Biologically Related Models for Treatment Planning

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Reference list as additional handout
• All treatment planning is biological in nature
  – What is a “biological” or “biologically related” model?
• An equation or algorithm that combines dosimetric and other factors to predict treatment outcome
  – “Other”: medical factors (type of cancer, chemo, age), ‘biological’ factors (FDG uptake, hypoxia, genomics)
  – Model may be
    • Descriptive (algorithmic reformulation of outcomes data)
    • Mechanistic (built on physiological or cellular data)
• Are biological models more reliable predictors of outcomes than dose/dose-volume plan features? — Especially when applied to your patients?

• Are optimizers based on biological models better?
  Better=More efficiently generated
  Better=plans the MD prefers
  Better= Plans with better outcomes

• Several commercial TPS have plan evaluation and optimization modules based on biological models
  — TG 166: biologically based treatment planning (BBTP)
    http://www.aapm.org/pubs/reports/RPT_166.pdf
• Endpoints of successful treatment planning
  – High tumor control (eradicate the irradiated tumor)
    • High Tumor Control Probability (TCP)
  – Low incidence of complications
    • Low Normal Tissue Complication Probability (NTCP)

• This talk will discuss several popular biological models
  – Generalized Equivalent Uniform Dose (gEUD)
    • Optimize and evaluate dose distributions for tumors and normal tissues
  – Linear-Quadratic (LQ) Model
    • Dose/fraction effects for tumors and normal tissues
  – TCP models- general nature
    • Predict TCP for given irradiation pattern; used for optimization and evaluation
  – NTCP models- general nature
    • Predict complication rates for given irradiation pattern; used for optimization and evaluation
gEUD (Generalized Uniform Dose)

• “The uniform dose that, if delivered over the same number of fractions as the non-uniform dose distribution of interest, yields the same radiobiological effect” (TG 166, Niemierko 1999)

• $gEUD = (\sum v_i (D_i)^a)^{1/a}$

• ‘$a$’: user-chosen parameter

• Convenient optimization term
gEUD dependence on “a”

- $a < 0$: cold spots dominate (use negative $a$ for tumors)
- $a = 1$: gEUD = mean dose
- $a$ large positive: hot spots dominate (use for normal tissues like spinal cord)

<table>
<thead>
<tr>
<th>$a$</th>
<th>gEUD (Gy)</th>
</tr>
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<tbody>
<tr>
<td>-20</td>
<td>34.8</td>
</tr>
<tr>
<td>0.2</td>
<td>49.3</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
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<tr>
<td>20</td>
<td>60.9</td>
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<tr>
<td>100</td>
<td>67.9</td>
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Linear-Quadratic (LQ) Model

- Observed: Same total dose delivered at high dose/fraction is more potent than at low dose/fraction
  - SBRT (hypofractionation) vs conventional fractionation (~ 2 Gy/fx)

- Radiobiology experiments:
  Surviving fraction (SF) of cells vs single dose D fits well to
  \[ SF = \exp(-\alpha D (1 + D/[\alpha/\beta])) \]

- \( \alpha \) (units Gy\(^{-1}\)) and \( \beta \) (units Gy\(^{-2}\)) are independent of D
  - Depend on type of cell or organ response and irradiation conditions
  - RBE, dose rate, hypoxia

- More complex versions of LQ not discussed here- see references
LQ Model: fractionated RT

- Dose $D$ delivered in $n$ fractions ($d = D/n$)
  
  $SF = \exp(-\alpha D \left(1 + \frac{d}{\alpha/\beta}\right))$

- $D \left(1 + \frac{d}{\alpha/\beta}\right) =$ Biologically Effective Dose (BED)

- Hypothesis: Regimens with the same LQ model BED have the same biological effect (isoeffective) on living tissues to which they are applied
  - In vitro, same BED means same SF

- $D_1$ in fractions $d_1$ is isoeffective to $D_2$ in fractions $d_2$ if
  
  $D_1 \left(1 + \frac{d_1}{\alpha/\beta}\right) = D_2 \left(1 + \frac{d_2}{\alpha/\beta}\right)$

- $LQED_2 =$ dose in 2 Gy fractions that is isoeffective to $(D,d)$
  
  $LQED_2 = D \left(1 + \frac{1}{\alpha/\beta}\right) / \left(1 + \frac{2}{\alpha/\beta}\right)$
Log10(SF) = -αD(1 + d/[α/β])

LQ model is suspect at low (≤ 1 Gy) and high (srs, sbrt) dose/fx

- There are other models but LQ is most commonly used because:
  - LQ fits decently over much of the clinical dose range
  - LQ is mathematically simple
**BED=D (1+d/α/β)**

- For fixed D
- BED > D
- Different α/β’s
  - α/β ↓, BED ↑

- Same α/β
- # fx ↓, BED ↑ because
  - # fx ↓, d ↑

**LQED2=BED/(1+2/α/β)**

- d < 2, LQED2 < D
- Rx/fx ~ 2 Gy,
  - LQED2_VH similar to DVH
• For MV photon and electron radiation, \( \alpha \) ranges from \( \sim 0.1 \text{ Gy}^{-1} \) [radioresistant] to \( \sim 0.7 \text{ Gy}^{-1} \) [radiosensitive]

