Biological Indices for IMRT Evaluation and Optimization

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Why biological indices?
• Dose distributions, DVHs- surrogates for outcome
• We want:
  high local control (TCP~100%)
  low complications (NTCP~0% for all tissues)
• Wanted! reliable mathematical models for TCP (D(t),V )
  NTCP(D(t),V )

Linear-Quadratic (LQ) model
SF(D)= mean fraction of cells surviving dose D

SF(D)=\(\exp(-[\alpha D+\beta D^2])\)

- Single track, non-reparable, lethal damage
- 2-track, partially repairable, sublethal damage

For low LET
  \(\alpha\): 0.1 Gy\(^{-1}\) – 1.5 Gy\(^{-1}\)
  \(\alpha/\beta\): 1.0 Gy - 20 Gy
  \(\alpha\) hard to measure vs \(\alpha/\beta\)

SF2 or SF=fraction of cells surviving a single 2 Gy dose
Back-of-envelope estimates
SF2~ 0.5

Fractionated Doses
SF(n,d)=[\(\exp(-[\alpha D+\beta D^2])\)]^n
SF(D,d)= \(\exp(-\alpha D[1+d/\alpha])\)

where n=# of fractions, d=dose/fx, D=nd

- Large \(\alpha/\beta\) (~10 Gy)->“Early responding” tissues
  - Insensitive to dose per fraction
  - most tumors, mucosa, skin- acute complications
- Small \(\alpha/\beta\) (<~4 Gy)->“Late responding” tissues
  - Sensitive to dose per fraction
  - spinal cord, lung, kidney – late complications
  - maybe prostate tumors (\(\alpha/\beta\) estimates from 1 Gy-10 Gy)
  - other slow growing tumors

Biological Effective Dose (BED)
Schedules with same BED have same biological effect

BED=D(1+d/\(\alpha/\beta\))

Tumor \(\alpha/\beta\)=10 Gy
Normal tissue \(\alpha/\beta\)=3 Gy
Standard schedule:D=60,d=2 Gy
BED\(_\text{tum}^\text{std}=72\) Gy BED\(_\text{nt}^\text{std}=100\) Gy

Hyperfractionation
At 1.2 Gy/fx
iso-tumor-effect->BED\(_\text{tum}=72\) Gy
Doses=72/1.2 = 60 Gy->iso-NT
iso-NT-effect->BED\(_\text{nt}=100\) Gy
Doses=100/1.4 = 71.4 Gy->NT damage
BED\(_\text{nt}=79.3\) Gy->higher tumor effect
Either way, better therapeutic ratio

LQED2 (or ED2)
Dose given at 2 Gy/fx with same bio-effect as (D,d)

LQED2=D(1+d/\(\alpha/\beta\))
(1+2(\(\alpha/\beta\)))

Transform each DVH dose bin separately.
LQED2 = total dose if d<2 Gy/fx
LQED2 > total dose if d>2 Gy/fx

Lung DVH - 80 Gy treatment (2 Gy/fx to 100% isodose) and LQED2-VH’s
\(\alpha/\beta=3\) Gy (red)
\(\alpha/\beta=2\) Gy (blue)
**Time Dependence: Sublethal Damage Repair**

“Treat at least 6 HOURS APART”

Occurs for tumors & normal tissue

Initial evidence - “split dose experiments”

At constant $(d, n)$

Short inter fraction time $\Delta T$

Less time for repair, higher $\beta$

Sublethal damage kinetics ~

$$\exp\left(-\frac{\ln2}{T_{1/2}}\right)$$

$T_{1/2}$ range ~0.3 hr to 4 hr

$T_{1/2}$ depends on the tissue

$$\beta(\Delta T)=\beta(1+h(n, \Delta T))$$

(particular concern for LDR)

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**Tumor Control Probability (TCP)**

TCP=“long-term” local control

$D_{50}$=local control dose for 50% of cases (also called TCD50)

$\gamma_{50}$ proportional to slope of TCP vs dose at $D_{50}$

$\gamma_{50}=\frac{\Delta TCP(%)}{\Delta(D/D_{50})}$

Parameter Range (Std Fx)

$D_{50}$: 20 Gy to $>100$ Gy

$\gamma_{50}$: 1-4

Example TCP curve

$D_{50}=60$ Gy, $\gamma_{50}=1.5$

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**TCP: Modeling problems**

- TCP endpoint=local control but at what time?
- Where is the tumor?
  - Tumor localization on planning images?
  - Multi-modality imaging?
  - “Local failure” or “marginal miss”?
- Which tumor cells determine local control?
- What was the delivered dose distribution?
  - Role of setup errors, organ motion?
- Uncertainty in radiobiological parameters.

