Why consider use of models?

- Are there problems that use of outcomes models could help resolve?
- Would their use make things easier or more consistent?
- Is this relevant today?
- Should I try to use this stuff?
Outline

- Tumor Control Probability (TCP) models
- Normal Tissue Complication Probability (NTCP) models
- Overall plan Evaluation / Implementation into optimization systems
- Caveats and Warnings regarding clinical use
3D CRT - PTV covered!

Target dose must be uniform to +/- 5%

Desired

Volume (%)

Dose (%)
RTOG IMRT target criteria

- The prescription dose is the isodose which encompasses at least 95% of the PTV.
- No more than 20% of any PTV will receive >110% of its prescribed dose.
- No more than 1% of any PTV will receive <93% of its prescribed dose.
Irregular Target Volume DVHs

% Dose (min PTV dose = 100%)

% Volume

Modality 1
Modality 2
Modality 3

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
Dose normalized to 95% of PTV

% Volume vs % Dose

Plan 1
Plan 2
Plan 3

Dose normalized to 95% of PTV
Dose normalized to 95% of PTV
Target volume issues

- Are target volume hot spots beneficial?
- Are target volume cold spots detrimental?
- How do cold spots and hot spots play off against each other?
- Use of TCP or EUD models could help us make rational decisions
Tumor Control Probability (TCP) Calculations
TCP Calculation Assumptions

- An inhomogeneously irradiated tumor volume is composed of smaller volume elements,
  - each with uniform dose,
  - each responding independently to radiation.
Basic TCP Models

- Complete “birth and death” models (M. Zaider and G. N. Minerbo, ...)
- Poisson (survival of clonogenic cells) models (Webb, Nahum, ...)
- “Tumorlet” models (Goitein, Brahme...)
- EUD type approaches
Tumour control probability: a formulation applicable to any temporal protocol of dose delivery

Abstract. An analytic expression for the tumour control probability (TCP), valid for any temporal distribution of dose, is discussed. The TCP model, derived using the theory of birth-and-death stochastic processes, generalizes several results previously obtained. The TCP equation is

\[
TCP(t) = \left[1 - \frac{(S(t) e^{(b-d)t})}{\left(1 + b S(t) e^{(b-d)t} \int_0^t \frac{dt'}{S(t') e^{(b-d)t'}}\right)^n}\right]
\]

where \(S(t)\) is the survival probability at time \(t\) of the \(n\) clonogenic tumour cells initially present (at \(t = 0\)), and \(b\) and \(d\) are, respectively, the birth and death rates of these cells. Equivalently, \(b = 0.693 / T_{pot}\) and \(d/b\) is the cell loss factor of the tumour. In this expression \(t\) refers to any time during or after the treatment; typically, one would take for \(t\) the end of the treatment period or the expected remaining life span of the patient. This model, which provides a comprehensive framework for predicting TCP, can be used predictively, or—when clinical data are available for one particular treatment modality (e.g. fractionated radiotherapy)—to obtain TCP-equivalent regimens for other modalities (e.g. low dose-rate treatments).

Poisson TCP Model

- Number of surviving clonogenic cells estimated for each dose level and summed to obtain total number of surviving cells
- Overall TCP related to total number of surviving clonogenic cells
Surviving Clonogenic Cells TCP Calculation

For uniform initial clonogenic cell density $\rho$, and uniform radiosensitivity $\alpha$, the number of surviving clonogenic cells for each bin of the DVH $\{V_j \text{ (cm}^3\text{)}, D_j \text{ (Gy)}\}$ is estimated as:

$$N_{s, j} = \rho V_j \exp \left[ -\alpha D_j (1 + \frac{\beta}{\alpha} \cdot d_i) \right]$$

$$\approx \rho V_j \exp \left[ -\alpha D_j \right] \quad \text{...for } \frac{\beta}{\alpha} \to 0$$
Surviving Clonogenic Cells TCP Calculation

The total number of surviving clonogenic cells is then the sum over all bins of the DVH:

\[ N_{s, \text{tot}} = \sum_j \rho V_j \exp \left( -\alpha D_j \right), \]

from which the TCP is estimated:

\[ TCP = \exp \left( -N_{s, \text{tot}} \right) \]
Inter-tumor radiosensitivity

The observed “population” TCP curves are not as steep as would be predicted for individual groups with equal radiosensitivity:

- (unless one assumes a very small number of clonogens, together with low radiosensitivity).

