The Radiobiological Four "R"s of Hypofractionation

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Overview of the presentation

- Definition of hypofractionation
- Radiobiology – 4 R's
  - Standard fraction dosing
- Linear quadratic (LQ) model – is it valid?
  - Radiosensitivity – 5th R of radiobiology
- 4 R's radiobiology of SBRT/SRS
  - Cell cycle, vascular effects, hypoxia, DNA repair
- Conclusions

Hypofractionation, SRS, SBRT [SABR]

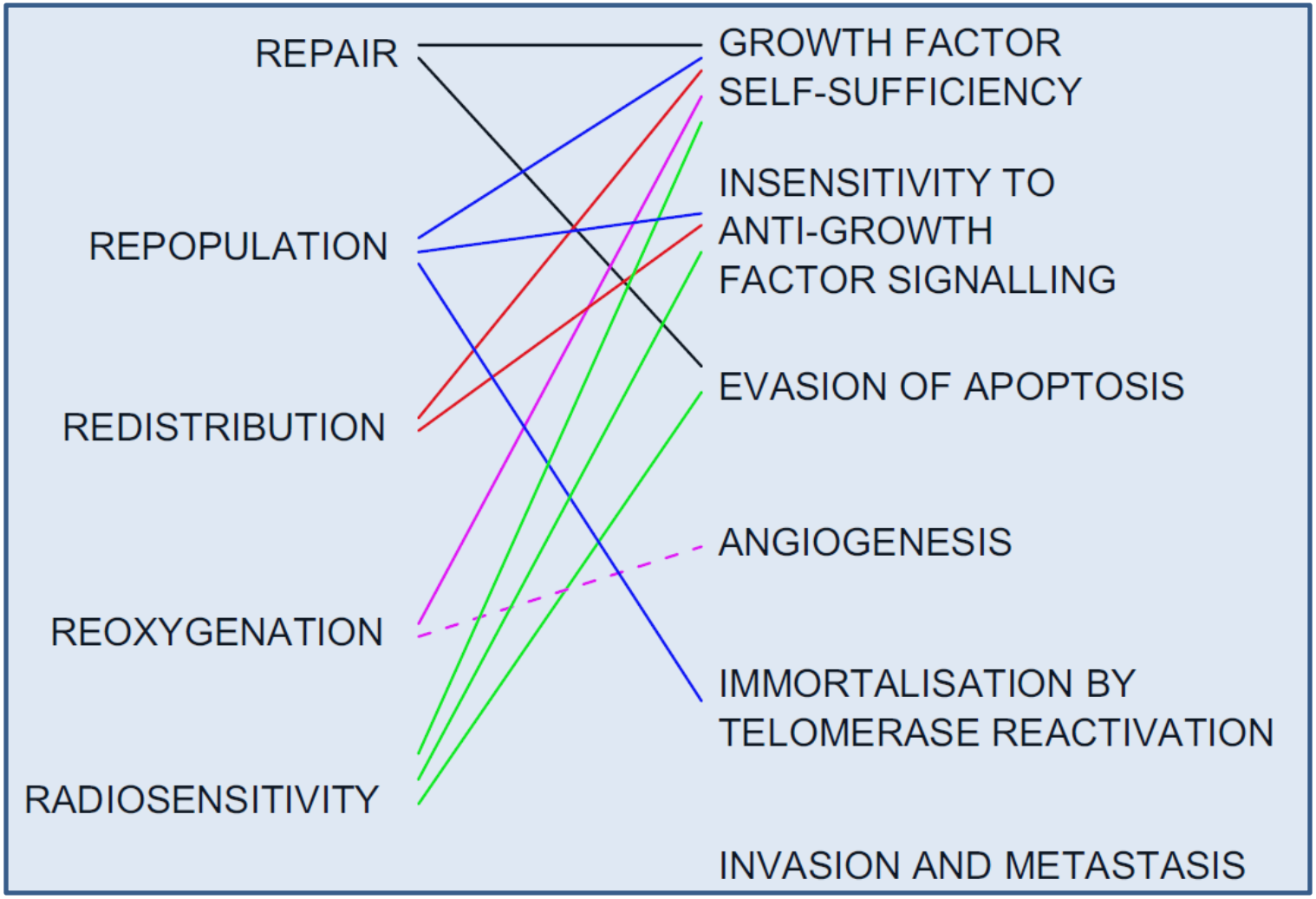
- **Conventional fractionation (1.8-2 Gy)**
- **Hypofractionation**
  - doses of 2.5 Gy and above
- **Stereotactic radiosurgery (SRS)**
  - entire dose is given in a single fraction
  - extreme example of SBRT– ablative doses of RT
- **Stereotactic body radiation therapy (SBRT)**
  - *a.k.a.* stereotactic ablative radiation therapy (SABR)
  - defined as treatment of tumors with 1 to 5/8 dose fractions
  - SBRT paradigm shift from the practice of radiation therapy
  - uncontested that conventional RT better for normal tissues

4 R's of radiobiology

- **R**epopulation, **R**edistribution, **R**epair & **R**eoxygenation
- Enabled development of safe and effective dose-fractionation regimens
  - along with a rudimentary appreciation of why treatment may succeed or fail (CHART v EORTC22851)
- Understanding the 4R's allows the concomitant use of drugs:
  - Repopulation, redistribution, repair and re-oxygenation
  - EGFR blockade by cetuximab in Head and Neck
    - Bonner *et al*. N Engl J Med 2006;354(6):
  - Use of DNA repair inhibitor
  - Inhibitors of neo-vascularization in glioma

Molecular Biology for the Radiation Oncologist: the 5Rs of Radiobiology meet the Hallmarks of Cancer

K. Harrington*†, P. Jankowska*, M. Hingorani†



Clinical Oncology (2007) **19:** 561–571 Clinical Oncology 25 (2013) 569–577

4(5) R's of conventional fractionated RT
"factors work in opposite directions"

- **Redistribution** (Reassortment)**: Sensitize tumors**
  - cell-cycle progression into RT-sensitive phases
- **Repopulation and Repair**
  - **tumors**: decreases radiation sensitivity
  - **early-reacting normal tissues**: increase in radiation tolerance with increasing overall treatment time
- **Reoxygenation: Sensitize tumors**
  - oxygenation of surviving hypoxic cells
- **Radiosensitivity (5^{th} R)**
  - intrinsic sensitivity of tumor: **modeled by LQ**

Steel, McMillan, Peacock. The 5Rs of radiobiology. *Int J Radiat Biol* 1989;**56**:1045-1048.

