Biologically Based Treatment Planning

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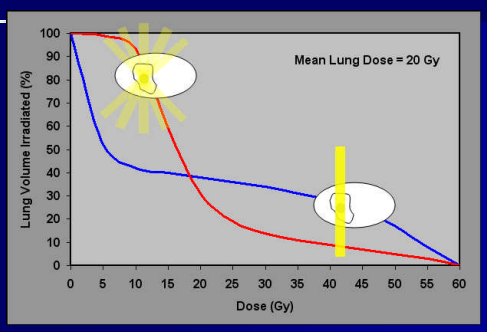
Limitations of dose-volume based treatment planning

- **DV metrics are merely surrogate measures of radiation response**
- **Commonly used DV constraints (e.g., V20 for lung)**

➢ More than one point correlates outcome (MLD, V5, V15,…)
➢ Specific to treatment techniques (3DCRT, static or rotational IMRT…)
➢ Plan optimization with multiple DV points is indirect, depending on planner's skill.
➢ Computerized optimization with multiple DV indices can be complex and can be trapped in a local mimimum.

A Little to a Lot or a Lot to a Little?



Biologically based treatment planning

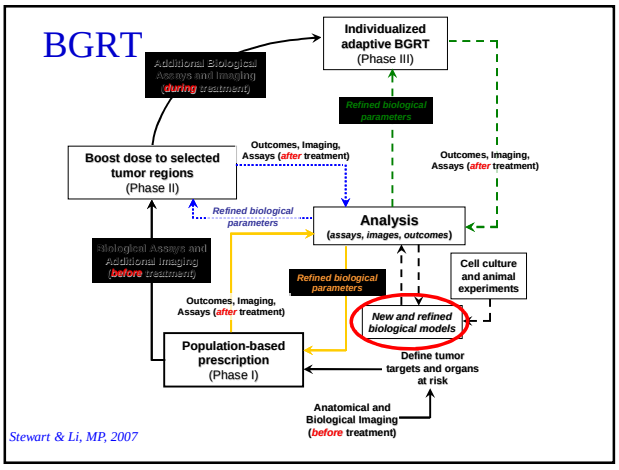
Feedback from biological response (outcome) models during the treatment planning process

Feedback may be either passive/automated in the case of inverse treatment planning, or with active participation from the planner in the case of forward treatment planning.

Evolution of biological (outcome-model) based treatment planning

Evolution stage	Plan optimization strategy	Plan evaluation strategy	Representative TPS
0	DV-based cost functions	DVHs	The majority of current TPS
1	EUD for OARs; EUD- and DV-based cost functions for targets	DVHs and relative values of TCP/NTCP	CMS Monaco Philips Pinnacle Varian Eclipse
2	EUD-based cost functions for all structures	Absolute values of TCP/NTCP	Future developments
3	Absolute values of TCP/NTCP	Absolute values of TCP/NTCP	Future developments

BGRT



Stewart & Li, MP, 2007

Why use outcome models?

- To fully describe responses as a function of any dose to any volume
- To predict responses based historical data
- To supplement or replace dose-volume criteria for plan optimization and evaluation.

Outcome modeling for treatment planning

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

Problems:

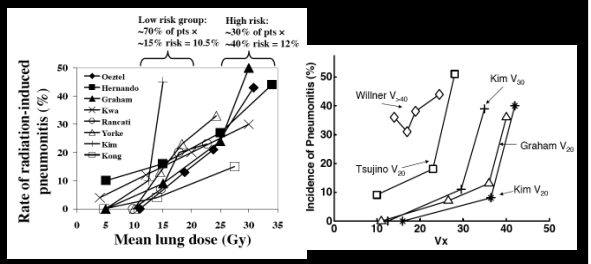
- Largely phenomenological rather than predictive
- Unreliable **model parameters, needs more clinical data (e.g., QUANTEC)**

But still useful (pushing individual DVHs towards less toxicity) !

