Outcome-Driven Automated Treatment Planning

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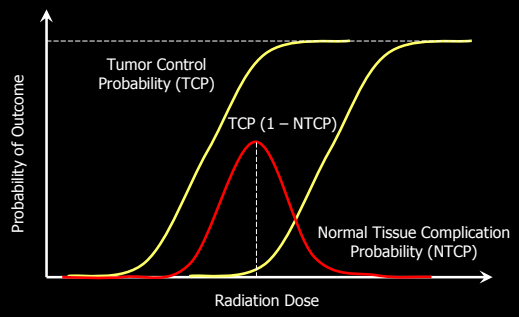
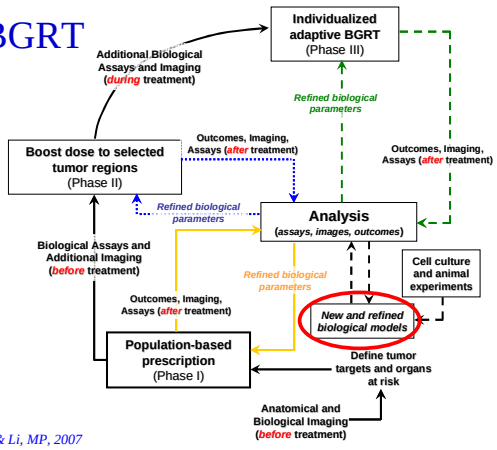
Goal of Radiation Therapy



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)**
- **TCP (Poisson model)**
- **NTCP (LKB, Serial, Parallel)**
- **EUD for both tumors and normal tissues**
- **Clinical Response Models (Maximum likelihood analysis)**

Problems:

Still phenomenological rather than predictive
Unreliable **model parameters (QUANTEC mission)**

Model parameterization based on clinical data

Breast cancer

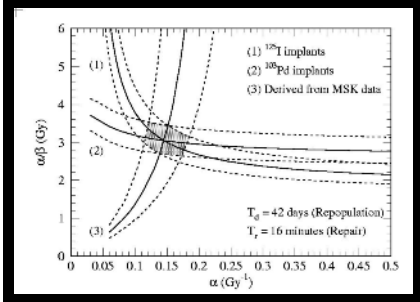
Three Clinical studies:

- **Resch *et al* (2002): BCS then 48Gy + 20Gy LDR or 52 Gy + 9.7Gy HDR. Same TCP.**
- **Fourquet *et al* (1995)*: RT alone*** **58Gy + 20Gy boost using ^{192}Ir LDR or ^{60}Co EBRT TCP_{Ir}=76% vs TCP_{Co}=61%.**
- **Mazeron *et al (1991)*: RT alone 45Gy + 37Gy 192Ir LDR R=0.32-0.49Gy/h TCP=60% R=0.5-0.59Gy/h TCP=72% R=0.6-0.9Gy/h TCP=84%**

$$\alpha = 0.3\ \text{Gy}^{-1}$$
$$\alpha/\beta = 10\ \text{Gy}$$
$$T_{rep} = 1\ \text{hour}$$

Guerrero & Li, PMB 3307,2003

Prostate cancer

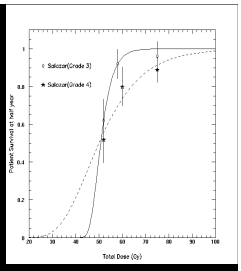


- **α = 0.15±0.05 Gy^{-1}**
- **α/β = 3.1 ± 2.0 Gy**
- **Clonogenic cell number: 10^6~10^7**

Wang, Guerrero & Li, *IJROBP* 2003

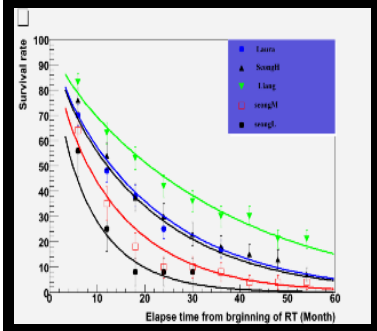
Malignant gliomas

MG	α = 0.06 ± 0.05 Gy^{-1} α/β= 10.0 ± 15.1 Gy
Grade 1&2	α = 0.35 ± 0.07 Gy^{-1} α/β= 4.3 ± 5 Gy
Grade 3	α = 0.11 ± 0.10 Gy^{-1} α/β= 5.8 ± 11.8 Gy
Grade 4	α = 0.04 ± 0.06 Gy^{-1} α/β= 5.6 ± 9.4 Gy



Qi, Schultz, Li , IJROBP, 2006.

