Implications of a mechanistic tumor control probability model applied to hypofractionated radiotherapy

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But first, can we use a simple model to understand TCP for standard Fx?

How can we estimate TCP for each patient?: *using an EUD model to describe TCP*

The 'cEUD' model

- EUD = same rate of LC as EUD given uniformly for tumor of vol. = Vref.
- EUD is less sensitive to parameter assumptions than TCP
- Using Niemierko's proposed model (1997)
- Cell-kill based, so we denote the model 'cEUD' vs. gEUD.

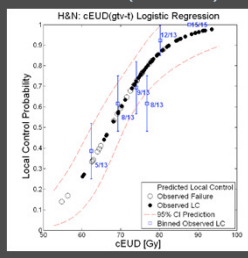
The cEUD equation

- Assume tumor homogeneity
- Single parameter model (SF2)

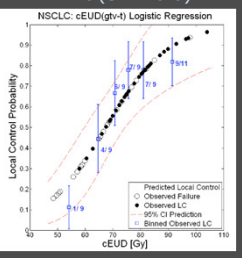
$$\mathrm{cEUD} = \frac{D_{ref}}{\ln(SF_2)} \ln\left[\frac{1}{V_{ref}} \sum_{i=1}^{bins} V_i \, SF_2^{\left(D_i / D_{ref}\right)}\right]$$

cEUD applied to Washington University data

WUSTL H&N original model fit (SF2=0.8)

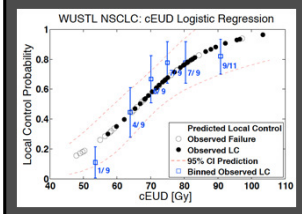


WUSTL lung original model fit (SF2=0.8)



But what about the high value of SF2?

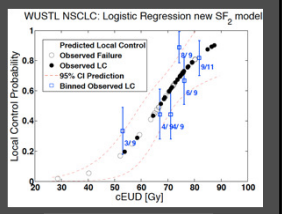
WUSTL NSLC fit: SF2 =0.8



But this is an unrealistically high SF2!

Perhaps it reflects increasing hypoxia with increasing volume.

Modified cEUD fit

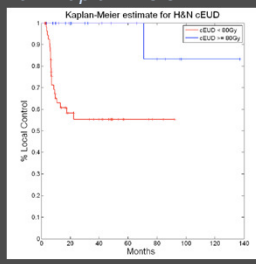


$$SF_{2\,effective} = SF_2\left(1 + k\frac{V_T}{V_{ref}}\right)$$

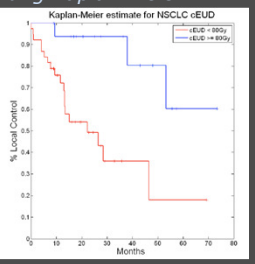
Steeper response, modestly better fit

How does this separate actuarial outcomes?

H&N Kaplan-Meier



Lung Kaplan-Meier



What does the basic competition between cells for resources imply about the response to radiotherapy? *We need a model.*

Goal: create a model of minimal complexity that captures

- Proliferation
- Hypoxia
- The competition for resources
- Empirically established concepts of growth fraction, cell loss factor, cell kill, and radioresistance due to hypoxia

Model uses

- Hypotheses generating: what are we missing? What seems to be implied?
- Integration of concepts
- Future: potential refinement to make actual predictions
- Possible guide to better understanding data lon standard Fx, SBRT, and FDG-PET vs. outcome.

State-based Simulations of Tumor Response to Radiotherapy

Jeho Jeong

Advisors: Dr. J. O. Deasy & Dr. S. K. Loyalka

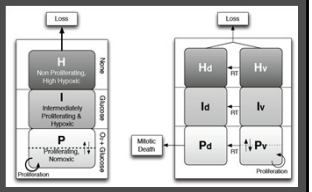
Apr 20th, 2012

A three compartment model to simulate the impact of micro-environmental conditions on radiotherapy response (J.Jeong)

Assumptions

- Assume oxygen and glucose can 'feed' a constant number of cells: i.e. blood supply is constant
- Proliferative component (P) of cells with adequate oxygen and glucose (a given % are proliferating)
- An extremely hypoxic state ('Denekamp hypoxia') where cells have neither adequate oxygen or glucose; cells are dying
- An intermediate compartment (I) where oxygen is low but glucose is adequate for survival.

