereotactic radiotherapy so successful?

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Presented at the Center for Radiological Research Centennial Symposium at Columbia University

Date: Thursday, April 28, 2016
Location: Columbia University, Lerner Hall 555, New York, NY
Conflict of Interest: None

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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 objective functions

What are the Big Questions for stereotactic RT?

- To what extent does classical radiobiology apply at high doses?
  - DNA repair, tumor hypoxia and reoxygenation, etc.

- 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?
The utilization of SBRT is rising

Why are clinical outcomes so good for SBRT?

Unique biological mechanisms have been suggested:

- 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 after high dose irradiation (Various authors)

Objective in **conventional RT** is to deliver uniform prescription 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 → **dose gradients outside target are sharp**
Tumor Control Probability (TCP) Model

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

\[ TCP = \exp\left(-N \cdot S(D)\right) \]

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

\[ N = \text{initial \# of tumor clonogens} \]

Clinical data from MSKCC

TCP Model Fit: \( N = 4.1 \times 10^6 \) cells
\( \alpha = 0.15 \text{ Gy}^{-1} \)
\( \alpha/\beta = 3.1 \text{ Gy} \)
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

How do we move towards hypofractionation?

**Isoeffect BED Example for Prostate Cancer**

- For standard fractionation of 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:

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

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*King et al. (2009)*  
*Yeoh et al. (2006)*  
*Kupelian et al. (2005)*  
*Standard Fractionation*  

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Factors that alter treatment effectiveness

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

- DNA repair
- Reoxygenation & Redistribution
- Repopulation
- Treatment duration

5th R: Intrinsic Radiosensitivity
Dose rate effects and DNA damage repair

- Cell killing decreases with decreasing dose rate
  \[ S(D) = \exp\left[-\left(\alpha D + \beta G[\mu, t]D^2\right)\right] \]
- 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 and during fractions
- Effect increases with increased delivery time

\[ \rightarrow \text{Can become important for SRS and SBRT} \]

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_α ~ OER_β**
  - Reasonable assumption for large number of *in vitro* data sets (Carlson et al. 2006)

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Clinical significance of tumor hypoxia

**Head and neck 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)

**Prostate cancer**

Hyperfractionation: 2 Gy/fx to 66-70 Gy
1.25 Gy/fx to 70-75 Gy

Primarily I-125 LDR brachytherapy to 145 Gy

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

Number of fractions

Surviving Fraction

Head and Neck Cancer
(α/β = 10 Gy)

Prostate Cancer
(α/β = 3.0 Gy)

Fully oxygenated cells

Hypoxia Imaging Clinical Trial at Yale

- IRB-approved protocol to perform serial $^{18}$F-fluoromisonidazole (FMISO) PET imaging in early-stage NSCLC cancer patients undergoing SBRT
Hypoxia Imaging at Yale: All analyzed patients to date

<table>
<thead>
<tr>
<th>Imaging Day</th>
<th>Patient #1</th>
<th>Patient #2</th>
<th>Patient #3</th>
<th>Patient #4</th>
<th>Patient #5</th>
<th>Patient #6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor Vol. = 23 cm³</td>
<td>Tumor Vol. = 8 cm³</td>
<td>Tumor Vol. = 3 cm³</td>
<td>Tumor Vol. = 5 cm³</td>
<td>Tumor Vol. = 2 cm³</td>
<td>Tumor Vol. = 94 cm³</td>
</tr>
<tr>
<td>HV (%) calculated on late summed 4D images (TBR &gt;1.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mon</td>
<td>69.1</td>
<td>23.5</td>
<td>0.0</td>
<td>0.0</td>
<td>16.6</td>
<td>37.4</td>
</tr>
<tr>
<td>Wed</td>
<td>–</td>
<td>40.4</td>
<td>0.0</td>
<td>0.0</td>
<td>45.2</td>
<td>56.0</td>
</tr>
<tr>
<td>Fri</td>
<td>–</td>
<td>23.1</td>
<td>0.0</td>
<td>0.0</td>
<td>41.9</td>
<td>74.9</td>
</tr>
</tbody>
</table>

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

Drug clinical trial

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

Targeted therapeutic trials:
- Hypoxic radiosensitizers
- Hypoxic cytotoxins

Alter radiation therapy treatment plan

Local Control for Early-Stage NSCLC and Brain Mets

- Data from literature over past 15 years reporting TCP at ≥1 year, fraction #, and dose
  - 33 studies (19 NSCLC, 14 brain mets) containing 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**

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

**Figure:**

- Dashed lines: LQ fits
- Solid lines: LPL fits

**HX118 melanoma cells (Steel et al 1987)**

A Step Backwards? “Correspondence within the past 3 years has questioned whether the simple LQ curve should be straightened beyond an arbitrary dose of 7 Gy...In practice, a good straightening can be simulated in the original simple LQ curve simply by assuming that $\alpha/\beta$ for lung tumours is 20 instead of 10 Gy...”

- Jack Fowler (BJR 2010; 83: 554)
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.

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 will provide a clearer picture.

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Conclusions

• **Available local control 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**
  – Available clinical data provide no clear evidence that a unique 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

• **LQ model provides 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 and error
Acknowledgements

- **Yale University**
  - Roy H. Decker, M.D., Ph.D.
  - Richard E. Carson, Ph.D.
  - Sara Rockwell, Ph.D.
  - Olivia J. Kelada, M.Sc.

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

- **Stanford University**
  - J. Martin Brown, Ph.D.
  - Paul J. Keall, Ph.D.

- **The Institute of Cancer Research**
  - Uwe Oelfke, Ph.D.

Work supported in part by the [Yale Cancer Center (YCC)](http://www.cancercenter.yale.edu) and the [Yale PET Center](http://www.petradiology.yale.edu)