Bentzen SM, Radiother Oncol 32:1-11, 1994
Inter-tumor radiosensitivity

- Assume that the radiosensitivity ($\alpha$) is normally distributed over the patient population.

$$g(\alpha, \sigma_\alpha) = \frac{1}{\sigma_\alpha \cdot \sqrt{2\pi}} \cdot e^{-\frac{(\alpha - \bar{\alpha})^2}{2\sigma_\alpha^2}}$$

Fitting Batterman et al ca. bladder data (Nahum and Tait 1992) (courtesy AE Nahum)

Key feature

\[ \sigma_\alpha = 0.08 \]

\[ \sigma_\alpha = 0.00 \]

Tumour Vol = 320 cm\(^3\)

Clinc. cell density = \(10^7\) cm\(^{-3}\)

\(\alpha = 0.35\) Gy\(^{-1}\)
“Tumorlet” TCP Model

- Tumorlet radiosensitivity estimated from the dose-response assumed for the entire tumor.
- Overall TCP predicted by product of the TCPs for each tumorlet.
“Tumorlet” TCP Assumptions

TCP of uniformly irradiated “tumorlet” with partial fractional volume $V_i$ is estimated from the dose response assumed for uniform irradiation of the entire tumor to the same dose $D_i$:

$$TCP ( D_i, 1) = \frac{1}{\{1 + (D_{50} / D_i)^4 \gamma_{50}\}}$$

using:

$$TCP ( D_i, V_i) = [TCP ( D_i, 1)]^{V_i}$$
“Tumorlet” TCP Assumptions

Overall TCP predicted by product of the TCPs for each tumorlet.

\[
\text{TCP}_{\text{total}} = \prod_i \text{TCP} \left( D_i, V_i \right)
\]
Equivalent Uniform Dose

- Uniform dose distribution that if delivered over the same number of fractions would yield the same radiobiological or clinical effect.
  - Niemierko 1996
  - Brahme 1991
  - Niemierko 1999 (abstract) gEUD
Equivalent Uniform Dose for Target Volume

\[
\text{EUD} = 2 \cdot \ln \left\{ \sum v_i (\text{SF}_2)^{D_i/2} \right\} / \ln (\text{SF}_2)
\]

- \(\text{SF}_2\) = Fx of clonogens surviving single 2 Gy dose
- \(v_i\) = fractional volume
- \(D_i\) = uniform dose to \(v_i\)

\(\text{Volume}\)

\(\text{Dose}\)
Generalized Equivalent Uniform Dose (gEUD)

ROI with \( N \) dose points \( d_i \)

\[
gEUD \equiv \left( \frac{\sum_{i=1}^{N} d^a_i}{N} \right)^{1/a} \equiv \left( \sum_i v_i d^a_i \right)^{1/a}
\]

DVH (fractional volume \( v_i \) receives dose \( d_i \))
gEUD

\[
gEUD \equiv \left( \frac{\sum_{i=1}^{N} d_i^a}{N} \right)^{1/a} \equiv \left( \sum_{i} v_i d_i^a \right)^{1/a}
\]

Tumors: \( a \) is \( \sim \) a negative number

Normal Tissues: \( a \) is a positive number

For \( a = 1 \), \( gEUD \) = mean dose

For \( a = 2 \), \( gEUD \) = rms dose

For \( a = -\infty \), \( gEUD \) = minimum dose

For \( a = +\infty \), \( gEUD \) = maximum dose

(discontinuous at \( a = 0 \))
$gEUD \equiv \left( \sum v_i d_i^a \right)^{1/a}$

Tumors:
Min < gEUD < Mean
$a$ is ~negative
- aggressive: $a = -20$
- non: $a = -5$

For $a = 1$, $gEUD = \text{mean dose}$
For $a = -\infty$, $gEUD = \text{minimum dose}$

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
The TCP as a function of uniform dose, \( EUD \), to the whole volume can then be described (for example) by the logistic function:

\[
TCP (EUD, 1) = \frac{1}{1 + (D_{50} / EUD)^{4\cdot\gamma_{50}}}
\]