5th R and LQ model – **conventional** RT

- The LQ model 'models' loss of reproductive ability: **Intrinsic Radiosensitivity**
- The LQ model is simple and convenient
  - **better fit in the low dose–high survival region**
  - **α (lethal/non-repairable) & β (sub-lethal/reparable)**
  - **α/β ratio for early and late reactions in human normal tissues consistent with results from experimental models**[1]
- Most useful means for isodose calculation with fractionated radiation therapy[2]
- LQ model used (and validated) in clinical trials of hyperfractionation [CHART/CHARTWEL]

[1]Thames *et al.* Radiother Oncol 1990;19:219; [2]Fowler Br J Radiol. 1989;62: 679-694;

5th R and LQ model – **hypofractionated** RT

- Implicit in LQ is full reoxygenation between each fraction
- LQ mathematical formulation gives a continually bending survival curve at high doses
- **Does LQ inherently overestimate cell death at high doses per fraction?**

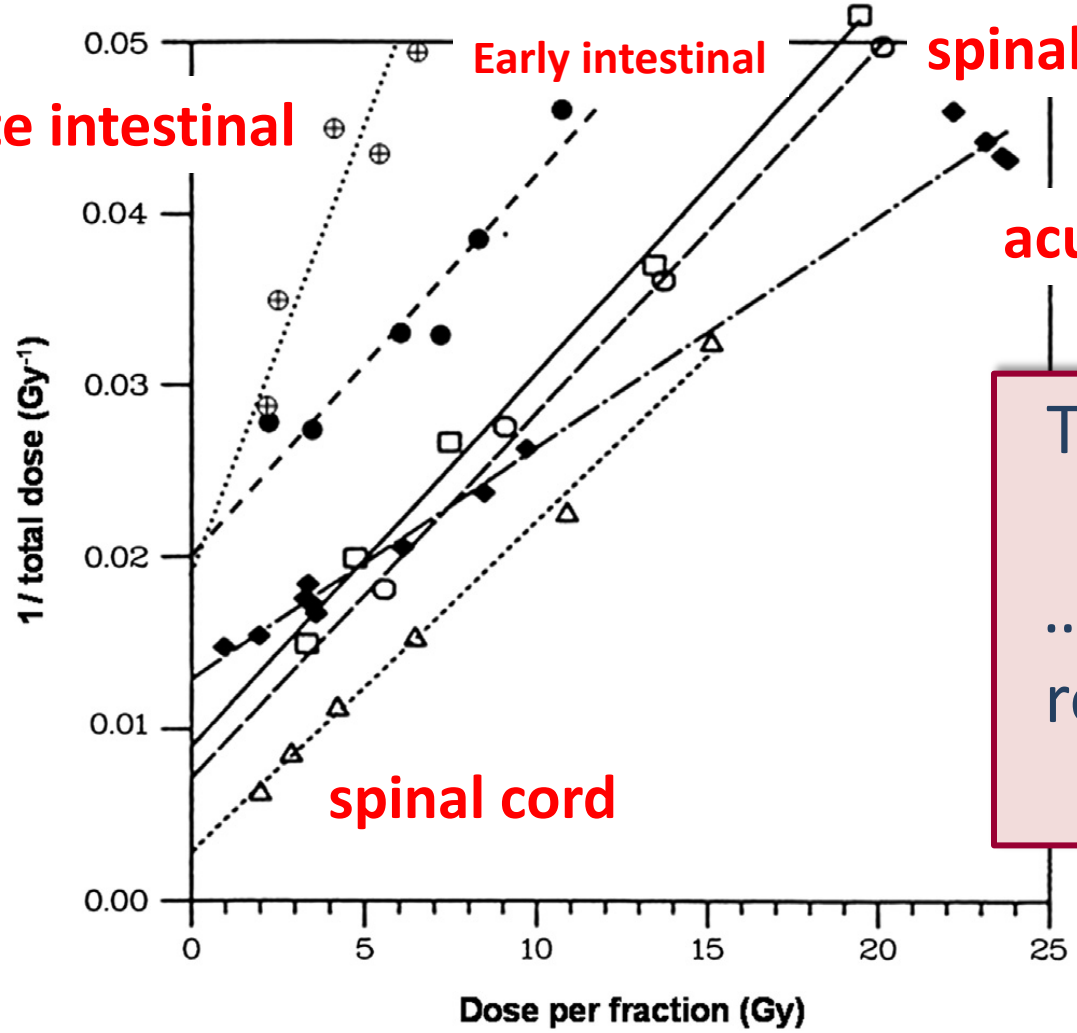
5th R and LQ model – **hypofractionated** RT

- Fundamental issues applying LQ to SBRT
  - Brenner[1] argues LQ holds up to 10 Gy, even 18 Gy
  - Kirkpatrick and colleagues[2], and others, argue LQ poor
- LQ-based models adapted to describe SBRT
  - LQ curve at low doses and high-dose linear component
  - Universal survival curve (USC) & single fraction equivalent dose[3]
  - USC greater sparing normal tissues outside PTV than LQ[4]
- High-dose linear component could be achieved by assuming a higher α/β[5]
  - rationale for higher α/β in rapidly proliferating & hypoxic tumors

1. Brenner DJ. Semin RO 2008;18:234-239 **2**. Kirkpatrick *et al*. Semin RO 2008;18:240-243
3. Park C *et al*. IJROBP 2008; 70(3):847–852 **4**. Wennberg and Lax, Acta Oncol. 2013 ;52(5):902-9
5. Fowler JF. Br J Radiol 2010; 83:554-568.

LQ **holds** for SBRT

Iso-effect data for normal tissues



The data are plotted as "reciprocal-dose" .....if data follow an LQ relationship, the points fall on a straight line.

Brenner DJ, *Semin Rad Onc* 2008;**18**:234-239

LQ **holds** for SBRT

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Critical Review

The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?