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**Time Dependence: Repopulation**

Cells proliferate during a course of treatment

Long RT course~more time to proliferate, lower tumor control

Growth ~ exponential over treatment course $T$

$$SF(n,d,T)=\exp\left(-\exp\left(1+d/\alpha/\beta\right)\right)\exp\left(\ln2\ T/T_{pot}\right)$$

$T_{pot}$ range: 2 days – 100 days

“Back-of envelope” BED lost to tumor growth ~ 0.5 Gy/day

**Continuous Hyperfractionated Accelerated RT (CHART)**

Control (H&N): 2 Gy/fx to 66 Gy, 1 Tx/dy, weekends off, $T=45$ dy

CHART: 1.5 Gy/fx to 54 Gy, 3 Tx/dy, $\Delta T>6$ hr, $T=12$ dys continuous

CHART expected to gain ~ 16 Gy of BED from reduced $T$

Clinical results: CHART “at least as effective” as control, trend shows benefit for advanced disease.

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**LQ Model Summary**

- Grounded in decades of in vitro, in vivo work
- Widely used to compare, devise Tx schedules
- Can include time-dependent effects
- Key parameters have large uncertainties, even for “common” systems (e.g. prostate cancer)
- Mechanistic understanding imperfect
- Not strictly “rigorous”

BUT it works and is clinically very useful

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**TCP: Poisson Model**

Only clonogenic cells can regrow the tumor

TCP=probability of no surviving clonogens

Let $N$ # clonogens, $SF(D)$=mean fraction clonogens surviving $D$ ($N SF(D)$) = mean # of surviving clonogens

Poisson distribution of surviving clonogens

$$TCP=\exp(-N SF(D))$$

compatible with models of SF such as LQ

$$TCP=\exp(-N SF^{2\gamma})$$

$$D_{50}=2\ Ln(Ln2/N) / Ln(SF^{2\gamma})$$

$\gamma_{50}=Ln(Ln2)/2\ Ln(SF^{2\gamma})$ independent of SF or $\alpha,\beta$
Problems, problems.....
Soft tissue cell density ~ 10⁹ cells/cc
Detectable tumors >1 cc (100 cc tumors are common)
If N=#cells, N>10⁹ -> γ_50>7.3
This contradicts clinical observation: γ_50~2
Two possible solutions
1. TCP controlled by a few radioresistant clonogens
   (N~200 ->γ_50~2)
2. TCP is a population average:
   (inter-tumor) different tumors have different radiosensitivities
   (intra-tumor) clonogens within a tumor vary in radiosensitivity.
   These are not mutually exclusive

Two ways to reduce γ_50

TCP for non-uniform dose distributions
Divide tumor into subvolumes (tumorlets)
- tumorlet volume = # density of clonogen n, \( n_i \)
- Dose and dose/fraction \( D, d_i \), surviving fraction \( SF(D, d_i) \)
- TCP=probability of no survivors in any tumorlet
Assume Poisson model, independence of each tumorlet
\[
TCP = \prod \exp(- n_i SF(D, d_i)) = \prod \exp(- \rho_i SF(D, d_i))
\]
Product over all the tumorlets
Geographic misses and deep cold spots are bad!
D~0 in a tumorlet -> TCP~ 0
Effect of cold spot has implications for use of TCP in plan optimization but.....

Effect of cold spot is model dependent

Small hotspots don’t help much
A model-robust conclusion
Small hot spots don’t improve TCP much UNLESS they coincide with small regions of radioresistant or a high density of clonogens (“dose painting”)
Big hot spots=Boosts

EUD: Equivalent Uniform Dose
EUD=uniform dose giving same clonogen survival as the true dose distribution (Niemierko, 1997)
For large \( \alpha/\beta \) and uniform clonogen density
\[
EUD = 2 \ln \left( \sum_v v_i (SF)^{1+\alpha/\beta} \right) \ln(SF)
\]
\( v_i = \) volume fraction receiving dose \( D_i \)
EUD is independent of # of clonogens
EUD is less model dependent than TCP.
\[
D_{min} \leq EUD \leq D_{mean}
\]
Generalized for spatial clonogen variation, general \( \alpha/\beta \), LQ+time dependence, population averaging
TCP Summary
Poisson statistics +LQ Model mathematically tractable
Applicable to general dose distributions

BUT
There are major conceptual questions
How many clonogens are there? How many control TCP? What LQ parameters? Importance of population averaging?
Spatial distribution of clonogens in tumor is unknown
If a cold/hot spot has no clonogens, TCP or EUD isn’t affected.
We assume uniform clonogen density out of ignorance.
Is there hope from molecular imaging?