\( D_{50} = 70 \text{ Gy} \)

\( \gamma_{50} = 2 \)
Normal Tissues
Easy!
Plan 2 is less toxic

Who knows?
Depends on tissue type

DVH Comparison - normal tissue

0 10 20 30 40 50 60 70 80
Volume (%)

0 10 20 30 40 50 60 70 80
Volume (%)

0 10 20 30 40 50 60 70 80
Dose (Gy)

0 10 20 30 40 50 60 70 80
Dose (Gy)
RTOG normal tissue dose criteria

- Small bowel < 30% to receive $\geq 40 \text{ Gy}$
  + minor deviation 30% to 40 Gy
- Rectum < 60% to receive $\geq 30 \text{ Gy}$
  + minor deviation 35% to 50 Gy
- Bladder < 35% to receive $\geq 45 \text{ Gy}$
  + minor deviation 35% to 50 Gy
- Femoral head $\leq 15\%$ to receive $\geq 30 \text{ Gy}$
  + minor deviation 20% to 30 Gy
Normal Tissue (Max Dose Constraint)

% Volume

Dose (Gy)

Spinal Cord

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
Normal Tissue (Single Point Constraint)

![Graph showing dose response for different plans.](image)

- Plan 1
- Plan 2
- Plan 3
Normal tissue issues

- The applicability of dose/volume criteria alone is dependent on:
  + Tissue type
  + Standardization of technique

- Use of models could assimilate effects of irregular dose distribution across the entire normal tissue/organ under consideration.
Normal Tissue Complication Probability (NTCP) Calculations
Why use an NTCP model?

- We would like to be able to fully describe complications as a function of any dose to any volume.
- Most clinical trials will only sample the low portion of any normal tissue complication probability (NTCP) frequency distribution.
- Start with a model based on normal statistical distributions
  - Try to parameterize the model for future use using a limited amount of information.
The Lyman NTCP Model

The Lyman NTCP Model

- The Lyman NTCP model attempts to mathematically describe complications associated with uniform partial organ irradiation.

- This implies:
  - A fractional volume, $V$, of the organ receives a single uniform dose, $D$.
  - The rest of the organ, $(1 - V)$, receives zero dose.
  - i.e., a single step DVH, $\{D, V\}$
For each uniformly irradiated fractional volume \( v_i \), the Lyman model assumes that the distribution of complications as a function of Dose \( D \) can be described by a normal distribution

\[ \text{with mean } TD_{50}(v_i) \]

\[ \text{with standard deviation } m \cdot TD_{50}(v_i) \]
The NTCP as a function of dose, $D$, to that uniformly irradiated volume, $v_i$, can then be described by the integral probability:

$$NTCP = (2\pi)^{-1/2} \int_{-\infty}^{t} \exp(-x^2/2) \, dx$$

where;

$$t = \frac{(D - TD_{50}(v_i))}{(m \cdot TD_{50}(v_i))}$$
Similarly for a different uniformly irradiated fractional volume ($v_j$):

$$NTCP = (2\pi)^{-1/2} \int_{-\infty}^{t} \exp(-x^2/2) \, dx$$

where;

$$t = \frac{(D - TD_{50}(v_j))}{(m \cdot TD_{50}(v_j))}$$
Lyman NTCP description

The final step:

- assume that the mean dose, $TD_{50}(v)$, for the distribution of complications for each uniformly irradiated fractional volume $v$,
- is related to the mean dose for the distribution of complications for uniform irradiation of the whole organ volume, $TD_{50}(1)$, through a power law "volume effect" relationship:

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n}$$
The Lyman NTCP Description

\[ NTCP = \left(2\pi\right)^{-1/2} \int_{-\infty}^{t} \exp\left(-x^2 / 2\right) \, dx, \]

where;

\[ t = \frac{D - TD_{50}(\nu)}{m \cdot TD_{50}(\nu)}, \]

and;

\[ TD_{50}(\nu) = TD_{50}(1) \cdot \nu^{-n} \]

Lyman Model dose-volume-response surface

Volume

Response

Dose

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
Dose-volume-response contours for a tissue with a large volume effect \((n = 0.80, \ m = 0.15, \ TD_{50} = 35 \text{ Gy})\)

The graphs illustrate the dose-volume-response contours for a tissue with a large volume effect. The parameters used are \(n = 0.80\), \(m = 0.15\), and \(TD_{50} = 35\) Gy. The graphs show the relationship between dose (in Gy) and NTCP (non-tumorigenic cell population) for different fractional volumes (V = 1.0, V = 0.75, V = 0.50, V = 0.25).