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"…..we conclude that the available preclinical and clinical data do not support a need to change the LQ model"

LQ **underestimates** for crypt cell survival

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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]

[a] *Department of Experimental Radiation Oncology;* [b] *Department of Radiation Oncology;* [c] *Department of Bioinformatics; and* [d] *Department of Biostatistics, UT MD Anderson Cancer Center, Houston, USA*

"The LQ model underestimates doses for iso-effective crypt-cell survival with fraction sizes >9 Gy. *This finding is consistent with the possibility that the target-cell survival curve is increasingly linear with increasing dose*".

Balance of evidence is that the LQ model is adequate for **modest dose** SBRT

…..with the odd exception

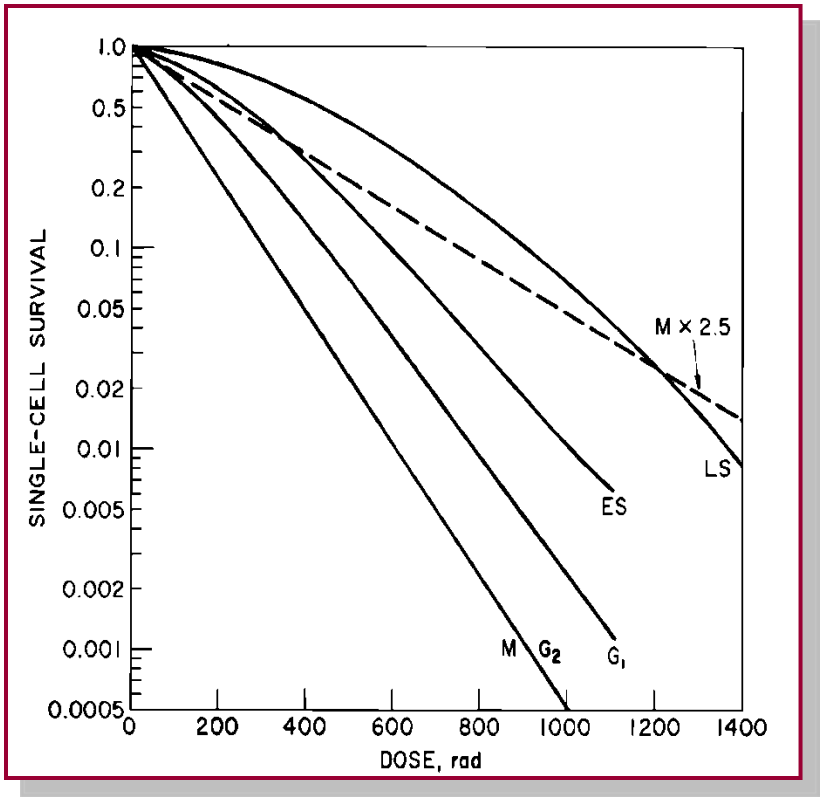
4 R's of conventional fractionated RT during the inter-fraction interval

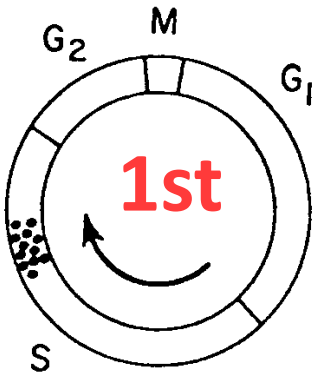
- **Redistribution** (Reassortment)**: Sensitize tumor**
  - cell-cycle progression into RT-sensitive phases
- **Repopulation and Repair**
  - **tumors**: decreases radiation sensitivity
  - **early-reacting normal tissues**: increase in radiation tolerance with increasing overall treatment time
- **Reoxygenation: Sensitize tumors**
  - oxygenation of surviving hypoxic cells

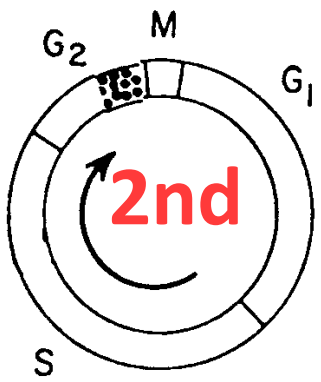
Steel, McMillan, Peacock. The 5Rs of radiobiology. *Int J Radiat Biol* 1989;**56**:1045-1048.

RT and **redistribution** (reassortment)

- Radiosensitivity of cells varies considerably as they pass through the cell cycle
- S phase most resistant
- Very late G2 and mitosis most sensitive
- Sinclair and Morton Biophys J. 1965;5:1-25.







