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

Presented at the 61st Annual Meeting of the AAPM in San Antonio, TX

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Thursday, July 18, 2019

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


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 (Fuchs and Kolesnick, MSKCC)
  - Vascular damage at high doses produces secondary cell killing (Song, UM)
- Enhanced antitumor immunity at high doses

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)

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

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

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 inter-patient heterogeneity is ignored, TCP model generally results in unrealistically steep dose-response curve

Factors that alter treatment effectiveness

4 R’s of Radiobiology give rise to “dose rate” effects:
- Repopulation
- Primary DNA repair
- Reoxygenation
- Radioresistance & Redistribution

What about tumor hypoxia at high doses?

- Oxygenation data are sparse
- OER values for cell death are relatively constant over a large dose range
- May actually decrease slightly with dose (Winters and Brown 1992)
- Statistically, OER<sub>dis</sub> = OER<sub>hyp</sub>
- Reasonable assumption for large number of in vivo data set (Carlson et al. 2004)

Clinical significance of tumor hypoxia

Head and neck cancer
- V79-719A 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 decrease slightly with dose (Winters and Brown 1992; Nahum et al. 2005)
  - Statistically, OER<sub>dis</sub> = OER<sub>hyp</sub>
  - Reasonable assumption for large number of in vivo data set (Carlson et al. 2004)

Prostate cancer
- Average oxygen levels within tumors:
  - ~90% of solid tumors have median values below normal (40-60 mmHg)
  - Half have median values below 5 mmHg

Effects of Hypoxia and Fractionation on Cell Survival

What happens to total cell killing if we include hypoxia?

- Dose fraction (F) is a multi-component tumour BED under conditions of hypoxia and fractionation
  - D<sub>t</sub> = (D<sub>red</sub> + D<sub>h</sub> + D<sub>rad</sub>) / R<sub>dis</sub> + R<sub>hyp</sub> + R<sub>rad</sub>

- Isotransform BED Example for Prostate
  - Conventional: 35 fractions of 4 Gy (a=0.2, b=0.5 Gy):
    - BED = D<sub>red</sub> + D<sub>h</sub> + D<sub>rad</sub>
    - BED = 78 Gy
  - Rearrange simplified BED equation:
    - D<sub>red</sub> = (D<sub>h</sub> + D<sub>rad</sub>) / (1 + D<sub>h</sub> / D<sub>rad</sub>)

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Hypoxia Imaging Clinical Trial at Yale

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

18F-FMISO PET (TBR)

18F-FMISO PET (Ki)

#1 SBRT 18Gy


Hypoxia Imaging at Yale: All analyzed patients to date

- Potential for increase in hypoxic fraction post-SBRT
- Heterogeneity between baseline levels of hypoxia is significant

Opportunity for therapeutic intervention

Imaging Day

Patient #1 | Patient #2 | Patient #3 | Patient #4 | Patient #5 | Patient #6

Tumor Vol. = 23 cm³

Tumor Vol. = 8 cm³

Tumor Vol. = 3 cm³

Tumor Vol. = 5 cm³

Tumor Vol. = 2 cm³

Tumor Vol. = 94 cm³

HV (%) calculated on late summed 4D images (TBR > 1.2)

Mon 89.1 23.5 0.0 0.0 16.6 21.7

Wed - 40.4 0.0 0.0 45.2 39.7

Fri - 23.1 0.0 0.0 41.9 18.1

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

SBRT delivery schedule

Hypoxic volume

> X% of tumor or

< X% of tumor

Hypoxic volume

Targeted therapeutic trials:

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

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 NSCLC, 937 brain mets)

- 59 dose regimens: 31% single fraction (median # of fractions is 3, max. # of fractions is 15)


Are conventional models valid at high doses?

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

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


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 with LQ, the shape of the survival curve shown in experimental and theoretical studies is different

- Consideration of potential “new biology” in vivo

What about single-fraction vs. multi-fraction?

- For brain metastases the analysis suggests 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.


Is there an optimal time course for lung SBRT?

Hypothesis: Nonconsecutive SBRT fraction delivery may be advantageous.

- Loyola University Chicago:
  - Hypothesis: Nonconsecutive SBRT fraction delivery may be advantageous.
  - Retrospective analysis comparing local controlled (LC) patients treated with consecutive daily fractions (5x5 Gy) vs. nonconsecutive two fractions (2x5 Gy) delivered two times per week.
  - Analysis of 127 stage I NSCLC patients (17 tumors).
  - LC was measured within 6 months of treatment completion.

- Hypothesis: Nonconsecutive SBRT fraction delivery may be advantageous.

- 5x5 Gy SBRT delivered over non-consecutive days yields similar LC rate to consecutive 5x5 Gy.

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- 127 stage I NSCLC patients (17 tumors) treated within 6 months of treatment completion.

- LC rate = 94.6% for consecutive 5x5 Gy.

- LC rate = 67.4% for nonconsecutive 5x5 Gy.

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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 homogenous, 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.

Acknowledgements

- **Yale University**
  - Roy D. Dickler, M.D., Ph.D.
  - Richard E. Carson, Ph.D.
  - Olu OJ. Roache, M.Sc.

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

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

Work supported in part by the Yale Cancer Center (YCC) and the Yale PET Center.