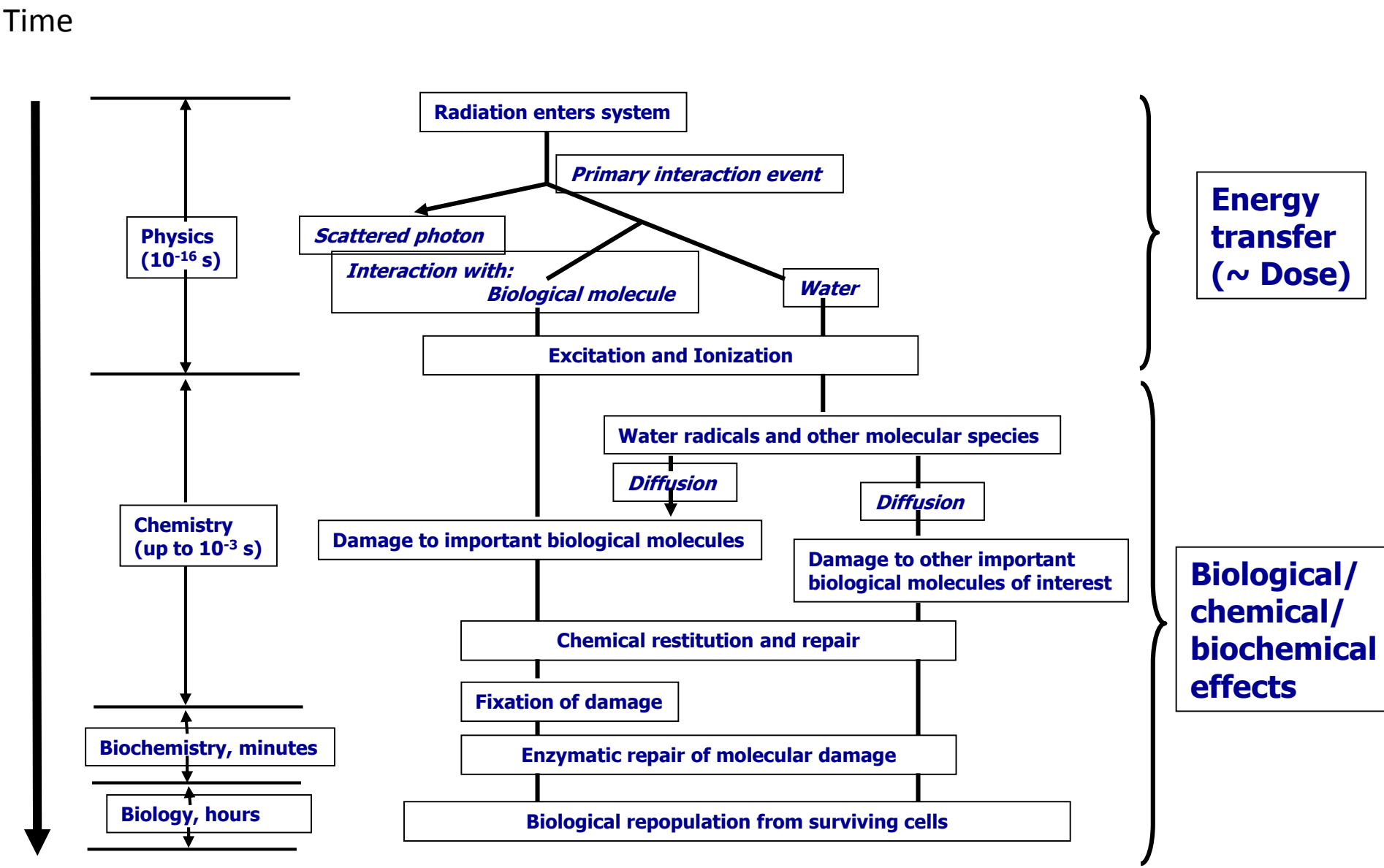
Classical Radiobiology and Normal Tissue Complication Analysis

Kamil M. Yenice, PhD

University of Chicago

From energy transfer to final biological damage



A. Vitkin, PhD (Univ. of Toronto)

Overview

- Review of Classical Radiobiology
  - Fractionation – 4Rs
  - Cell survival curves and modeling
    - Multi-target model
    - Linear quadratic (LQ) model
    - BED Concept
- NTCP

Rationale For Fractionation: 4Rs

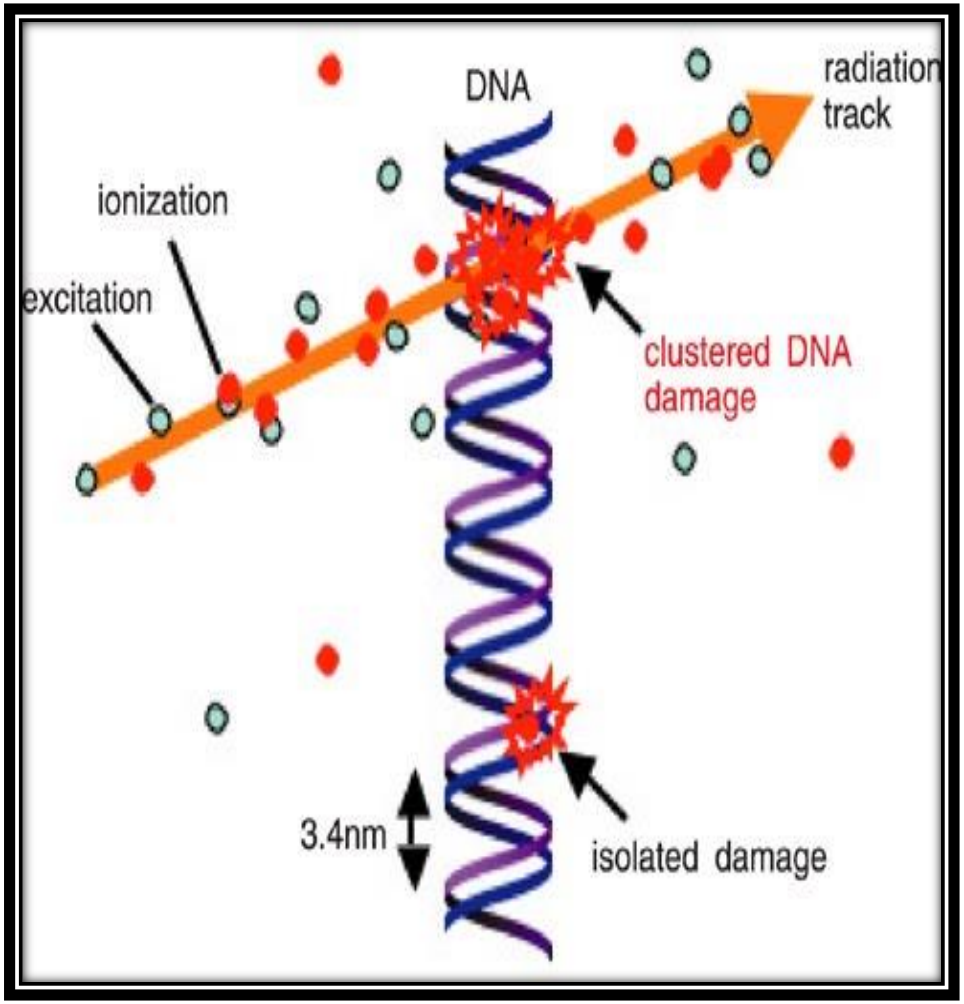
- **R**epair
  (few hours)
- **R**edistribution
  (few hours)
- **R**eoxygenation
  (hours to few days)
- **R**epopulation
  (5-7 weeks)

→ **R**adiosensitivity

Withers HR (1975), Adv Radiat Biol5: 241-7

Radiation Induced DNA Damage

- Radiation generates highly reactive oxygen species from water molecules. They are short lived and rapidly interact with biomolecules in cells.
- The clusters of ionizations occurring at the end of electron tracks, if happened within a few base pairs of DNA are very important in causing DNA damage



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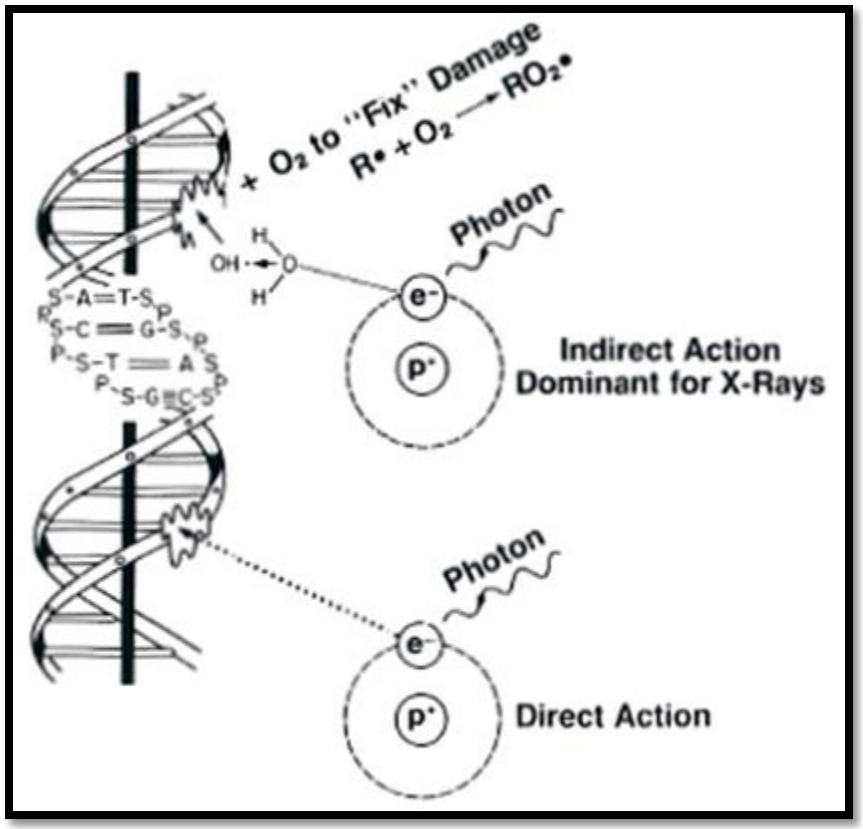
Types of Damage

- Lethal – irreversible, irreparable, leads to cell death (loss of reproductive capacity)
- Sub-lethal (SLD*) – can be repaired within hours unless additional SLD occurs (such as a second dose of radiation); represents shoulder on cell survival curve.
- Potentially Lethal Damage – can be modified by the post-irradiation environment

*Repair of SLD spares late responding normal tissue preferentially

Reoxygenation

- Increases tumor damage, no effect in normal tissues



- Oxygen "fixes" the damage (making it permanent)
- Extends the lifetime of free radicals
- Fractionation allows O_2 to diffuse into the usually hypoxic center of an expanding tumor during the interval between fractions, and thus enables more tumor killing during subsequent treatment

