# TCP Modeling for Lung SBRT

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AAPM, TU-A-BRD-01, July 22, 2014

## Acknowledgement

MCW

- Feng Liu, Ph.D
- An Tai, Ph.D

WGSBRT – Lung TCP Group

- Percy Lee – Co-Chair
- Allen Li – Co-chair
- Billy Loo – Co-chair
- Jimm Grimm
- Ellen Yorke
- Tithi Biswas
- Issam El Naqa
- Timothy Solberg
- George Ding
- Andy Jackson
- Spring Kong
- Moyed Miften
- Chang Song
- Tamara LaCouture

## Data Analyzed

- Pooled clinical data from 118 studies
- Data with stages > T2 were excluded.
- Treatment doses were converted to isocenters, 80% prescription was assumed if unspecified.
- For the data with unknown portion of T1, 50% was assumed.

## Models considered

1) LQ: $BED = D(1+\frac{d}{\alpha/\beta})$

d: fraction dose; D: total dose

## Model: USC


BIOLOGY CONTRIBUTION

UNIVERSAL SURVIVAL CURVE AND SINGLE FRACTION EQUIVALENT DOSE: USEFUL TOOLS IN UNDERSTANDING POTENCY OF ABLATIVE RADIOTHERAPY

Clint Park, M.D. M.S., Lech Papiez, Ph.D., Shichuan Zhang, M.D., Ph.D., Michael Story, Ph.D., and Robert D. Timmerman, M.D.

2) Universal survival curve (USC):

$$BED = \begin{cases} D\left(1+\frac{d}{\alpha/\beta}\right), & d < d_T \\ \frac{1}{\alpha D_0}\left(D - nD_q\right), & d \geq d_T \end{cases} \quad \left(\beta = \frac{(1-\alpha D_0)^2}{4D_0 D_q}, d_T = \frac{2D_q}{1-\alpha D_0}\right)$$

**Two classic models**
- **LQ**
- **Multitarget**

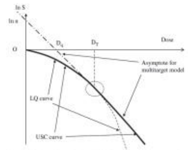
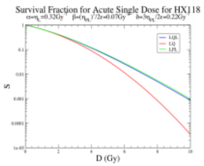



Fig. 2. Universal survival curve (USC) and transition between dose range at which linear quadratic (LQ) model is valid and dose range at which multitarget model is valid. Below transition dose $D_T$, USC curve is identical with LQ model curve and above $D_T$, USC curve is identical with terminal linear portion of multitarget model curve.

## Model: LQL

3) LQ-Linear: $BED = \begin{cases} D\left(1+\frac{d}{\alpha/\beta}\right), & d < d_T \\ nd_T\left(1+\frac{d_T}{\alpha/\beta}\right) + n\left(1+2\frac{d_T}{\alpha/\beta}\right)(d-d_T), & d \geq d_T \end{cases}$

**Guckenberger et al, Radiotherapy & Oncology, 109, 13-20 (2013)**





Institute of Physics Publishing — Physics in Medicine and Biology

Extending the linear–quadratic model for large fraction doses pertinent to stereotactic radiotherapy

M Guerrero[1] and X Allen Li[2]

$S_{LQL}=\exp(-\alpha D-\beta D^2 G(\mu T+\delta D))$

**Guerrero and Carlone, Med. Phys. 37, 4173-81 (2010)**

## Model: MA-LQ

4) Modified LQ (MA-LQ): $BED = D\left(1 + \frac{d}{\frac{\alpha}{\beta}(1+\frac{\beta}{\gamma}D)}\right)$

$$\ln S = -\alpha D - \beta D^2 \frac{1}{1 + \frac{\beta}{\gamma}D}$$

**LQ, when D << γ/β**

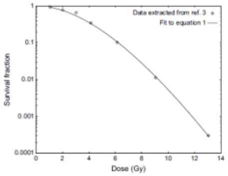



Fig. 1. Data from Carmichael *et al.* (3) and fit of Eq. 1 to NCI-H841 (variant) small-cell lung cancer.