The left graph plots NTCP against dose (in Gy), while the right graph plots fractional volume against dose (in Gy). The contours indicate the dose levels at which certain percentages of the volume are expected to exhibit a response, such as 1%, 5%, 20%, 50%, 80%, 95%, and 99%.

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
Volume Effect (partial volume contours)

NTCP Surface \( [n = 0.10, m = 0.20, TD50 = 40.0] \)

Volume Contours \( [n = 0.10, m = 0.20, TD50 = 40.0] \)
Volume Effect (partial volume contours)

NTCP Surface \[ n = 1.00, m = 0.20, \text{TD}50 = 40.0 \]

Volume Contours \[ n = 1.00, m = 0.20, \text{TD}50 = 40.0 \]
Volume Effect (Iso-NTCP contours)
Volume Effect (Iso-NTCP contours)
Using the Lyman NTCP description

- The Lyman NTCP description attempts to describe uniform partial organ irradiation.

- This implies:
  + A fractional volume, $V$, of the organ receives a single uniform dose, $D$.
  + The rest of the organ, $(1 - V)$, receives zero dose.
  + i.e., a single step DVH, $\{D, V\}$
DVH reduction schemes

- For non-uniform irradiation, the 3D dose volume distribution (or DVH) must be reduced to a single step DVH that could be expected to produce an identical NTCP.
  + Wolbarst & Lyman schemes reduce DVHs to uniform irradiation of entire organ ($V=1$) to some reduced effective dose, $D_{\text{eff}}$.
  + Kutcher & Burman scheme reduces a DVH to uniform irradiation of an effective fraction of the organ, $V_{\text{eff}}$, to some reference dose, $D_{\text{ref}}$. 
\[ V_{\text{eff}} = \sum \{ v_i \cdot \left( \frac{D_i}{D_{\text{ref}}} \right)^{1/n} \} \]
Single step \( \{D_{\text{ref}}, V_{\text{eff}}\} \) DVHs

Direct DVH

Cumulative DVH

\( V_{\text{eff}} \)

\( D_{\text{ref}} \)
$V_{eff}$ DVH reduction $\rightarrow$ NTCP evaluation

Cumulative DVH

$V_{eff}$

Dose (Gy)

Volume (%)  

0 25 50 75 100

Dose (Gy)

Fractional Volume

$V_{eff}$

$D_{ref}$

0 20 40 60 80 100

1% 5% 20% 50% 80% 95% 99%

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
**Generalized Equivalent Uniform Dose (gEUD)**

ROI with $N$ dose points $d_i$

$gEUD \equiv \left( \frac{\sum_{i=1}^{N} d_i^a}{N} \right)^{1/a} \equiv \left( \sum_i v_i d_i^a \right)^{1/a}$

DVH (fractional volume $v_i$ receives dose $d_i$)
\[ g_{EUD} \equiv \left( \sum_i v_i d_i^a \right)^{1/a} \]

Normal Tissues:
Mean < gEUD < Max
\( a \) is positive

Relationship to Lyman Model: \( a = 1/n \)

For \( a = 1 \), \( g_{EUD} \) = mean dose
For \( a = 2 \), \( g_{EUD} \) = rms dose
For \( a = +\infty \), \( g_{EUD} \) = maximum dose
EUD NTCP description

For uniform irradiation of the whole organ, assumes that the distribution of complications as a function of dose can be described by a normal distribution

\(+\) with mean \(\text{TD}_{50}\)
\(+\) standard deviation \(m \cdot \text{TD}_{50}\)
The EUD NTCP description

The NTCP as a function of uniform dose, $EUD$, to the whole volume can then be described by the integral probability:

$$NTCP = (2\pi)^{-1/2} \int_{-\infty}^{t} \exp(-x^2/2) \, dx$$

where;

$$t = \frac{(EUD - EUD_{50})}{(m \cdot EUD_{50})}$$
Local response function

- Required to change non-uniformly irradiated volume to equivalent uniform dose EUD