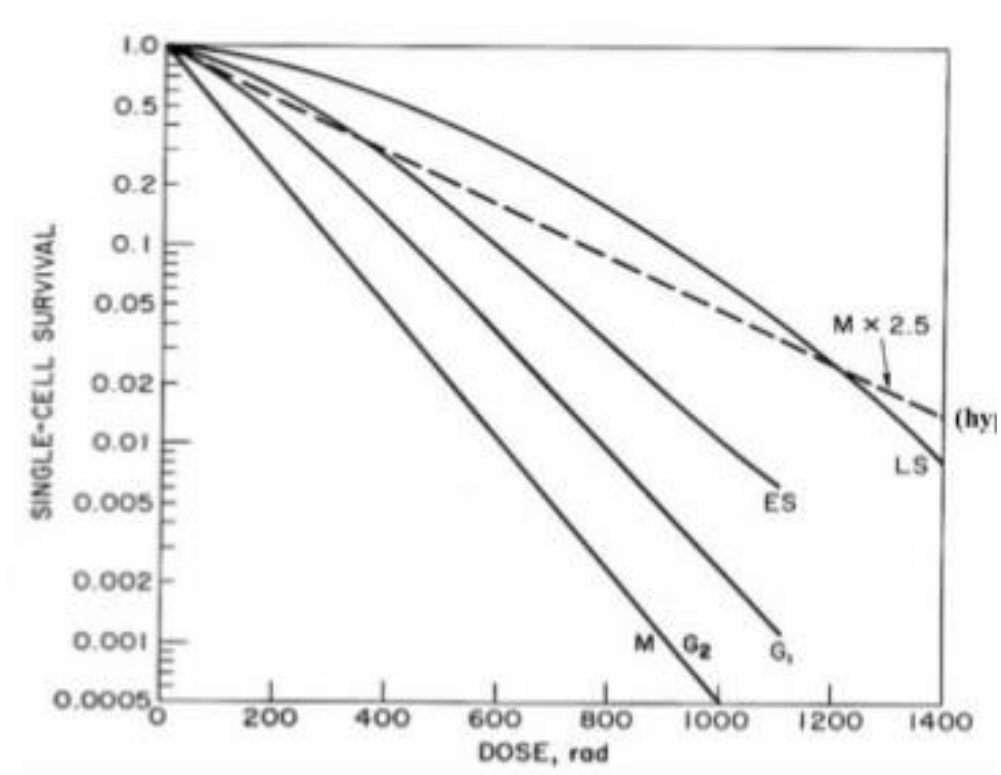
Repopulation

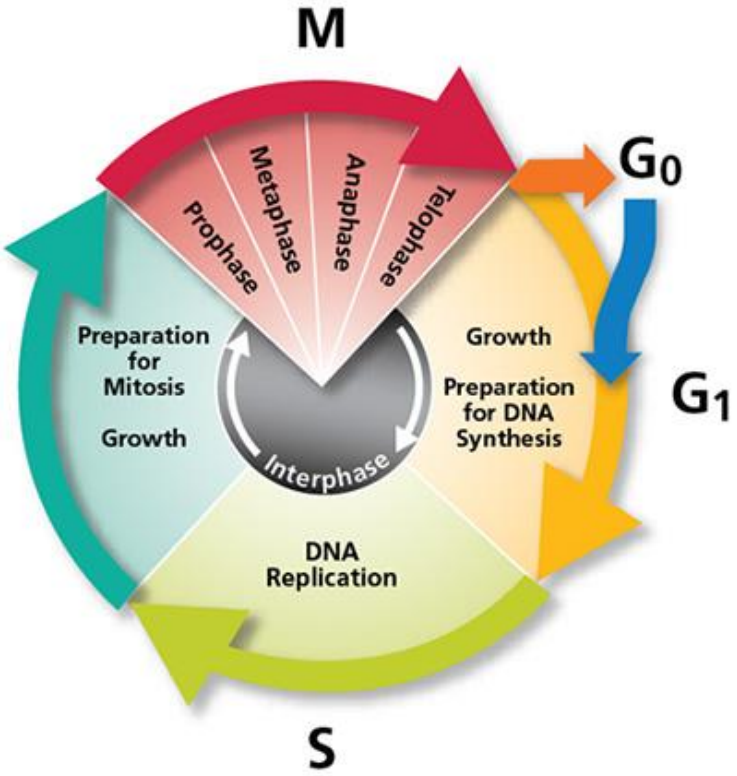
- Acute responding normal tissue
  - Prolonging treatment time spares acute responding normal tissue
  - As treatment time is reduced, acute responding tissue becomes dose-limiting
- Late responding normal tissue
  - Prolonging overall treatment time beyond 6 weeks has little effect, but prolonging time to retreatment my increase tissue tolerance
- Danger of tumor population

Redistribution

- Cells exhibit differential radiation sensitivity while in different phase of the cell cycle
- After an initial fraction of dose the cells at a resistant phase may survive but then proceed in time eventually to the sensitive phases
- Increases acute and tumor damage, no effect on late responding normal tissue

Experiments of Warren Sinclair: Survival curves during cell cycle





M > G2 > G1 > early S > Late S for sensitivity
Most radiosensitive: G2 and M
Mammalian cell cycle times: 10-20 hrs (G1 – most variable)

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Meaning of survival-how to quantify damage?

MEANING of SURVIVAL

for differential cells,
loss of a specific function
for proliferating cells,
loss of ability to divide
infinitely

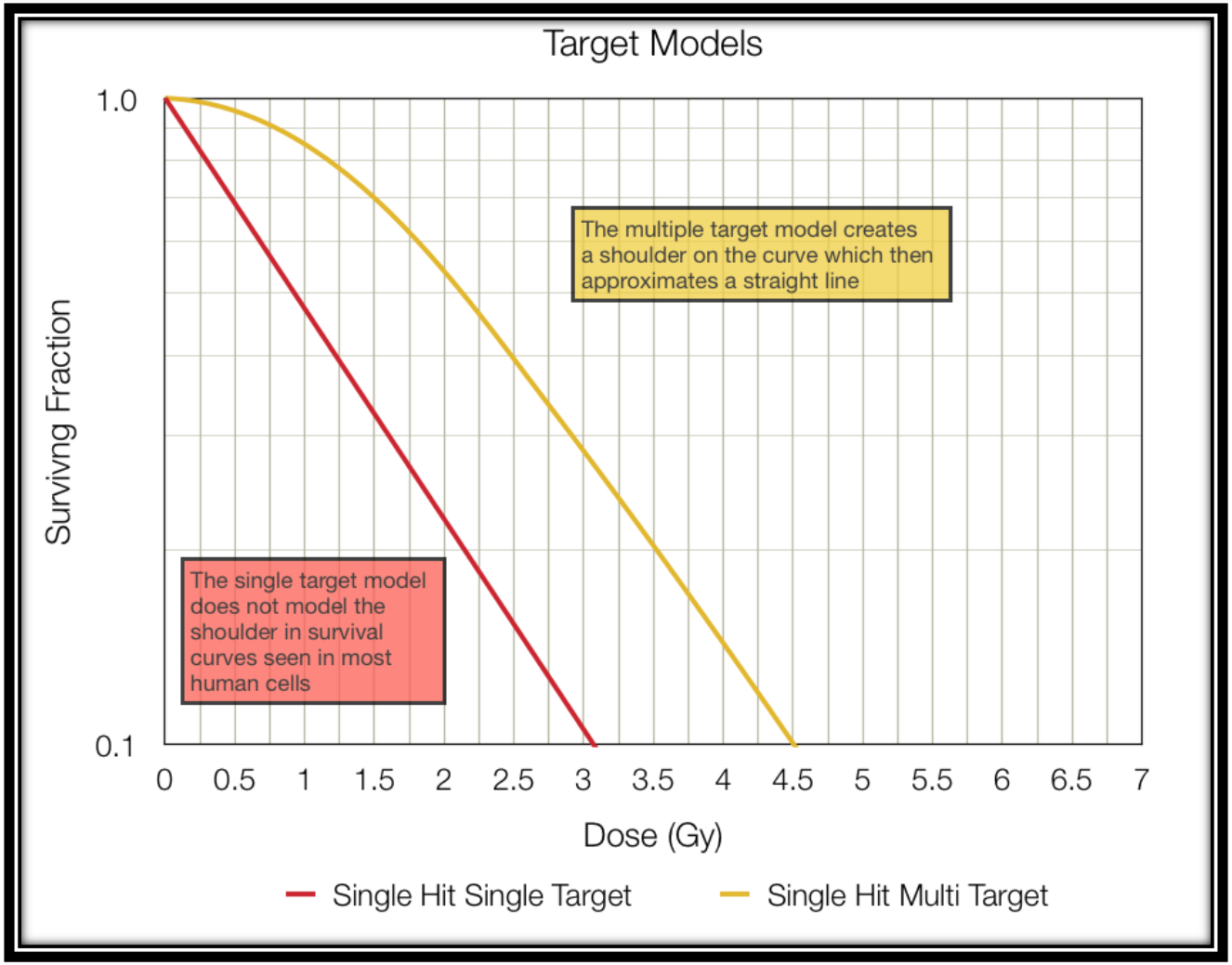
for a tumor to be eradicated, it is only necessary to destroy its proliferating capacity

in general, we need an average ~ 100 Gy to destroy cell function but ~ 2 Gy or less to destroy proliferating capacity
dependence on oxygen, repair, cell kinetics (the 4R's)

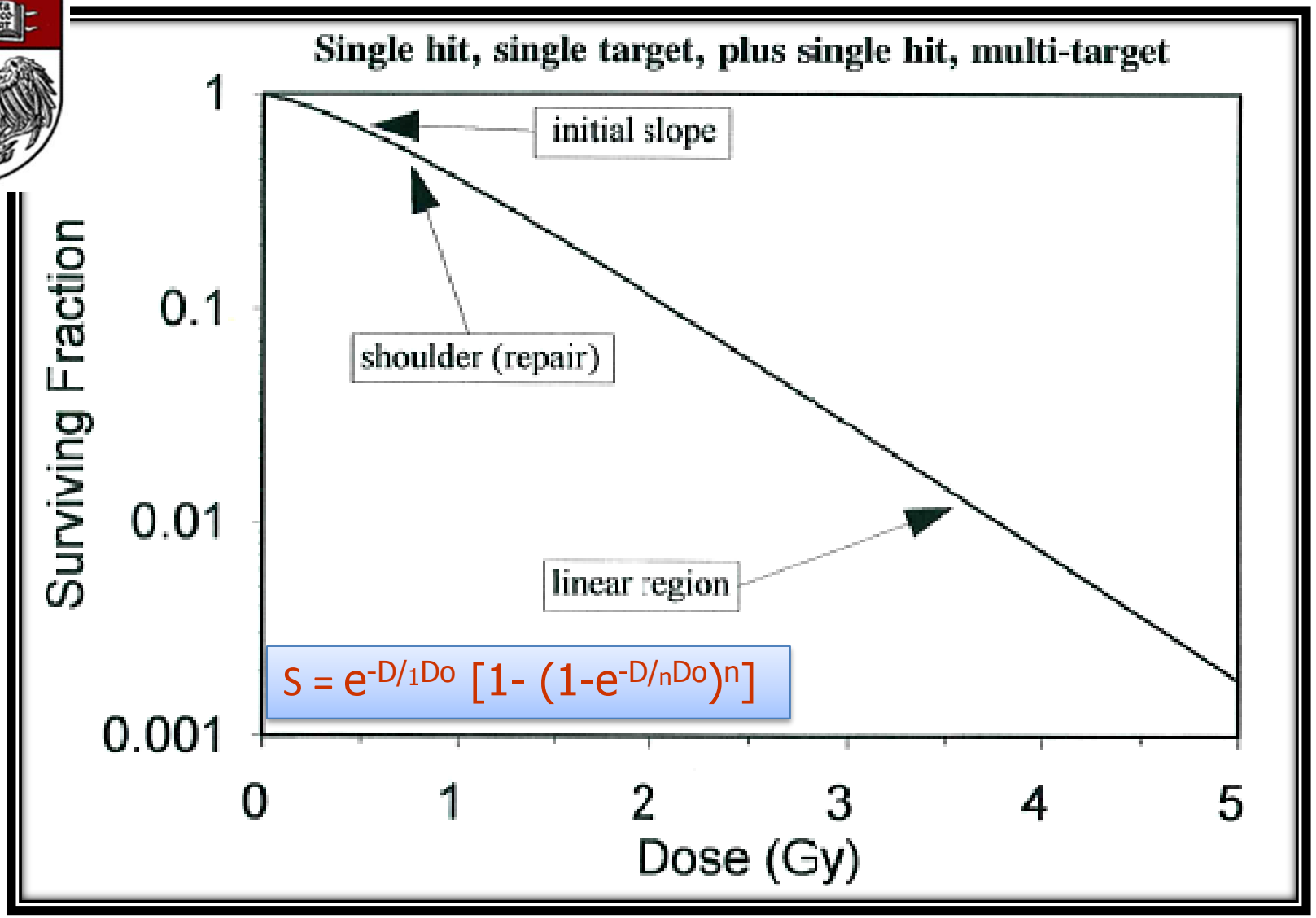
Cell Survival Curves

- Biological effect can be quantified as a function of radiation dose
- Target-cell hypothesis
  - There exist within each cell critical targets, which when hit by ionizing radiation in a random fashion may lead to consequential loss of cellular reproductive integrity

Cell Survival Curve Models



Most experimental survival curves have an initial slope whereas the multi-target/single-hit model predicts no initial slope