IOP Publishing — Physics in Medicine and Biology
Phys. Med. Biol. 54 (2009) 1593–1608 — doi:10.1088/0031-9155/54/6/013

**Fitting techniques of cell survival curves in high-dose region for use in stereotactic body radiation therapy**

F W McKenna and S Ahmad

## Model: Regrowth

5) Regrowth model: $BED = D\left(1 + \frac{d}{\alpha/\beta}\right) - \gamma T/\alpha$,

T: treatment time, $\gamma = \frac{ln2}{T_d}$, $T_d$: the doubling time,

- Local control rate: $LCR = 1 - \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx$
  where $t = \frac{K - K_{50}}{\sigma_K}$, $K = K_0 e^{-[\alpha D\left(1+\frac{d}{\alpha/\beta}\right) - \gamma T - (\gamma(\tau - T))^{\delta}]}$, $\tau - T$: follow-up time, K/$K_0$/$K_{50}$ : tumor colonogens.
- $\gamma T/\alpha$ controls LCR -> 1

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 900–907, 2008
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0360-3016/08/$–see front matter
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doi:10.1016/j.ijrobp.2007.10.037

PHYSICS CONTRIBUTION

**ESTIMATE OF RADIOBIOLOGIC PARAMETERS FROM CLINICAL DATA FOR BIOLOGICALLY BASED TREATMENT PLANNING FOR LIVER IRRADIATION**

An Tai, Ph.D., Beth Erickson, M.D., Kevin A. Khater, Ph.D, M.D., and X. Allen Li, Ph.D.

**Regrowth Model**

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 900–907, 2008
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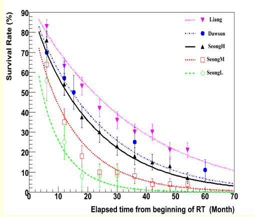


| | |
|---|---|
| $K_{50}/K_0$ | 2.03±0.04 |
| $\alpha$ | 0.010±0.001 (Gy$^{-1}$) |
| $\alpha/\beta$ | 15.0±2.0 (Gy) |
| $T_d$ | 128+12 day |
| $\sigma_K/K_0$ | 0.65±0.06 |
| δ | 0.20±0.01 |

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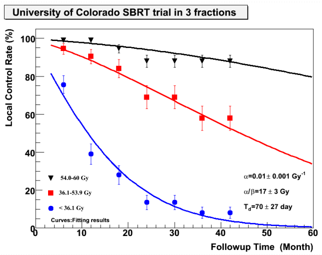
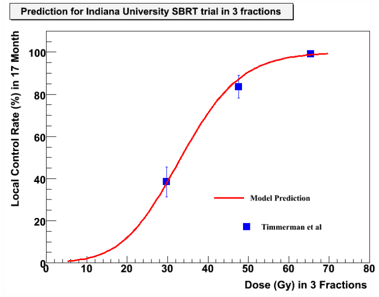
## Lung Cancer: TCP with the Regrowth model




| Model parameters | Fitting results |
|---|---|
| $K_{50}/K_0$ | $2.60 \pm 0.34$ |
| $\sigma_k/K_0$ | $0.74 \pm 0.10$ |
| $\delta$ | $0.21 \pm 0.02$ |
| $\alpha$ | $0.010 \pm 0.001$ ($Gy^{-1}$) |
| $\alpha/\beta$ | $17 \pm 2.8$ (Gy) |
| $T_d$ | $70 \pm 27$ (day) |

## Lung Cancer: TCP with the Regrowth model




## Models Considered

| Model | BED | parameters | TCP |
|---|---|---|---|
| LQ | $D(1+\frac{d}{\alpha/\beta})$ | $\alpha, \alpha/\beta$ | $e^{-K*e^{-\alpha*BED}}$ |
| Universal Survival Curve | $\begin{cases} D\left(1+\frac{d}{\alpha/\beta}\right), & d<d_T \\ \frac{1}{\alpha D_0}(D-nD_q), & d \geq d_T \end{cases}$ $(\beta=\frac{(1-\alpha D_0)^2}{4D_0D_q}, d_T=\frac{2D_q}{1-\alpha D_0})$ | $\alpha, D_0, D_q$ | $e^{-K*e^{-\alpha*BED}}$ |
| LQ-L | $\begin{cases} D\left(1+\frac{d}{\alpha/\beta}\right), & d<d_T \\ nd_T\left(1+\frac{d_T}{\alpha/\beta}\right)+n\left(1+2\frac{d_T}{\alpha/\beta}\right)(d-d_T), & d \geq d_T \end{cases}$ | $\alpha, \alpha/\beta, d_T$ | $e^{-K*e^{-\alpha*BED}}$ |
| MA-LQ | $D\left(1+\frac{d}{\frac{\alpha}{\beta}(1+\frac{\beta}{\gamma}D)}\right)$ | $\alpha, \beta, \gamma$ | $e^{-K*e^{-\alpha*BED}}$ |
| Regrowth | $D\left(1+\frac{d}{\alpha/\beta}\right)-\gamma T/\alpha$, $\gamma=\ln 2/T_d$, | $\alpha, \alpha/\beta, T_d$ | $1-\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-\frac{x^2}{2}}dx$ |