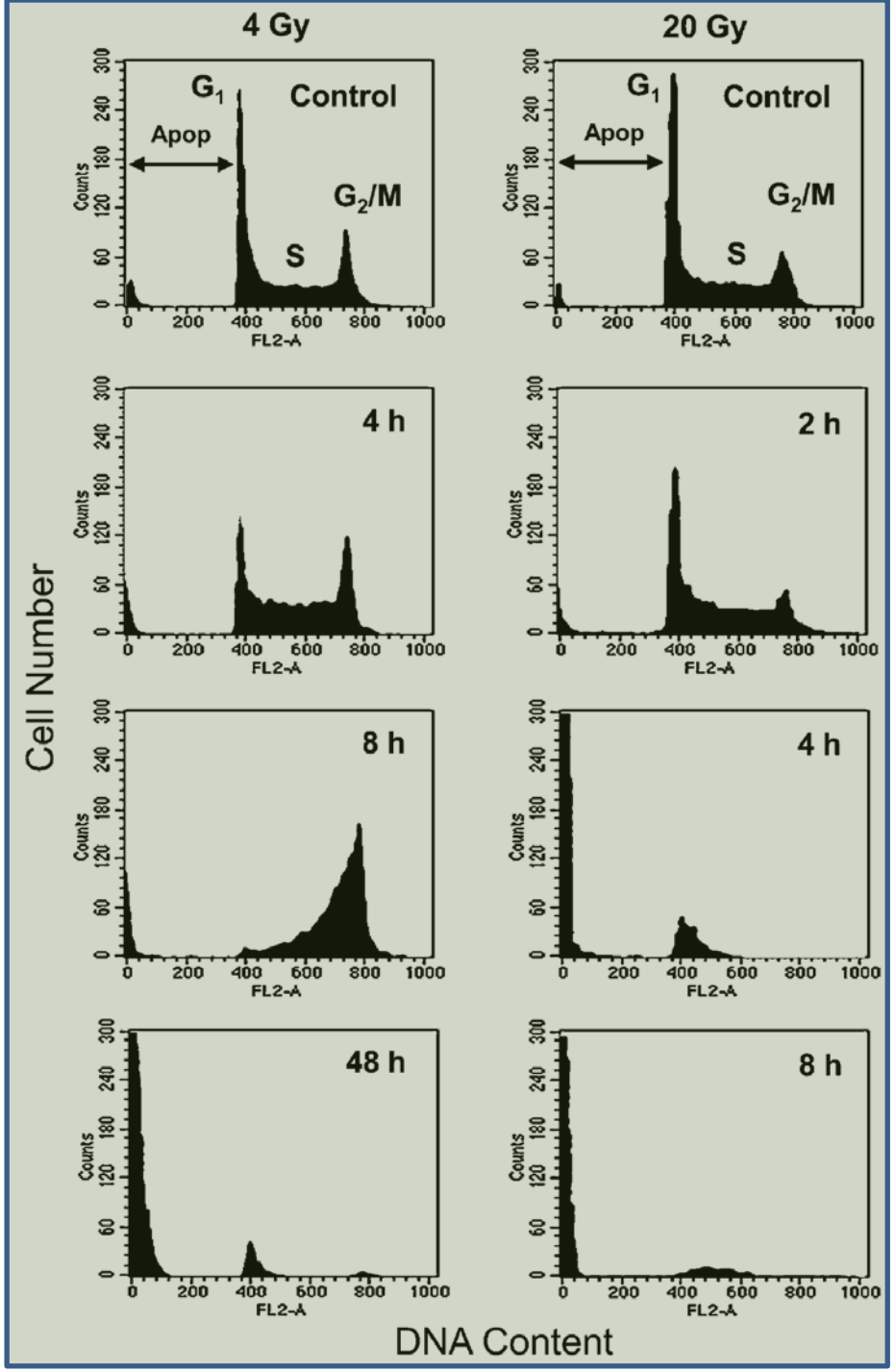
SBRT and **redistribution**

Progression of HL-60 cells measured after 4 or 20 Gy

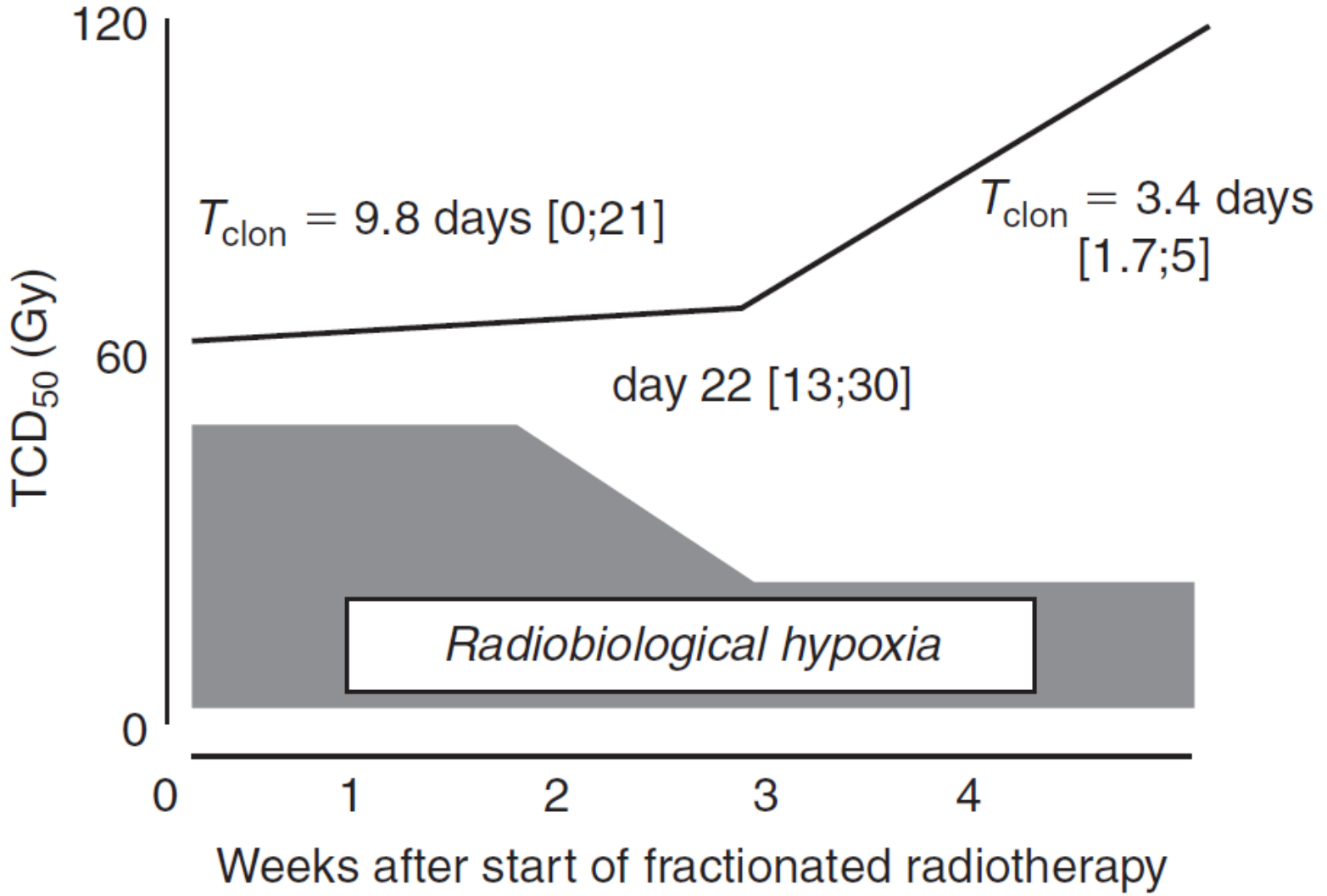
Cells in late S and G2 died of apoptosis: 4 h after 4 Gy

After 20 Gy, ***no cell cycle progression***. Cells died an ***interphase death*** in the cell cycle phase they where in at the time of irradiation

Park *et al.* Radiat Res (2000) 153:295–304



Biphasic course of clonogen **repopulation** during fractionated RT



Petersen *et al*. IJROBP (2001) 51: 483–93.