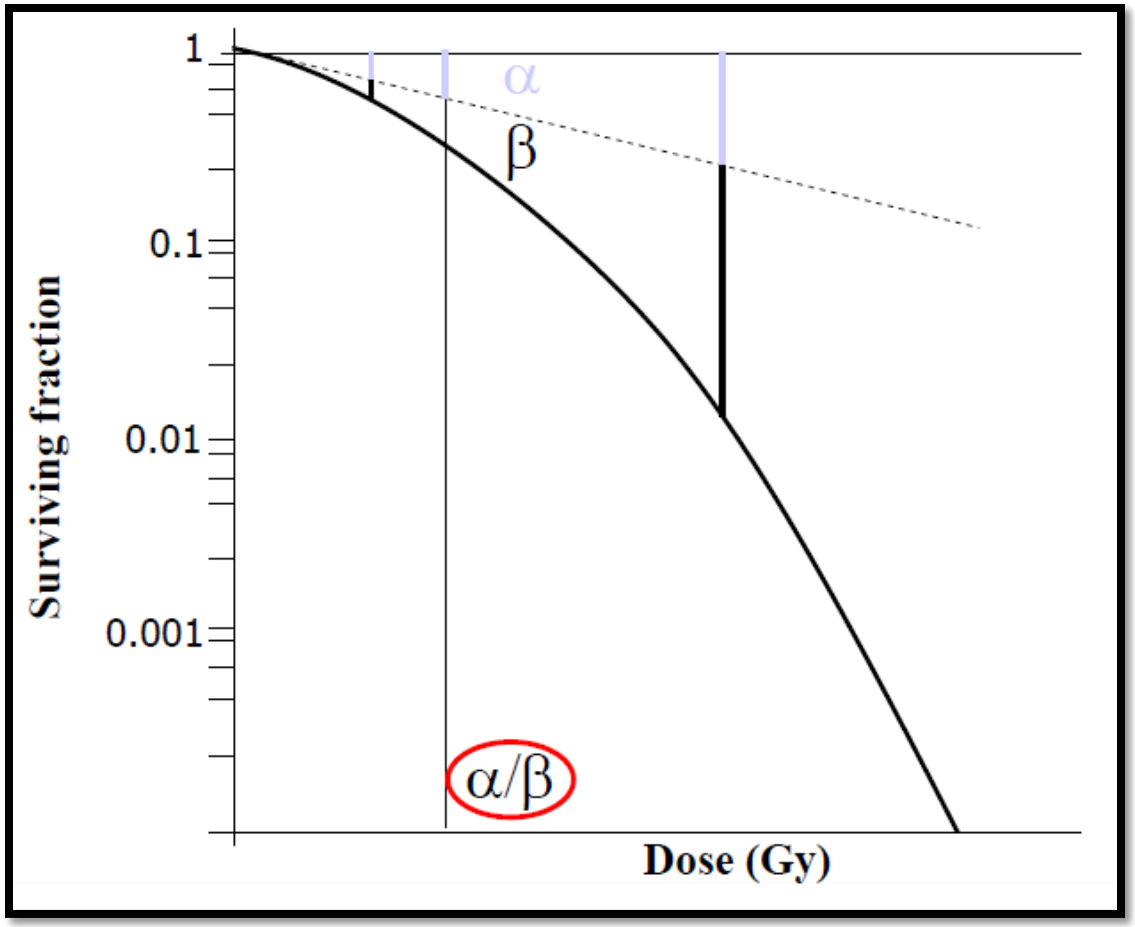
Can further refine the target model by assuming that there are two independent methods by which a cell can be inactivated:

1) *accumulation of sublethal lesions via single hit, multi-target mechanisms*
2) *a single-hit, single-target*

Linear Quadratic Model

- Lea and Catchside (1942): “Radiation-induced chromosome aberrations in …..”
- Originally called the “Theory of Dual Radiation Action” by Kellerer and Rossi in describing high vs. low LET radiation (1972)
- Cell kill contributions from linear and quadratic terms - Fits the shoulder very well
- DNA double strand breaks incorporated as mechanism of cell inactivation

The Linear Quadratic Model



- Linear (α) component: a double chromosome break caused by the passage of a single charged particle e.g. high-LET electron:

$$S = e^{-\alpha D}$$

- Quadratic (β) component: two separate chromosome breaks caused by separate charged particles:

$$S = e^{-\beta D^2}$$

α/β is the dose at which death due to single lethal lesions = death due to accumulation of sublethal lesions i.e. $\alpha D = \beta D^2$ and $D = \alpha/\beta$ in Gy

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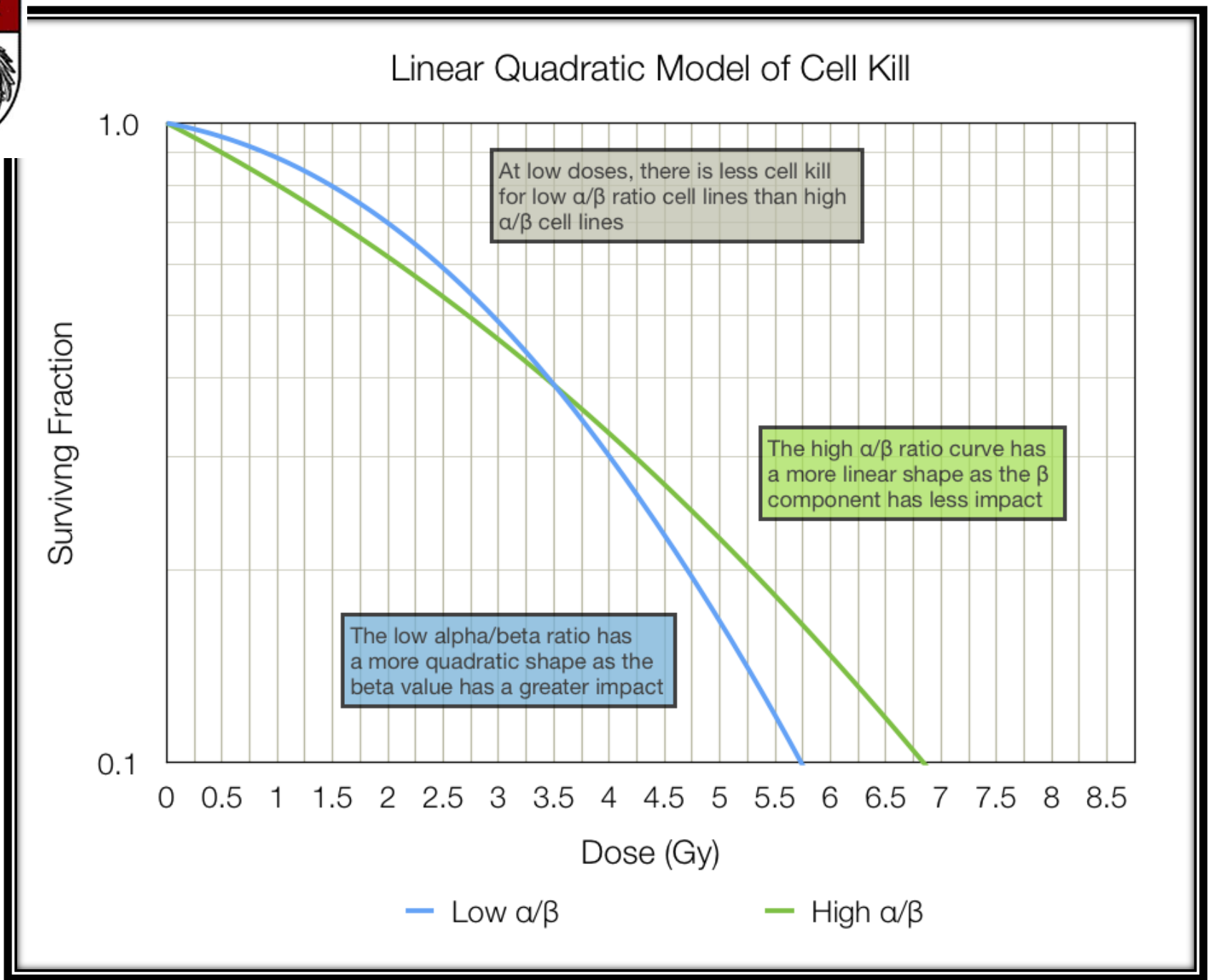
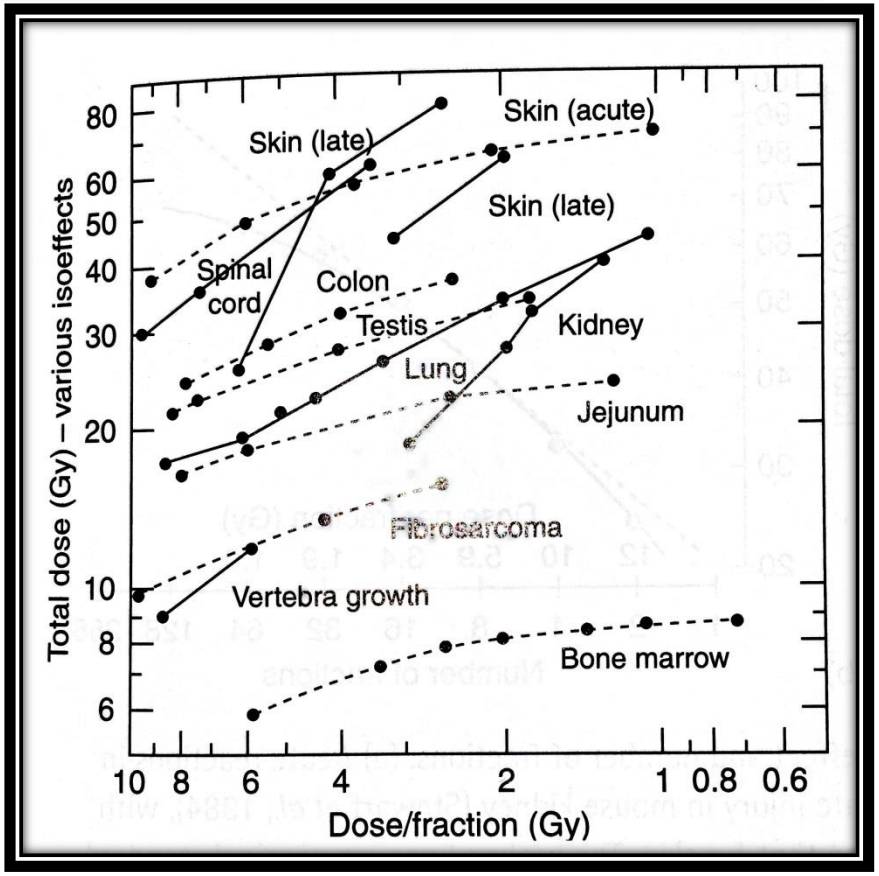
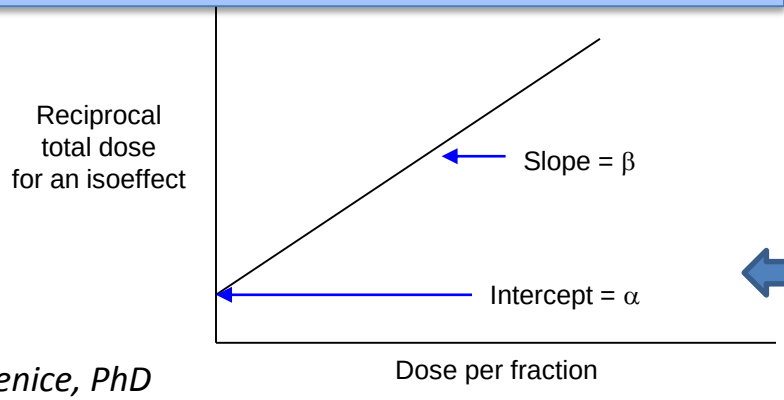

Linear Quadratic Model of Cell Kill
1.0
0.1
Surviving Fraction
At low doses, there is less cell kill for low α/β ratio cell lines than high α/β cell lines
The high α/β ratio curve has a more linear shape as the β component has less impact
The low alpha/beta ratio has a more quadratic shape as the beta value has a greater impact
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5
Dose (Gy)
Low α/β
High α/β

Response to Radiation

- The slope of an isoeffect curve changes with size of dose per fraction depending on tissue type (Thames et al IJROBP 8: 219, 1982)
- Acute responding tissues have flatter curves than do late responding tissues
- α/β measures the sensitivity of tumor or tissue to fractionation i.e. it predicts how total dose for a given effect will change when you change the size of dose fraction