- gEUD is one very general form of this function (there can be many others):
  
2 parameters

3 parameters

4 parameters

3 parameters

\[ t = \frac{EUD - EUD_{50}}{m \cdot EUD_{50}} \]

\[ t = \frac{rdV - rdV_{50}}{m \cdot rdV_{50}} \]

\[ NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \]

\[ NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \]

\[ NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \]

\[ NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \]
Local Radiation Response - Organ Functional Reserve Models

- Offer the potential for a more direct visualization of the relationship between the DVH and radiation damage
- May (ultimately) offer the possibility of linking cellular and organ subunit radiobiology to the prediction of radiation complications.
Local Radiation Response - Organ Functional Reserve Models

Fraction (f) of a macroscopic volume element incapacitated by a dose D can be described by a simple response function:

\[
f = \frac{1}{(1 + (D_{50} / D)^k)}
\]

where \(D_{50}\) is the dose which incapacitates half the volume and "k" describes the steepness of the "local damage" function.
Local Damage Function

Volume (%) vs. Dose (Gy)

Fx Incapacitated

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
Total Estimated Damage

Total fraction \( F \) of the organ that is incapacitated is equal to the sum of the fractions of the individual macroscopic volume elements destroyed.

\[
F = \sum f_i
\]
Organ Injury Function

$$NTCP = (2\pi)^{-1/2} \int_{-\infty}^{t} \exp \left( -x^2 / 2 \right) dx,$$

where

$$t = \left( F - F_{50} \right) / \sigma_v$$

$F_{50}$ is the fraction of the total organ damaged which would produce a 50% complication rate,

$\sigma_v$ describes the steepness of the “organ” response function
Overall Plan Evaluation
Overall Plan Evaluation

- Optimization of IMRT is an inherently multicriteria problem as it involves multiple planning goals for target volumes and their neighboring critical tissue structures.

- Successful achievement of one planning goal often competes with those of other planning goals.
Overall plan evaluation?

![Graph showing dose-volume histograms for different plans.]

- Target Plan 1
- Target Plan 2
- Normal Plan 1
- Normal Plan 2

Dose (%) vs. Volume (%) graph.
Models could make things easier

- Thanks to the prevalence of 3D CRT, considerable data exist relating tumor and normal tissue outcomes with planned dose distributions.

- From the purely technical perspective, such information could supplement or replace simple dose-volume criteria for inverse planning and/or treatment plan evaluation.
Implementation within optimization systems
Implementation

- Issues related to implementing and using the biological models within optimization systems
- Short survey of existing software tools that utilize the biological models
General optimization problem

\[ \min_{x \in \mathbb{R}^n} f(x) \]

Objective Function

Opt. Variables

subject to

\[ \begin{cases} 
  c_i(x) = 0, & i \in \mathcal{E}, \\
  c_i(x) \geq 0, & i \in \mathcal{I}.
\end{cases} \]

Constraints
IMRT Optimization problem

1. Beamlet intensities, $x$
   Opt. variables (100s ~ 1000s)
   Dose-to-Point calculations (Linear)

2. Dose distributions, $d_i(x)$
   Biological Models (Nonlinear)

3. Obj. & Constraint functions, $f(d_i), c(d_i)$
Example functions to minimize

- **Physical Dose**

\[ \sum_{i \in PTV} w_{PTV} (d_i - d_{PTV})^2 + \sum_{i \in OAR} w_{PTV} (d_i - d_{OAR})^2 + \ldots \]

- **Biological Models**

\[ \prod_{OAR} NTCP_{OAR} - TCP_{PTV} \]
Minima are not necessary
Global minimum.