Normal Tissue Toxicity
Sample QUANTEC data

organ	tolerance	toxicity rate (%)
lung	V20 < 30%	20
spinal cord	Dmax=50Gy	0.2
parotid	mean dose < 25 Gy	<20
esophagus	mean dose < 34 Gy	5-20
heart	V25 < 10%	<1
liver	mean dose < 30Gy	<5
kidney	mean dose < 15-18Gy	<5
rectum	V50<50%, V70<20%	<15

Pneumonitis: multiple fractions whole lung irradiation

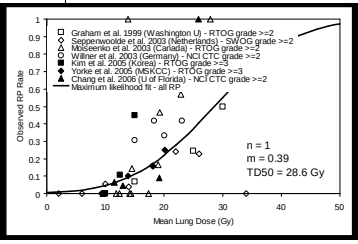


- Fractionation increases lung tolerance.
- Strong correlation with dose-volume parameters
- Strongly fraction size dependence

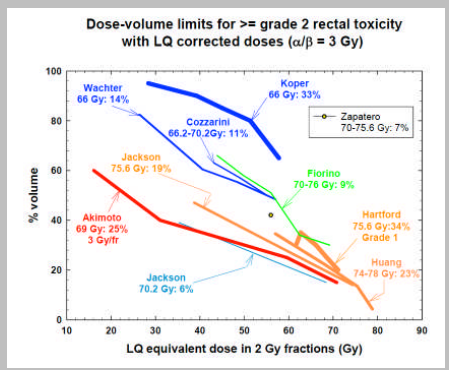
Courtesy: Marks et al, QUANTEC Lung

Derive LKB NTCP model parameters based on clinical and lab data

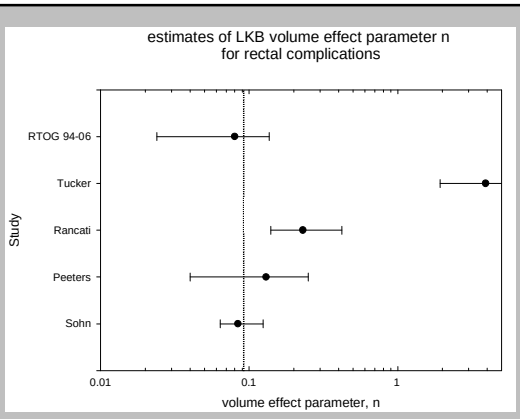
Reference	n	m	TD_{50} (Gy)	Endpoint	Fractionation Scheme
Lung					
Burman *et al.* 1991	0.87	0.18	24.5	Pneumonitis	1.8-2 Gy q.d.
Martel *et al.* 1994	0.87	0.18	28	SWOG grade ≥ 1 RP	1.8-2 Gy q.d.
Kwa *et al.* 1998	1	0.30	30.5	SWOG grade ≥ 2 RP	1-2.7 Gy q.d.; normalized to 2 Gy/fr using α/β of 2.5 or 3 Gy
Seppenwoolde *et al.* 2003	0.99 1	0.37 0.28	30.8 43	SWOG grade ≥ 2 RP SWOG grade 3 RP	1-2.7 Gy q.d.; normalized to 2 Gy/fr using α/β of 2.5 or 3 Gy
Moiseenko *et al.* 2003	1.02 0.80	0.26 0.37	21.0 21.9	Symptomatic pneumonitis Radiographic and symptomatic pneumonitis	1-2 Gy q.d.; normalized to 2 Gy/fr using α/β of 3 Gy



Semenenko & Li 2007



QUANTEC, IJROBP 2010 (Slide courtesy J. Deasy)



(Slide courtesy A. Jackson et al.)

(Note: a = 1/n)

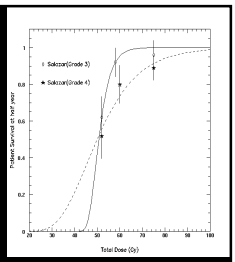
LQ parameters: Malignant gliomas

MG $\alpha = 0.06 \pm 0.05\ Gy^{-1}$
$\alpha/\beta = 10.0 \pm 15.1$ Gy

Grade 1&2 $\alpha = 0.35 \pm 0.07\ Gy^{-1}$
$\alpha/\beta = 4.3 \pm 5$ Gy

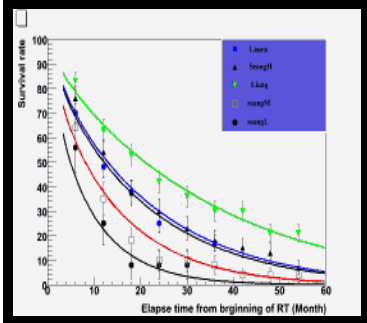
Grade 3 $\alpha = 0.11 \pm 0.10\ Gy^{-1}$
$\alpha/\beta = 5.8 \pm 11.8$ Gy