Douglas and Fowler Rad Res 66:401, 1976

Showed and easy way to arrive at an α/β ratio

Sensitivity of Tissue to Dose Fractionation: α/β ratio

Early-Responding Tissues	α/β	Late-Responding Tissues	α/β
Jejunal mucosa	13	Spinal cord	1.6-5
Skin epithelium	10	Kidney	0.5-5
Spermatogenic cells	13	Lung	1.6-4.5
Bone marow	9	Liver	1.4-3.5
Melanocytes	6.5	Human skin	1.6-4.5
Tumors		Dermis	1.5-3.5
Mouse fibrosarcoma metastases	10	Bladder	5.0-10.0
Human Tumors	6-25	Bone	1.8-2.5

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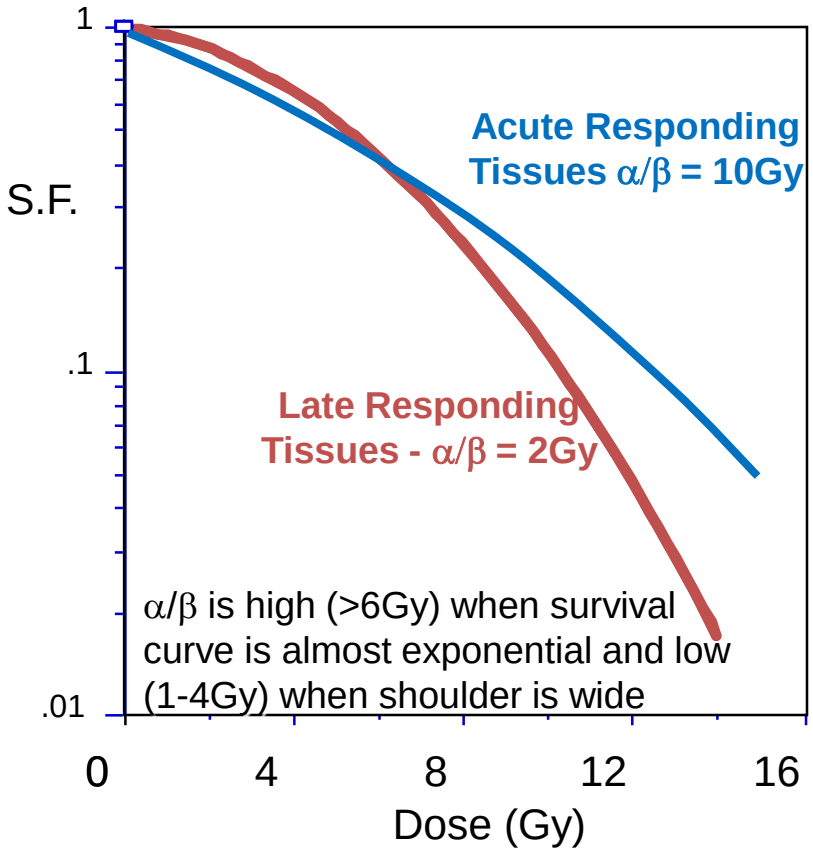
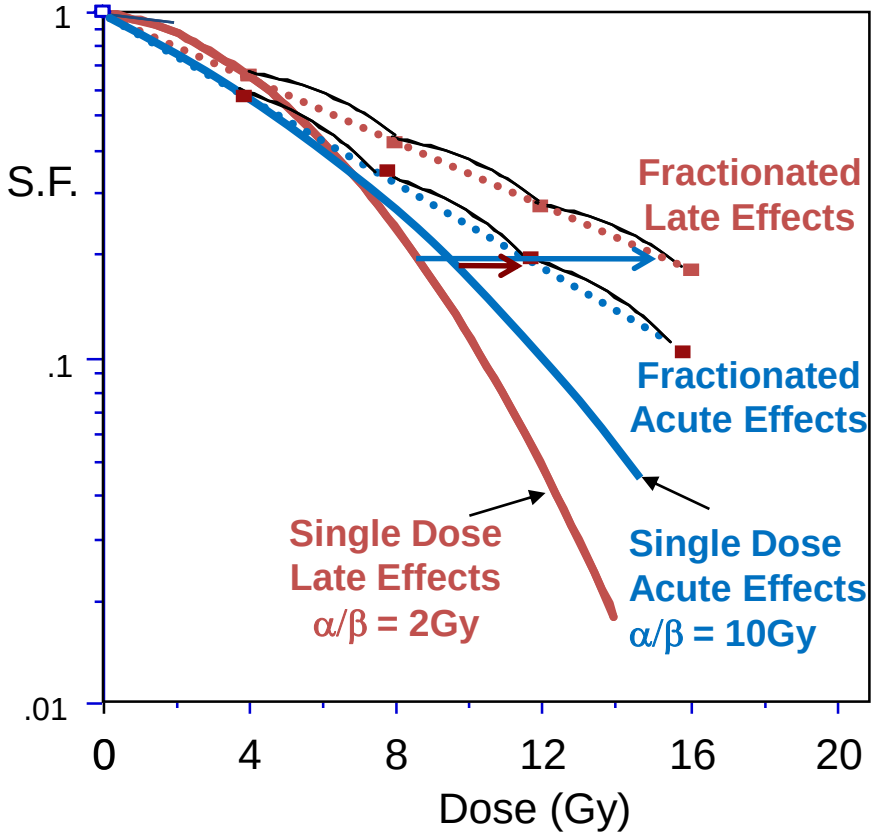
Response to Fractionation Varies With Tissue





If α/β ratio of tumor is the same or less than that of the critical normal tissue, then a larger dose per fraction *(hypofractionation)* is preferred, i.e., prostate cancer, breast cancer

If α/β ratio of tumor is high (often 10 or greater) and > α/β ratio of normal tissue (often < 5) a lower dose per fraction *(hyperfractionation)* is preferred, i.e., squamous. Ca. H&N

The LQ Model and Dose Fractionation Schedules

- For fractionated delivery of total dose D in n equal fractions of dose (D = n·d), the surviving fraction:

  $S = \exp [- n (\alpha d + \beta d^2)]$

  $\Rightarrow \ln S = - n (\alpha d + \beta d^2)$ (accounts for repair only)

- If tumor cell repopulation is assumed to be an exponential function of time, with doubling time for repopulation of the cycling cells T_{pot}:

  $\ln S = - n (\alpha d + \beta d^2) + (0.693/T_{pot}) T$

  Effect = - ln (surviving fraction)

The LQ Model and Dose Fractionation Schedules

Biologically equivalent dose (BED):

$$-(\ln S)/\alpha = BED = nd\left(1+\frac{d}{\alpha/\beta}\right)-\frac{0.693T}{\alpha T_{pot}}$$

α and T_{pot} vary considerably from patient to patient. A generic repopulation parameter (k) is more useful. Typically, k varies from 0.1 Gy to 0.6 Gy for slowly growing and rapidly repopulating tumors, respectively

$$BED = nd\left(1+\frac{d}{\alpha/\beta}\right)-k(T-T_k)$$

T_k = kick-in time; k =0 for $T < T_k$

The LQ Model and Dose Fractionation Schedules

Two treatment schedules have the same biological effect provided:

$$n_1 d_1 \left(1+\frac{d}{\alpha/\beta}\right) - k(T-T_k) = n_2 d_2 \left(1+\frac{d}{\alpha/\beta}\right) - k(T'-T_k)$$

where n_1 an d_1 are number of fractions and fractional dose for schedule and similarly for schedule 2.

Biologically Effective Dose (BED)

$$S.F. = e^{-E} = e^{-(\alpha D + \beta D^2)}$$

$$E = nd(\alpha + \beta d)$$

$$E/\alpha = nd(1+d/_{\alpha/\beta})$$

Biologically Effective Dose

Total dose

Relative Effectiveness

35 x 2Gy = B.E.D.of $84Gy_{10}$ and $117Gy_3$

NOTE: 3 x 15Gy = B.E.D.of $113Gy_{10}$ and $270Gy_3$

Equivalent to 162 Gy in 2Gy Fx -unrealistic!
(Fowler et al IJROBP 60: 1241, 2004)

Normalized total $dose_{2Gy}$

= BED/RE

= BED/1.2 for α/β of 10Gy

= BED/1.67 for α/β of 3Gy

What total dose (D) to give if the dose/fx (d) is changed

New **Old**

$$D_{new}\,(d_{new} + \alpha/\beta) = D_{old}\,(d_{old} + \alpha/\beta)$$

So, for late responding tissue, what total dose in 1.5Gy fractions is equivalent to 66Gy in 2Gy fractions?

$$D_{new}\,(1.5+2) = 66\,(2 + 2)$$

$$D_{new} = 75.4\text{Gy}$$

NB: Small differences in α/β for late responding tissues can make a big difference in estimated D!

NTCP Analysis (Example: Lung Toxicity)

- Dose fractionation varies and cannot simply add different schemes to come up with dose guidelines.
- Normalized Total Dose (NTD) (Lebesque and Keus, Radiother.Oncol. 1991)
  - total dose, given in 2Gy fractions, that has same biological effect as actual treatment schedule under consideration

$$NTD = nd\ [(\alpha/\beta + d) / (\alpha/\beta + 2)]$$

α/β = 3 Gy for lung tissue

NTCP Modeling for Radiation Pneumonitis

(Kwa et al IJROBP 1998)

Biologically adjusted DVH for partially irradiated lung:

$NTD_{mean} = \sum NTD_i v_i$

Lyman model for incidence of RP in terms of NTD_{mean}:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2}\, dx,$$

$$t = \frac{NTD_{mean} - NTD_{50}}{m \times NTD_{50}}$$

NTD_{50} = NTD that results in 50% probability for RP

m = steepness of the dose response curve

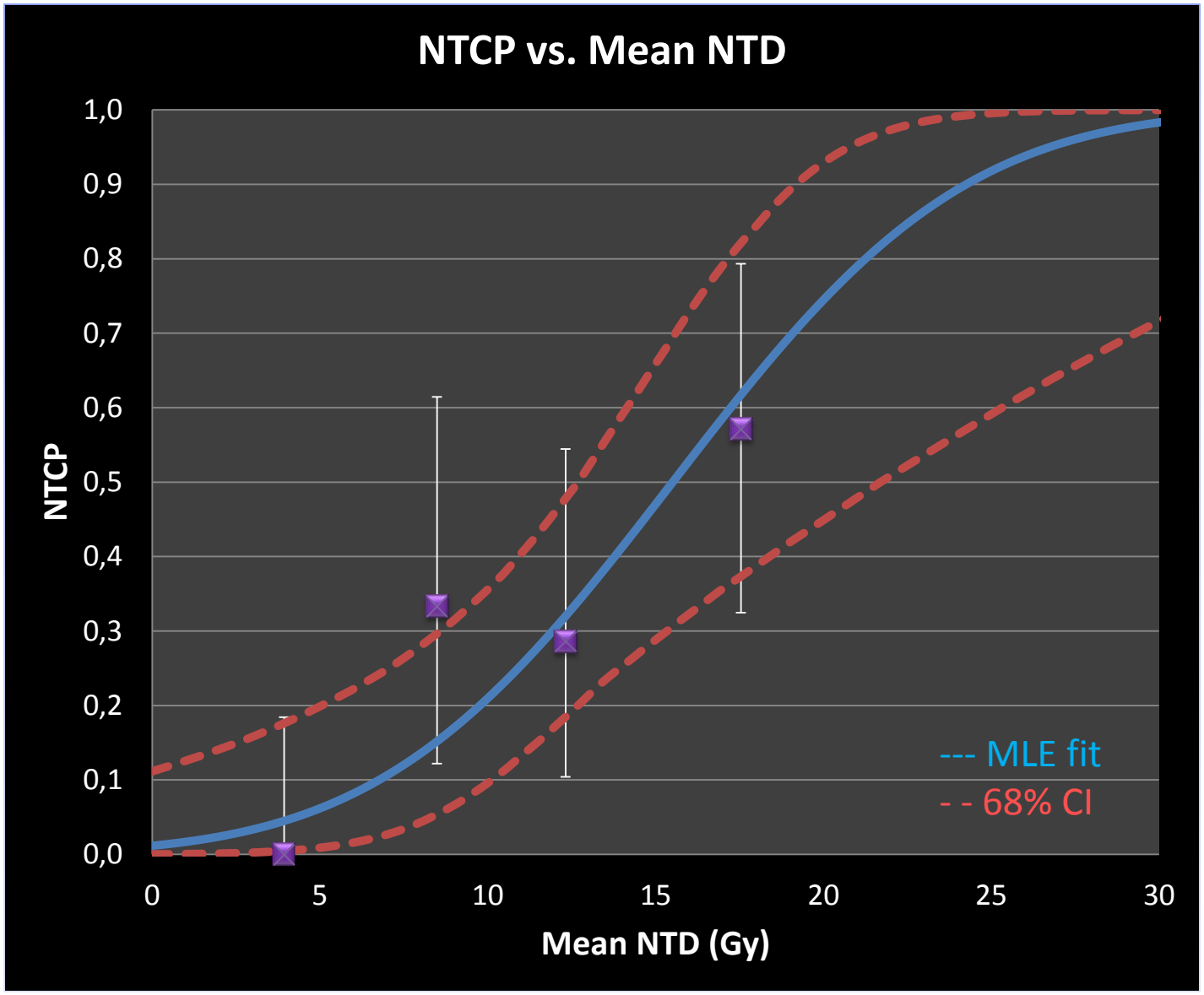
Maximum Likelihood Fit of NTCP Model to Data

Statement of the Problem: Given the outcome of each individual patient in this study [RP (Gr≥2) =0 or 1], what is the overall likelihood that our NTCP model is "right"?