The 'PIH' model schematic

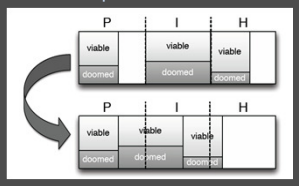


Before RT During RT

Assume re-compartmentalization: *this leads to reoxygenation*

- Assume oxygen and glucose can 'feed' a constant number of cells
- Then re-distribution constantly occurs that assumes P is the preferred state, then I, then H.
- This implies a 'reoxygenation' process

After an (exaggerated) time step:



$$\alpha_X = \alpha_P / OER_X \quad \text{and} \quad \beta_X = \beta_P / OER_X^2$$

$$SF_{hyp} = \exp\left(-\frac{\alpha_{eff}}{OER_{eff}} d - \frac{\beta_{eff}}{OER_{eff}^2} d^2\right) = \exp\left(-\frac{\alpha_{ref}}{OER} d - \frac{\beta_{ref}}{OER^2} d^2\right)$$

Accounting for the OER

(Carlson and Stewart, Med Phys 2006)

How do we find the initial clonogen distributions? *The clonogen distribution is (almost) fixed by knowing CLF and GF.*

The PIH model has nice properties

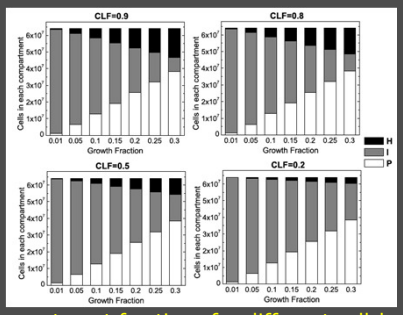
- A more complicated model would be underspecified by CLF and GF
- A less complicated model cannot include cell loss and GF
- In this sense, the I-state is *implied* by CLF+GF.

The equations

$$N^p(t) = \frac{GF}{f_{pp}^p} \cdot N^{total}(t)$$

$$N^{dl}(t) = CLF \cdot GF \cdot \frac{T_{1/2,death}}{T_C} \cdot N^{total}(t)$$

$$N^I(t) = \left[1 - GF\left(\frac{1}{f_{pp}^p} + CLF \cdot \frac{T_{1/2,death}}{T_C}\right)\right] \cdot N^{total}(t)$$



Compartment fractions for different cell-loss factors and growth fractions

Parameter values from the literature were used that *also* resulted in results consistent with clinical data.

Table 1. The parameters used to demonstrate the model for HNSCC

Parameters	Values
Tumor cell density (ρ_t)	10^6 mm^{-3} (Joiner and van der Kogel 2009)
Volume of a tumorlet (v_t)	64 mm^3 (based on typical PET voxel size)
Total number of cells in a tumorlet (n_t)	6.4×10^7 ($\rho_t \cdot v_t$)
Stem cell fraction (f_s)	0.01 (Hemmings 2010)
Cell cycle time (T_c)	2 days (Joiner and van der Kogel 2009)
Initial proliferation fraction in P ($f^0_{p,a}$)	0.5[a]
Cell loss half-time in H ($T_{1/2,loss}$)	2 days (Ljungkvist *et al* 2005)
Survival rate of progeny after mitosis (k_a)	0.3[a]
Linear radiosensitivity coefficient (α_p)	0.41 Gy^{-1} (Søvik *et al* 2007)
Quadratic radiosensitivity coefficient (β_p)	0.041 Gy^{-2} (Søvik *et al* 2007)
OER of I compartment (OER_I)	1.2, 1.37 or 2.0[a]
OER of H compartment (OER_H)	1.37 (Chan *et al* 2008)
Lysis half-time ($T_{1/2,lysis}$)	3 days[a]
Time step of the calculation (Δt)	15 min

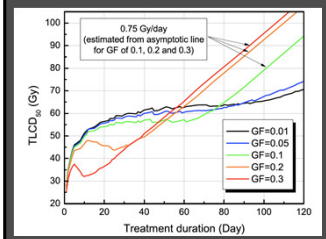
[a] Assumed parameters

PIH-model parameters from the literature

Parameter values from the literature were used that *also* resulted in results consistent with clinical data.