Grade 4 $\alpha = 0.04 \pm 0.06\ Gy^{-1}$
$\alpha/\beta = 5.6 \pm 9.4$ Gy



Qi, Schultz, Li , IJROBP, 2006.

LQ parameters: Liver Cancer

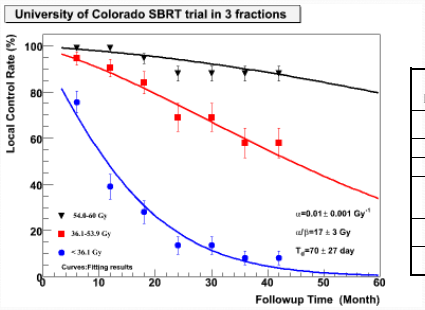


$\alpha = 0.029 \pm 0.004\ Gy^{-1}$
$\alpha/\beta = 9.9 \pm 1.8$ Gy
$T_d = 100 \pm 18$ days

	Patient no.	Median Dose (Gy)	Fraction scheme (Gy/fx)	Reference
Liang	128	53.6	4.88	Cancer Vol103,218 (2005)
Dawson	128	61.5	1.5	J. Clin Onco Vol18, 2210 (2000)
Seong H	83	55	1.8	Int. J. Rad. Onco Biol. Phys. 55 329 (2003)
Seong M	51	45	1.8	
Seong L	24	32.5	1.8	

Tai et al, IJROBP, 2008

Data fitting with modified LQ for NSCLC



Model parameters	Fitting results
K_{50}/K_0	2.60 ± 0.34
σ_K/K_0	0.74± 0.10
δ	0.21± 0.02
α	0.010± 0.001 (Gy^{-1})
α/β	17 ± 2.8 (Gy)
T_d	70 ± 27 (day)

16

Updated model parameters for tumor

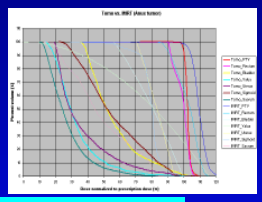
Tumor	α/β ratio (Gy)	α (Gy-1)	Repair time Tγ (h)	Doubling Time Td (d)	Reference
Prostate	3.1	0.15	0.27	42	Wang et al. (2003)
Breast	10	0.3	1.0	15	Guerrero et al. (2003)
Glioma	6.0	0.06	0.5	50	Qi et al. (2005)
H&N	8.3	0.22	0.267	2	Qi et al. (2006)
Liver	9.9	0.03	1.0	100	Tai et al. (2006)
AVM	2.1	0.02	—	—	Qi et al. (2005)
…					

Use of outcome models in computerized treatment planning

- Plan evaluation
- Plan optimization

Problems to evaluate complex plans with DVH

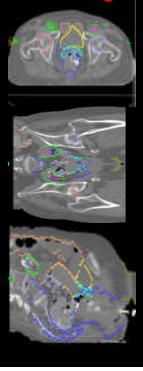
- Complicated anatomy, multiple OARs
- Complicated/crossing DVHs
- Difficult for visual inspection
- Plan merit not quantified
- DVH failure for spatial tumor heterogeneity

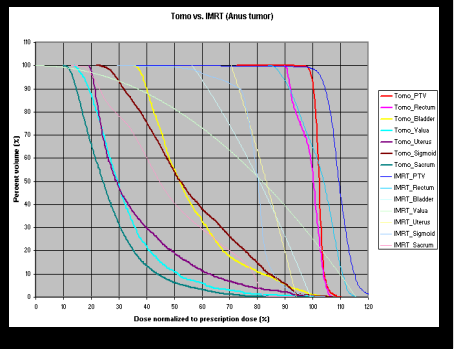


Quantitative evaluation and comparison of complicated plans based on biological effectiveness are desirable.