Maximize the objective function:

$$\ln(L) = \sum_{i=1}^{n} [ep_i \ln(NTCP_i) + (1 - ep_i)(1 - \ln(NTCP_i))]$$

Obtain the best fit parameters: NTD_{mean} and m



Confidence intervals calculated by profile maximum likelihood method

Summary

- LQ model is useful in the fractional dose regime of 1-8 Gy
- It provides a simple and operational mechanistic model
- Explains the clinical data in terms of classical radiobiological concepts
- NTCP/TCP models provides more reasonable tools for design of appropriate treatment schedules

Radiobiology of SBRT/SRS

Kamil M. Yenice, PhD

University of Chicago

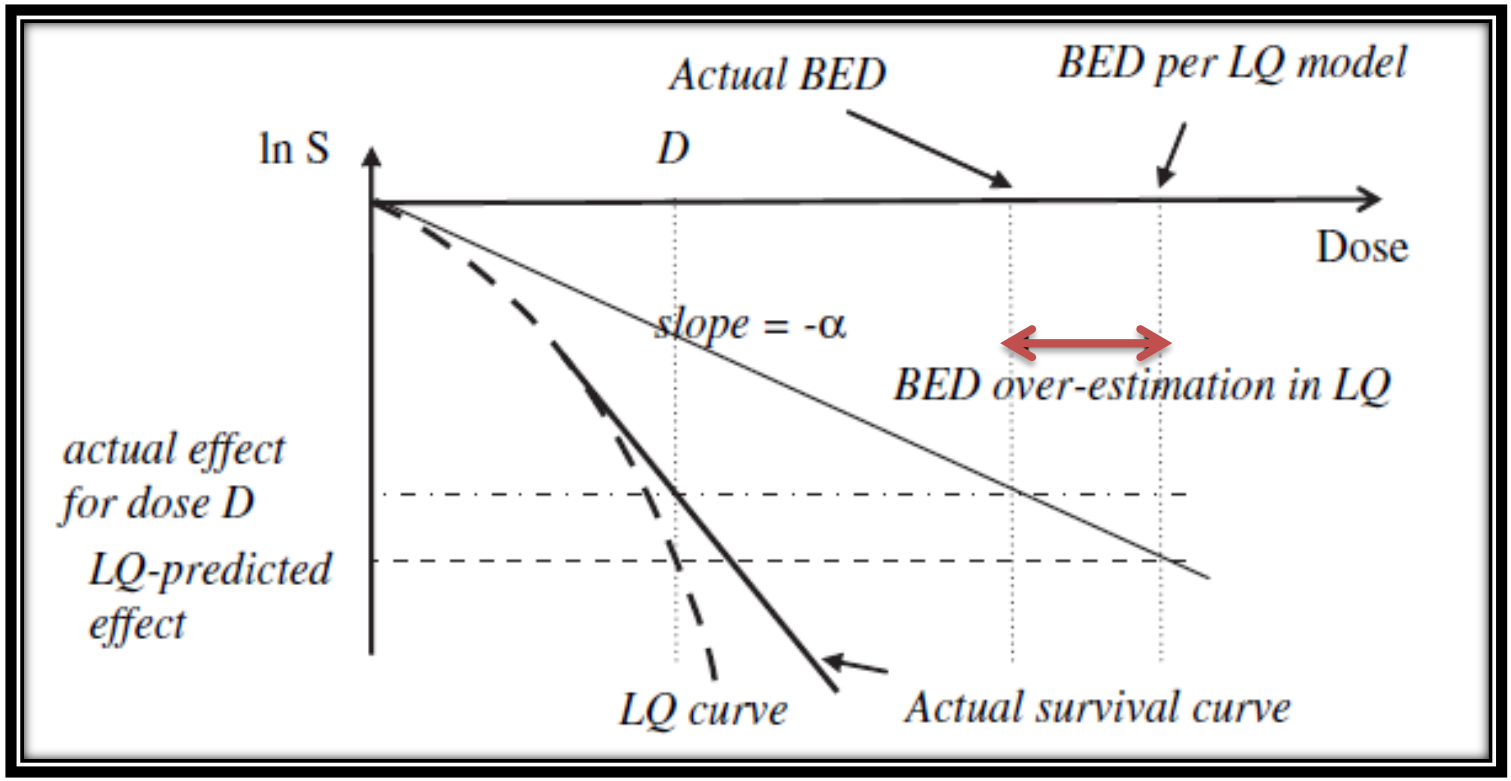
Current issues

- What is the biological basis of potent hypofractionation used in SRS and SBRT?
- Does LQ model work at high doses?
- What effect does occur increasingly at higher doses per fraction?
- Are “4Rs” of radiobiology still relevant to SRS/SBRT regimens?

Fractionation Schemes

- Conventional
  - Daily dose: 1.8 – 2 Gy
  - Total Dose: 40 – 70 Gy
  - increase dose to the tumor while PRESERVING NORMAL TISSUE FUNCTION
- Hypofractionation
  - Dose per fraction > 2.2 Gy (3-6 Gy)
  - Reduced total number of fractions (10-15)
  - Rationale: tumor has low α/β ratio and there is no therapeutic advantage to be gained with respect to late complications
- Extreme Hypofractionation/SRS/Ablative
  - Daily dose: 10-30 Gy
  - Number of fractions: 1-5
  - Overwhelm tumor repair capacity
  - Causes “late” effects that may be intolerable

Comparisons between the effects of different dose-fractionation schemes.



$$BED = D \cdot \left(1 + \frac{d}{\alpha/\beta}\right)$$

Total dose delivered in an infinite number of infinitesimally small dose fractions that has the same biologic effect as the dose-fractionation scheme in question.

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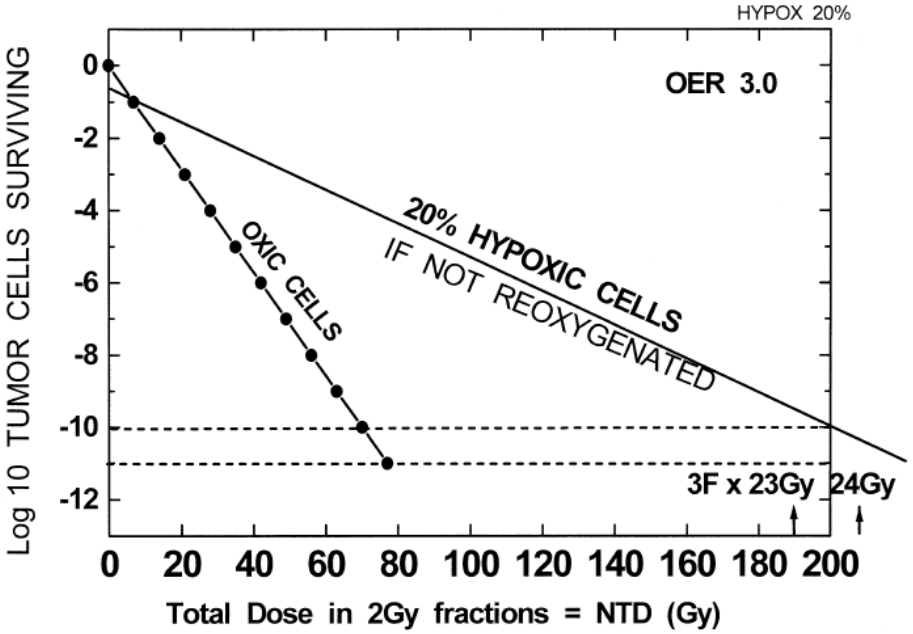
Predictions of Mathematical Modeling

Fractionation regimens currently in use (refs)	Predicted logs of cell kill			
	Without hypoxia		With hypoxia	
	LQ	USC	LQ	USC
25 Gy/1fraction (11, 12)	13.3	8.1	3.3	3.2
50 Gy/4 fractions (13)	17.1	14.9	6.7	6.7
60 Gy/3 fractions (14, 15)	27.4	19.0	7.7	7.7

Brown et al 2010 IJROBP: V 78, pp 323-327



Fowler et al 2004 IJROBP V60, pp1241-1256

Both studies suggested: if cell population is assumed to be mixed (20% hypoxic) and no reoxygenation occurs, then currently used dose fractionations (SBRT) are not sufficient to control tumor!

SRS: Clinical Outcome

Trigeminal Neuralgia

Series	No. of Patients	Follow-up (mo)	Dose (Gy)	Pain Relief (%)	Recurrence (%)	Numbness (%)
Seattle[7]	110	19	70 to 80	95	34	2.7
Pittburgh[8]	220	24	60 to 90	82	13	10.2
University of Maryland[9]	112	30	70 to 80	77	29	7.3
University of Virginia[10]	151	19	50 to 90	90	27	9
Medical College of Ga[11]	106	34	70 to 85	85 to 92	23	16

AVM Radiosurgery

Series	No. of Patients	Follow-up (mo)	Size	Dose	Obliteration (%)	Rebleed (%)	Complications (%)
Pittsburgh[25]	351	36-132	5.7 mL (0.2 to 24)	20 Gy (12 to 30)	75	4	4
Prague[26]	330	38 (1-118)	3.9 mL (0.1 to 28.6)	20 Gy (8 to 32)	74	6	7
Tokyo[27]	531	88	2.1 cm (4.8 mL)	21 Gy	81	5	6.6

Acoustic Neuroma

Series	No. of Patients	Prior Surgery	Median Dose (Gy)	Median Volume (mL)	Median Follow-up (mo)	5-Year Progression Free	Cranial Nerve Injury	Serviceable Hearing Preservation
Munich[32]	111	33%	13 (10-16)	1.6	84	95%	V:8% VII:3%	NS
Taipei[33]	187	37%	13 (11-18)	4.1	30	93%	V:1% VII:1%	60%
Pittsburgh[34]	313	NS	13 (12-13)	1.1	24	93%	V:4% VII:0%	78%
University of Florida[35]	149	28%	14 (10-22)	4.8	34	87%	V:11% VII:9%	NS

SRS: Clinical Outcome

Meningioma

Series	No. of Patients	Follow-up (mo)	Volume	Margin Dose	Progression Free (%)	Complications (%)
JCRT[39]	127	31 (1-60)	4.1 mL	15 Gy (9-20)	89 (3 year)	4.7
Pittsburgh[40]	934	48	7.4 mL	14 Gy	93 (10 year)	5.7
Mayo[41]	330	43 (2-138)	7.3 mL (0.5-50.5)	16 Gy (12-20)	94 (crude)	8