Liver Cancer



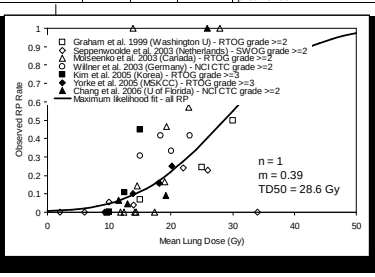
α = 0.029±0.004 Gy^{-1}
α/β = 9.9±1.8 Gy
T_d = 100±18 days

	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

LKB NTCP: Lung

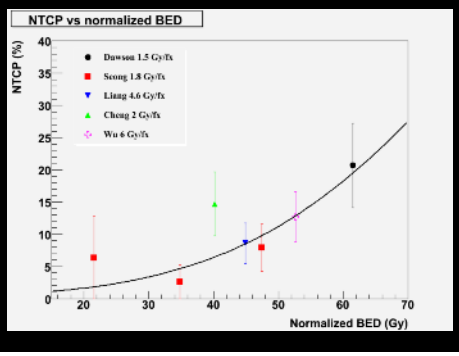
Reference	n	m	TD_{50} (Gy)	Endpoint	Fractionation Scheme
Lung					
Burman *et al.* 1991	0.87	0.18	24.5	Pneumonitis	1.8-2 Gy q.d.
Martel *et al.* 1994	0.87	0.18	28	SWOG grade ≥ 1 RP	1.8-2 Gy q.d.
Kwa *et al.* 1998	1	0.30	30.5	SWOG grade ≥ 2 RP	1-2.7 Gy q.d.; normalized to 2 Gy/fr using α/β of 2.5 or 3 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

Liver NTCP: BED=D(1+d/α/β+f*N)*

D: total dose, d: fraction dose, N: # of fractions



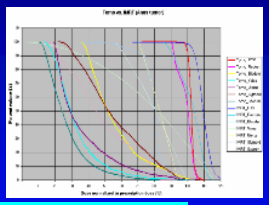
Tai et al, 2008

Use of outcome models in computerized treatment planning

- Plan evaluation
- Plan optimization

Problems to evaluate complex plans with DVH

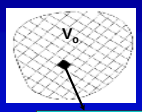
- Complicated anatomy, multiple OARs
- Complicated/crossing DVHs
- Difficult for visual inspection
- Plan merit not quantified
- DVH failure for spatial tumor heterogeneity



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

Equivalent Uniform Dose

EUD: the dose that, if distributed uniformly, will lead to the same biological effect as the actual non-uniform dose distribution. ……..*Niemierko. MP. 1997*



V_i: a volume element

$$S = \sum_i \frac{V_i}{V_o} S(D_i)$$

$$S = \exp(-(\alpha \cdot EUD + \beta d \cdot EUD - 1.4\gamma \frac{EUD}{d}))$$

$$EUD = \frac{-\ln(S)}{\alpha + \beta d - 1.4\gamma / d}$$

Alternatively:

$$\mathrm{EUD} = \left(\sum_i v_i D_i^a \right)^{\frac{1}{a}},$$

EUD-based Figure-of-merit index (*fEUD*)

$$fEUD = \frac{1.0}{1.0 + k \cdot \frac{\sum_{i=1}^{n} \omega_i \cdot EUD_{OAR}^{i}}{\sum_{j=1}^{m} \omega_j \cdot EUD_{Tumor}^{j}}}$$

n, m : number of OARs and targets;
ω_i, ω_j : weighting factors for each OAR and target;
k : the relative importance factor between tumor and OAR.

- ***Condensing complex DVHs into one # (range: 0-1)***
- ***The larger fEUD, the superior the plan***

Plan Optimization

- Cost Functions
  - Mathematical forms of treatment goals
  - Increase if goal is not met
  - Good if value less than or equal to 0
- Physical (dose-based) cost functions
  - Overdose/underdose volume constrains
  - Maximum/minimum doses
- Biological (dose-response model based) cost function.
  - Target/OAR EUDs
  - TCP/NTCP.