SBRT and **redistribution/repopulation**

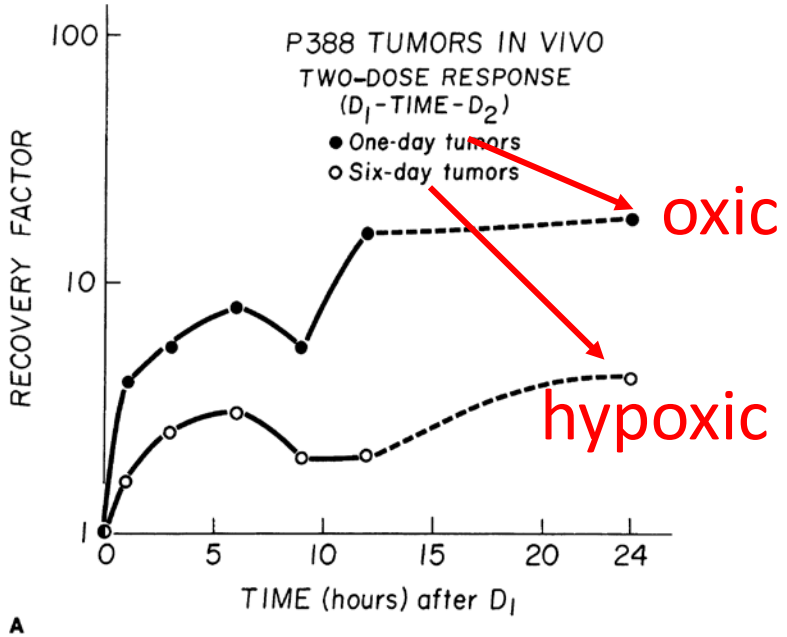
- Conventional RT delivery repopulation evident 3-4 weeks after initiation
- **Repopulation:** SBRT complete with 1-2 weeks
  - Negligible or no substantial role after high-dose SBRT
- **Redistribution** after high dose SBRT
  - Dose-dependent arrest checkpoints
  - Cells die an inter mitotic death (apoptosis or necrosis) or indefinitely arrested[1]
  - Negligible or no substantial role after SBRT

1. Park *et al* Radiat Res (2000) 153:295–304

Repair (Elkind recovery) from sublethal damage (SLD)

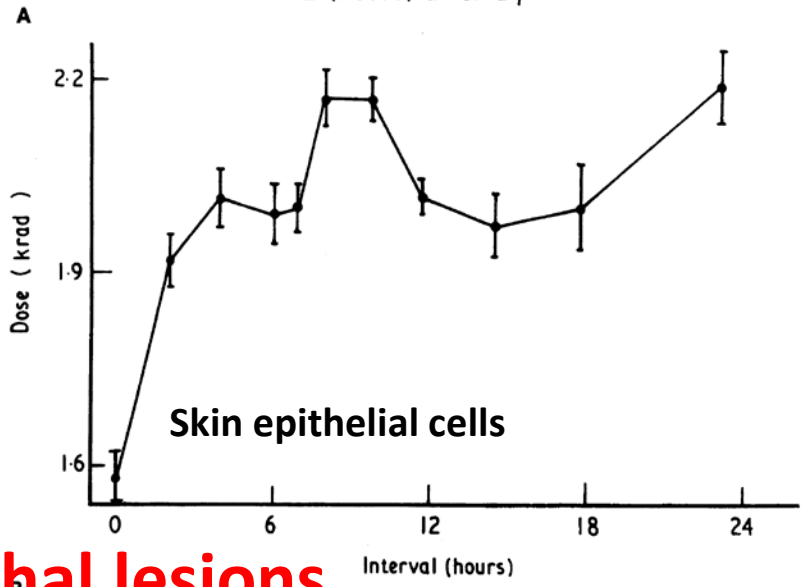
Radiation response of mammalian tumor cells. I. Repair of sublethal damage in vivo.

Belli et al. *J Natl Cancer Inst*. 1967 **38**(5):673-82.



Survival of mouse skin epithelial cells following single and divided doses of x-rays.

Emery et al. *Radiat Res*. 1970 **41**(3):450-66.



Interaction and repair of sub-lethal lesions

SBRT and **repair**

- SBRT → high levels of DNA damage, repair evident @ 80 Gy
  - No evidence of repair saturation
- High-dose radiation-induced foci (RIF) formed relatively faster and resolved slower than low-dose RIF[1]
  - high doses of radiation larger and more intense clusters of DNA repair proteins formed (repair centers), in fewer locations
- Gerwick *et al.* (2006)[2]
  - Established tumors from DNA-PKcs-/- and DNA-PKcs+/+ cells
  - 4 x 5 Gy, 15 Gy and 30 Gy – measure tumor growth delay
  - DNA-PKcs–/– cells - significantly longer growth delay
  - Tumor radiosensitivity is a major determinant of response after 15-30 Gy not cell stroma