Regrowth mode: $t=\frac{K-K_{50}}{\sigma_K}, K=K_0 e^{-[\alpha D\left(1+\frac{d}{\alpha/\beta}\right)-\gamma T-(\gamma(\tau-T))^{\delta}]}$, T: elapsed Tx time, $T_d$: doubling time, $\tau-T$: follow-up time

## Data fitting

Local control rate:

$$LCR = e^{-K \cdot e^{-\alpha \cdot BED}} \qquad LCR = 1 - \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx$$

Least $\chi^2$ method was used to fit the clinical LCR data

$$\chi^2 = \sum_{i=1}^{n} \frac{[LCR_i^{data}(D_i, d_i, \tau_i) - LCR_i^{model}(D_i, d_i, \tau_i)]^2}{\sigma_i^2}$$

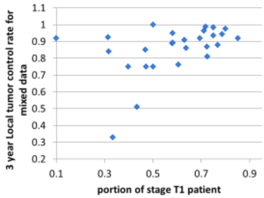
With error

$$\sigma_i = LCR_i^{data} \sqrt{\frac{1 - LCR_i^{data}}{N_i}}$$

**The fitting considers goodness and sample size of each data point.**

## Difference between T1 and T2

- 3 year LCR v.s. portion of T1 in mixed data: T1 portion ↑, LCR ↑

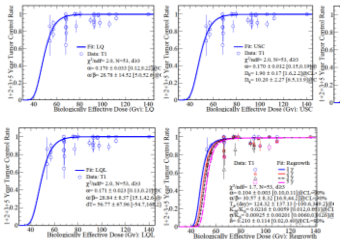



## Fit to data w/ T1&T2

- $LCR^{model} = f_{T_1} * LCR_{T_1}{}^{model} + f_{T_2} * LCR_{T_2}{}^{model}$, $f_{T_1}(f_{T_2})$: portion of T1 (T2) patient w/ $f_{T_1}$+$f_{T_2}$=1
- Two sets model parameters for T1 and T2
- Simultaneous fits to all data

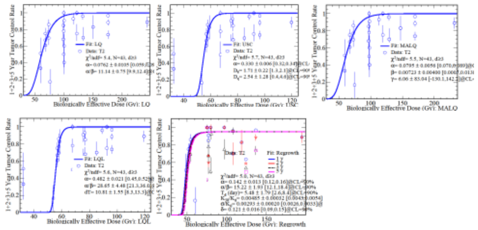
## Fits to T1 data

**Fit with LQ, USC, MA-LQ, LQ-L, and regrowth models (para. ranges @CL=90%)**



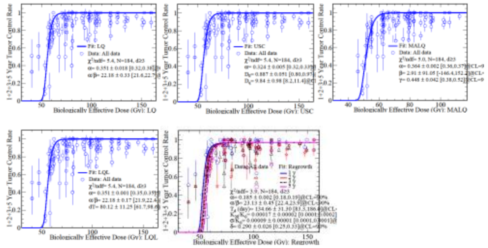
## Fits to T2 data

**Fit with LQ, USC, MA-LQ, LQ-L, and regrowth models (para. ranges @CL=90%)**



## Fits to All data

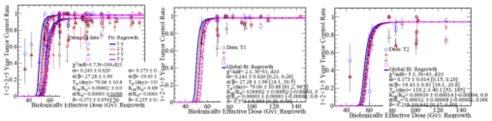
**Fit with LQ, USC, MALQ, LQ-L, and regrowth models (para. ranges @CL=90%)**



## Fits to data w/ T1&T2 mixed

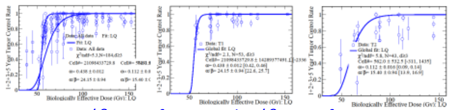
- Simultaneous fit to all data w/ parameters for T1&T2 (BED in left panel calc. with w/ T1 paras for plotting)

Notice: $\alpha_{T_1} > \alpha_{T_2}, \alpha/\beta_{T_1} > \alpha/\beta_{T_2}, T_{d\,T_1} < T_{d\,T_2},$ (para. ranges @CL=90%)

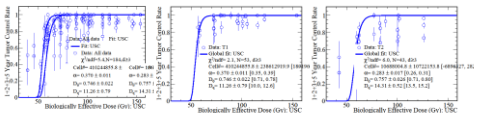


## Fits to data w/ T1&T2 mixed

- LQ: $\alpha_{T_1} > \alpha_{T_2}, \alpha/\beta_{T_1} > \alpha/\beta_{T_2},$ (paras @CL=90%)