Brain Metastases

Author	Diameter (cm)	Dose (Gy)	BED_{12} (Gy)	6 month local control (%)	12 month local control (%)
Matsuo (1999) [31]	0–3	25	[b]53.0	100	93
Chang (2003) [25]	0–2	20–24	41.0–50.7	Na	69
	0–1	20–24	41.0–50.7	97	86
	1–2	20–24	41.0–50.7	82	56
Lutterbach (2003) [30]	0–3	18	[b]36.0	93	91
Chang (2005) [26]	1–3	15–18	28.6–36.0	Na	38
Vogelbaum (2006) [34]	0–2	24	[b]50.7	92	85
	2–3	18	[b]36.0	87	49
	3–4.5	15	[b]28.6	71	45
Chao (2008) [27]	0–2	22–24	45.9–50.7	97	92
	2–4	15–18	28.6–36.0	83	62
Molenaar (2009) [6]	0–2	21	[b]43.4	100	82
	2–3	18	[b]36.0	95	65
	3–4	15	[b]28.6	95	37

6-Mo LC>80% for all, 12-Mo LC: >80% (Rx≥21Gy); >60% (Rx ≥ 18Gy); <50% (Rx≤15Gy)

SBRT: Clinical Outcome

Phase II trials of SBRT in early stage lung cancer

Series	No. of Patients	Follow-up (mo)	Volume	Dose	Local Control	Survival	Toxicity Grade ≥3
Indiana[48]	70	32	PTV: 46 mL (10-150)	T1: 60 Gy/3 T2: 66 Gy/3	95% (2 year)	55% (2 year)	Central: 46% (2 year) Peripheral: 17% (2 year)
Japan[49]	31	32 (4-87)	PTV: 62 mL (4-156)	45 Gy/3 (20 pts) 60 Gy/8 (11 pts)	71% (crude)	71% (3 year)	3% (crude)

Phase II trials of SBRT for liver metastases

Series	No. of Patients	Follow-up (mo)	Volume	Dose	Local Control	Survival	Toxicity Grade ≥3
Colorado[56]	21 (28 tumors)	19 (6-29)	14 mL (1-98)	60 Gy/3 (36-60/3)	93% (18 months)	NS	4% (crude)
Denmark[57]	65* (142 tumors)	2-75	3.5 cm (1.0-8.8)	45 Gy/3	79% (2 year)	1.6 years (median)	6% (crude)
Heidelberg[58]	37 (60 tumors)	6 (1-26)	10 mL (1-132)	14-26 Gy/1	71% (1 year)	72% (1 year)	0%

Attempts to Modify LQ Model

- Guerrero-Li Modified LQ model and Curtis Lethal-Potentially-Lethal Model

$$S = \exp(-\alpha D - \beta G(\lambda T) D^2) \qquad G(\lambda T) = 2(\lambda T + e^{-\lambda T} - 1)/(\lambda T)^2$$

- Potentially-Lethal Model
  - Mathematically sound
  - Too complicated for everyday clinical use.
  - Modification factors not well characterized.
- Using extremely large α/β ratio (~ 20 Gy)
  - Valid?
  - The curve straightens, but the low-dose fit suffers.

Guerrero, Phys Med Biol, 2004, 49:4825
Curtis, Radiat Res, 1986, 106:252

Universal Survival Curve

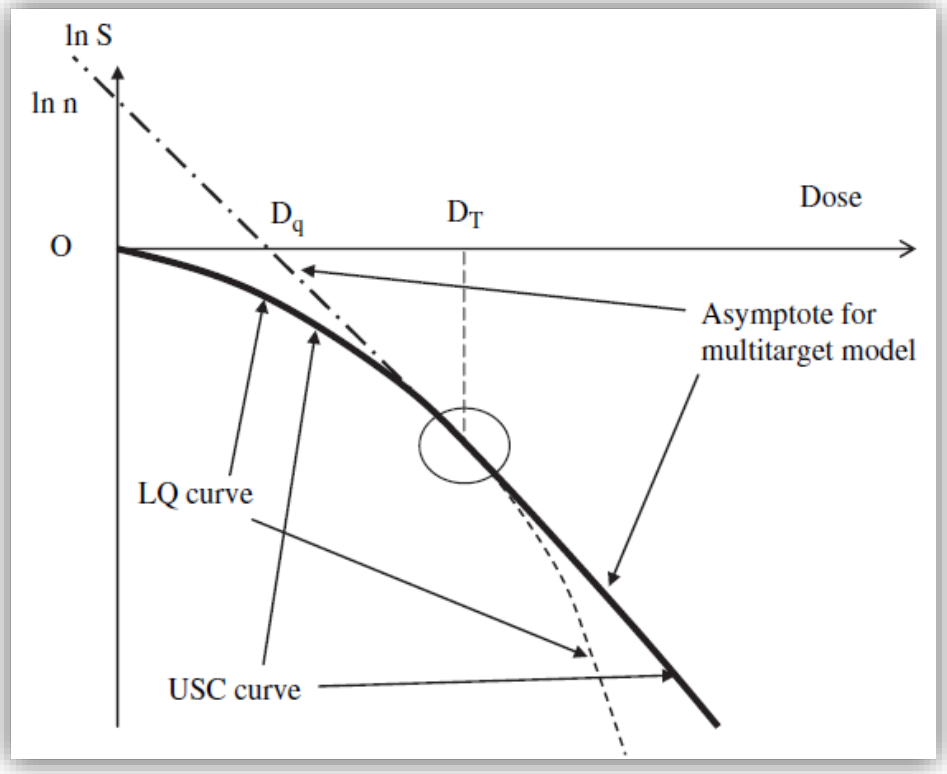
(Park et al IJROBP, Volume 70, Number 3, 2008)

- Combine the LQ model with multi-target model at high dose

$$S = e^{-d/d_1} \cdot \left\{1 - \left(1 - e^{-d/D_0}\right)^{\bar{n}}\right\}$$

$$\ln S \approx -\frac{1}{D_0} d + \ln(\bar{n}) = -\frac{1}{D_0} d + \frac{D_q}{D_0}$$

$$\ln S = \begin{cases} -(\alpha \cdot d + \beta \cdot d^2) & \text{if } d \le D_T \\ -\frac{1}{D_0} d + \frac{D_q}{D_0} & \text{if } d \ge D_T \end{cases}$$



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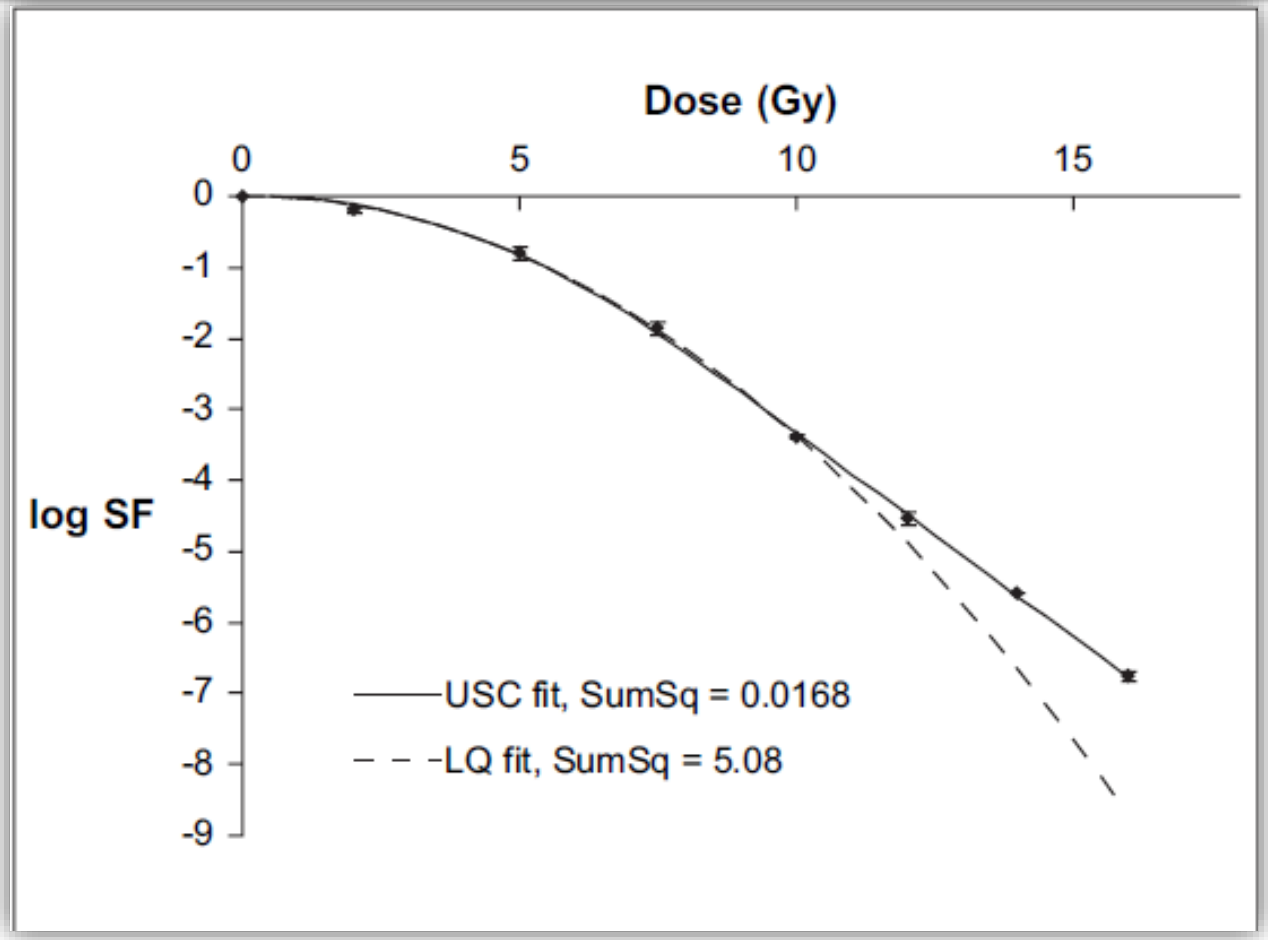
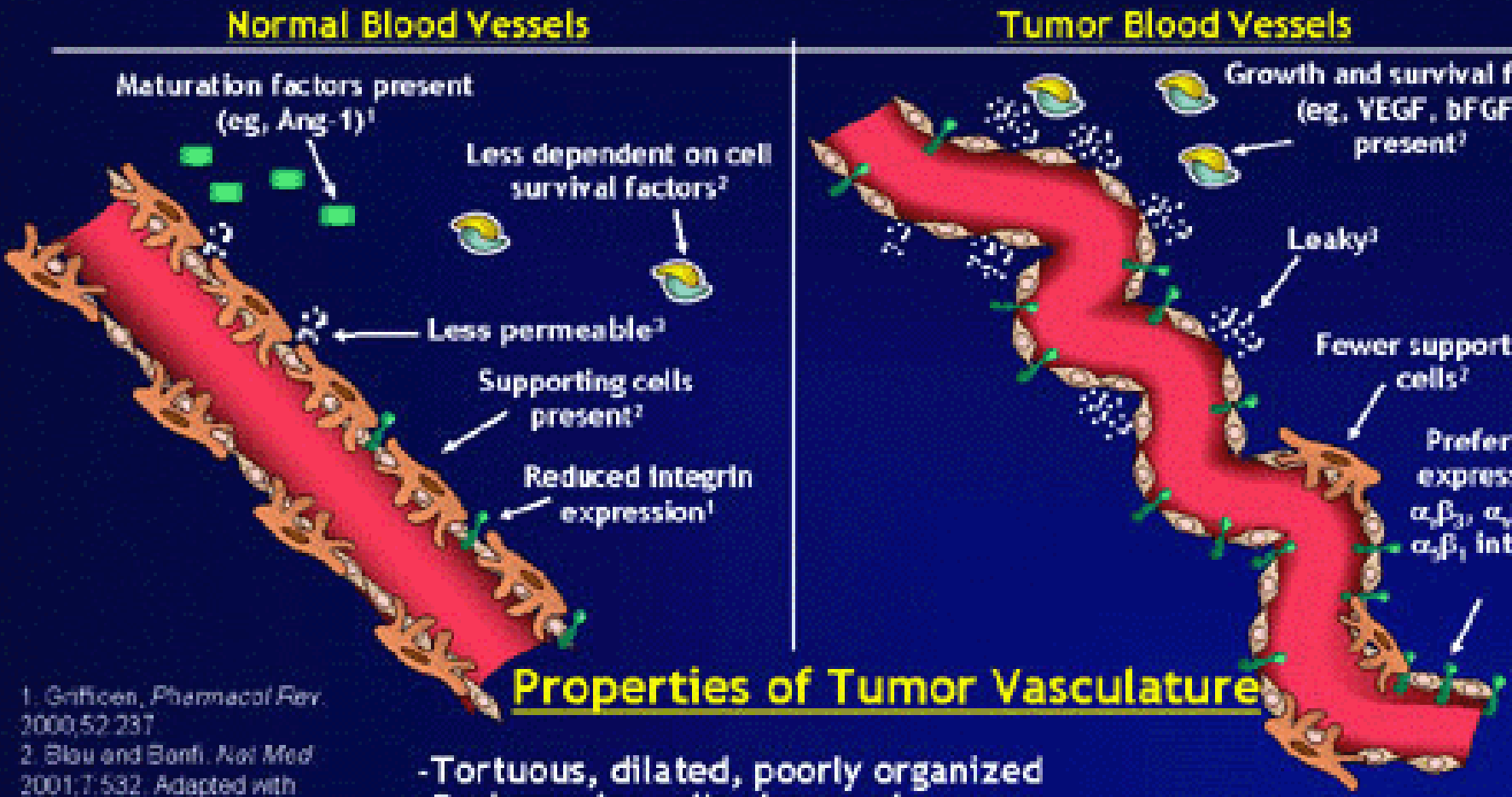


Survival curve of H460 fitted with linear quadratic (LQ) model (using points ≤8 Gy) and with universal survival curve (USC) model.