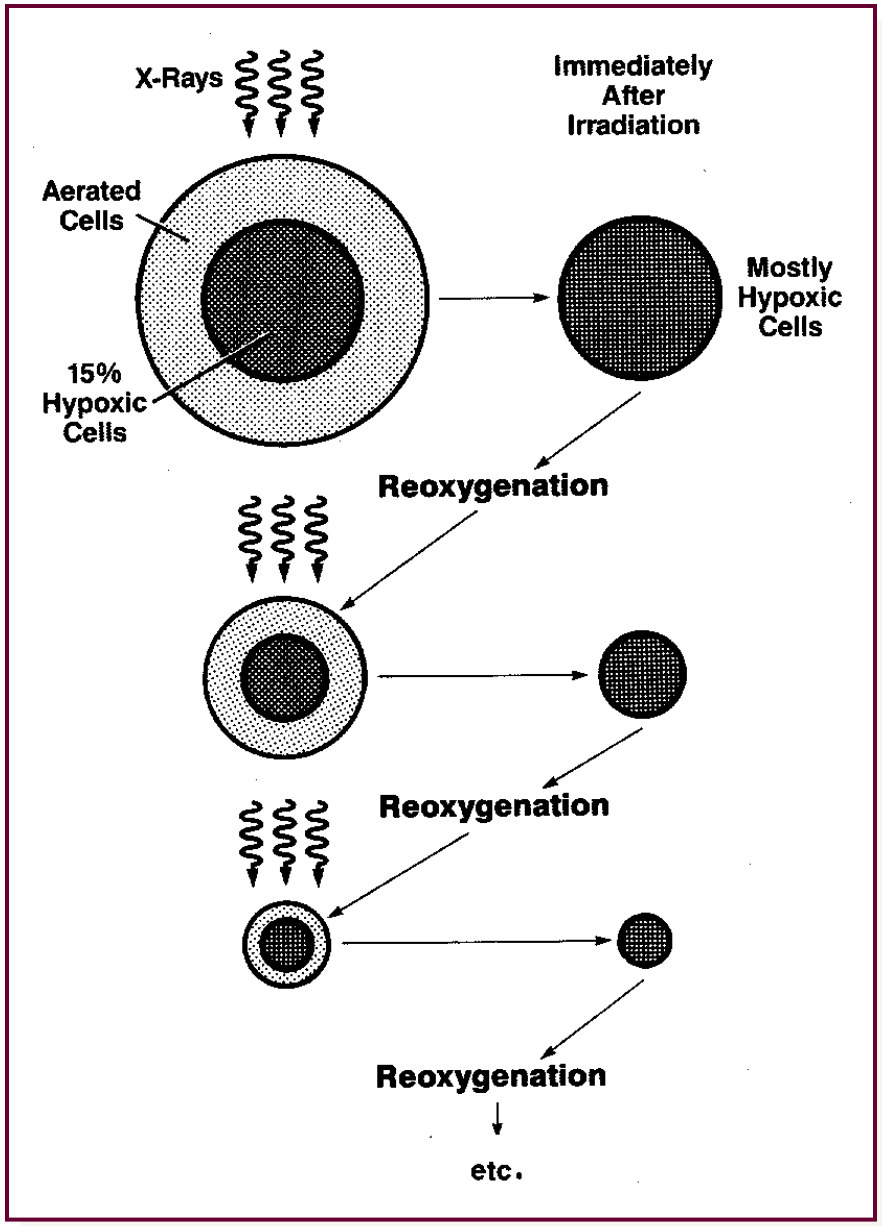
1. Neumaier *et al*. Proc Natl Acad Sci USA 2012; 109(2):443–448

2. Gerweck *et al.* Cancer Res 2006; 66:8352–5.

Reoxygenation most likely the important radiobiological ‘R’ when comparing SBRT with conventional RT

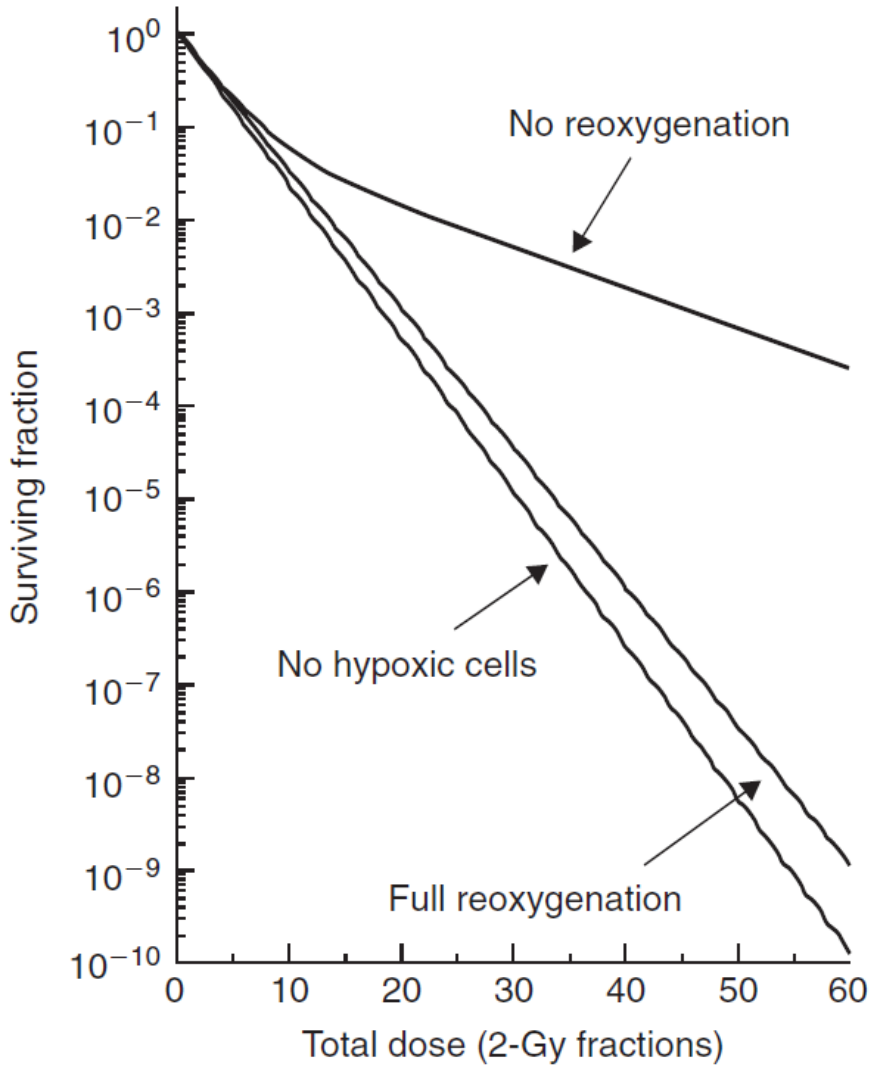
…..if one assumes the tumor is hypoxic

Conventional RT and **reoxygenation**



- Tumors contain a mixture of aerated and hypoxic cells
- A dose of x-rays kills a greater proportion of the aerated cells as they are more radiosensitive (OER)
- Immediately after RT most cells in tumors are hypoxic
- However pre-irradiation patterns tend to return because of reoxygenation
- Fractionation **tends** to overcome hypoxia

Conventional RT and **reoxygenation**



- Hypoxia can be chronic or acute
- Hypoxic cells are less sensitive to radiation
- Important cause of treatment failure
- Reoxygenation has been shown to occur in animal tumors
- Evidence for reoxygenation in human tumors is less direct.