Two commercial biological TPS

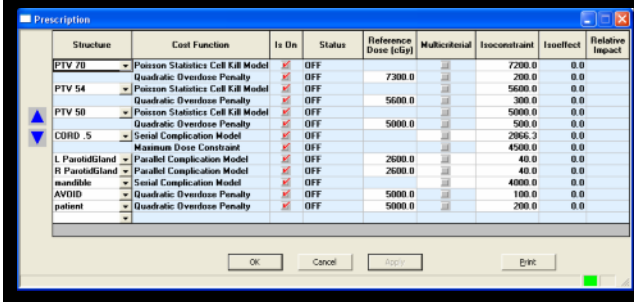
CMS Monaco

Phillips Pinnacle

Models used in Monaco

	Model		
	Name / description	**Parameters required**	**Comments**
Tumor	**Poisson cell kill model**	**1. Cell sensitivity (0.1-1.0) 2. EUD prescription (Gy)**	**Mandatory cost function for targets; no penalty for hot spots**
OAR	**Serial complication model**	**1. Power law exponent a (≥ 1) 2. EUD (Gy)**	**Penalizes for hot spots**
	Parallel complication model	**1. Reference dose (Gy) 2. Power law exponent a (≥ 1) 3. Mean organ damage (%)**	**Effective for reducing mean organ dose**

Monaco



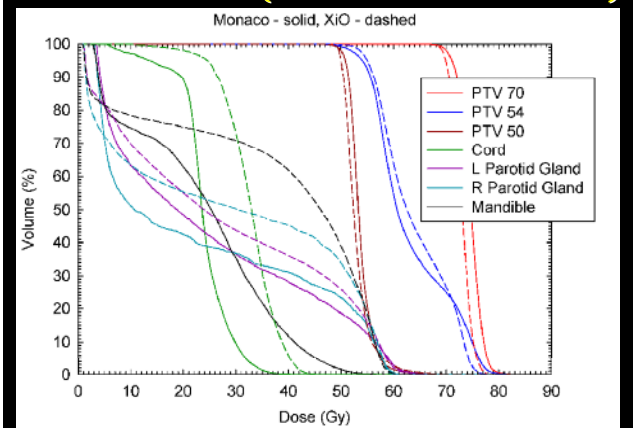
Models used for optimization in Pinnacle

Structure	model	Parameters	Objectives/ constraints	Comments
Target	**Min EUD**	**Volume parameter (a<1)**	**EUD**	**Penalizes for too low EUD**
	Target EUD	**Volume parameter (a<1)**	**EUD**	**Penalizes for any deviation from the desired EUD**
OAR	**Max EUD**	**Volume parameter (a≥1)**	**EUD**	**Penalized for too high EUD; can be used with both serial and parallel structures**

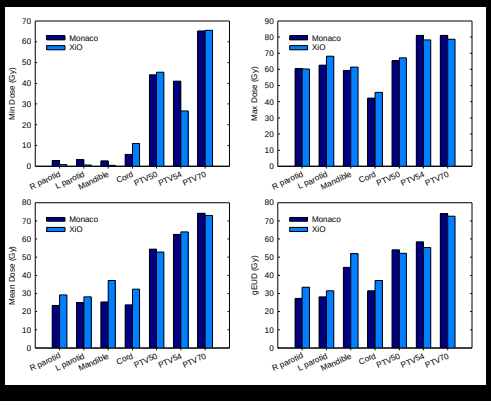
Models used for plan evaluation in Pinnacle

Tool	Structure type	Name/description	Parameters	Comments
NTCP/ TCP Editor	Target	Empirical TCP model	D_{50}, m	Sigmoid curve represented by the integral of a normal distribution
	OAR	Lyman-Kutcher model	D_{50}, m, n	Database of model parameters supplied
Biological Response panel	Target	Poisson/LQ-based TCP model	D_{50}, Gamma, Alpha/Beta	Database of model parameters supplied
	OAR	Källman S-Model	D_{50}, Gamma, Alpha/Beta, Seriality	Database of model parameters supplied
	Multiple targets	Composite TCP	---	$TCP = \prod_i TCP_i$
	Multiple OARs	Composite NTCP	---	$NTCP = 1 - \prod_i (1 - NTCP_i)$
	Targets & OARs	Uncomplicated tumor control, P_+	---	$P_+ = TCP - NTCP$