Convex $f()$
Are biological models convex?

\[ g\text{EUD}(d;a) \]

- Concave: \(-\infty \leq a \leq 0\)
- Convex: \(1 \leq a \leq \infty\)


\[ \text{EUD}(d;\alpha) \]

- Concave: \(0 \leq \alpha\)


\[ \text{NTCP-Lyman} \]

- Quasi-convex

Börgers C 1997 Proceedings of IMA Workshop

\[ \text{TCP-Possion} \]

- Locally concave at high dose regions

\[ \ln(\text{TCP-Possion}) \]

- Strictly concave

But a little can be said about the obj. function itself...

\[ P_+ = TCP - \prod_i NTCP_i + \delta(1-TCP)\prod_i NTCP_i \]

\[ f = \left[1+\left(\frac{EUD_{t,0}}{EUD_t}\right)^n\right]^{-1}\prod_i \left[1+\left(\frac{EUD_{OAR,i}}{EUD_{OAR,0,i}}\right)^n\right]^{-1} \]

Brahme A. 1993 Med. Phys. 20 1201-10  

non-convex
Most TPS solves nonlinearly constrained optimization problem

What we do..
Preemptive NL-Goal programming

- Multicriteria optimization strategies based on soft-constraints with priority
- Solves a sequence of nonlinearly constrained optimization sub-problems (SQP)
- Maintains convexity at least locally...
Soft-constraint example
Make the heart NTCP less than 5%

\[ f = \text{Max}[0, (NTCP_{\text{heart}} - 5)]^2 \]
Soft-constraint example
Make the PTV EUD greater than 80 Gy

\[ f = \text{Max}[0, (80 - EUD_{PTV})]^2 \]
NSCLC Example
Priority 1: Protect Critical Tissues
Limit PTV dose

\[ \text{NTCP}_{\text{Lung}} < 15\% \ (5.3\%) \]
\[ \text{NTCP}_{\text{Heart}} < 5\% \ (0\%) \]
\[ \text{NTCP}_{\text{Esophagus}} < 5\% \ (1.1\%) \]
\[ \text{Max}_{\text{Cord}} < 45 \text{ Gy} \ (45\%) \]
\[ \text{Max}_{\text{PTV}} < 90 \text{ Gy} \ (90\%) \]
NSCLC Example
Priority 2: Achieve Target Dose

\[ \text{EUD}_{\text{PTV}} > 80 \text{ Gy} \ (80 \text{ Gy}) \]
\[ \text{NTCP}_{\text{Lung}} = 7.9\% \]
\[ \text{NTCP}_{\text{Heart}} = 0\% \]
\[ \text{NTCP}_{\text{Esophagus}} = 5.0\% \]
\[ \text{Max}_{\text{Cord}} = 44 \text{ Gy} \]
\[ \text{Max}_{\text{PTV}} = 90 \text{ Gy} \]
Plan Evaluation Software

- Adelaide Bioeffect Planning System (Wigg D)
- Bioplan (Sanchez-Nieto B, Nahum A at Royal Marsden)
- TCP_NTCP_CALC module (Warkentin B, Fallone B at U of Alberta)
- Albireo (Wals A at Regional U. Carlos Haya Hospital)
- DREES (Naqa I, Deasy J at Washington U.)
- EUCLID (Gayou O, Mifftten M at Drexel U.)

and probably more..
Bioplan
TCP_ NTCP_ CALC module
Albireo

Inputs:
formatted text or TPS exported plans

Outputs:
fx size normalized dose, Seriality, Critical Volume, Poisson NTCP & TCP

Model parameter database

Outcome Model Building Tools

- Multivariate regression
- Fitting to NTCP/TCP
- Uncertainty Estimation

A clinical example
A clinical example

- Patients at our institution with tumors in the liver or lung have been treated according to IRB approved protocols that seek to escalate \textit{homogeneous} dose (+7\%, -5\%) to the PTV at a fixed normal liver/lung iso-NTCP.
Difficulties in implementation

- Frequently the risk to other OARs (e.g., stomach-duodenum / esophagus) limits the tumor dose to below that which could be justified based solely on liver/lung NTCP,
  - especially when there is an overlap between the PTV and an external (to the liver/lung) OAR.
Liver tumor PTV-OAR overlap
Lung tumor PTV- OAR overlap
Can we do better?

- Optimized beamlet IMRT may benefit these patients.
- However, even with IMRT, in order to increase the mean PTV dose above the maximum tolerated dose of one of these OARs, it is necessary to relax PTV homogeneity constraints.
- But, how does one do this in a logical – meaningful way?
Can we do better?

- Objective function adjustment of beamlet intensities simply using PTV mean dose often leads to deep cold spots beyond those associated with the overlapping OAR.