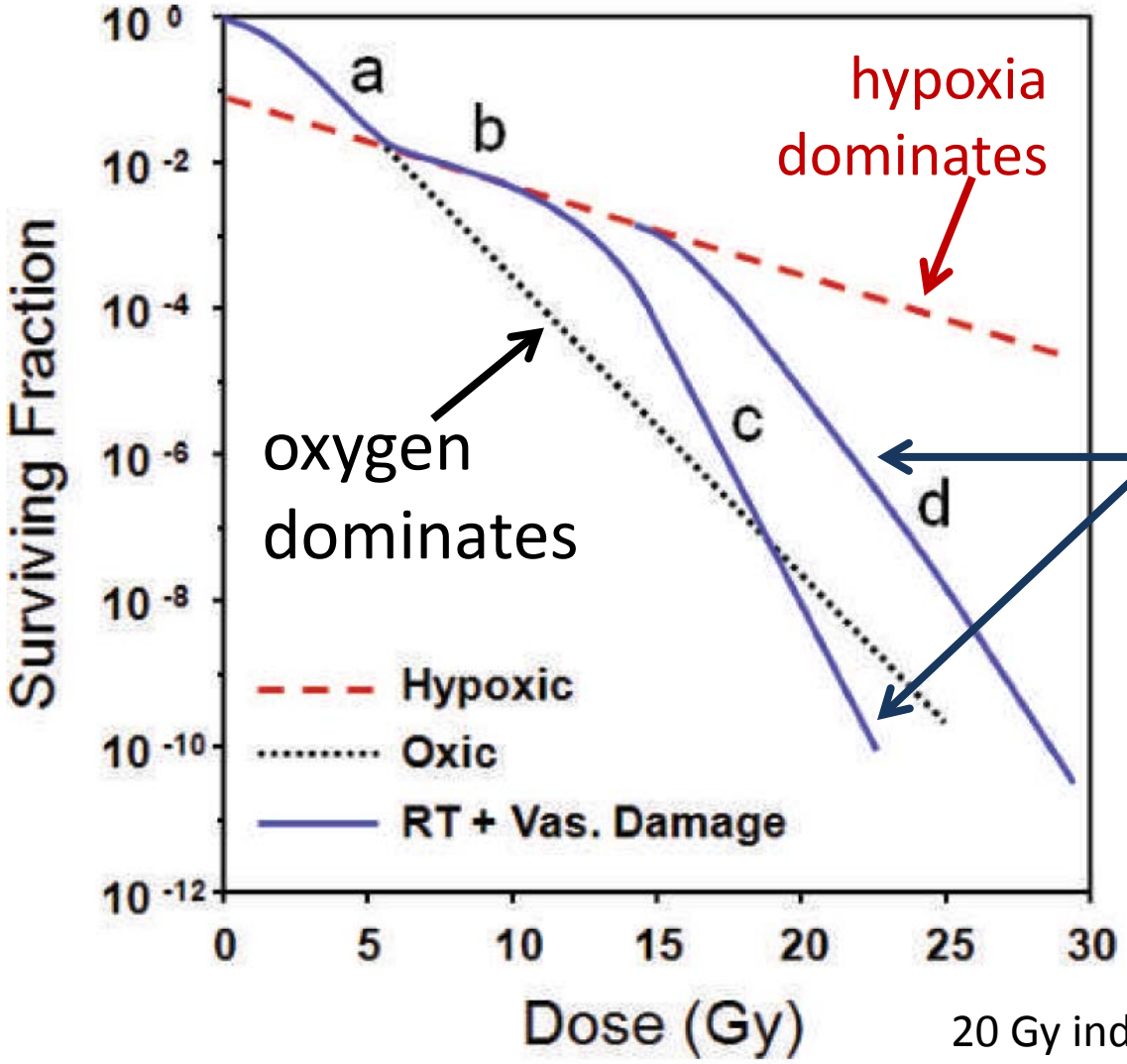
Wouters and Brown, Radiat Res 1997 147: 541–50

Reoxygenation (hypoxia) and SBRT

- Carlson *et al*. report predictions for hypoxic situations[1]
  - 3 logs of cell kill lost up to single doses to 18-24 Gy
  - Can be overcome with hypoxia dose boosting[2,3]
- Brown *et al*. (2010) evaluated the expected level of radiation-mediated cell killing by different SBRT regimens[4]
  - 20 Gy x 3 was barely sufficient due to hypoxia
- Clinical outcomes for NSCLC with SBRT are good
  - Indicative of mechanisms ***in addition to*** direct cell killing
  - Anti-tumor immune responses, secondary effects from vascular damage

1. Carlson *et al*. IJROBP. 2011; 79: 1188; **2**. Ruggieri *et al*. Acta Oncol 2010; 49:1304
3. Ling *et al*. IJROBP 2000; 47: 551–560; **4**. Brown *et al.* IJROBP 2010; 78: 323–327

Hypothetical cell death mechanisms after SBRT – direct and **indirect vascular effects**



