

**“Non-classical” radiobiology
relevant to high-doses per
fraction**

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Why reconsider high dose fractions?

- Because we can: Physics
- Patient convenience and demand
- Lower cost of whole treatment
- Evidence that it is very effective
- Evidence of low α/β in some sites

The radiobiology has not yet caught up



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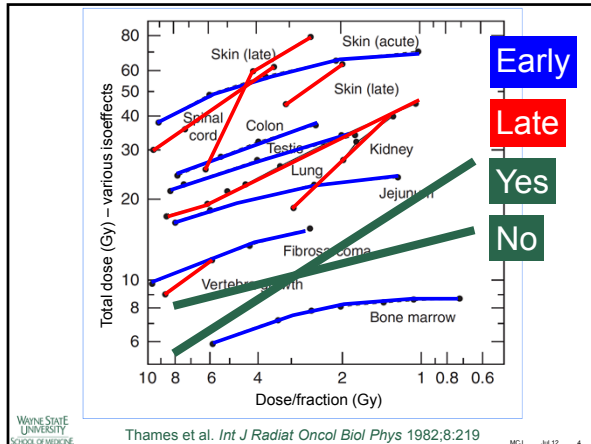
Why not LQ at high doses?

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

Answers likely depend on tissue type
and tumor type / stage



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Semin Radiat Oncol 2008;18:234-9

SEMINARS IN RADIATION ONCOLOGY

The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction

David J. Brenner, PhD, DSc

1. Mechanistic, biologically based **No**
2. Few parameters → practical **Yes**
3. Other models predict similar dose-fractionation **No**
4. Well-documented predictive value in Lab **Yes**
5. Validated up to 10 Gy per fraction, OK to 18 **No**

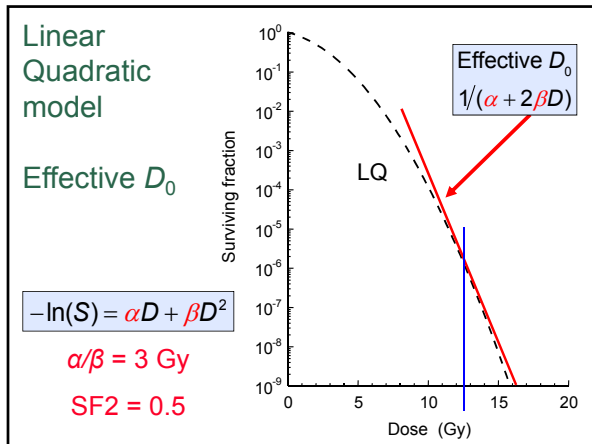
Semin Radiat Oncol 2008;18:240-3

SEMINARS IN RADIATION ONCOLOGY

The Linear-Quadratic Model Is Inappropriate to Model High Dose per Fraction Effects in Radiosurgery

John P. Kirkpatrick, MD, PhD, Jeffrey J. Meyer, MD, and Lawrence B. Marks, MD

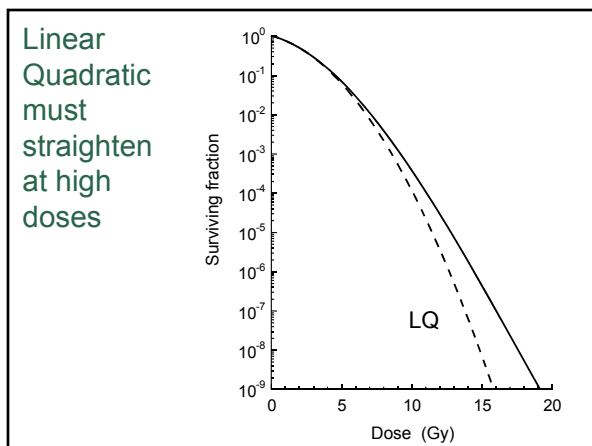
1. LQ model derived mostly in vitro **No**
2. LQ underestimates high-dose tumor control **???**
3. LQ ignores cell subpopulations **Yes**
4. LQ mechs don't reflect vascular, stromal **Yes**
5. Need understanding mol mechs and stem cells **No**