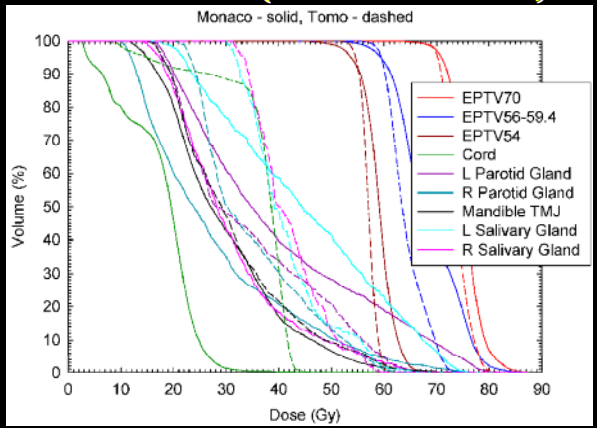
Case 1 – H&N (XiO IMRT vs Monaco)



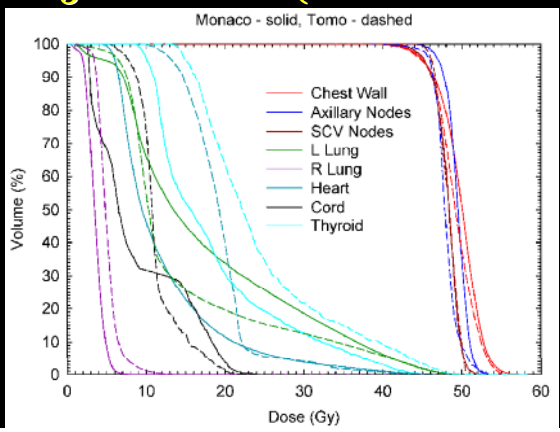
Case 1: H & N



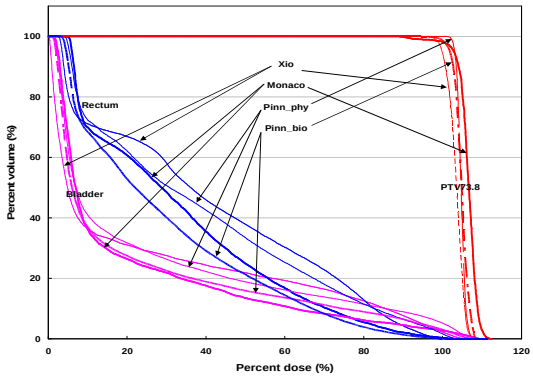
Case 2: H&N (Tomo vs Monaco)



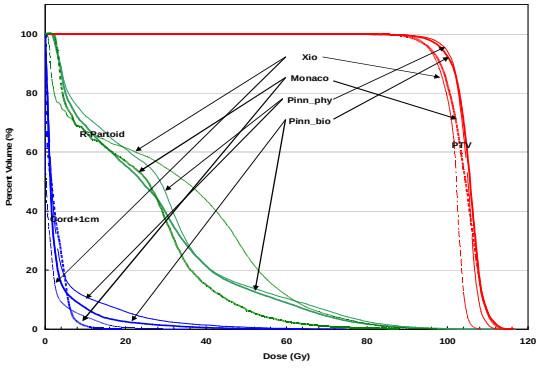
Case 3 – Chest Wall (Tomo vs Monaco)



Pinnacle vs Monaco: Prostate



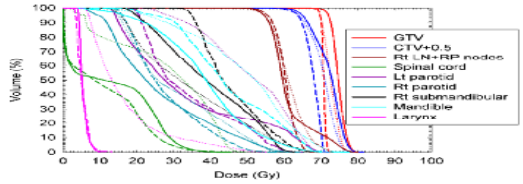
Monaco vs Pinnacle: H & N



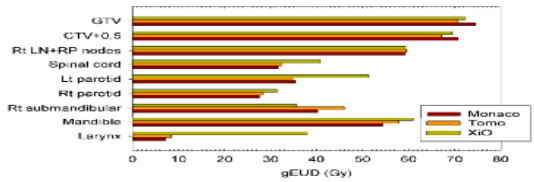
Pinnacle vs. Monaco: *f*EUD

	XiO	Monaco	Pinn_Phy	Pinn_Bio
fEUD (H&N)	0.38	0.42	0.37	0.40
fEUD (Prostate)	0.26	0.31	0.27	0.29

Monaco vs Tomo vs XiO
H&N site 1 – oropharynx



Comparison of DVHs in Monaco (solid lines), Tomo (dashed lines) and XiO (dotted lines) plans.