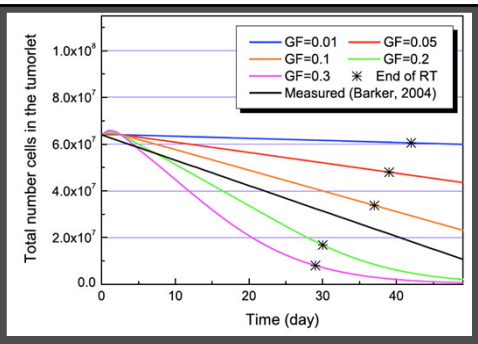
What does the model imply with respect to overall time?

Tumorlet-D50 for CLF = 0.9; daily delivery simulation



Simulation results show

- 'Dog-leg effect' due to reoxygenation
- Loss of local control of 0.75 Gy/day, similar to clinical data
- But depends critically on assumed GF (less dependent on CLF)
- Note that tumor heterogeneity tends to matter least at ~7 wks



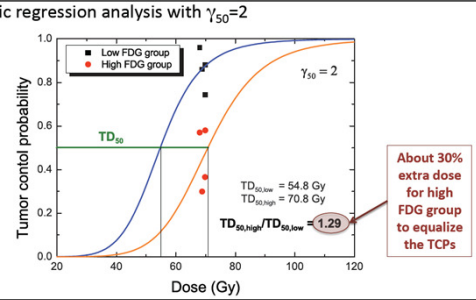
Simulated regression patterns

2 Gy/day.

State-driven mathematical model simulations of tumor response to radiotherapy: *how does high FDG uptake relate to classical radiobiological principles?*

Summary analysis of local control data vs.FDG/SUV status

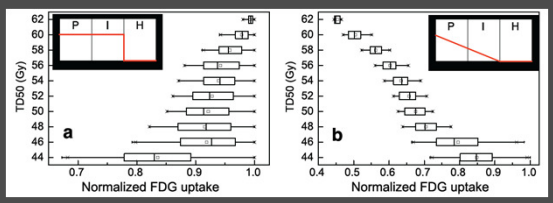
- Logistic regression analysis with $\gamma_{50}=2$



Predicted relationship between FDG uptake and TCD50: *what is the effect of differing FDG uptake vs. compartment?*

Equal P-state and I-state uptake

Preferential *P-state* uptake

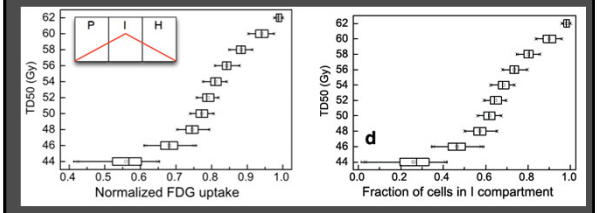


Neither result agrees with clinical observation

Predicted relationship between FDG uptake and TCD50: *what is the effect of differing FDG uptake vs. compartment?*

Preferential I-state uptake

So FDG uptake reflects cells density in I-state



Agrees with clinical observation

Modeling stereotactic body radiation therapy (SBRT) including cell cycle-dependent radiosensitivity, hypoxia, reoxygenation and proliferation: are SBRT local control rates explainable based on classical radiobiological factors?

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SBRT & Radiobiology

- Insufficient radiobiological understanding
- Outcome usually analyzed in terms of biologically effective dose (BED)
  - Does not consider established radiobiological factors (e.g., hypoxia, reoxygenation, repopulation…)

Objective

- **Simulate SBRT tumor response considering classical radiobiological factors**
  - **Using the state-based tumor response model**
- **Answer the question:**

"Is SBRT tumor response explainable based on classical radiobiological factors?"

