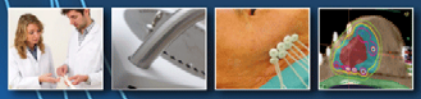
AS1

BrachyNext
Working Together to Shape the Future of Brachytherapy



Hidden Issues in the Use of LQ and Other Models

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Disclosure

William H. McBride, PhD, DSc, does not have any financial relationships or products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

Slide 1

AS1 CME comment was:
*Are there references for these slides? 18, 32, 33, 34, 37, 40, 41, 43, 44

NOTE: I inserted a new slide (Disclosures) so the slide numbers will have changed
A. Schreiber, 5/23/2014

Where Are We Now and Where Are We Going?

Increasing use of non-homogeneous, non-conventional dose delivery by brachytherapy (HDR/LDR), IMRT, IGRT, SRS, SRT, SBRT, Cyberknife, Gammaknife, Tomotherapy, protons, heavy ions, etc.

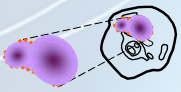
Why the Change?

High precision dose delivery allied with:

- More accurate definition of the target through anatomical and biological imaging
- Repeated imaging during treatment: **adaptive RT**
- Tracking/gating to reduce margins and normal tissue dose

Leads to:

- More high dose rate/high dose/fraction
- More non-homogenous dose distributions
  - Dose painting



How do our radiobiological concepts fit these advances in physics?

- Are better machines, better planning systems, better imaging, better computers, better physics going to rewrite the past lessons learned in clinical radiobiology?
- Are QUANTEC guidelines suited to all delivery schemes?
- Is the LQ formula still appropriate for assessing dose-time relationships for all delivery schemes?
- Note: Classically trained radiation oncologists associate high dose per fraction/HDR with:
  - Late effects that can affect QoL or even be deadly
  - Increased vascular injury and chronic inflammation
  - Increased damage to acute responding tissues from accelerated treatment

Linear Quadratic Model

- Biological effect of radiation is based on a linear and quadratic terms – linear quadratic (LQ) model

Barendson (1982), Thames and Withers (1982), Fowler (1989)

$$S.F. = e^{-(aD+bD^2)} = e^{-E}$$

$$E = nd(a + bd)$$

n = # fractions
d = dose per fraction
D = total dose

$$E/a = nd(1+d/_{a/b})$$

Biologically Effective Dose or $EQD0_{a/b}$

Total dose (D)

Relative Effectiveness

ICRU – Equi-effective dose ($EQDX_{a/b}$) is the total absorbed dose delivered by a reference dose with a fraction size X that leads to the same biological effect as a test treatment with dose per fraction of d and total dose D where a/b is specific for an endpoint and radiation quality

$EQDX_{a/b} = D*(d + a/b)/(X + a/b)$

Normalized total dose 2Gy = BED/RE = BED/1.2 for α/β of 10Gy and BED/1.67 for α/β of 3Gy

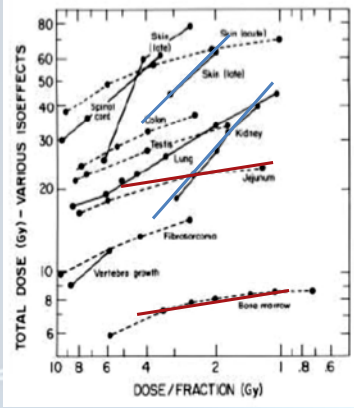
Lea and Catchside: J. Genet. 44: 216,1942

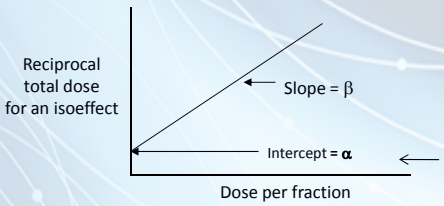
The LQ Model: Strengths

- Takes account of differences in the way tissues with rapid ("acute") and slow ("late") turnover respond to changes in size of dose fraction or in dose rate
- Focused attention on the most serious normal tissue complications (those that occur late), warning clinicians of the dangers of generating "hot spots" in such tissues
- Gives a simple way to change total dose with change in fraction size, especially around 2 Gy, using α and β parameters—neither of which needs to be known!
  - You only need an estimate of the α/β ratio for the tissues in the field
  - Tissues with rapid turnover ("acute") have a high α/β ratio (estimated at around 10 Gy)
  - Tissues with slow turnover ("late") have a low α/β ratio (around 2 Gy)

The Evidence for the Differences Between Tissues

- Late responding tissues respond more than acute responding tissues to change in size of dose per fraction (or dose rate)
- The α/β ratio is a measure of this change
- The steeper the slope of total dose for an isoeffect with change in Fx size (or dose rate), the lower the α/β ratio





Douglas and Fowler, Rad Res 66:401, 1976

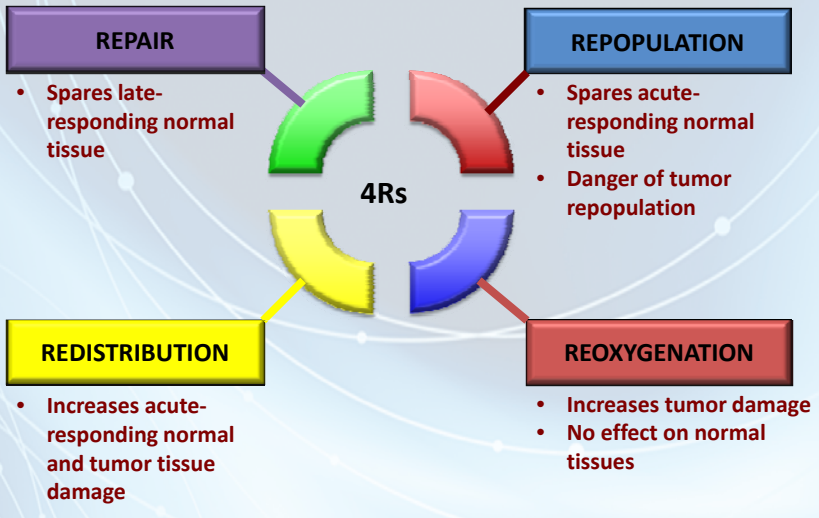
Show how to derive α and β - Fe plot

Thames et al. Int J Radiat Oncol Biol Phys 8: 219, 1982.

The LQ Model: Weaknesses

- Tissues do not all fall into high or low α/β ratio categories—it is a continuum
- The *in vivo* data on which the LQ model is based comes primarily from studies on normal tissue isoeffects; its application to tumors *in vivo* and to *in vitro* clonogenic assays is far less certain
- The α/β ratio is an estimate derived from data from large patient cohorts or from animal studies. It says nothing about values for individuals. This is especially relevant for tumors
- It is superior to other models for data around 2 Gy and LDR, but its application to HDR and other fraction sizes is uncertain. Withers 1989 stated "It is inappropriate at high doses. This matters little since such doses (e.g., >8 Gy) are of limited relevance to radiotherapy"
- The mechanisms why the α/β ratio differs for "late" and "acute" tissues is unclear
- The LQ model assumes
  - The endpoint is well defined and has sufficient precision for isodose calculations
  - The endpoint is related to cell kill
  - The relationship of survival to dose does not change with time
    - » i.e., equal biological effect per dose fraction

Interfraction Events Affecting Isodoses for Fractionated RT



Withers - Adv Radiat Biol 5:241 (1975)

Parameters for the 4Rs Can Be Incorporated into the LQ Equations Allowing Dose Rate to Fraction Size Equivalence Calculation

$S = \exp [- a.D$ one-track killing

$- b.G(t_r).D^2$ two-track killing i.e., "repair"

$+ (1/2s^2).G(ts).D^2$ resensitization (redistribution

$+ T/t_p]$ repopulation

where:

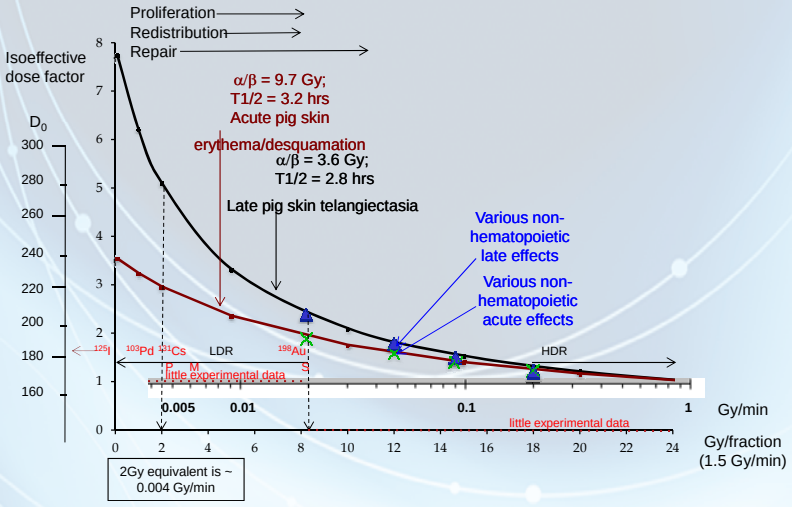
- a is average of a Gaussian distribution with va
- G is the generalized Lea-Catcheside funct ts alteration in damage due to repair or resensitization
- t_r is repair time in minutes - ho
- ts is resensitization time i
- t_p is the repopulati
- with a total do time T

Introduces additional unknowns...and the LQ model begins to lose its innocence!

Brenner et al. Int. J. Rad. Oncol. Biol. Phys. 32:379, 1995

Isoeffect Dose Factors for Different Dose Rates and Fraction Sizes

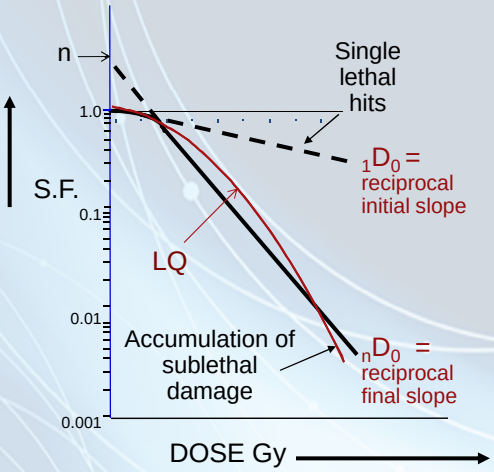
(ratio isoeffect doses for low dose rate to high dose rate or single to Fx dose)



Scaling between fractionated size and dose rate is possible but parameters such as repair $T_{1/2}$ is a problem

After: Turesson Radiotherapy and Oncology 19: 1 (1990)

What Is the Shape of the Survival Curve?



The LQ model describes a curve that continuously bends downwards

The single target, single hit + multi-target (n), single hit model describes a curve that is linearly related to log SF

$$S.F. = e^{-D/{}_1D_0[1-(1-e^{-D/{}_nD_0})^n]}$$

Single hit | Accumulated damage | Extrapolation Number

Does it Matter?

Doses isoeffective for 60 Gy in 2 Gy Fx to lung

Dose/fx	Gy LQ (no time correction)	Gy LQ (time correction)	Gy TC (no time correction)	Gy TC (time correction)
5	37.5	40.2	37.6	39.6
10	23.1	25.1	27.6	29.5
15	16.7	18.3	24.8	26.6
20	13.0	14.4	23.6	25.4
25	10.7	11.8	22.9	24.7

Yes, when extrapolating from low to high dose per fraction.

Courtesy: Howard Thames

Prompted Development of the "Universal" Survival Curve, Multi-target Model

$$D_{SBRT} = \alpha \times D_0 \times D_{CFRT} \times (1 + d_{CFRT}/\alpha/\beta) + n_{SBRT} \times D_q$$

UNIVERSAL SURVIVAL CURVE AND SINGLE FRACTION EQUIVALENT DOSE: USEFUL TOOLS IN UNDERSTANDING POTENCY OF ABLATIVE RADIOTHERAPY

Clint Park, M.D. M.S., Lech Papiez, Ph.D., Shichuan Zhang, M.D., Ph.D., Michael Story, Ph.D., and Robert D. Timmerman, M.D.

Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX

Truthfully, I do not know the shape of the *in vivo* survival curve for normal tissues over the full dose range.
For tumors, the final portion of the curve seems to vary depending in part on what oncogenes are activated

Some Rationale for the Use of High Dose/fx or HDR

- If the sensitivity of a cancer to changes in fraction size or dose rate is similar to that for dose-limiting normal tissues, there may be little to be gained from trying to exploit the 4Rs
- Ablative fractionated RT and HDR brachytherapy make most of the 4Rs irrelevant. But,
  - Shorter treatment time may minimize any effect of accelerated tumor repopulation
  - Dose coverage is less likely to change with treatment time
- Economics
  - Significant reduction in machine time
  - Less time consuming for the physicists
  - Saves patients time and travel

What Is "High"?

- Hypofractionation
  - Dose per fraction higher than 2.2 Gy????
  - 10–20 fractions????
  - The aim is generally curative with ...rvation
- Oligofractionation
  - 1–5 fractions of 7...
  - Greater dos... ...wer prescription isodose
  - These a... ...e doses

These are different endpoints and different aims with different constraints!

If the sensitivity of a cancer to changes in fraction size or dose rate is similar to that for dose-limiting normal tissues, there may be little to be gained from trying to exploit the 4Rs...

What Are the α/β Ratios for Human Cancers?

- The Phase III clinical trials of altered fractionation confirmed that HNSCC tumors had high α/β ratios
- Slowly turning over tumors such as melanoma, soft tissue sarcoma, and liposarcoma have long been known to have low α/β ratios, but the finding that prostate and breast α/β ratios may also be low, combined with the introduction of IMRT, increased enthusiasm for hypofractionation

Prostate

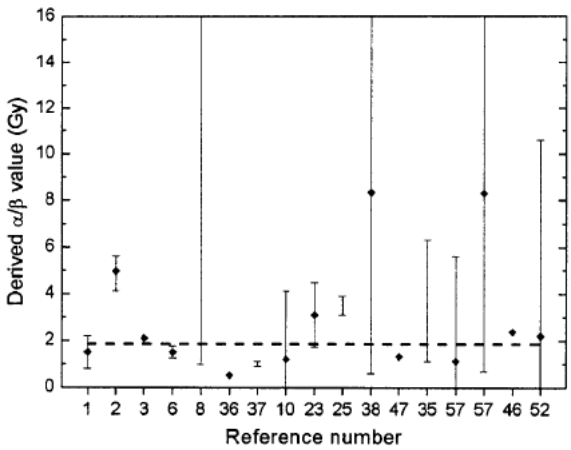
- Brenner and Hall IJROBP 43:1095, 1999
  - Comparing implants with EBRT
  - α/β ratio is 1.5 Gy (0.8, 2.2)
- Lukka JCO 23: 6132, 2005
  - Phase III NCIC 66 Gy 33F in 45 days vs 52.5 Gy 20F in 28 days
  - Compatible with α/β ratio of 1.12 Gy (-3.3-5.6)

Breast

- UK START Trial Lancet. 2008 371;1098-107
  - α/β ratio = 4.6 Gy (1.1-8.1) for tumor control and 3.4 Gy (2.3-4.5) for late breast appearance

Caveats…
What is the α/β ratio for a human cancer?

Prostate Cancer α/β Values



17 studies since Brenner & Hall (1999)

- 9 EB-LDR
- 1 EB-HDR
- 5 EB
- 2 *in vitro*

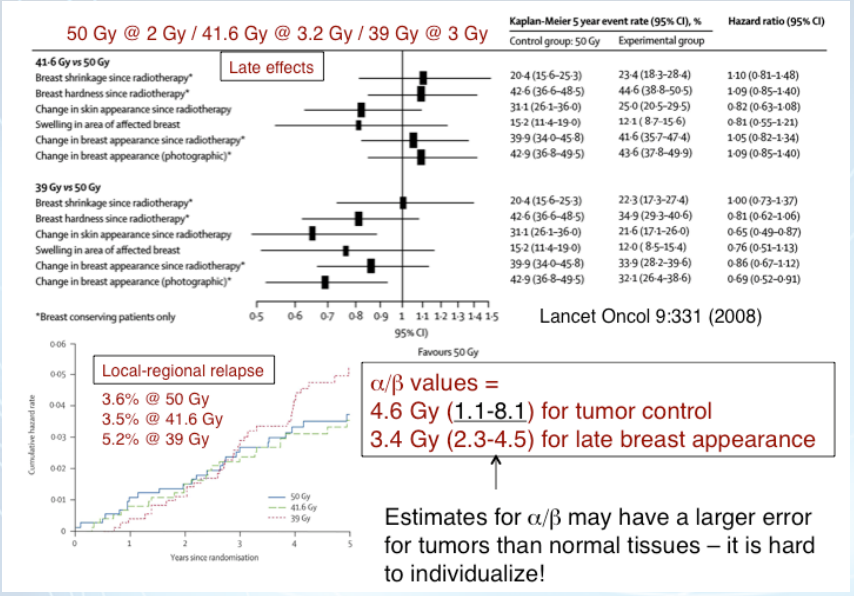
Modeling: *RBE, repair, repopulation, dose heterogeneity*

α/β = 1.85 Gy

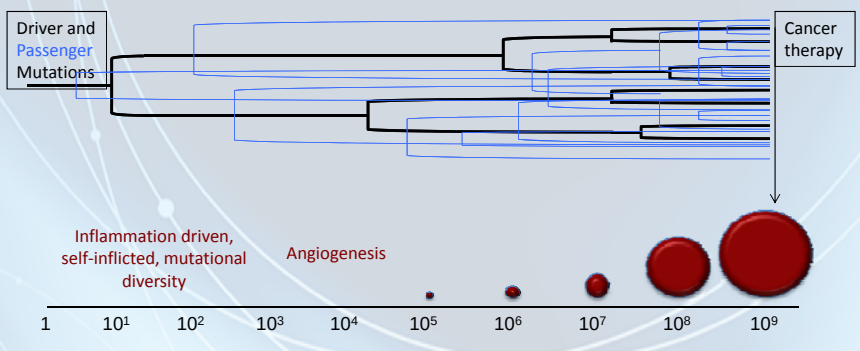
Dasu A *Clinical Oncology* 2007;19:289-301

Note the large error bars in many studies!

START A Breast Cancer Trial



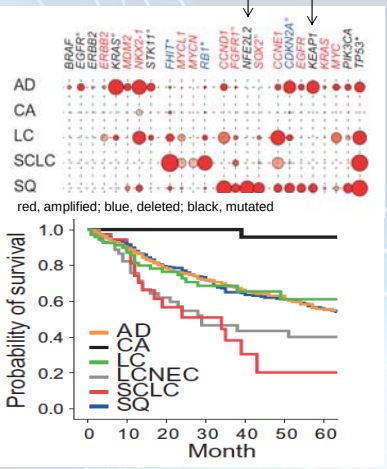
Where does the heterogeneity come from?

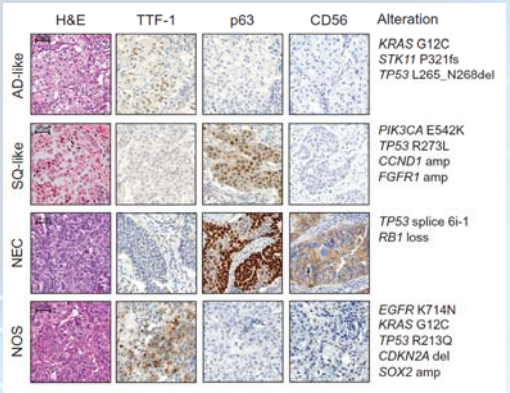


What is the effect of tumor mutations on tumor turnover, response to therapy, and α/β values?

A Genomics-Based Classification of Human Lung Tumors
The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM),
Sci Transl Med **5**, 209ra153 (2013);
DOI: 10.1126/scitranslmed.3006802

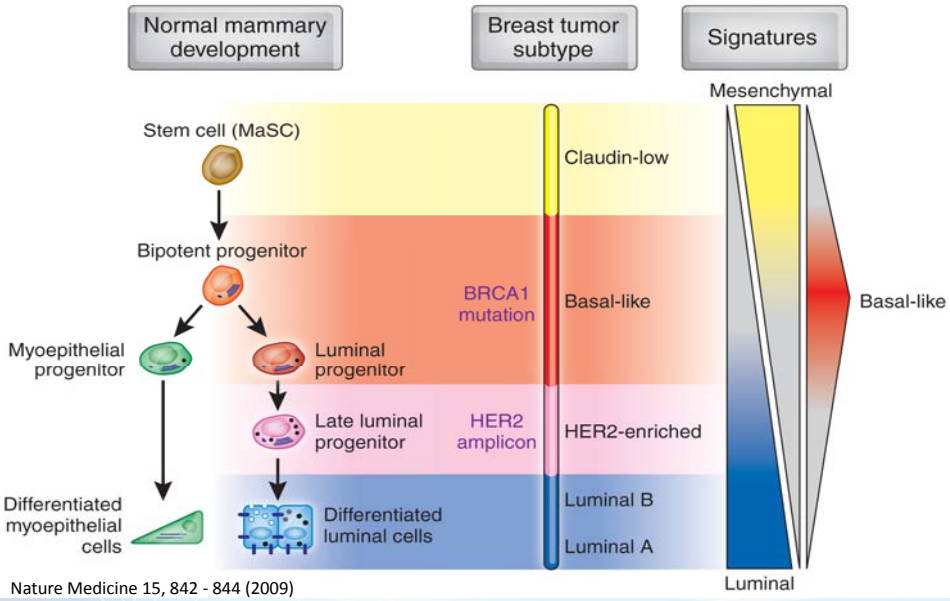
The major players in determining anti-oxidant response are frequently mutated in many cancers





Any estimate of α/β ratio for "lung cancer" should take molecular features into account

Aren't These Different Diseases?



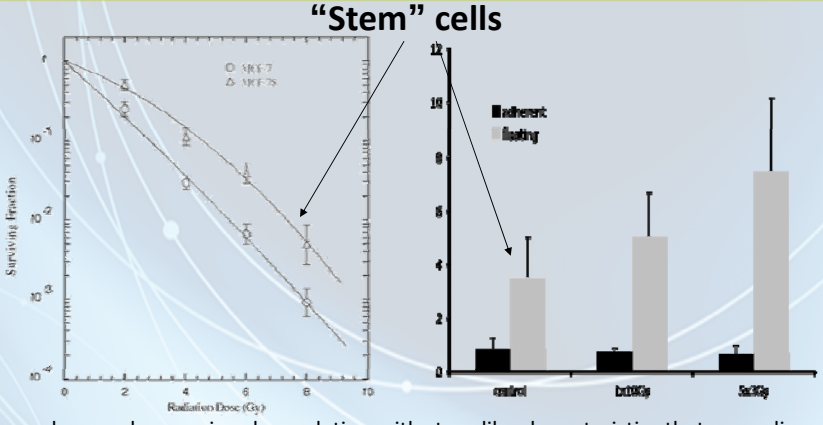
Nature Medicine 15, 842 - 844 (2009)

Heterogeneity Due to Cell Hierarchies

Many tumors contain cancer "stem" cells that are:

- Highly tumorigenic
- Responsible for metastases, accelerated repopulation during therapy, and recurrence
- Have high free radical scavenger levels
- Resistant to killing by chemo- and radiotherapy
- Can be derived by reprogramming of non-stem cells

Response to Radiation

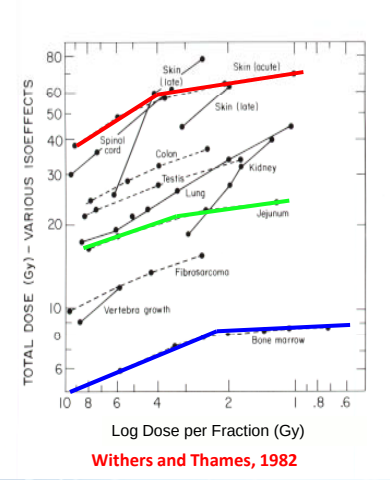


Tumors have a clonogenic subpopulation with stem-like characteristics that are radioresistant and are selected for by fractionated irradiation.

Phillips et al J Natl Cancer Inst 98:1777, 2006
Stem Cells. 2012 May;30(5):833-44. doi: 10.1002/stem.1058.
Radiation-induced reprogramming of breast cancer cells.
Lagadec C, Vlashi E, Della Donna L, Dekmezian C, Pajonk F.

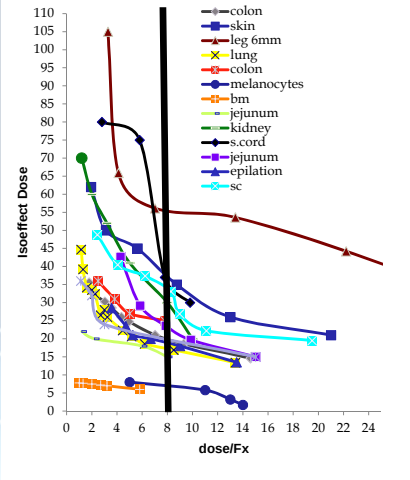
What are the radiobiological consequences of increasing fraction size/dose rate?

Decreased Repair: Above ~8 Gy the Differences in Slopes of the Isoeffect Curves Fade



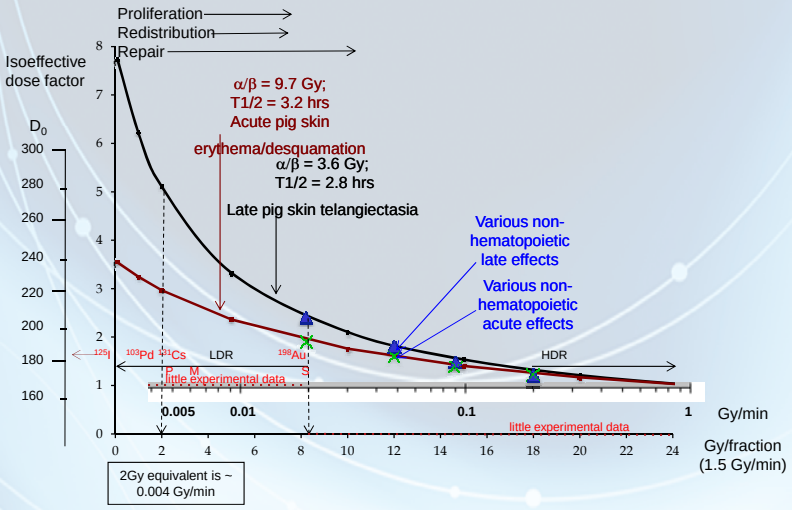
Withers and Thames, 1982

Log – Log scale



Linear – Linear scale

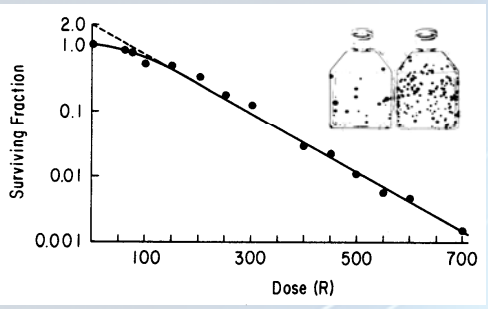
Isoeffective Dose Factors for Different Dose Rates and Fraction Sizes (ratio isoeffect doses for low dose rate to high dose rate or single to Fx dose)



Scaling between fractionated size and dose rate is possible but repair $T_{1/2}$ is a problem

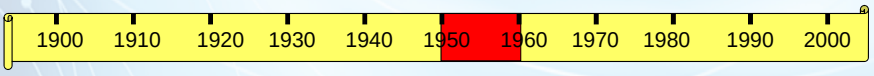
After: Turesson Radiotherapy and Oncology 19: 1 (1990)

Decreased Number of Cell Cycles: T.T. Puck and P.I. Marcus

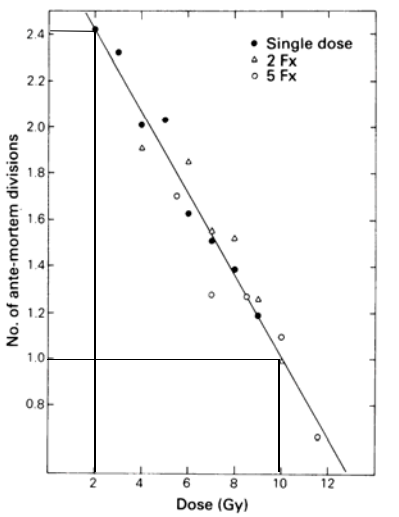


"Cells in which the ability to reproduce has been destroyed by doses below 800 r can still multiply several times. At higher doses even a single cell division is precluded."

Puck and Marcus JEM vol. 103: 653-666, 1956



Ante-mortem Proliferation Kinetics

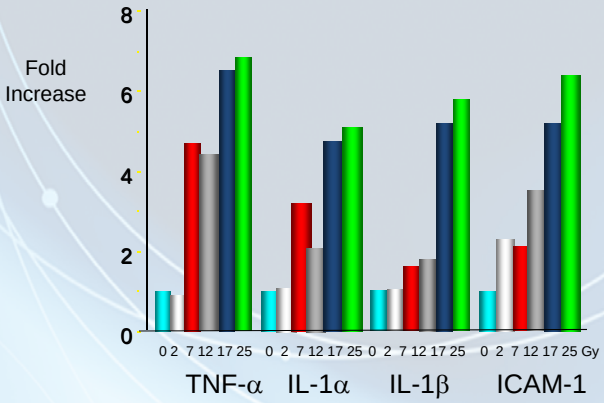


In vitro K562 cells
divisions at an isoeffective dose

- Dose fractionation has little effect on the number of ante-mortem divisions at isoeffective survival, but total dose does
- ≥8–10 Gy prevents cells dividing. One might expect:
  - More rapid tumor responses
  - More effects on acute responding tissues
  - The time to a late endpoint to decrease as dose increases
  - Tumor repopulation to be of less importance but to be accelerated

McBride and Withers Br J Cancer 53:386 (1986)

Increased Inflammation at ≥7 Gy

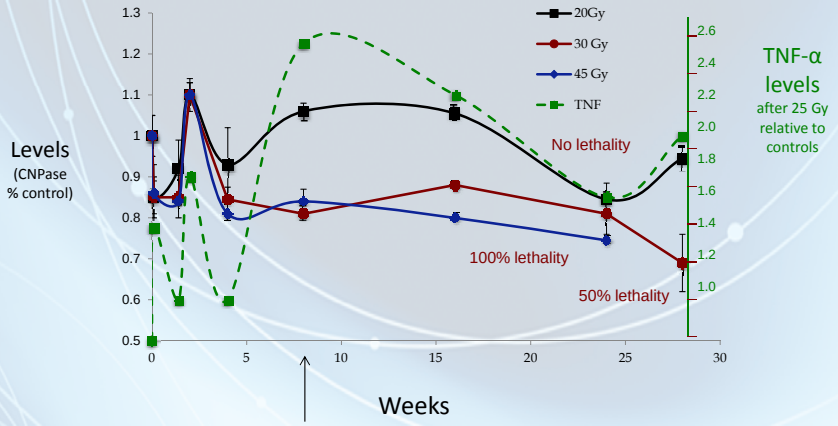


≥7 Gy is needed to generate robust brain inflammatory markers in mice

6 hours after RT

Chiang et al. Brain Research, 566, 265 (1991).

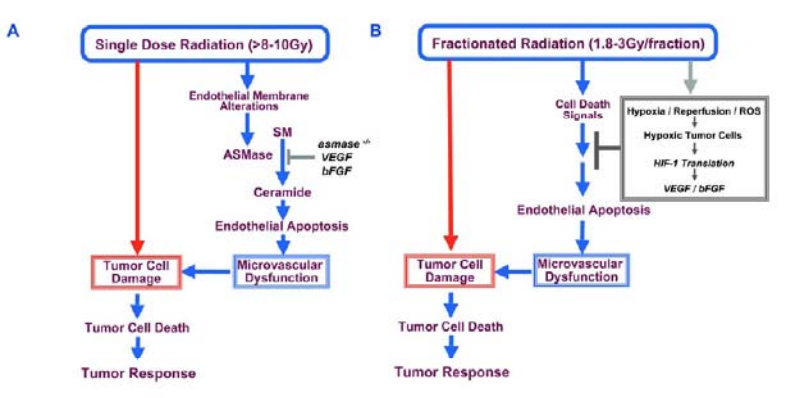
Cell Death, Proliferation, and Inflammation With Time After Brain Irradiation



C3H mice

After: Chiang et al. Int. J. Radiat. Biol 72, 45 (1997)

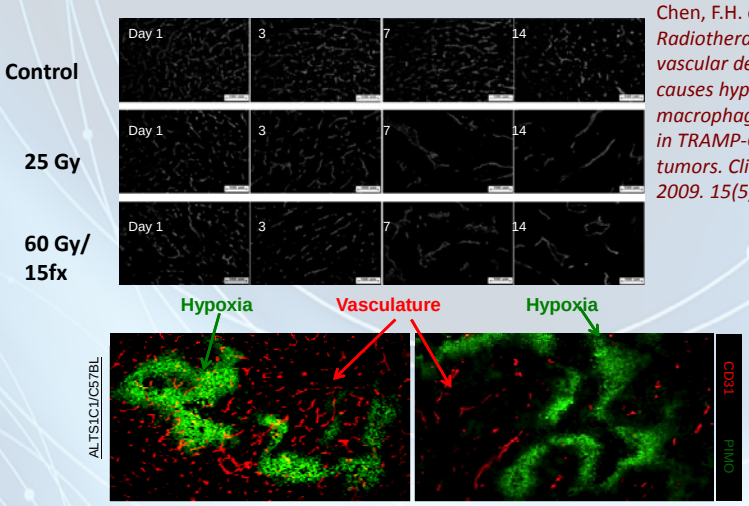
Increased Vascular Damage?



"The endothelial responses in mouse and human tumor specimens both display an apparent threshold at 8–10 Gy and a maximal response at 20–25 Gy."

Zvi Fuks and Richard Kolesnick - Cancer Cell 8:89, 2005

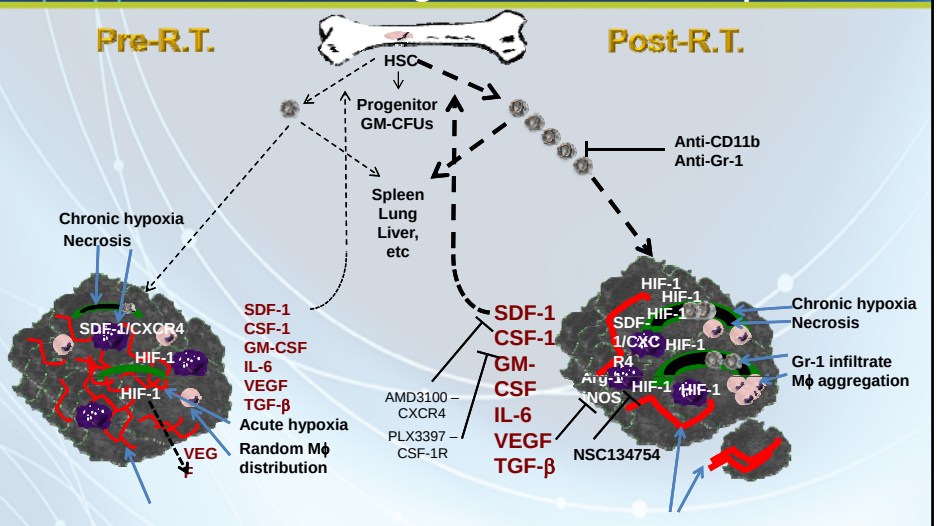
Vascular "Pruning" After RT



Chen, F.H. et al, *Radiotherapy decreases vascular density and causes hypoxia with macrophage aggregation in TRAMP-C1 prostate tumors. Clin Cancer Res, 2009. 15(5): p. 1721-9.*

Acute hypoxia → **Chronic hypoxia**

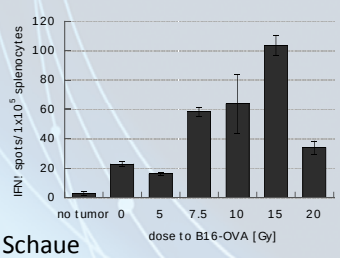
Tumor Vascular Changes After RT Are Complex!

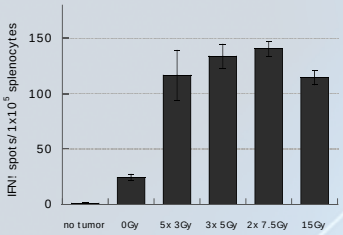


Angiogenesis → **Vasculogenesis**

McBride unpublished

Increased Radiation-Induced Tumor Immunity?





Dorthe Schaue

Multiple fractions may prime for adaptive responses

One benefit of hypofractionation may be increased immune/abscopal effects
"Fractionated but Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect when Combined with Anti–CTLA-4 Antibody."
Dewan et al Clin Cancer Res 15; 5379, 2009

3 x 8 Gy > 5 x 6 Gy or 1 x 20 Gy

- Models to extrapolate from low dose/fraction data to >8 Gy/fraction are flawed
- But it is hard (for me!) to escape the conclusion that the radiobiology at >8 Gy/ fraction is different from that at 2 Gy

Is There Any Biological Advantage for Very High Dose/HDR Rationale if Tumor and Normal Tissue Have Similar α/β Ratios?

Moderate doses of <8 Gy may

- Still provide some sparing for late responding tissues
- Allow some proliferation of acute responding tissues
- Minimize vascular damage
- Minimize inflammation
- Optimize anti-tumor immunity

High doses of >10 Gy may cause

- Greater acute and late damage
- Greater vascular damage and inflammation
- Suppress anti-tumor immunity

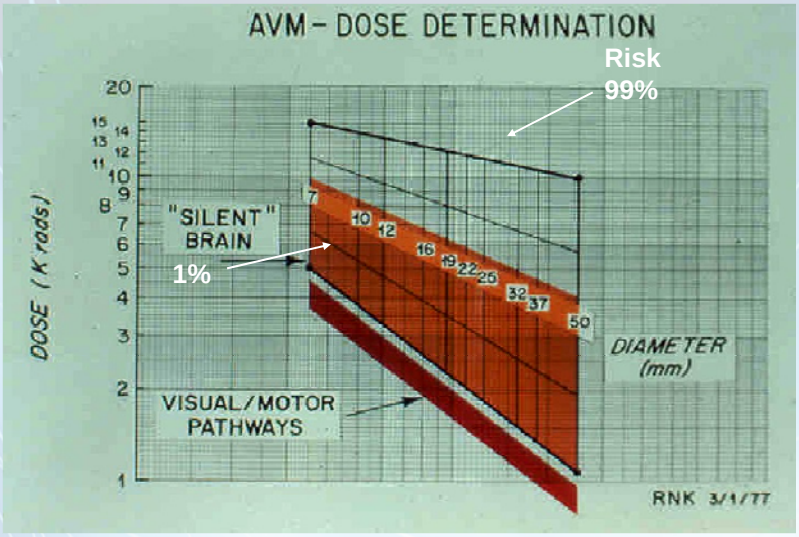
Oligofractionation — Ablative SBRT

- According to Fowler, 3 x 20 Gy is enough dose for 27 logs of kill!

  Int. J. Radiation Oncology Biol. Phys., 60, pp. 1241–1256, 2004

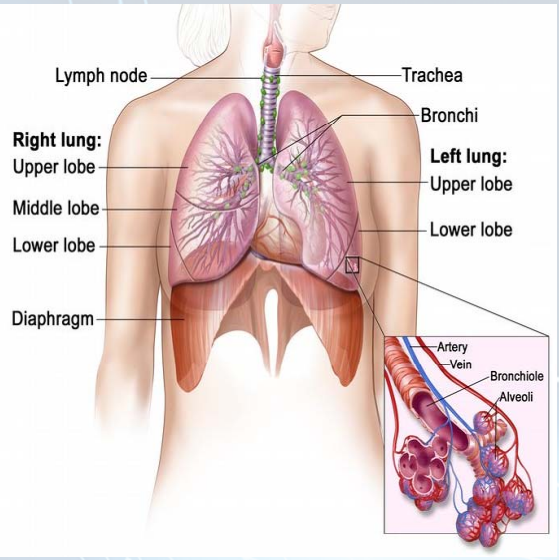
- Is the dose excessive?
- If tumor recurs locally is it because of hypoxia, "intrinsic" radioresistance, or geographic miss?
- Doses of 3 x 20 Gy will ablate most normal tissues, but the structure of the tissues will matter

Dose/Volume Matters More With Oligofractionation



Kjellberg N Engl J Med 309:269-274, 1983

As Does Tumor Location



Tissue tolerance is affected by

- The number of clonogens that make up an FSU
- The organization of FSUs in series or in parallel in a tissue

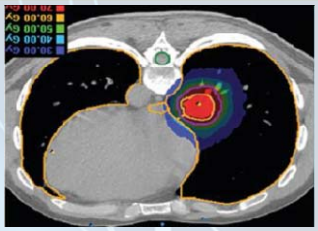
(By definition, for an FSU to survive, at least one clonogen must survive)

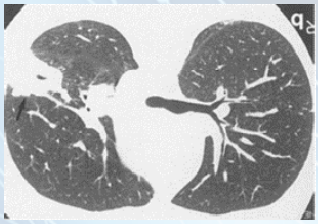
(McBride and Withers In Perez & Brady's Principles and Practice of Radiation Oncology p61, 2013)

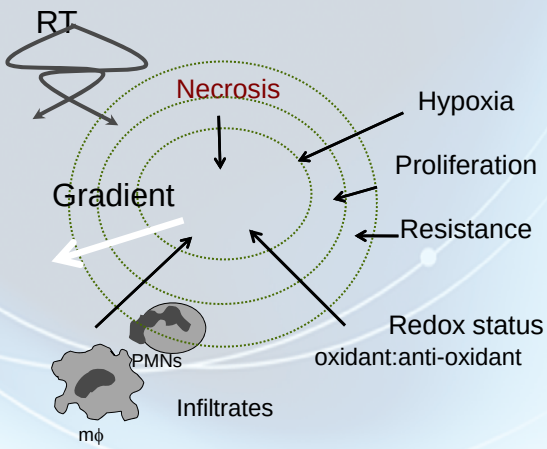
General need to avoid critical serially organized structures

Less dose can be given by SBRT for centrally located tumors in lung

The Shape of the Lesion Caused by IMRT/Brachytherapy Differs From Conventional Fractionation







The ability to deliver RT to defined smaller volumes may alter the tumor-host relationship—think outside the field!

Schaue and McBride Frontiers in Oncol 2:1 (2012)

Conclusions

- Consider the aim—normal tissue preservation/ablation/palliation
- Tight margins can result in missed tumor extensions!
- Hypofractionation without excessive complications is probably feasible for tumors with a slow turnover—melanoma, prostate, breast, and maybe other sites
- Oligofractionation may be useful where there are no critical structures in the field, provided the volume is limited. May be useful for "picking off" a few metastases, e.g., after chemo/biological therapies
- High and low dose fractions/HDR and LDR/large and small volumes will have different radiobiological effects
  - Tumor cell proliferation
  - Tumor vasculature
  - Pro-inflammatory/anti-inflammatory cytokine production
  - Anti-tumor immunity
- Tumors are heterogeneous—so is their response to RT. We need to correlate response with molecular markers…desperately!
- The 4Rs are still relevant in many cases, even hypofractionation, but individualization of therapy is needed