Affect on TCP predictions for evaluation & optimization ??

Poisson model breaks down for proliferating cells (worse for short $T_{pot}$)
Impact on optimization/evaluation unknown
(see Stavrev et al, Med Phys May 2003)

Problems with modeling NTCP
(Normal tissue complication probability)

- Reported clinical data mostly for low NTCP and low (<70 Gy) doses.
  - If NTCP increases sigmoidally with dose, most data are on the early “tail”- extrapolation is troublesome
- Several types of complications per organ
  - Different onset times, dose-volume dependences
- Reports use different scoring systems
- Non-radiation factors affect NTCP
- Most models quantize the complication
  - Most complications show severity continuum

Main data source – Emami et al, 1991

- Critical review and summary of dose limiting complications literature up to 1991 for 28 normal tissues
- Predates 3D-CRT era (time for new look?)
- Tolerance doses: TD50/5 and TD5/5
  - Doses for complication probability of 50% and 5% respectively at 5 years, tx at 1.8-2 Gy/Fx

Volume dependence of tolerance doses

Partial organ irradiation
Volume fraction $v$ gets full dose
Remainder of organ gets zero dose

Emami et al tabulated TD50/5 and TD5/5 for partial organ irradiations of $v=1, 2/3$ and $1/3$.

NTCP Volume Dependence

- For most normal tissues iso-complication dose increases if irradiated volume fraction decreases
- Power law approximation
  $TDc(v)=TDc(1)/vn$
  $n>0$
- Small $n$-weak volume depdce, $D_{max}$ dominates
- High $n$-strong volume depdce ($n=1$->mean dose depdce)

Low $n$-spinal cord, brainstem
High $n$-lung (pneumonitis), parotids (xerostomia), liver (RILD)
Mid $n$-rectum (bleeding), heart

Normal Tissue Complications
Spinal Cord

- Complication= Radiation myelitis
- Clinically-want NTCP<<5%
- 1991(E&B) TD5~47-50 Gy,TD50~70Gy, n=0.05
  Updates
  - TD5=57 Gy
  - Weak volume dependence confirmed
  - Evidence for slow repair component (>8 hr)
  - Small $\alpha/\beta$ (~2 Gy)
  - Some occult injury recovery (~ 2 yrs)
Normal Tissue Complications

Lung
- Complication: severe radiation pneumonitis
  - Requiring serious medical care
- NTCP ~ 20-25% (steroids) accepted
- Onset within 6 months of Tx
- 1991 TD50(1)=24.5 Gy, TD5(1)=17.5 Gy, n=0.87
- Updates
  - n~1, TD50(1)~28 Gy
  - Good DVH correlates for treatment planning:
    $D_{\text{mean}}$, Volumes receiving >13 Gy, >20 Gy, >30 Gy
  - $\alpha/\beta$ ~ 2-4 Gy
  - Are some subvolumes more sensitive than others??

Late rectal complications
- Complications: severe proctitis, rectal bleeding, ulceration, stricture, fistula
- Onset latency up to 2-3 yrs post treatment
- NTCP ~ 10-20% (bleeding) are accepted
- 1991 TD50=80 Gy, TD5=60 Gy, n=0.12
- Updates
  - $\alpha/\beta$ ~ 3-4 Gy
  - More complex volume dependence (not just $D_{\text{max}}$)
  - MSK: Restrict volume >75 Gy, volume >50 Gy
  - DV constraints: "Planning" rectal wall 1 slice above and below PTV; <30% to >75.6 Gy, <53% to >47 Gy
  - $D_{\text{mean}}$ < 84-86 Gy

NTCP Models: Lyman Model
4-parameter sigmoidal function for all complications
$$ NTCP = \int \exp(-t^2/2)dt/\sqrt{2\pi} $$
Parameters: TD50(1), m, volume exponent n, $V_{\text{reference}}$

Histogram reduction schemes
DVH -> equivalent partial organ or uniform irradiation
KB: use equivalent uniform dose $D_{\text{eq}}$ ($\Sigma v_i (D_i)^m/n$)
Lyman: use equivalent partial irradiation of $v_{\text{eff}}$ to $D_{\text{max}}$
  $$ v_{\text{eff}} = \Sigma v_i (D_i/D_{\text{max}})^{1/n} $$

Tissue Architecture Models
Tissue made of independent functional subunits (FSUs)
NTCP depends on FSU radiosensitivity and organization
Unfortunately FSUs remain speculative and un-identified!