Plan Ranking: Tomo vs IMRT
Case example: Female Anus

Figure-of-merit TOMO: *fEUD* = 0.613 IMRT: *fEUD* = 0.600





Plan Optimization

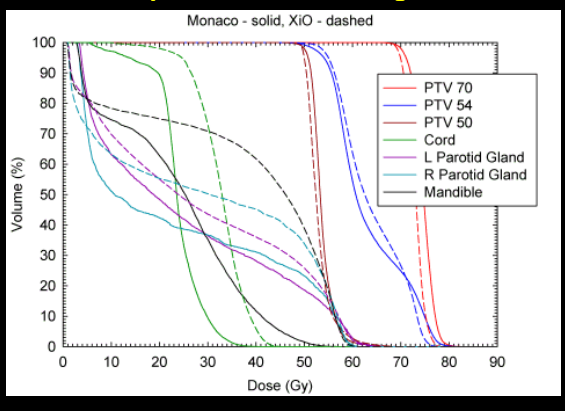
Cost Functions: Mathematical forms of treatment goals

- Physical (dose-volume based) cost functions
  - Overdose/underdose volume constrains
  - Maximum/minimum doses
  - V20, mean dose
- Biological (outcome-model based) cost function.
  - Target/OAR EUDs
  - TCP/NTCP.

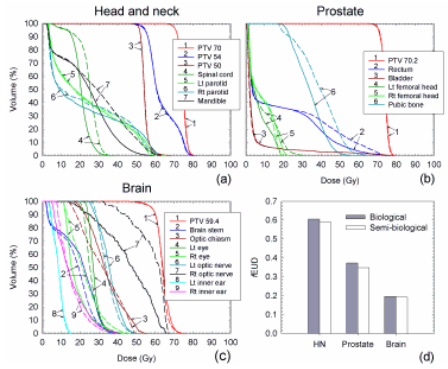
Three commercial treatment planning systems with tools for biologically based plan evaluation and optimization

CMS Monaco
Phillips Pinnacle
Varian Eclipse

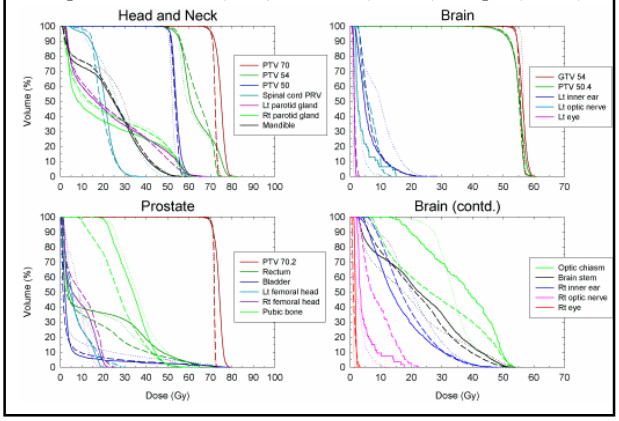
H&N case: Physical (XiO) vs Biological (Monaco)



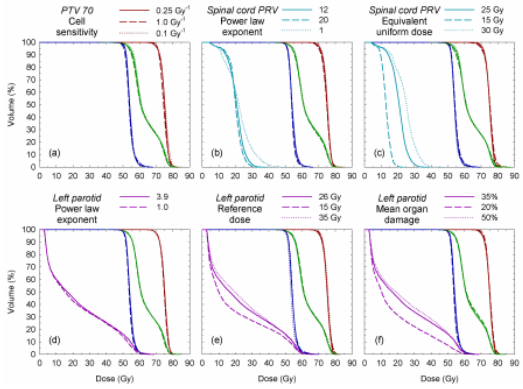
Biological (solid) vs. dose-based (dashed) cost functions for OARs
Monaco



Comparison: Monaco (solid), Pinnacle (dashed), Eclipse (dotted)



Sensitivity on model parameters: Monaco



Why do outcome models work?

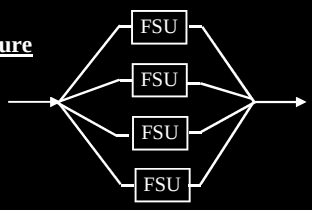
We know how to ask and what to ask !