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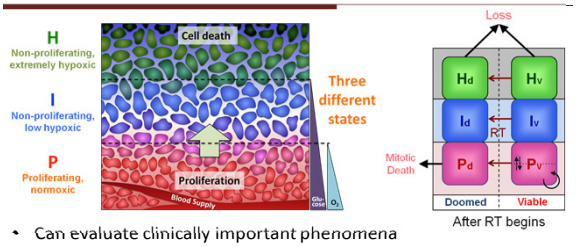
State-based tumor response model



- Can evaluate clinically important phenomena
  - Fraction size effect
  - Tumor reoxygenation effect
  - Tumor repopulation effect
  - Tumor regression pattern

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Inclusion of cell cycle effect into model

- Cell cycle effects: might be considerable at high fractional dose
- Radiosensitivity
  - Cell cycle dependent (G2/M > G1 > S)
  - No cell cycle redistribution within a fractional dose
  - **Fraction size dependent: reduced for high fractional dose**
- Oxygen enhancement ratio (OER)
  - Proliferating cells (*P-comp*): in cell cycle → varying radiosensitivity
  - Hypoxic cells (*I-* & *H-comp*): resting phase (G0/G1) → fixed radiosensitivity
  - **Fraction size dependent: reduced for high fractional dose**
- Cell cycle effect in the model
  - Fraction-size-dependent effective radiosensitivity
  - Fraction-size-dependent effective OER

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RADIATION RESEARCH 36, 45–54 (1968)

X-Ray Sensitivity of Synchronized Chinese Hamster Cells Irradiated during Hypoxia[1]

JACK KRUUV[2] AND WARREN K. SINCLAIR

Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois

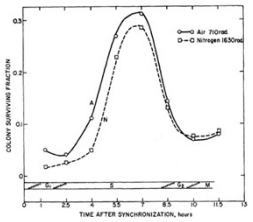

FIG. 2. Colony surviving fraction after irradiation of cells at different points in the cell cycle, either in air with 710 rads (curve *A*) or in nitrogen with 1630 rads (curve *N*). The approximate lengths of the fractions of the cell cycle (as determined by pulse labeling with ^{3}H-thymidine) are indicated at the foot of the graph. Survival data were not corrected for the average cellular multiplicity (1.78) during the first cell cycle.

Model parameters for Lung cancer

Parameter	Value
Growth fraction (GF)	0.25[a]
Cell loss factor (CLF)	0.92[a]
Cell cycle time (T_C)	2 days (Joiner & Kogel, 2009)
Fraction of cells in P compartment (f^P)	50 %[b]
G1-phase in P (f_{G1})	28 % (Volm *et al.*, 1985)
S-phase in P (f_S)	12 % (Volm *et al.*, 1985)
G2/M-phase (f_{G2M})	10 % (Volm *et al.*, 1985)
Fraction of cells in I compartment (f^I)	27 %[b]
Fraction of cells in H compartment (f^H)	23 %[b]
Ratio of alpha of G1- to S-phase (α_{G1}/α_S)	2[c]
Ratio of alpha of G2/M- to S-phase (α_{G2M}/α_S)	3[c]
Reference radiosensitivity at 2 Gy/fx (α_{ref})	0.35 Gy^{-1} (Mehta *et al.*, 2001)
Alpha-beta ratio (α/β)	3 or 10 Gy[c]
Reference OER of I compartment at 2 Gy/fx ($OER_{ref,I}$)	2[c]
Reference OER of H compartment at 2 Gy/fx ($OER_{ref,H}$)	1.4 (Chan *et al.*, 2008)

[a] estimated from potential doubling time and volume doubling time measured for lung cancer (Tinnemans *et al.*, 1993; Shibamoto *et al.*, 1998)
[b] estimated from GF and CLF of the model
[c] assumed parameters

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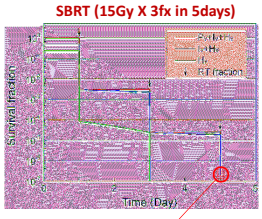
Model-predicted equivalent dose at 2 Gy/fx

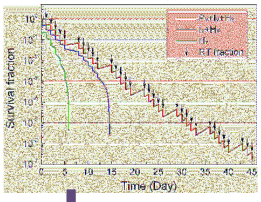
- Find dose required to achieve the same level of survival in 2 Gy/fx

SBRT (15Gy X 3fx in 5days)



Survival Fraction (SF) = 2.3×10^{-7}

Conventional (2 Gy/fx, 5fx/wk)



$EQD_{2,model}$ = 66 Gy

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Clinical outcome of SBRT

escalating doses from 24Gy to 72Gy (all 3 fractions)