• \( \alpha/\beta \) ranges from \( \sim 1 \text{ Gy} \) [effect depends strongly on the dose per fraction] to 15 Gy [effect depends only weakly on dose per fraction]

• The LQ model is semi-mechanistic; related to DNA damage mechanisms
  – Model refinements account for repair during the delivery time and proliferation between fractions
    • See Hall & Giaccia, Joiner & van der Kogel (good references and good source of LQ parameters)

• Stay tuned for a future ICRU Report (#25) which aims to bring order to the LQ-model terminology wilderness
Tumor Control Probability (TCP)

- Tumor control: irradiated tumor doesn’t grow after radiation treatment course ends.
- TCP is sigmoidally increasing function of dose.
- For given tumor type and irradiation conditions:
  - $D_{50}$ = dose for 50% TCP of uniformly irradiated tumors
  - $\gamma_{50}$ = % $\Delta$TCP /% $\Delta$(d/D50) evaluated at d/D50=1
    - Typical $\gamma_{50}$ range: 1 (shallow curve) – 5 (steep curve)

Many equations are used for TCP
- Some have no mechanistic basis- just approximately right shape
- For example _ the Log Logistic

$$TCP = \frac{100}{1 + (D_{50}/D)^{4\gamma_{50}}}$$
Poisson-LQ cell kill TCP model

• **Assume** $N$ clonogenic cells (cells that can regrow tumor)
  – **Assume** LQ: $SF = \exp(-\alpha D(1+d/\alpha/\beta))$
  – **Assume** the number of clonogens that survive treatment is Poisson distributed
  – **Assume** $TCP = \text{probability of no surviving clonogens}$

• $TCP = \exp(-N \exp(-\alpha D(1+d/\alpha/\beta)))$

• $N$ can be calculated from $\gamma_{50}$; with these assumptions, $N$ is very small for observed $\gamma_{50}$’s
  – $\sim < 100$ cells, independent of tumor size

• **Two different approaches to this puzzle:**
  – There really are very few clonogens – just carry on
  – There are many clonogens ($\sim 10^7$/cc) but observed $TCP$ is a population average over a range of sensitivities ($\alpha$’s); averaging smears out the slope (Niemierko & Goitein 1993; Webb & Nahum, 1993)
TCP for non-uniform radiation

- Break tumor into ‘tumorlets’, each with uniform dose
  - Which structure to use: PTV? CTV? GTV?
- Start from differential DVH $\{D_i, v_i\}$
- $TCP = \Pi_i (TCP(D_i,d_i))^{v_i}$
- This approach can model non-uniform tumor characteristics as well as non-uniform doses
  - (D50’s, clonogen densities, etc)
  - Can we use information from molecular imaging?
    - Location? LQ parameters? Relevant cell density?
    - Dose-painting guided by PET, etc?
- For tumors, given current knowledge are fancier models (TCP) than dose or BED/volume metrics or gEUD with consistent ‘a’ useful for tx planning?
Normal Tissue Complication Probability (NTCP)

$\gamma_{50} =$ Normalized slope at TD50
Slope (Gy$^{-1}$) = 100 $\gamma_{50}/TD50$ (Gy)

Most clinical data at low NTCP

The assumed sigmoidal shape is rarely evidence-based

TD5: dose for 5% complication probability

TD50: Dose for 50% complication probability
Most organs have more than one complication, each with different dosimetric correlates
- Lung: pneumonitis, fibrosis
- Rectum: bleeding, incontinence, fistula

Acute complications: during or soon after treatment
Late complications: many months-years latency

A complication can be mild, intermediate, or severe
- Toxicity grading: 1 (mild, asymptomatic) – 5 (fatal)
- CTCAE 4.03*, RTOG, SWOG

‘Tolerable’ complication rate depends on impact of toxicity on quality of life and on treatment tradeoffs
- Serious risk more acceptable in last-chance scenarios

NTCP: Tolerance Doses

Tolerance dose (or dose/volume metric) depends on:

- The complication
- The dose/fraction
  - LQ model generally used
  - Acute complications: $\alpha/\beta$ typically large ($\sim 10$ Gy)
    - Weak dependence on dose/fx
  - Late complications: $\alpha/\beta$ typically small ($< 5$ Gy)
    - Strong dependence on dose/fx
- The dose distribution
- And other things which we won’t handle here
  - Dose rate (external beam vs LDR)
  - Medical factors (chemo, smoking, co-morbidities)
  - RBE (protons, heavy ions)
Tolerance dose-volume dependence

Partial organ irradiation (see Emami 1991)

Zero dose
Volume fraction = 1 - v

Uniform Dose D
Volume fraction = v

5% complication vs irradiated volume fraction

- Observed
  - Iso-complication dose increases as irradiated volume fraction decreases
  - Weak vs strong volume effects