- Additional, trial and error, dose-volume objective function aided planning sessions are required to adjust the dose distribution. These are time consuming, and generally leave the planners with unsatisfying (or at least unresolved) impressions about how optimal the resulting solution actually is.
Use of models in optimization

- Models for target and normal tissues could aid in planning, as their use would integrate the contributing effects of all parts of target and normal tissues dose distributions.
Use of models in optimization

- We explored IMRT optimization utilizing:
  + gEUD costlets for the PTVs to maximize anti-tumor effects,
  + NTCP costlets to maintain OAR doses within protocol limits.


PTV DVHs for liver patient

![Graph showing dose-volume histograms for different treatment techniques]

- **CONFORMAL**
- **IMRT ORIG ANG**
- **IMRT 7 FLD**
- **IMRT STAND ANG**

**DOSE (Gy)**

**VOLUME (%)**

*Source: NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08*
## Heterogeneous PTV dose assessment

<table>
<thead>
<tr>
<th>Patient number</th>
<th>gEUD $a = -20$ CRT (Gy)</th>
<th>gEUD $a = -20$ IMRT (Gy)</th>
<th>gEUD $a = -5$ CRT (Gy)</th>
<th>gEUD $a = -5$ IMRT (Gy)</th>
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<tr>
<td>1</td>
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<td>63.8</td>
<td>60.7</td>
<td>69.3</td>
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<td>75.7</td>
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<td>57.3</td>
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<td>64.1</td>
<td>57.3</td>
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<td>75.3</td>
<td>117.7</td>
</tr>
<tr>
<td>8</td>
<td>60.5</td>
<td>73.3</td>
<td>66.9</td>
<td>92.7</td>
</tr>
<tr>
<td><strong>mean</strong></td>
<td><strong>61.7</strong></td>
<td><strong>72.8</strong></td>
<td><strong>63.7</strong></td>
<td><strong>81.7</strong></td>
</tr>
<tr>
<td><strong>t test</strong></td>
<td><strong>p=0.001</strong></td>
<td><strong>p=0.003</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NTCP, TCP, EUD Tutorial, Univ of Michigan, Dept of Radiation Oncology: RK Ten Haken, K-W Jee, 2002-08
IMRT optimization conclusions

- We suggest that the use of biological parameters directly as costlets within the optimizing process should be able to produce IMRT plans that:
  - utilize heterogeneous PTV coverage to maximize tumor gEUD,
  - while maintaining NTCP limits for dose limiting normal tissues and other OARs.
IMRT optimization conclusions

- It appears that the direct use of “outcome” cost functions for both target and normal tissues should allow:
  - significant \((i.e., \text{ multi-fraction})\) increases in the calculated gEUD for the PTV,
  - in a much more intuitive (and efficient) manner than might be realized using multiple dose/volume based optimization sessions.
Caveats and Warnings
NTCP/TCP modeling

We’ve come a long way......
But.......

OK, beware! mostly personal opinion may follow

cast of thousands here... would you believe 100’s?? ...maybe tens?
Conceptually Simple

- Pick a Model
- Look at some Patients
  - Have 3-D Dose Distributions
  - Have 3-D Volumes
  - Have Outcomes
- Use patient data to parameterize and/or test model
¿No Problemo?

DVH  Veff
3-D   Functional Reserve
NTCP
Well........
Biologists and Physicians and Physicians Agree the Models are:

- **Too simple or naive** *(papa bear)*
  + Biology is more complex than this
  + Not enough parameters

- **Too complex** *(mama bear)*
  + Too many parameters
  + Is this still biology?

- Still looking for *baby bear’s model*
Modeling

- Model vs. Theory
  - **Models** interpolate
  - **Theories** extrapolate

- Mathematics vs. Biology
  - K.I.S.S.
Models?

- Probably best to say that at this point much of this is still phenomenological and “descriptive” rather than predictive.

- It can be dangerous to use the models for treatment situations different from the circumstances in which their parameters were derived.
Model Fitting

- Generally not enough solid data points (complications) to yield quantitative results
- Large confidence limits on model parameters
- No effective means of determining “goodness of fit”
Model Fitting (the good news!)