H&N Monaco vs Tomo vs XiO: *fEUD*

Site	Monaco	Tomo	XiO
1. Oropharynx	0.51	0.49	0.44
2. Paranasal sinus	0.12	0.13	0.08
3. Nasal cavity	0.12	0.19	0.16
4. Oral cavity	0.52	0.50	0.47
5. Larynx	0.771	0.766	0.73
6. Nasopharynx	0.27	0.25	---

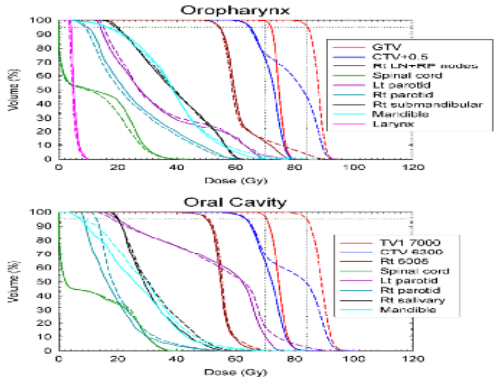
Greatest *fEUD* Smallest *fEUD*

Monaco vs Tomo vs XiO
Heterogeneity Index (HI) for primary target

Site	Monaco	Tomo	XiO
1. Oropharynx	1.16	1.03	1.13
2. Paranasal sinus	1.19	1.08	1.22
3. Nasal cavity	1.45	1.06	1.31
4. Oral cavity	1.23	1.04	1.14
5. Larynx	1.17	1.09	1.15
6. Nasopharynx	1.23	1.15	---

Greatest HI Smallest HI

Dose escalation to GTV using Monaco



DVHs corresponding to a conventional (GTV dose = 70 Gy; solid lines) and escalated dose (GTV dose = 84 Gy; dashed lines) plans.

Why biologically-based is better

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

The standard formulation of biological cost functions

All cost functions can be expressed as

$$F = \frac{1}{N}\sum_{i=1}^{N} f(D_i)$$

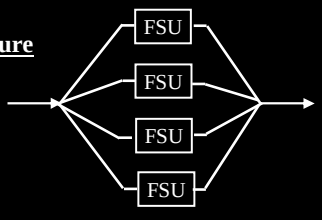
where

D_i	Dose in volume element *i* of an organ/tumour
N	Number of volume elements
$f(D)$	objective density = badness factor

The properties of f fully define the behaviour of the cost function !

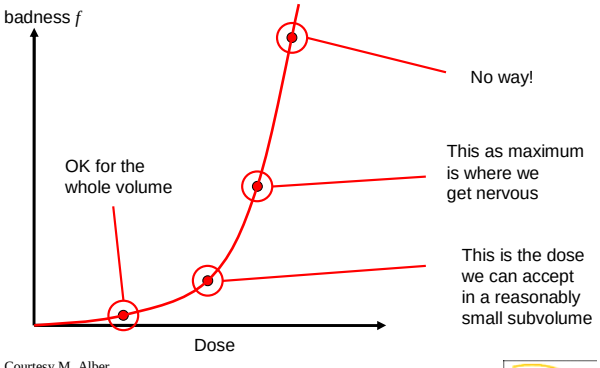
Serial structure (spinal cord, rectum)

Parallel structure

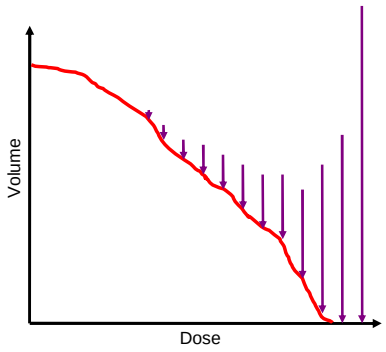


lung, liver

How to make a biological cost function: serial models



How does a serial complication model control the DVH ?



The length of the weight arrow grows as

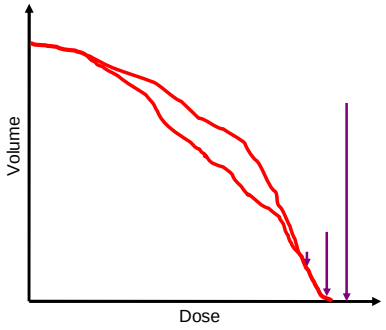
D^{k-1}

$\exp(\alpha D)$

or similar functions

Courtesy M. Alber
Bloemfontein 2006

In contrast, a quadratic penalty:



DVH control only for doses greater than threshold

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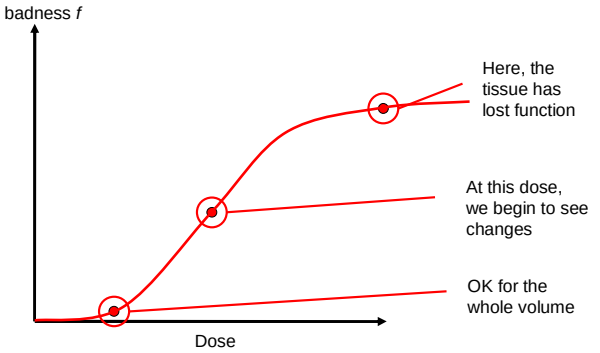
Not all organs are serial: parallel complication models



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

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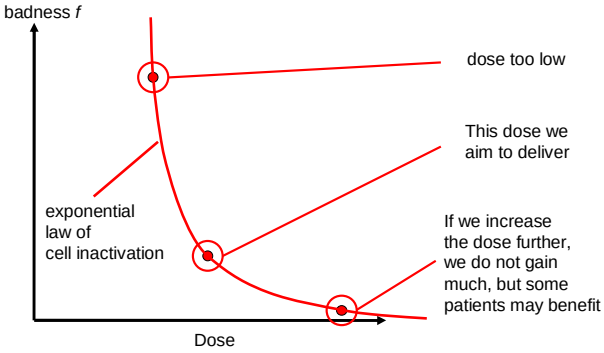
targets



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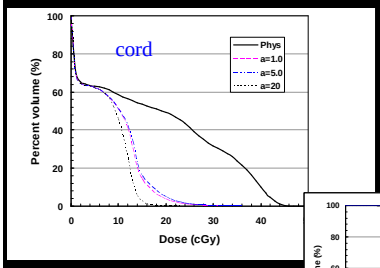
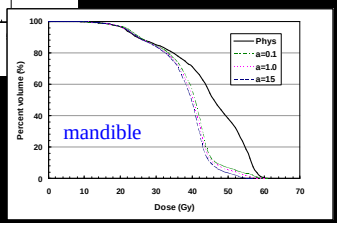
Dependence of model parameter



Pinnacle



Cautions for using BBTP

- Cold and hot spots (evaluating with DVHs and 3D dose distribution)
- Sensitivity of model parameters
- Extrapolation/interpolation between fractionations (EUD, DVH)
- ……

Evolution of biologically based TPS

Evolution stage	Optimization strategy	Evaluation strategy	Example
0	Dose-volume-based objectives/constraints	DVHs EUD/TCP/NTCP	The majority of TPS currently in use
1	EUD for OARs, EUD+dose-constraints for targets	DVHs and/or relative values of TCP/NTCP/P_+	CMS Monaco Philips Pinnacle
2	EUD	Absolute values of TCP/NTCP/P_+	Future developments
3	Absolute values of TCP/NTCP/P_+	Absolute values of TCP/NTCP/P_+	Future developments

AAPM Task Group 166:

THE USE AND QA OF BIOLOGICALLY RELATED MODELS FOR TREATMENT PLANNING

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Summary:

Biologically based treatment planning

- Is more effective to generate plans with better normal tissue sparing
- Needs to be implemented with cautions
- Requires more data/work for outcome modelling
- Is coming into clinic and is here to stay !

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