Normal and Tumor Vasculature



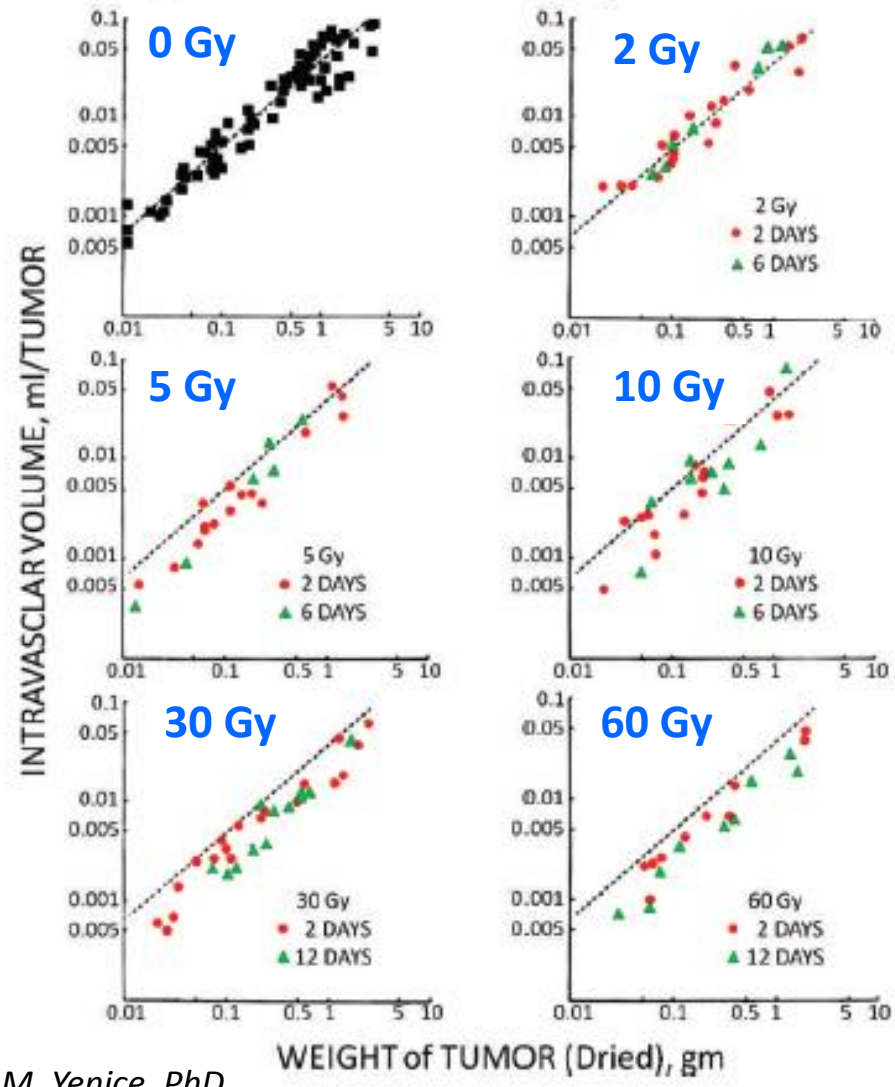
Properties of Tumor Vasculature

- Tortuous, dilated, poorly organized
- Perivascular cells abnormal
- Hyperpermeable
  - Results in increased interstitial pressure
  - Decrease in diffusion of drugs into the tumor

1. Griffioen, *Pharmacol Rev.* 2000;52:237.
2. Blau and Banfi. *Nat Med* 2001;7:532. Adapted with permission from MacMillan Publishers.
3. Jain. *Nat Med.* 2001;7:987. Adapted with permission from MacMillan Publishers.

- vasculature associated with tumors is not normal
  - The blood vessels in a tumor bed, generally speaking, are tortuous, dilated, and poorly organized
  - The surrounding pericytes are abnormal. They tend to be hyperpermeable and leaky

Vascular effects occur at high doses

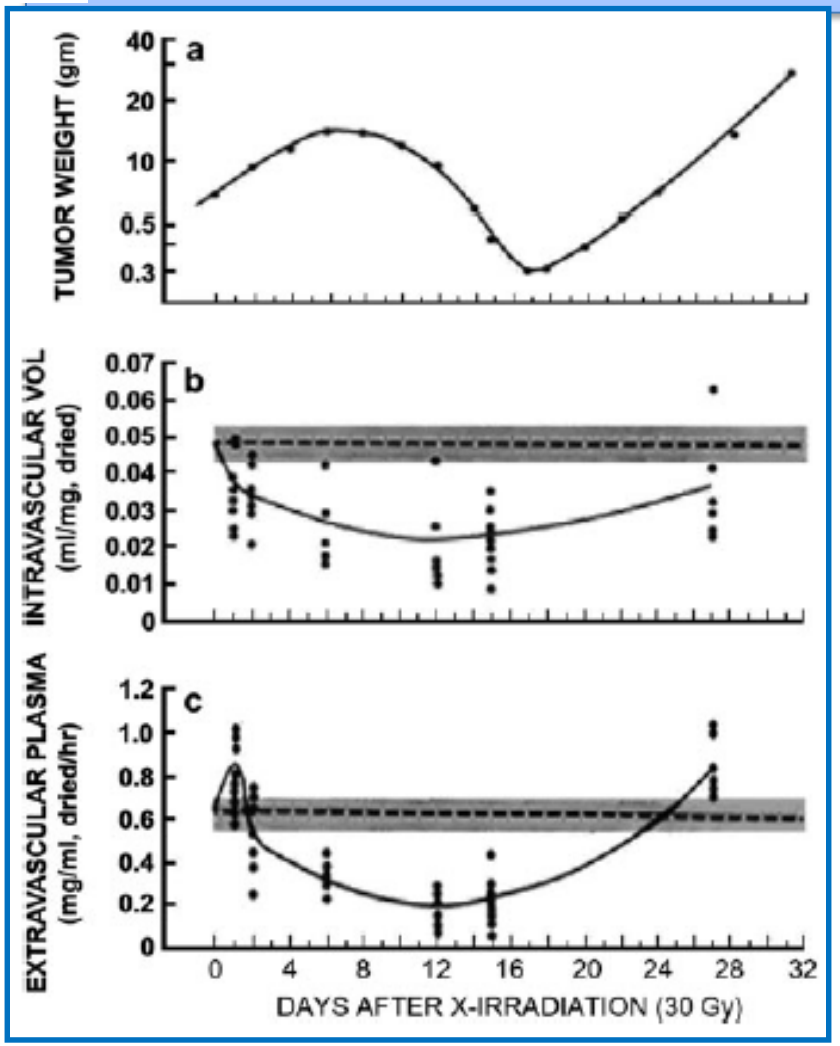


- Functional intravascular Volume
- Walker 256 tumors (s.c.) grown in legs of Sprague-Dawley rats
- Single dose radiation

Park HJ et al. *Radiat Res* 2012;177:311–27

Kamil M. Yenice, PhD

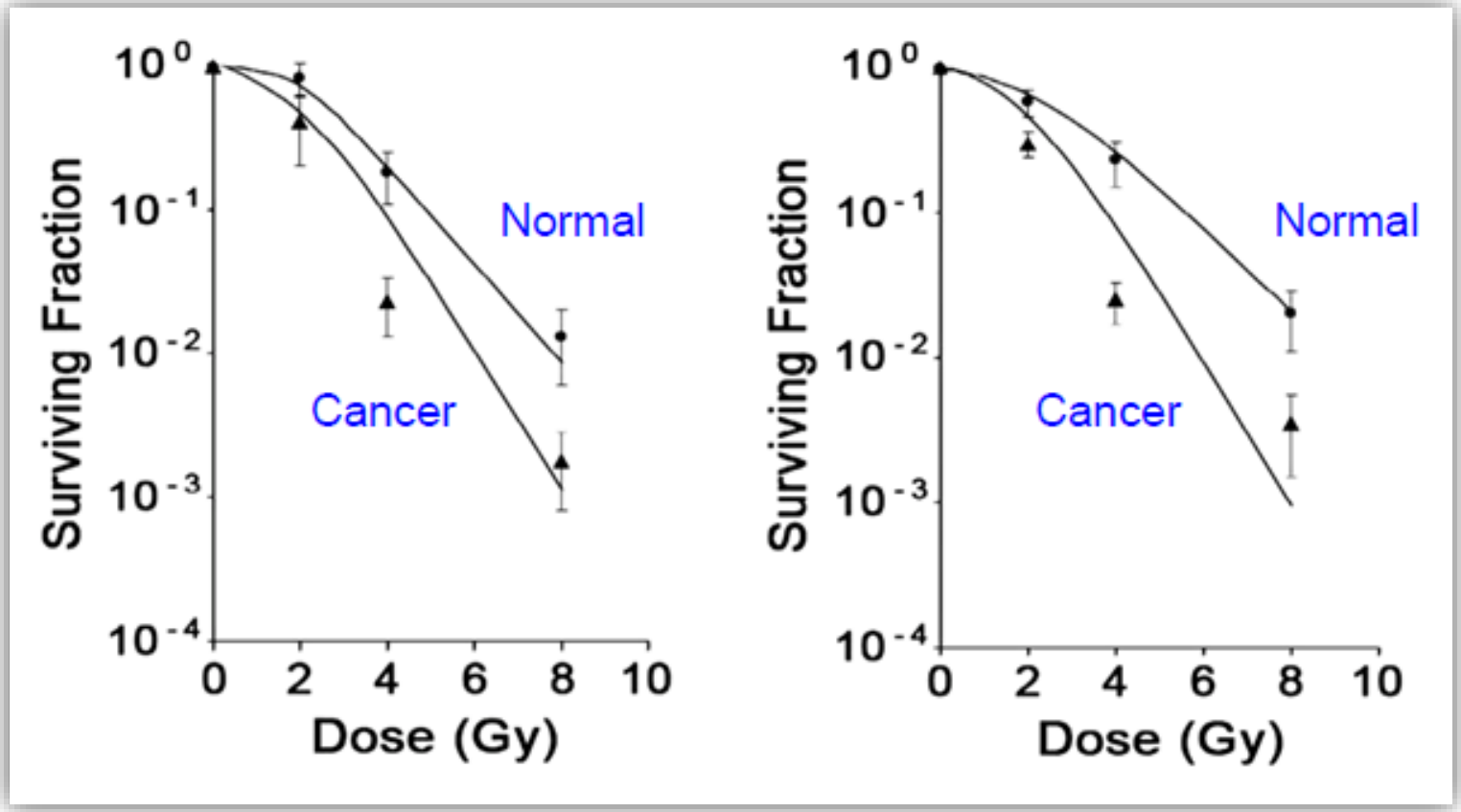
Vascular Changes in Tumor by Radiation



- Walker 256 carcinoma grown subcutaneously in the leg of Sprague–Dawley rats.
- The functional vascularity in tumors decreases within several hours after irradiation with doses higher than 10–15 Gy.