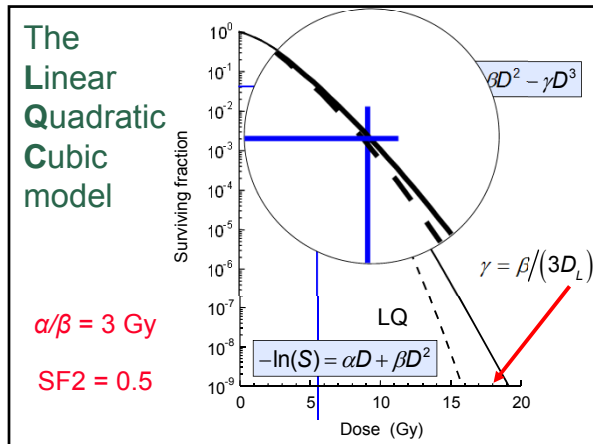


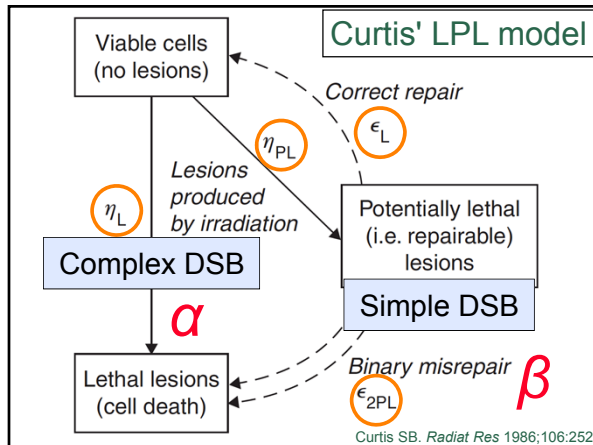
Effective D_0 is too small at high doses

α/β	SF2 = 0.5					SF2 = 0.6					SF2 = 0.7				
	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

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Why can't the LQ model describe the response to very high doses?

- 23% 1. The mathematics is too complex
- 17% 2. It doesn't explain the response of stem cells
- 20% 3. Predicted radiosensitivity would be too great
- 27% 4. It must be based on understood mechanisms
- 13% 5. It is derived only from in vitro data

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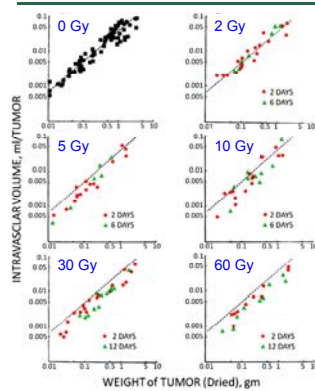
Answer 3

Refs: Brenner DJ. *Semin Radiat Oncol* 2008;18:234-9
Kirkpatrick JP et al. *Semin Radiat Oncol* 2008;18:240-3

Response heterogeneity

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

Vascular effects occur at high doses



Functional
intravascular
volume

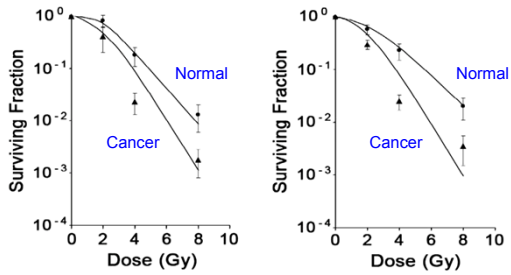
Walker 256 tumors (s.c.)
grown in legs of
Sprague-Dawley rats

Single dose radiation

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

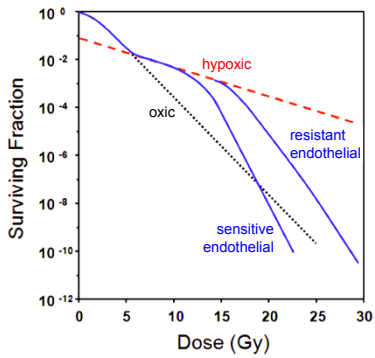
Vascular effects occur at high doses

Breast cancer patients
Endothelial cells from normal breast or cancer



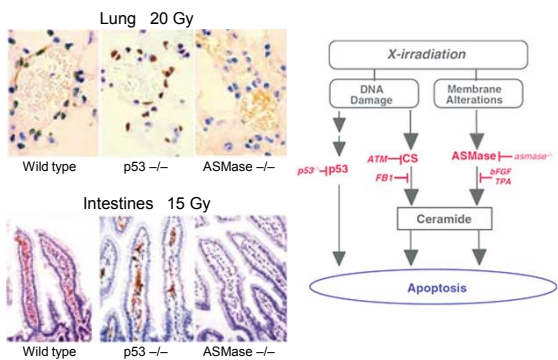
Park HJ et al. *Radiat Res* 2012;177:311-27

Vascular effects occur at high doses



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

Endothelial cell apoptosis at high doses



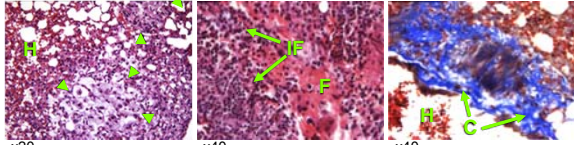
Kolesnick R & Fuks Z. *Oncogene* 2003;22:5587-906

Immunological effects at high doses

A549 Human NSCLC in lungs of nude mice
27 days after 12 Gy single dose

Hematoxylin-Eosin

Masson-Trichrome



x20

Tumor

x40

Normal lung

x40

Normal lung

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

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

Extensive fibrotic tissue [C] and hemorrhages [H]

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

What effect occurs increasingly at higher doses per fraction?