Emami, 1991
Power Law ‘Fit’ to Volume Dependence

Inverse relationship between tolerance dose TDc% and irradiated volume fraction, v

$$TDc(v)=TDc(1)/v^n$$

Descriptive (not mechanistic)

Serial-type response
Low n-> weak volume dependence, $D_{\text{max}}$ dominates

Parallel-type response
High n-> strong volume dependence

Low n-> myelitis, brainstem necrosis
High n-> pneumonitis, xerostomia, RILD
Mid n-> rectal bleeding, pericarditis

n=1: mean dose dependence
NTCP: Lyman Model
Most popular in USA

• Power law volume dependence
• 4 complication-specific parameters: n, TD50(1), slope parameter m, reference volume for v=1

\[
\text{NTCP} = (2\pi)^{-1/2} \int_{-\infty}^{(D - \text{TD50}(v))/(m \text{TD50}(v))} \exp(-t^2/2) \, dt
\]

• Also called Lyman-Kutcher or LKB (Lyman-Kutcher-Burman) Model
• Histogram reduction converts general DVH, \{D_i, v_i\}, to an equivalent uniform or partial irradiation
  
  \(-\) \quad D_{\text{eff}} = (\sum v_i (D_i)^{1/n})^n, \ v = 1 \ (\text{whole organ})
  
  • Use \(D_{\text{eff}}\) for \(D\) and 1 for \(v\) in upper limit of integral
  
  \(-\) \ or \ \(v_{\text{eff}} = \sum v_i (D_i/D_{\text{ref}})^{1/n}\)
  
  • Use \(V_{\text{eff}}\) for \(V\) and \(D_{\text{ref}}\) for \(D\) in upper limit of integral
Lyman Model $D_{\text{eff}}$ is gEUD

- Lyman $D_{\text{eff}} = (\sum v_i (D_i)^{1/n})^n$
- $g\text{EUD} = (\sum v_i (D_i)^a)^{1/a}$

- $a = 1/n$
  - Serial-type response: large $a$, small $n$ ($n < 1$)
  - Parallel-type response: small $a$, large $n$ ($n \geq 1$)

- There are Lyman model parameters in the literature for many complications
  - Watch for ongoing research
NTCP: Källman s-model (Relative seriality)


• Popular in Europe – implemented on some commercial TPS
• Organ responds to radiation damage in combined serial and parallel fashion
• 4 parameters (and $\alpha/\beta$ if use LQ)
  – $D_{50}$ and $\gamma_{50}$ for whole organ response to uniform dose
  – $s$ = ‘seriality parameter’; $s=1$ for weak volume dependence, small $s$ for strong dependence
• With proper parameters, NTCP curves similar to Lyman
• Planners routinely include volume dependences as planning goals for many organs
  – This is not new!
  – Cord: $D_{\text{max}} < 50$ Gy (avoid myelitis)
  – Parotid: Mean dose $< 26$ Gy (avoid xerostomia)
  – Lung: Mean dose $< 20$ Gy (avoid pneumonitis)

• Where do these numbers come from?
  – Literature
    • Emami, QUANTEC, subsequent publications

• Red and Green Journals and meetings are good sources of updates
Pitfalls and cautions

• To use models for plan evaluation
  – Use reliable sources of parameters
    • Cautiously update as knowledge evolves
  – Your patients may be different so.....
  – Test carefully against your clinic’s outcomes before changing your plan acceptance criteria

• Hypofractionation is a vast unknown
  – TG101 and floods of peer-reviewed literature

• To use models to drive optimization
  – If you get qualitatively similar, ‘good’ plans faster with biological optimizations, that’s great but....
  – Watch out for unusual distributions
    • For example, gEUD may steer hot or cold spots to odd places

• Clinical outcomes still the best criteria for ‘good’ plans
• General References on Biological Models


3. The “Emami paper” (NTCP)


8. Normal tissue guidelines for SBRT: Table III of the report of TG 101 [http://www.aapm.org/pubs/reports/RPT_101.pdf](http://www.aapm.org/pubs/reports/RPT_101.pdf). It is very important to note that the TG itself says “The doses are mostly unvalidated, and while most are based on toxicity observation and theory, there is a measure of educated guessing involved as well.”

9. TCP-Population averaging


10. Brachytherapy (especially LDR brachy) is quite different and is not covered by TG166: In addition to the radiobiology text references, look at the report of AAPM TG 137 [http://www.aapm.org/pubs/reports/RPT_137ExecSummary.pdf](http://www.aapm.org/pubs/reports/RPT_137ExecSummary.pdf)
NTCP since QUANTEC

- QUANTEC cites consensus-selected NTCP references, up to ~ 2009, covering mostly conventional fractionation. Here are a few standard-fractionation NTCP modeling studies published since QUANTEC that look interesting (PubMed search). Hypofractionation (sbrt) is in such vigorous flux that I don’t dare make suggestions!

- Rectal toxicity:

- Lung toxicity: