Radiobiology of high dose per fraction

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Historically

- Research focused on clinically relevant doses per fraction of **1–3 Gy**
- Radiobiology at these doses is quite "mature"
- Little incentive/funding for high-dose research up until now

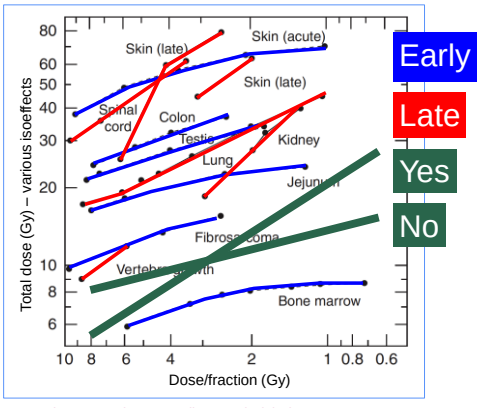
Why now use/test high-dose fractions?

- Because we can: Physics
- Patient convenience and demand
- Lower cost of whole treatment
- Evidence that it can be very effective
- Evidence of low α/β in some tumors, *e.g*. prostate, breast
- Other tumors…? Lets hypothesize: esophagus, melanoma, liposarcoma, *GBM*, *Pancreatic* ?

So why not LQ at high doses?

- Response is really linear at higher doses?
- Vascular damage?
- Immunological effects?
- Increased apoptosis?
- Mixed tumor cell populations with different response characteristics?

Answers will depend on tissue type and tumor type / stage



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

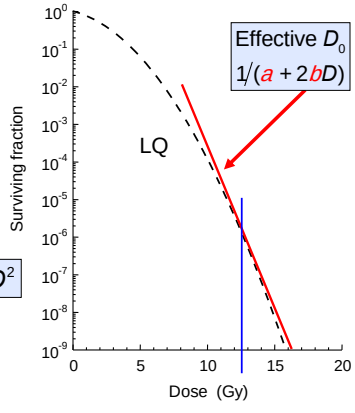
Linear Quadratic model

Effective D_0

$$-\ln(S) = aD + bD^2$$

α/β = 3 Gy

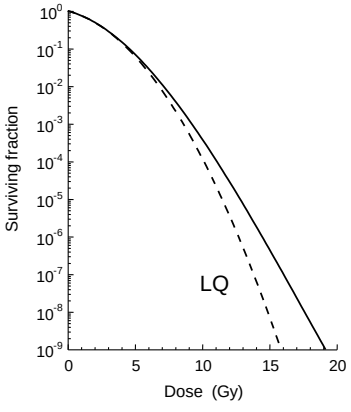
SF2 = 0.5



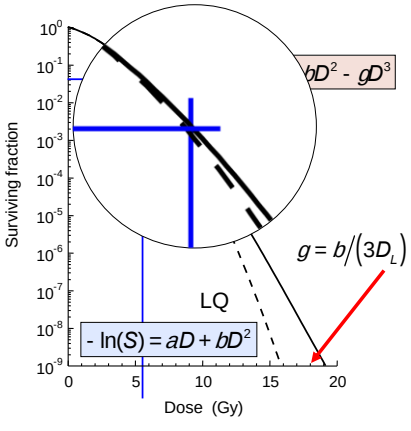
Effective D_0 is too small at high doses

	SF2 = 0.5					SF2 = 0.6					SF2 = 0.7				
α/β / Dose	1.5	2	3	6	10	1.5	2	3	6	10	1.5	2	3	6	10
1.8	2.0	2.1	2.2	2.4	2.5	2.7	2.8	3.0	3.3	3.5	3.9	4.0	4.2	4.7	4.9
2	1.8	1.9	2.1	2.3	2.5	2.5	2.6	2.8	3.1	3.4	3.6	3.7	4.0	4.5	4.8
4	1.1	1.2	1.3	1.6	1.9	1.5	1.6	1.8	2.2	2.6	2.1	2.2	2.5	3.2	3.7
6	0.8	0.8	1.0	1.3	1.6	1.0	1.1	1.3	1.7	2.1	1.5	1.6	1.9	2.5	3.1
9.5	0.5	0.5	0.7	0.9	1.2	0.7	0.7	0.9	1.3	1.6	1.0	1.1	1.3	1.8	2.3
12	0.4	0.4	0.5	0.8	1.0	0.5	0.6	0.7	1.0	1.4	0.8	0.9	1.0	1.5	2.0
19	0.3	0.3	0.4	0.5	0.7	0.4	0.4	0.5	0.7	1.0	0.5	0.6	0.7	1.0	1.4
20 Gy	0.2	0.3	0.3	0.5	0.7	0.3	0.4	0.5	0.7	0.9	0.5	0.5	0.7	1.0	1.3

Linear Quadratic must straighten at high doses

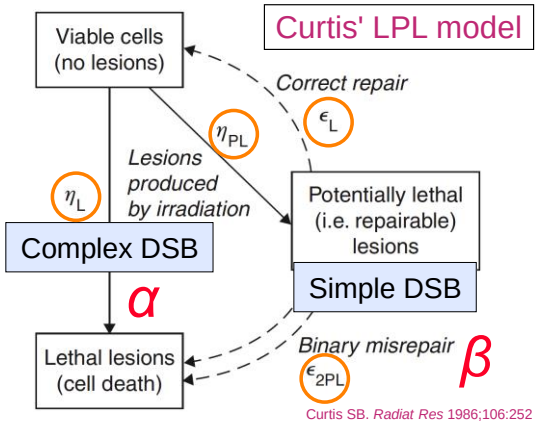


The **L**inear **Q**uadratic **C**ubic model



α/β = 3 Gy

SF2 = 0.5

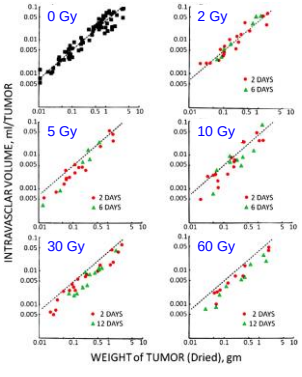


Curtis SB. *Radiat Res* 1986;106:252

Response heterogeneity

Alternative damage response pathways and/or cell types which are dose dependent?

Vascular effects occur at high doses



Functional intravascular volume

Walker 256 tumors (s.c.) grown in legs of Sprague-Dawley rats

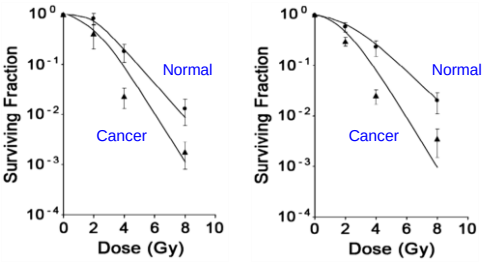
Single dose radiation

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

Vascular effects occur at high doses

Breast cancer patients

Endothelial cells from normal breast or cancer

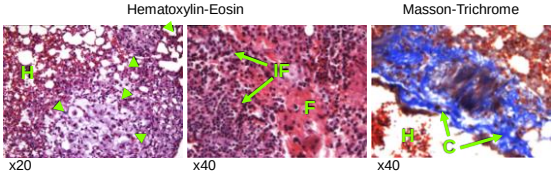


Park HJ et al. *Radiat Res* 2012;177:311-27

Immunological effects at high doses

A549 Human NSCLC in lungs of nude mice

27 days after 12 Gy single dose



Tumor

Small tumor nodules (arrows) with degenerative changes in nuclei and cytoplasm. Multiple large vacuoles, hemorrhages [**H**] and scattered inflammatory infiltrates

Normal lung

Heavy infiltration of inflammatory cells [**IF**] mostly lymphocytes and neutrophils. Fibrous tissue [**F**] in midst of inflammatory infiltrates

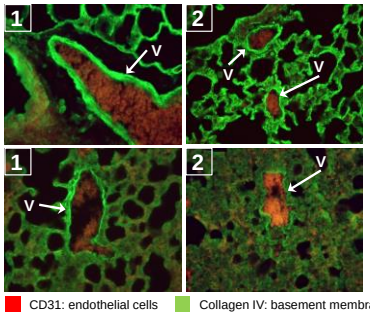
Normal lung

Extensive fibrotic tissue [**C**] and hemorrhages [**H**]

Hillman GG et al. *Radiother Oncol* 2011;101:329-36

Immunological effects at high doses

Normal lung in tumor-bearing lungs 50 days after 10 Gy



Damaged Vessels

Control 29%

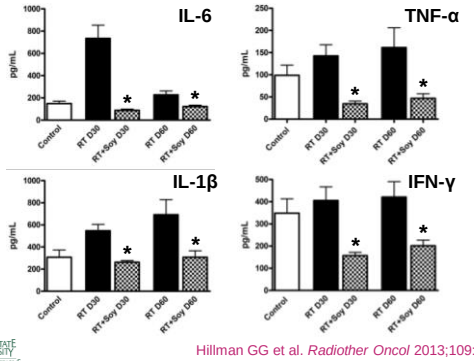
Rad 42%

Disruption and distortion of basement membrane of vessels (1 & 2) and thickened, inflamed and hemorrhagic septa (2)

CD31: endothelial cells Collagen IV: basement membrane SMA: pericytes

Hillman GG et al. *Radiother Oncol* 2013;109:117-25

Inflammatory cytokines at high doses



Hillman GG et al. *Radiother Oncol* 2013;109:117-25

Response heterogeneity

Mixed target cell populations with different sensitivities?

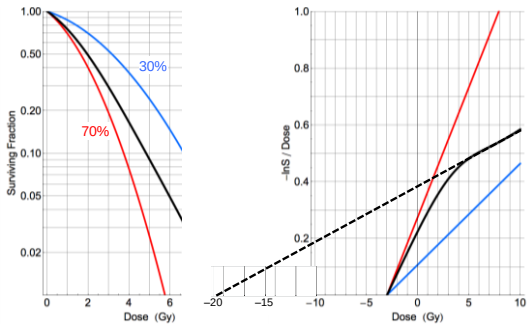
Radiotherapy and Oncology, 9 (1987) 241- 248
Elsevier
241
RTO 00341

An explanatory hypothesis for early- and late-effect parameter values in the LQ model

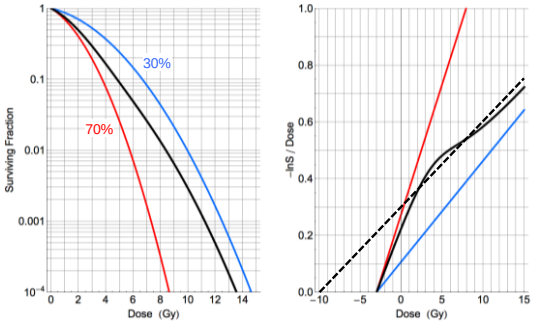
T. E. Schultheiss, G. K. Zagars and L. J. Peters
Division of Radiotherapy, The University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, TX 77030, U.S.A.

1. Higher-order terms (*e.g.* LQC) result from response heterogeneity
2. Leads to increase in "measured" value of *α/β*
3. Leads to "linearization" of the "cell survival curve" at higher doses
4. Explains the higher *α/β* for early effects and in some tumors

Response heterogeneity



Response heterogeneity



The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved? *Int J Radiat Oncol Biol Phys* 2014;88:254-62

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**Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California; †Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut, and ‡Center for Radiological Research, Columbia University Medical Center, New York, New York*

Received

LQ applies at high dose per fraction

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), are rapidly becoming accepted practice for the radiation therapy of certain tumors. Typically, SRS and SBRT involve the delivery of 1 or a few large-dose fractions of 8 to 30 Gy per fraction: a major paradigm shift from radiation therapy practice over the past 90 years, when, with relatively large amounts of normal tissues receiving high doses, the goal was to maximize tumor response for an acceptable level of normal tissue injury. The development of SRS and SBRT have come about because of technologic advances in image guidance and treatment delivery techniques that enable the delivery of large doses to tumors with reduced margins and high gradients outside the target, thereby minimizing doses to surrounding normal tissues. Because the results obtained with SRS and SBRT have been impressive, they have raised the question whether classic radiobiological modeling, and the linear-quadratic (LQ) model, are appropriate for large doses per fraction. In addition to objections to the LQ model, the possibility of additional biological effects resulting from endothelial cell damage, enhanced tumor immunity, or both have been raised to account for the success of SRS and SBRT. In this review, we conclude that the available preclinical and clinical data do not support a need to change the LQ model or to invoke phenomena over and above the classic 5 Rs of radiobiology and radiation therapy, with the likely exception that for some tumors high doses of irradiation may produce enhanced antitumor immunity. Thus, we suggest that for most tumors, the standard radiobiology concepts of the 5 Rs are sufficient to explain the clinical data, and the excellent results obtained from clinical studies are the result of the much larger biologically effective doses that are delivered with SRS and SBRT.

Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Modelling of fractionation

Use of the LQ model with large fraction sizes results in underestimation of isoeffect doses

Tommy Sheu [a], Jessica Molkentine [a], Mark K. Transtrum [c], Thomas A. Buchholz [a,b], Hubert Rodney Withers [a], Howard D. Thames [a,d,*], Kathy A. Mason [a]

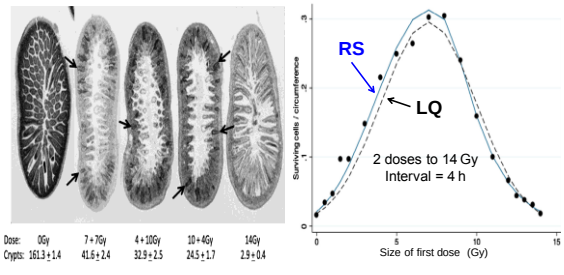
…consistent with hypothesis that use of the LQ model to estimate tolerance doses for SBRT treatments with large fraction sizes is likely to lead to underestimation of those doses. This finding is consistent with the possibility that the target-cell survival curve is increasingly linear with increasing dose.

Stereotactic body radiotherapy
Linear-quadratic model
Tolerance calculations
Microcolony assay

using the LQ model, the lethal potentially lethal (LPL) model, and a repair-saturation (RS) model.
Results: Cell kill was greater in the group receiving the larger fraction first, creating an asymmetry in the plot of survival vs size of first dose, as opposed to the prediction of the LQ model of a symmetric response. There was a significant difference in the estimated βs (higher β after larger first doses), but no significant difference in the αs, when large doses were given first vs small doses first. This difference results in underestimation (based on present data by approximately 8%) of isoeffect doses using LQ model parameters based on small fraction sizes. While the LPL model also predicted a symmetric response inconsistent with the data, the RS model results were consistent with the observed asymmetry.
Conclusion: The LQ model underestimates doses for isoeffective crypt-cell survival with large fraction sizes (in the present setting, >9 Gy).

Radiother Oncol 2013; 109:21-5

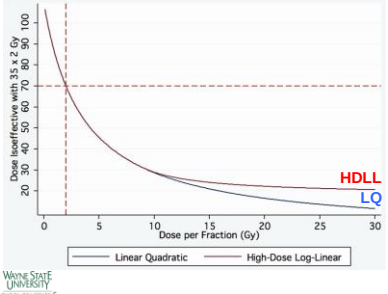
Repair Saturation fits better than LQ



Sheu T et al. *Radiother Oncol* 2013;109:21-5

Why does this make a difference?

High-dose log-linear (HDLL) model predicts higher isoeffect dose than LQ as the curve goes linear



At what dose does this divergence become significant?

Courtesy: HD Thames

Approach

- Consider three tumor sites (breast, prostate, lung) where hypofractionation or SBRT is being used
- Identify relevant α/β values of tumor and NTs, and doses per fraction used clinically
- Choose HDLL models consistent with parameters
- Estimate size of dose per fraction at which 10% or greater disparity between predicted isoeffect doses occurs
- Compare this with doses actually in use clinically

Results

Breast: For dose/fraction 2.7-3.3 Gy, LQ predictions of isoeffect doses are approximately correct for tumor response and toxicity, but too low for higher doses per fraction (>6 Gy)

Prostate: For dose/fraction of 2.7-3.1 Gy, LQ predictions of isoeffect doses are approximately correct for tumor response and toxicity, but too low for higher doses per fraction (>4 Gy). This undermines to some extent the LQ-predicted therapeutic gain from hypofractionation

Lung: For dose/fraction < 10 Gy, LQ predictions of isoeffect doses are approximately correct for tumor response and early toxicity, but too low for higher doses per fraction (>12 Gy)

Courtesy:
HD Thames

Hypofractionation: Research to do

- Physics + Biology
  - superb dose definition: QA
  - optimizing image guidance
  - rapid delivery: high dose-rate effects?
- Biology + Physics
  - can low tumor "α/β" be exploited clinically?
  - is LQ still good for high-dose fractions?
  - vascular and immunological effects?