- Since, by definition, there are an infinite # of DVHs that lead to an EUD for a given organ, outcome-model based cost functions can lead to the desired EUD directly.
- Can get the best possible result (not just any acceptable result) and will get it more quickly and easily

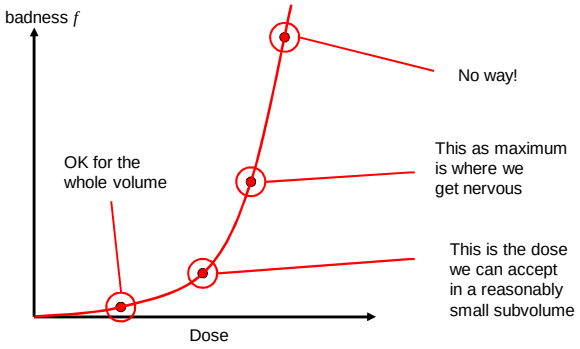
Serial structure (spinal cord, rectum)

Parallel structure

lung, liver



How to make a biological cost function: serial models

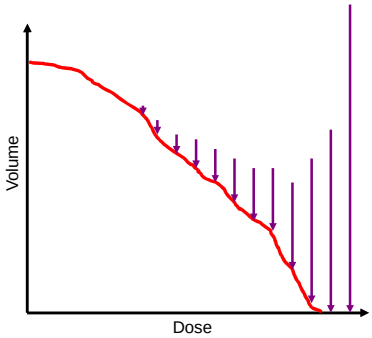


Courtesy M. Alber

Bloemfontein 2006

HYPERION

How does a serial complication model control the DVH ?



The length of the weight arrow grows as

D^{k-1}

$\exp(\alpha D)$

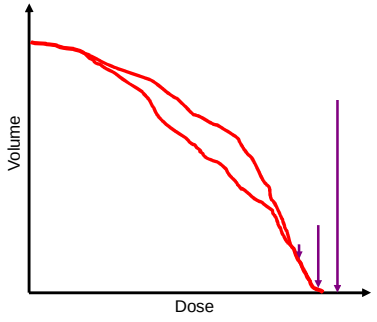
or similar functions

Courtesy M. Alber

Bloemfontein 2006

HYPERION

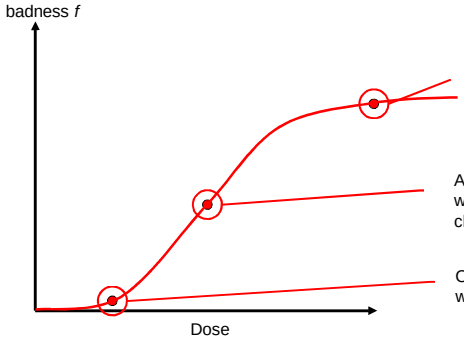
In contrast, a quadratic penalty:



DVH control
only for doses
greater than threshold

Courtesy M. Alber
Bloemfontein 2006

Not all organs are serial: parallel complication models



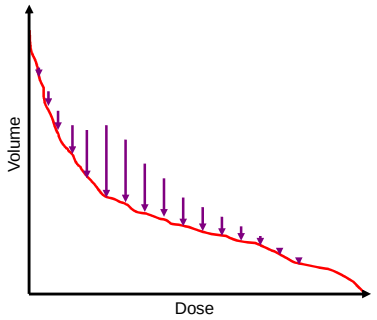
Here, the
tissue has
lost function

At this dose,
we begin to see
changes

OK for the
whole volume

Courtesy M. Alber
Bloemfontein 2006

How does a parallel complication model control the DVH ?