TABLE 2. Dose Fractionation Regimens and Crude Local Control in Phase I & II Studies

	Patient (#)	Median FU (mo)	Tumor Size (cm)	Prescribed Dose/# Fractions	Prescription	BED_{tm}/EQD_2 (Gy_{10})	$BED_{periphery}/EQD_2$ (Gy_{10})	Crude Local Control
McGarry et al 05[41]	47	15.2	≤7	MTD 66 Gy/3	80% isodose at the PTV periphery	309.4/257.8	211.2/176	78.7%
Le et al 06[42]	Stage I: 20/32	18	≤6.2 Median 3.9	15–30 Gy/1	100% dose at the PTV periphery	64.1–215.6/53.4–179.7	37.5–120/31.25–100	75%
Onimaru et al 03[43]	Stage I: 25/45	18	≤6	60 Gy/8 48 Gy/8	Isocenter	105/87.5 76.8/64	76.8/64 56.8/47.3	80%
Nagata et al 05[44]	63	39	n/a	48 Gy/4	Isocenter	105.6/88	n/a	98%
Zimmermann et al 06[45]	68	17	n/a	37.5 Gy/3 35 Gy/5	60% isodose at the PTV periphery	193.4/161.2 126.8/105.7	84.4/70.3 59.5/49.6	94%
Hoyer et al 06[46]	40	29	≤6	45 Gy/3	Isocenter	112.5/93.75	60.5/50.4	92.5%
Fakiris et al 09[47]	70	50.2	≤7	T1: 60 Gy/3 T2: 66 Gy/3	80% isodose at the PTV periphery	262.5/218.8 309.4/257.8	180/150 211.2/176	94.3%
Baumann et al 09[48]	57	35	≤5 Median 2.5	45 Gy/3	67% isodose line at PTV periphery	219.4/182.8	112.5/93.75	93%

(Fowler et al., IJROBP 2006)

Reference	Patient setup	PTV margin (cm) (axial/long)	Treatment Duration	RTP system
McGarry et al. 05	SBF in VP+ DC (≤1cm)	0.5/1.0	once daily with fractions separated by 2-3 days	RenderPlan 3-D planning system (Elekta) Forward-planning intensity modulation for parabolic dose profiles across each beam
Le et al. 06	A vacuum-set moldable Styrofoam	2mm (first 10 pts) → 5mm	single fraction (2-6 hours with CyberKnife)	A radiosurgical treatment plan was generated based on tumor location and geometry
Onimaru et al. 03	None	3 CTs: 0.5/1.0 (add 0.5cm for 1 CT)	2 wks	Focus (Computerized Medical Systems) with considerations made for inhomogeneity in pulmonary density
Nagata et al. 05	SBF + DC	0.5/0.8-1.0	median 12 days (5-13)	CADPLAN Ver 3.1 & ECLIPSE Ver 7.1(Varian)
Zimmermann et al. 06	vacuum couch and low pressure foil	Individual	5 days (3-10)	Siemens Helax system with pencil beam algorithm
Hoyer et al. 06	Aarhus: SBF + DC Copenhagen(8 pts): custom-made VP	0.5/1.0	5-8 days	Aarhus: Helax, TMS (Nucletron) Copenhagen: CadPlan Plus/Eclipse (Varian)
Fakiris et al. 09	SBF in VP+ DC (≤1cm)	0.5/1.0	once daily with fractions separated by 2-3 days	3D RTP w/o non-homogeneity correction
Baumann et al. 09	SBF + DC (≤0.5cm)	CTV: 0.1-0.2cm PTV: 0.5-1.0/1.0	every second day, median 5 days (4-15 days)	Helax-TMS (Nucletron) or Eclipse (Varian) Pencil beam algorithms with heterogeneity correction

SBF: Stereotactic Body Frame (Elekta, Stockholm, Sweden)
VP: Vacuum Pillow
DC: Diaphragm Control

Several typical SBRT regimes

$\alpha/\beta = 10$

EQD_2 and cell kill effect are too low to explain clinically observed high local control rate