- 20% 1. Survival of stem cells
- 23% 2. Increased cell proliferation
- 13% 3. Lowered inflammatory and immune response
- 23% 4. Vascular destruction
- 20% 5. Decreased apoptosis

What effect occurs increasingly at higher doses per fraction?

- 1. Survival of stem cells
- 2. Increased cell proliferation
- 3. Lowered inflammatory and immune response
- 4. Vascular destruction
- 5. Decreased apoptosis

Answer 4

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

Response heterogeneity

Mixed target cell populations with different sensitivities

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

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RTO 00341

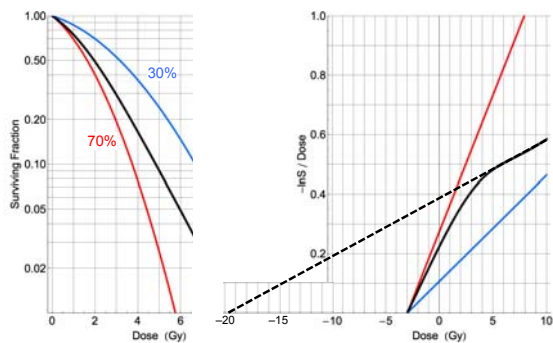
An explanatory hypothesis for early- and late-effect parameter values in the LQ model

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.

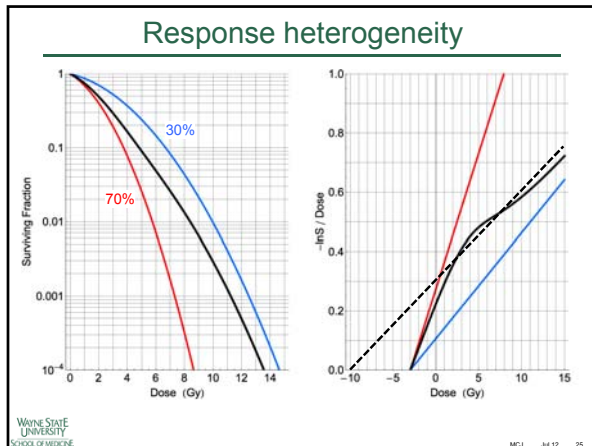
1. Higher-order terms (e.g. LQC) result from response heterogeneity
2. Leads to increase in "measured" value of α/β
3. Leads to "linearization" of the "cell survival curve" at higher doses
4. Explains the higher α/β for early effects and in some tumors

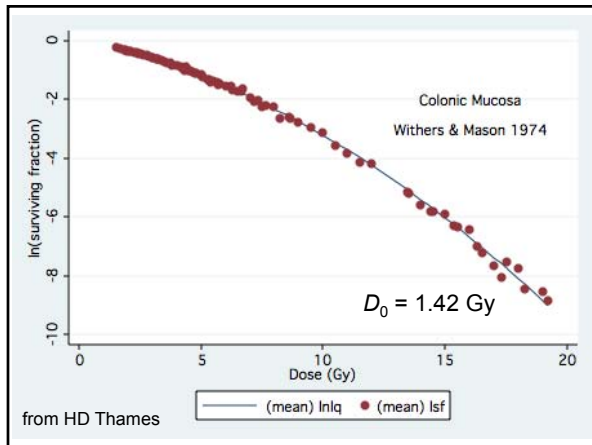
Response heterogeneity



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In vivo survival curves "linear" at high dose

Tissue	D_0 (Gy)	Ref
Cartilage growth plate	1.65	Kember 1965, 1967
Skin	1.3-1.4	Withers 1967
Colon	1.42	Withers 1974
Spermatogenic tubules	1.74	Withers 1974
Telogen hair follicles	1.35	Griem 1979
Jejunum	1.3	Hendry 1983
Kidney tubules	1.25	Withers 1986

from HD Thames

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Response heterogeneity can give rise to:

1. Increase in measured α/β ratio
2. Increase in cell proliferation
3. Increased chance of metastatic spread
4. Increased curvature in cell survival curves
5. Increase in radiosensitivity

Answer 1

Ref: Schultheiss TE. *Radiother Oncol* 1987;9:241-8

Hypofractionation can work in 2012 ?

- Physics enables:
 - improved dose definition
 - image guidance
- Biology is catching up:
 - low " α/β " of some tumors...
 - vascular and immunological effects
 - is LQ good for high dose fractions?