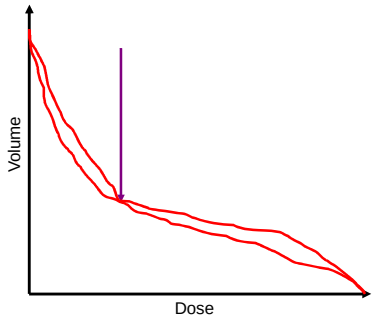
The length of
the weight arrow
grows as

$$\frac{\exp(-\alpha D)}{(1+\exp(-\alpha D))^2}$$

or similar functions

Courtesy M. Alber
Bloemfontein 2006

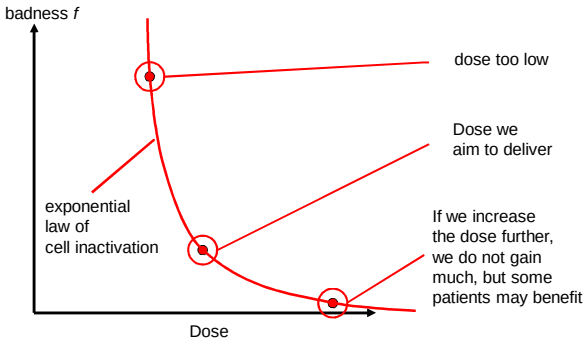
In contrast, a DVH constraint :



The constraint
controls only a
single point

Courtesy M. Alber
Bloemfontein 2006

targets



dose too low

Dose we
aim to deliver

exponential
law of
cell inactivation

If we increase
the dose further,
we do not gain
much, but some
patients may benefit

Courtesy M. Alber
Bloemfontein 2006

AAPM Task Group 166:

The use and QA of biologically related models for treatment planning

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Vladimir Semenenko
Joseph O. Deasy
Kyung-Wook Ken Jee
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TG-166 General Recommendations

- **Outcome-model based cost functions for OARs can be *more effective* towards OAR sparing**
- **Outcome-model based TPS could generate highly non-uniform dose distributions.** Unless for deliberate and tested situations, such highly non-uniformity should be avoided by using min and/or max dose constraints.
- **At present, plan evaluation should base on established dose-volume criteria (3D dose distribution, DVH)**. Biological indices may be used to help select rival plans. Use of absolute estimates of TCP/NTCP as main indicators of plan quality is not warranted at this time.

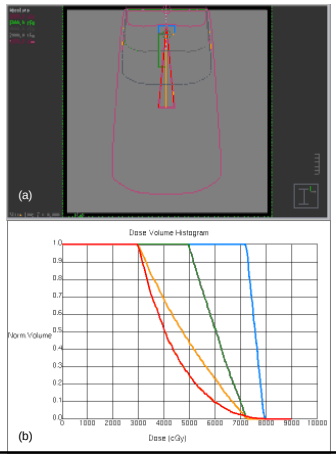
Cautions for using outcome-model based TPS

- **Cold and hot spots**
- **Sensitivity of model parameters**
- **Extrapolation/interpolation between fractionations (EUD, DVH)**

Commissioning of biologically based TPS

- **Verification of model calculations (EUD/TCP/NTCP)**
  - Benchmark phantom (suggested by TG-166)

Benchmark Phantom for verification of EUD, TCP and NTCP calculation



TCP/NTCP calculated for benchmark phantom

Structure	PTV Rectangle	Rectangle 1	PTV Rectangle	Rectangle 1	Rectangle 2	Triangle 1
D50 (Gy)	63.3	44.2	80	75.1	55.3	46
γ	5	1.6	3	2.8	3.1	1.8
α/β (Gy)	10	10	3	3	3	3
Seriality	N/A	N/A	0.18	8.4	0.69	1
Function	TCP	TCP	NTCP	NTCP	NTCP	NTCP
Value (%)	94.1	80.3	26.6	18.1	23.5	29.5

Commissioning of biologically based TPS

- **Verification of model calculations (EUD/TCP/NTCP)**
  - Benchmark phantom (suggested by TG-166)
  - Test cases (head & neck, prostate and brain cases available from TG-166 site)
  - Independent software tools (e.g., CERR (http://radium.wustl.edu/CERR/about.php), BioPlan (Sanchez-Nieto and Nahum), BioSuite (Uzan and Nahum).
- **Double planning for first several cases from each representative tumor site using the outcome-model based TPS and the standard dose-based TPS**

Summary on BBTP:

Outcome-model based treatment planning

- Can be more effective to optimize plan towards normal tissue sparing.
- needs to be implemented with caution.
- requires more data/work for outcome modelling.
- is coming into our clinics and is here to stay !

Acknowledgement

Members of TG-166

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