- We now have collaborations with genuine bio-statisticians who are applying valid statistical methods to the data analyses and the new protocol designs.
Input Data: Dose

- Calculational algorithms are better
- Can compute 3-D distributions
- Dose distributions are complex
  + Non-uniform
  + Daily variations not easily included
Using published model parameters..

- Model parameters are obtained from a specific cohort of patients, irradiation conditions.
- Outcome models should account for fractionation schedule. (e.g., NTCP vs. fx size)
Dose per fraction corrections

Normalized Iso-effective Dose ($NID$) at standard dose per fraction $d_0$ is equivalent to total dose $D$ given at dose per fraction $d$:

$$NID_{d_0} = \frac{\alpha}{\beta} = D \left( \frac{(\alpha/\beta) + d}{(\alpha/\beta) + d_0} \right)$$
Dose per fraction corrections to model

Primary Liver Cancer

NTCP for RILD

Mean Liver Dose (Gy)

0.0 0.2 0.4 0.6 0.8 1.0

0 1 02 03 04 05 06 0

1.5 Gy fractions
2.0 Gy fractions
3.0 Gy fractions

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Dose per fraction corrections

\[ \text{NID}_{d_0, \alpha/\beta} = D \cdot \left( \alpha/\beta + d \right) / \left( \alpha/\beta + d_0 \right) \]

Normalized Isoeffective Dose \( \text{NID}_{d_0, \alpha/\beta} \)
alpha / beta Ratio \( \alpha/\beta \)
nominal dose per fraction \( d_0 \)
for local Total Dose \( D \)
and local dose per fraction \( d \)
Normal Liver DVH

Volume (cc)

Dose (Gy)

Physical Dose
**Normalized Dose - 40 Fractions**

- **Physical Dose**
- **2 Gy Eq Dose**

**Graph Details:**
- **Volume (cc)**
- **Dose (Gy)**

**Values:**
- **EUD** = 27.5 Gy
- **EUD** = 23.6 Gy
- **EUD** = 19.5 Gy
- **NTCP** = 8.1%
- **NTCP** = 1.8%
- **NTCP** = 0.2%
Normalized Dose - 20 Fractions

EUD = 27.5 Gy
EUD = 31.9 Gy
EUDx = 23.6 Gy
NTCP = 8.1 %
NTCP = 26.7%
NTCPx = 1.9 %
Fraction Size Dependence

- EUD (Gy) or NTCP (%)
- # of Fractions

Graph showing the dependence of EUD and NTCP on the number of fractions. The graph includes lines labeled EUDb, NTCPb, EUDp, and NTCPp.
Input Data: Volume

- 3-D yields Volumes
  + Physical Volume (size and shape)
  + Position

- How accurate are the input data?
  + For first treatment?
  + As a basis for the whole treatment?
Input Data: Dose-Volume

- Difficult to track which volume receives what dose
  + Time factors often ignored
- Changes not easily accommodated
  + Tumor shrinkage
  + Inter and Intra treatment changes and processes
Modeling Summary

- Careful studies of the partial organ tolerance of normal tissues to therapeutic ionizing radiation are emerging, as are attempts to model these data.

- We should be encouraged by the progress in this area.
Modeling Summary

• However, the ability to use the NTCP models themselves reliably, and in a predictive way is still an area of active research and should be approached with great caution in a clinical setting.
Summary

• Higher quality input data coupled with valid statistical considerations should help in resolving some of our outstanding issues in the assessment of dose-limiting normal tissue toxicity and tumor control.
QUANTEC Workshop

- QUantitative Analysis of Normal Tissue Effects in the Clinic
- October 5-7, 2007, Madison, WI
- Red Journal supplement due 2008
TCP Workshop

• Modeling Tumor response to irradiation

• May 28-31, 2008, Edmonton, AB

• Preliminary plans for articles to be published in Acta Oncologica early 2009
Work in progress

Report of the AAPM Task Group 166:

THE USE AND QA OF BIOLOGICALLY RELATED MODELS FOR TREATMENT PLANNING

X. Allen Li, Medical College of Wisconsin (Chair)
Markus Alber, Uniklinik für Radioonkologie Tübingen
Joseph O. Deasy, Washington University
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Ellen D. Yorke, Memorial Sloan-Kettering Cancer Center

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“All models are wrong, but some are useful.”

G.E.P. Box, 1979*