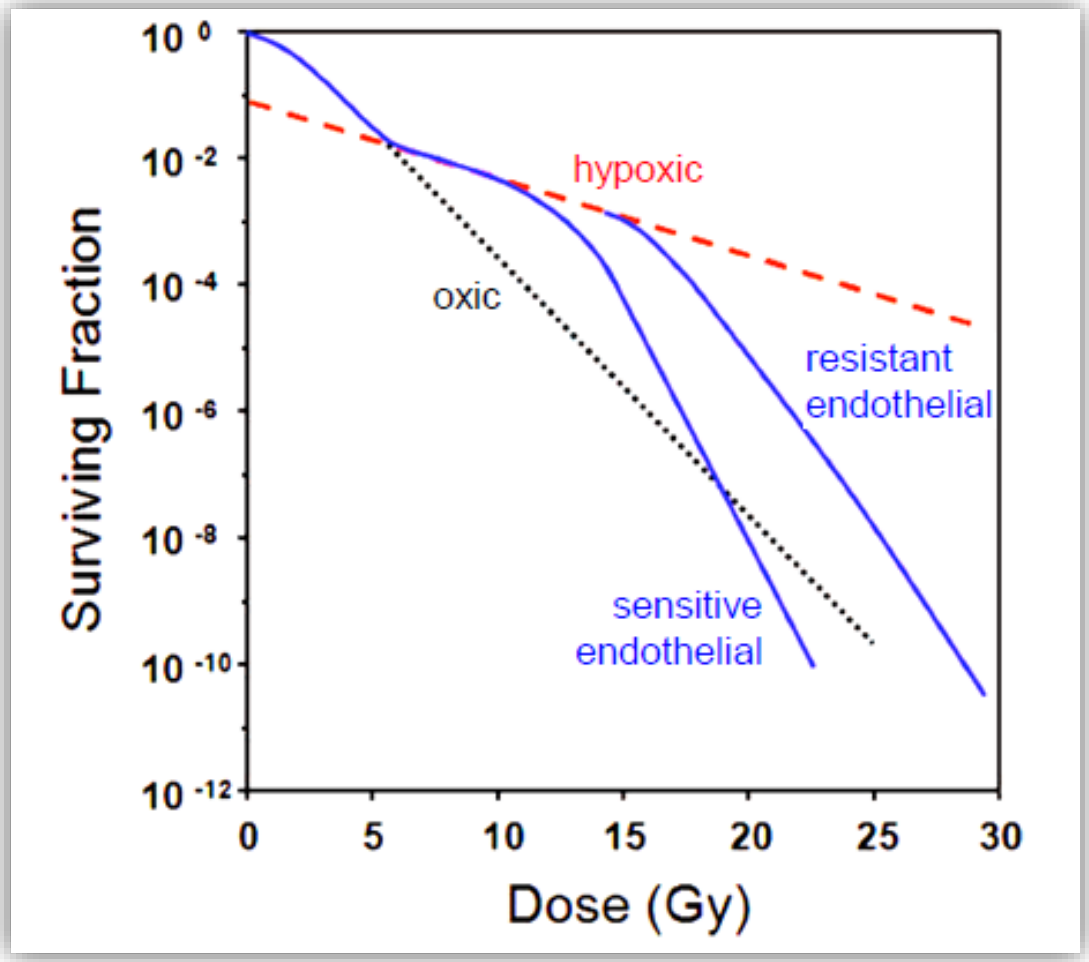
Vascular effects occur at high doses

Breast cancer patients
Endothelial cells from normal breast or cancer



Park HJ et al. *Radiat Res* 2012;177:311–27

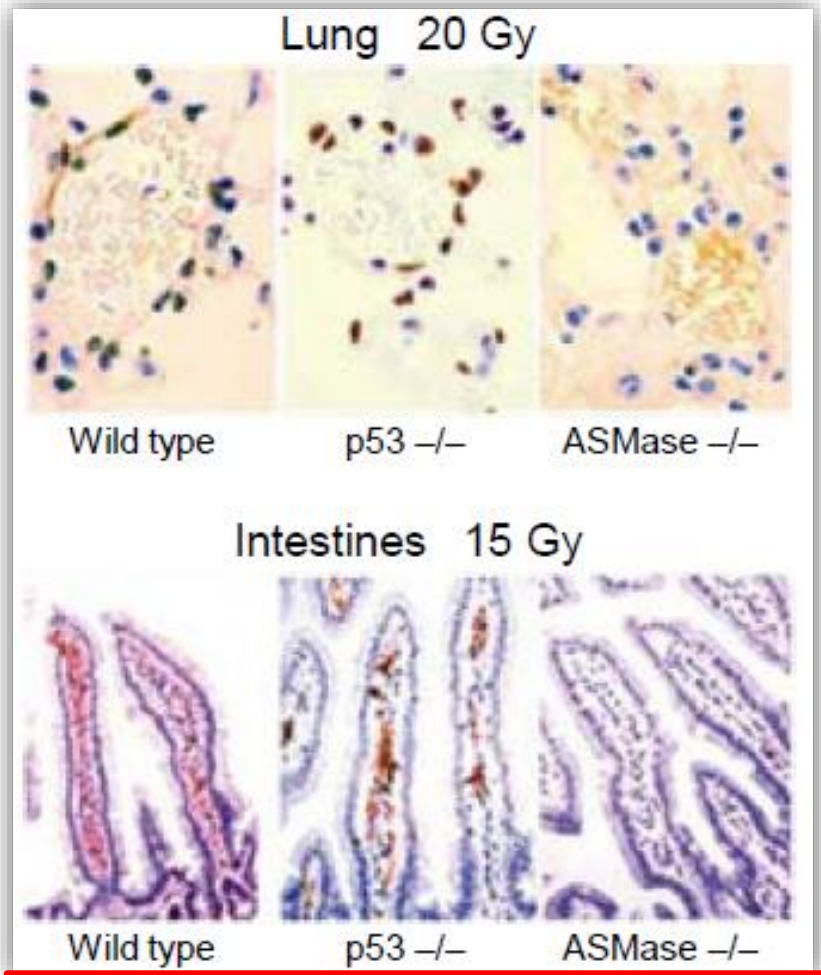
Vascular effects occur at high doses

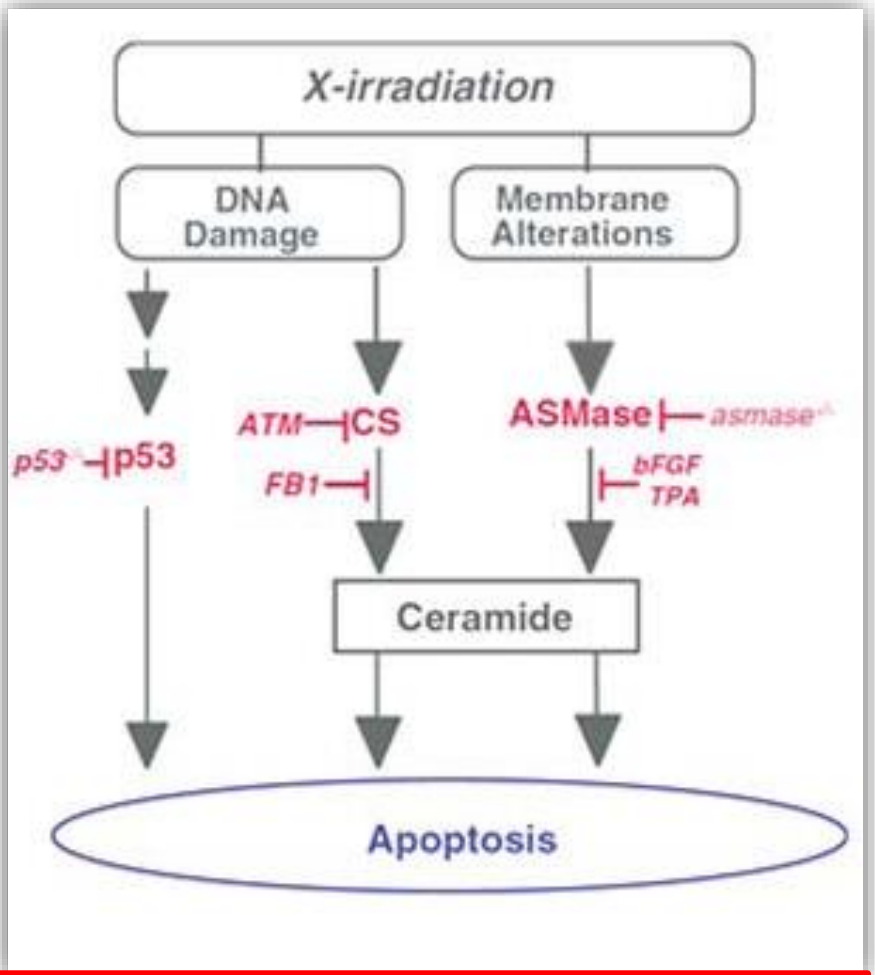


- Hypothetical cell death mechanism after doses of single fraction radiation
- 10% hypoxic population
- For < 5Gy fully oxygenated cells die
- For > 5Gy hypoxic cell death dominates
- For >10 Gy vascular damage begins to occur in tumors (endothelial cells relatively sensitive)

Park HJ et al. *Radiat Res* 2012;177:311–27

Endothelial cell apoptosis at high doses





HYPOTHESIS: Ceramide mediated Endothelial Apoptosis causes indirect cell kill at >10Gy!

Kolesnick R & Fuks Z. *Oncogene* 2003;22:5587–906

The Role of Cancer Stem Cells

Cancer Cell
Article

A Perivascular Niche for Brain Tumor Stem Cells

Christopher Calabrese,[1] Helen Poppleton,[1] Mehmet Kocak,[2] Twala L. Hogg,[1] Christine Fuller,[3] Blair Hamner,[4] Eun Young Oh,[1] M. Waleed Gaber,[5] David Finklestein,[6] Meredith Allen,[1] Adrian Frank,[1] Ildar T. Bayazitov,[1] Stanislav S. Zakharenko,[1] Amar Gajjar,[7] Andrew Davidoff,[4] and Richard J. Gilbertson[1,7,*]

SUMMARY

Cancers are believed to arise from cancer stem cells (CSCs), but it is not known if these cells remain dependent upon the niche microenvironments that regulate normal stem cells. We show that endothelial cells interact closely with self-renewing brain tumor cells and secrete factors that maintain these cells in a stem cell-like state. Increasing the number of endothelial cells or blood vessels in orthotopic brain tumor xenografts expanded the fraction of self-renewing cells and accelerated the initiation and growth of tumors. Conversely, depletion of blood vessels from xenografts ablated self-renewing cells from tumors and arrested tumor growth. We propose that brain CSCs are maintained within vascular niches that are important targets for therapeutic approaches.

Cancer Cell 11, 69–82, January 2007

4Rs Revisited for SRS

- Reoxygenation
  - When tumors are treated with SRS/SBRT the intratumor environment will become hypoxic leading to secondary cell death due to vascular damage
- Repair
  - Vascular damage and ensuing chaotic intratumor environment may significantly hinder repair of radiation damage
- Redistribution
  - after irradiation with extremely high doses of radiation (>15-20 Gy), in a single fraction, cells are indefinitely arrested in the phases of cell cycle where they were irradiated and undergo interphase cell death
- Repopulation
  - Since SRS/SBRT treatment courses substantially short (1-2 weeks) repopulation of tumor cells will not be substantial during the course of SBRT

Not significant factors. Differential biological effect between tumor and normal tissue is largely gained through minimization of normal tissue volume in SRS and SBRT

Summary

- The LQ model cannot describe the response to very high doses because the predicted radiosensitivity would be too great
- Vascular effects occurs increasingly at higher doses per fraction
- Extreme hypofractionated RT (SBRT/SABR) seems to be capable of overcoming hypoxic radioprotection through mechanisms other than directly killing tumor cells via DNA damage.
- An important mechanism for cell inactivation has been *hypothesized* to be ceramide-mediated endothelial cell apoptosis which becomes important at doses >10 Gy
- A truly mechanistic radiobiological model for SRS/SBRT is currently lacking. The correct dosages for SS/SBRT should be chosen based on clinical experience and prospective trials that balance treatment efficacy against normal tissue toxicity

Perspectives

Physicist

Oncologist/Biologist

Kamil M. Yenice, PhD