Introduction:
Outcome Modeling and Response Prediction
from Analytic to Data-Driven

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Stewart RD, Li XA. BGRT: biologically guided radiation therapy-the future is fast approaching! Med Phys. 2007; 34:3739-51
Why outcome modeling?

- To fully describe responses as a function of any dose to any volume
- To predict responses based on historical data
- To better design treatment, e.g., supplementing or replacing dose-volume criteria for RT plan optimization and evaluation.

Outcome modeling: Analytical-Empirical

- Survival probability (LQ)
- Equivalent Uniform Dose (EUD/gEUD)
- TCP (Poisson model)
- NTCP (LKB, Serial, Parallel)
- Clinical Response Models (Maximum likelihood analysis)

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<table>
<thead>
<tr>
<th>Model</th>
<th>BED</th>
<th>parameters</th>
<th>TCP</th>
<th>comments</th>
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</thead>
<tbody>
<tr>
<td>Linear-quadratic (LQ)</td>
<td>$D(1 + \frac{d}{\alpha/\beta})$</td>
<td>$\alpha, \beta, K_0$</td>
<td>$e^{-K_0}e^{-\alpha \cdot \text{BED}}$</td>
<td></td>
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<tr>
<td>Universal Survival Curve (USC)</td>
<td>$\left{ \begin{array}{l} D \left(1 + \frac{d}{\alpha/\beta}\right), \quad d &lt; d_r \ \frac{1}{\alpha K_0} (D - nD_0), \quad d \geq d_r \end{array} \right.$</td>
<td>$\alpha, D_0, D_q, K_0$</td>
<td>$e^{-K_0}e^{-\alpha \cdot \text{BED}}$</td>
<td>LQ @ low dose, multitarget model @ high-dose</td>
</tr>
<tr>
<td>LQ-L</td>
<td>$D \left[ 1 + G \left( \frac{d + \Delta d}{\alpha/\beta} \right) \right]$</td>
<td>$\alpha, \beta, \gamma, \frac{\alpha}{\beta}, K_0$</td>
<td>$e^{-K_0}e^{-\alpha \cdot \text{BED}}$</td>
<td>$\Delta$ adjustable to reproduce lethal potentially-lethal</td>
</tr>
<tr>
<td>Modified LQ-L (mLQ)</td>
<td>$\left{ \begin{array}{l} D \left(1 + \frac{d}{\alpha/\beta}\right), \quad d &lt; d_r \ nD_c \left(1 + \frac{d_r}{\alpha/\beta}\right) + n \left(1 + \frac{2 d_r}{\alpha/\beta}\right) (d - d_r), \quad d \geq d_r \end{array} \right.$</td>
<td>$\alpha, \beta, \gamma, K_0$</td>
<td>$e^{-K_0}e^{-\alpha \cdot \text{BED}}$</td>
<td>LQ to exponential inactivation</td>
</tr>
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<td>Modified LQ (mLQ)</td>
<td>$D \left(1 + \frac{d}{\alpha/\beta}\right)$</td>
<td>$\alpha, \beta, \gamma, K_0$</td>
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<td>LQ to exponential inactivation</td>
</tr>
<tr>
<td>Regrowth model</td>
<td>$D \left(1 + \frac{d}{\alpha/\beta}\right) - \gamma T / \alpha, \gamma = \ln 2 / T_d$</td>
<td>$\alpha, \beta, \gamma, K_0, \delta, T_d, \frac{\alpha}{\beta}$</td>
<td>$1 - \frac{1}{\gamma T_d} \cdot e^{-\gamma T d}$</td>
<td>$\gamma$ adjustable to reproduce lethal potentially-lethal</td>
</tr>
</tbody>
</table>

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Examples of Biophys Models
TCP of SBRT for T1 & T2 NSCLC

Fitting 1-, 2-, 3-, and 5-year TCP data simultaneously using the regrowth model

HyTEC: Organ-Specific Paper

Local Control following Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer

Percy Lee, M.D.1, Billy W. Loo, Jr., M.D., Ph.D.2, Tithi Biswas, M.D.3, George X. Ding, Ph.D.4, Issam M. El Naqa, Ph.D.5, Andrew Jackson, Ph.D.6, Feng-Ming Kong, M.D., Ph.D.7, Tamara LaCouture, M.D.8, Moyer Mitten, Ph.D.9, Timothy Solberg, Ph.D.10, Wolfgang A. Tome, Ph.D.11, An Tai, Ph.D.12, Ellen Yorke, Ph.D.6, X. Allen Li, Ph.D.12


Required PTV physical doses to reach the TCP asymptotic plateau for SBRT of NSCLC
RILT < 10-15% if bilateral MLD < 8 Gy in 3-5 fractions and V20Gy < 10-15%.

QuanTEC: Pneumonitis/multiple fractions whole lung irradiation

Courtesy: Marks et al, QUANTEC Lung
Outcome modeling: Analytical-Empirical

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Problems:

- Largely phenomenological rather than predictive
- Unreliable model parameters
  - Need more outcome data (e.g., QuanTEC, HyTEC, PenTEC)
- Population based, rather individualized
  - Need more patient-specific data (e.g., profiling, imaging)

Lung cancer: patient-specific info from images

Early Assessment of Treatment Responses During Radiation Therapy for Lung Cancer Using Quantitative Analysis of Daily Computed Tomography.
Machine learning based delta-radiomics process

CT delta radiomics features (DRF) predict treatment response for chemo-RT of pancreatic cancer

Delta radiomics + clinical factor CA19-9

Concordance statistics


Prediction of treatment response for chemo-RT of pancreatic cancer with combined DRFs (Entropy, cluster tendency and coarseness) and CA19-9

Combined biomarker leads to earlier prediction, reducing from 4th week with CA19-9 alone to the 3rd week with the combined.
Prediction of treatment pathology response for chemo-RT of pancreatic cancer

*Combined biomarkers: Delta radiomics + CA19-9 + CEA*


**Take home message**

Radiation treatment outcome modeling conventionally with analytical and biophysical methods is being revolutionized by incorporating data-driven machine learning techniques, *transitioning from population-based into individualized response prediction.*
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