Serial: X X X X X and X X X X X give same effect
- NTCP = probability of no FSUs destroyed
  - Mathematically tractable (FSU response directly from whole organ)
  - Low volume dependence, applied to spinal cord

Parallel: Complication only if > a critical % of FSUs destroyed
- Applied to strong volume dependence organs (lung, liver, kidney)
- Need population averaging (over critical %) to reduce $\gamma_{50}$
- NTCP saturates for high dose partial organ irradiation
  (e.g. partial irradiation of 25% of organ volume -> NTCP < 25%)

The model can affect clinical decisions
An example for lung treatment plans with outcomes-based criteria.
- $f_{\text{dam}}$: fraction damaged FSUs in parallel model
- $D_{\text{eff}}$: fraction irradiated

Generalized EUD for normal tissues
Calculated from the DVH, $\{v_i, D_i\}$
$$ EUD = (\Sigma v_i (D_i)^{a/n})^{1/a} $$
(Nomoto, 1999)

Advantages
- Computationally simpler than model NTCPs
- Only one parameter/complication
- Same formalism for tumors and normal tissues
  (a = large negative # for tumors so EUD is determined by the cold spot)
NTCP: Summary

Bad news
NTCP models are much too simplistic to describe the physiology of radiation damage. Maybe we shouldn’t try!

Good news—maybe we don’t need very sophisticated models
Crudely, there are 3 types of normal tissues
“Max dose” (serial?) tissues (cord, optic structures, bowel)
“Mean dose” (parallel?) tissues (lung, liver, parotids)
Mixed tissues (rectum) – look at middle parts of DVH

Such surrogates for NTCP are easily obtained from DVH
They are used in clinical decisions and IMRT optimization.
(mean lung dose<21 Gy, Max cord dose<50 Gy, <30% RW over 75 Gy)
More good news: Lots of data from modern clinical studies!

Biological models in optimization score functions

Common features
– All the uncertainties associated with biological models
– Is the whole PTV equally important for TCP?
– False normal structure to limit hotspots in target
– More computation-intensive than dose, dose-volume

1. Uncomplicated Control [Agren et al, 1990]
Probability of local control (benefit) without injury

\[ P_c = P_B - P_I \delta \]

\[ P_B = TCP, P_I = 1 - \Pi (1 - NTCP) \]
\[ \delta = \text{independent B and I} \]

\[ \delta = 1 \rightarrow P_c = P_B (1 - P_I) \]

Problem: does not discriminate against serious complications (5% TCP decrease same as 5% myelitis increase)

2. TCP and NTCP with prioritization
Maximize F where

\[ F = TCP \Pi_{NT} s_{NT} \]

\[ s_{NT} \text{ is constant until NTCP of ith organ hits first threshold; falls to zero at second threshold} \]

Any TCP, NTCP model.

Results were compared with dose but not dose-volume constraints [Wang et al. 1995]

3. Generalized EUD : \( (\sum v_i (D_i)^a)^{1/a} \)
EUD constraint values set for each structure (e.g. for tumor, EUD = the prescription dose)
Generalized EUD for each tissue of interest (a<0 for tumors) calculated in each optimization iteration.

Quadratic score function (difference of calculated and constraint EUDs rather than doses) [Jones & Hoban, 2001]

Product of logistics score function [Wu et al, 2001]

\[ S = \prod \left[ \frac{1}{1 + (EUD_{i,\text{min}}/ EUD_{i,\text{max}})^n} \right] \]

Better than dose/dose volume methods?
Wu et al find advantages:
Better normal tissue protection (protection throughout optimization, larger search space explored).
Only one constraint per tissue (vs several for dose, dose-volume constraints).

In a later report, cited need to combine EUD with dose-based score function to “fine tune” the plan for ultimate clinical use [Wu et al PMB 48, 2003]

Jones & Hoban: EUD gave no advantage.

Many questions remain......

Do objective functions using biological models give better or more efficient IMRT distributions than dose/dose-volume functions?

How to do a fair comparison?

Plan evaluation with models or D-V correlates or both? How realistic do models need to be?
Can we beat biologists at their own game (should we be trying)?

If multiple normal tissues compete with tumor control, how to weight models vs “clinical judgement” factors?