- USC: $\alpha/\beta$=23.7 for T1 and $\alpha/\beta$=19.9 for T2



## Model Parameters from fitting

Model parameters @ 90% confidence level

| Model | $\chi^2$/ndf | T1 | | | T2 | | |
|---|---|---|---|---|---|---|---|
| | Fit to all data | $\alpha$ (Gy$^{-1}$) | $\alpha/\beta$ (Gy) | Td/$D_q$/Y | $\alpha$ (Gy$^{-1}$) | $\alpha/\beta$ (Gy) | Td/$D_q$/Y |
| regrowth | 3.7 | 0.24±0.02 [0.21,0.28] | 27.3±2.0 [24.1,30.5] | Td=79±11 [61,97] days | 0.173±0.014 [0.15,0.20] | 19.43±0.81 [18.1, 20.8] | Td= 119±40 [53,185] days |
| LQ | 5.3 | 0.44±0.01 [0.42,0.46] | 24.2±0.9 [22.6,25.7] | | 0.112±0.016 [0.09,0.14] | 15.4±0.9 [13.9,16.9] | |
| LQ-L | 6.1 | 0.156±0.001 [0.15, 0.16] | 22.9±0.5 [22.1,23.7] | dT=27.6±1.6 [24.9, 30.2] Gy | 0.208±0.001 [0.21,0.21] | 19.68±0.22 [19.3, 20.0] | dT=87.9±0.1 [87.6, 88.1] Gy |
| USC | 5.4 | 0.370±0.011 [0.35, 0.39] | $D_0$=0.746±0.022 [0.71,0.78] Gy | $D_q$=11.3±0.8 [10.0, 12.6] Gy | 0.283±0.017 [0.26, 0.31] | $D_0$=0.757±0.0262 [0.71,0.80] Gy | $D_q$=14.3±0.5 [13.5, 15.2] Gy |
| MALQ | 5.0 | 0.411±0.009 [0.40, 0.43] | $\beta$ =39.0±15.8 [13.1, 64.9] Gy$^{-2}$ | Y=0.454±0.024 [0.41,0.49] Gy$^{-1}$ | 0.346±0.008 [0.33, 0.36] | $\beta$ =30.6±31.7 [-21.3, 82.5] Gy$^{-2}$ | Y=0.499±0.024 [0.46,0.54] Gy$^{-1}$ |

## Model predictions

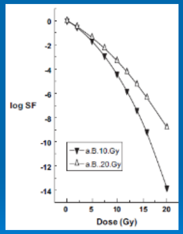
Required prescription (physical dose) (Gy) predicted based on the models considered

(Regrowth: Tx time 7d for 3fx, 14d for 5fx)

| Model | stage | 2-year LCR= 95% | | asymptotic (Plateau) | |
|---|---|---|---|---|---|
| | | 3 fx | 5 fx | 3 fx | 5 fx |
| Regrowth | T1 | 39.2 Gy | 44.0 Gy | 45.0 Gy | 50.9 Gy |
| | T2 | 46.4 Gy | 53.7 Gy | 46.2 Gy | 53.5 Gy |
| LQ | T1 | 39.6 Gy | 44.7 Gy | | |
| | T2 | 43.4 Gy | 50.8 Gy | | |
| USC | T1 | 39.5 Gy | 44.6 Gy | | |
| | T2 | 40.5 Gy | 46.3 Gy | | |
| LQ-L | T1 | 40.3 Gy | 45.5 Gy | | |
| | T2 | 40.1 Gy | 45.8 Gy | | |

## Discussion

LQ




Jack Fowler

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 3, pp. 957–959, 2008

## More Models

Int J Radiation Oncol Biol Phys, Vol. 84, No. 3, pp. e379–e384, 2012

**Modeling Local Control After Hypofractionated Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer: A Report From the Elekta Collaborative Lung Research Group**

Nitin Ohri, MD,* Maria Werner-Wasik, MD,* Inga S. Grills, MD,† José Belderbos, MD, PhD,‡ Andrew Hope, MD,§ Di Yan, DSc,† Larry L. Kestin, MD,† Matthias Guckenberger, MD,‖ Jan-Jakob Sonke, PhD,‡ Jean-Pierre Bissonnette, PhD,§ and Ying Xiao, PhD*

Medical Physics, Vol. 39, No. 1, January 2012

**A generalized linear-quadratic model incorporating reciprocal time pattern of radiation damage repair**

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## Summary

- Regrowth model seems yielding better fitting to the data, fits yield large $\alpha/\beta$ for all models
- Models predict that the required physical doses are 39.2-41.0 (or 40.1 -46.4) Gy in 3 fractions in order to achieve a 2-year local control of 95% for T1 (or T2) lung cancer.