SBRT regimen	BED (Gy)	NTD_2 (Gy)	$EQD_{2,model}$[a] (Gy)	$EQD_{2,mod}/NTD_2$	Estimated SF at the end of RT
26 Gy × 1 fx (single)	93.6	78	46	59 %	1.1×10^{-5}
30 Gy × 1 fx (single)	120	100	58	58 %	8.2×10^{-7}
12 Gy × 3 fx (in 9 days)	79.2	66	48	73 %	4.3×10^{-8}
15 Gy × 3 fx (in 5 days)	112.5	93.75	66	70 %	2.3×10^{-7}
20 Gy × 3 fx (in 8 days)	180	150	108	72 %	1.2×10^{-10}
22 Gy × 3 fx (in 8 days)	211.2	176	126	72 %	5.4×10^{-12}
12 Gy × 4 fx (in 12 days)	105.6	88	78	89 %	2.3×10^{-8}

BED: biologically effective dose, NTD_2: normalized total dose at 2 Gy fraction, SF: survival fraction
[a] model predicted equivalent dose in 2 Gy/fx including cell cycle, proliferation and hypoxia effects

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Very low α/β ratio

$\alpha/\beta = 3$

SBRT regimen	BED (Gy)	NTD_2 (Gy)	$EQD_{2,model}$[a] (Gy)	$EQD_{2,model}/NTD_2$	Estimated SF at the end of RT
26 Gy × 1 fx (single)	251.3	150.8	68	45 %	2.1×10^{-11}
30 Gy × 1 fx (single)	330	198	88	44 %	2.2×10^{-14}
12 Gy × 3 fx (in 9 days)	180	108	56	52 %	8.0×10^{-10}
15 Gy × 3 fx (in 5 days)	270	162	78	48 %	4.4×10^{-13}
20 Gy × 3 fx (in 8 days)	460	276	130	47 %	9.3×10^{-21}
22 Gy × 3 fx (in 8 days)	550	330	154	47 %	3.1×10^{-24}
12 Gy × 4 fx (in 12 days)	240	144	82	57 %	1.3×10^{-13}

BED: biologically effective dose, NTD_2: normalized total dose at 2 Gy fraction, SF: survival fraction
[a] model predicted equivalent dose in 2 Gy/fx including cell cycle, proliferation and hypoxia effects

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Interim Summary

- Included cell cycle effect into the state-based model
  - Based on fraction-size-dependent effective radiosensitivity and effective OERs
  - In single shot Tx, cells in resistant cell-cycle phases may affect outcome more than hypoxic cells
- Model predicted EQD_2 & cell-kill effect (for α/β=10): significantly lower compared to clinical outcome
- Consistent with very low α/β (<3) & with LQ model validity to 25 Gy.
- Other non-classical effects might exist in SBRT
  - Vascular endothelial cell apoptosis (Garcia-Barros *et al.*, 2003)
  - Immune stimulation after SBRT (Lee *et al.*, 2009)

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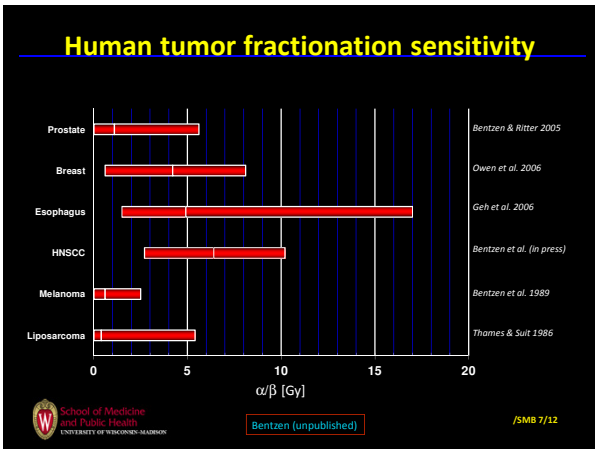
Questionable assumptions

- LQ holds to high doses, apart from other mechanisms
  - Makes it more likely that cell kill is over-estimated
- Differences in LQ parameters over the cell cycle
  - Cells in late-S may have a different high-dose response
  - Late-S survival may be crucial
- Alpha/beta might be low for NSLC



"No matter what the fractionation scheme is, local control is ~90%"

- Likely key issue is hitting all the disease
- Implies over-treatment for many dose fractionation schemes
- Many studies (e.g., Timmerman's IU experience) were pre-image guidance and pre-accurate dosimetry.