10% hypoxic cells

Size of effects dependent on fraction size

Park *et al* Radiat Res (2000) 153:295–304

20 Gy indiscriminately caused apoptosis in all cell cycle phases

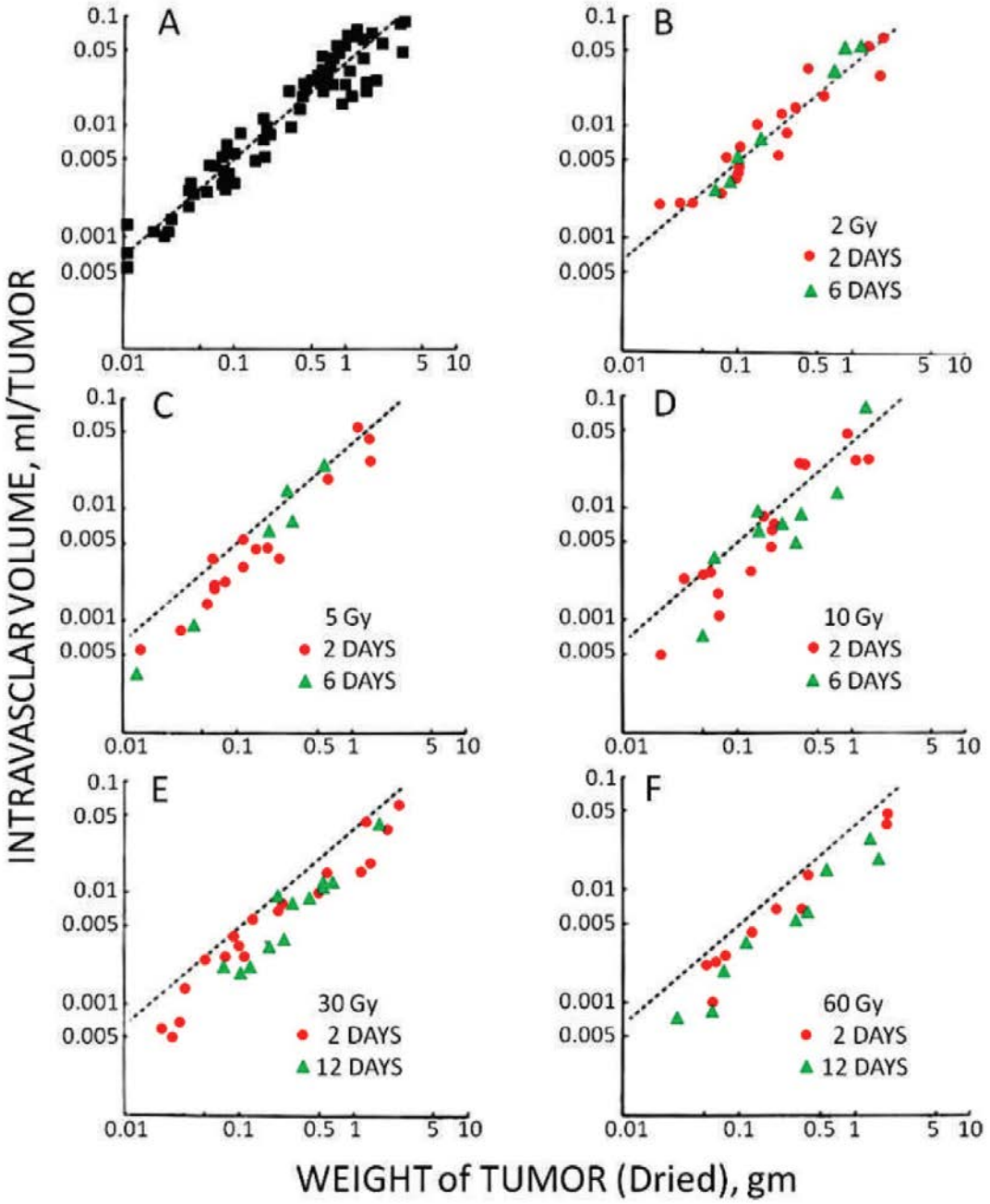
SBRT: **Indirect vascular effects**

- Vascular damage less significant ~3-8 Gy/fractions
- Large fraction size SBRT may prohibit reoxygenation of hypoxic tumor cells
  - Reoxygenation between fractions – requires fractions!
  - Heterogeneous vascular damages above ~10 Gy/fraction[1]
  - Decrease is vascular function with 24 hours[2], loss of vascular function < 7 days[3], but perfusion recovers via CD11b+ cells[4]
  - <2.5 Gy – decrease for 6-12 hours then returns to normal
  - 5-10 Gy – tumor blood flow decreases, returns in 2–3 days
  - 10-15 Gy (1/2) blood flow initially decreases for 1–7 days
  - 15-20 Gy (1) blood flow decreases rapidly

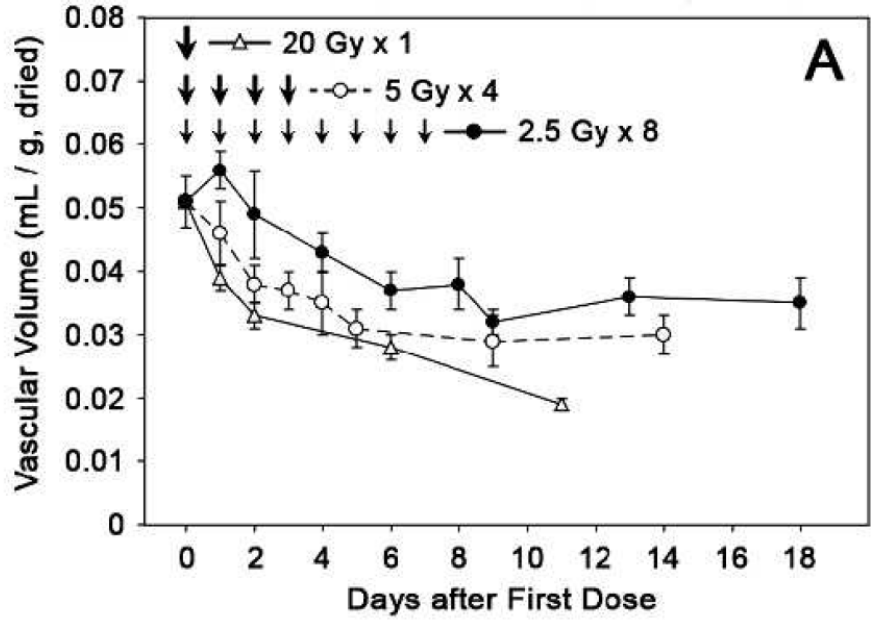
1. Garcia-Barros et al. Science 2003; 300:1155-1159.
2. Bussink *et al*. Radiat Res 2000; 153:398–404.
3. Solesvik *et al*. Radiat Res 1984; 98:115–28.
4. Kioi *et al*. J Clin Invest 2010; 120:694–705.

Walker 256 tumors

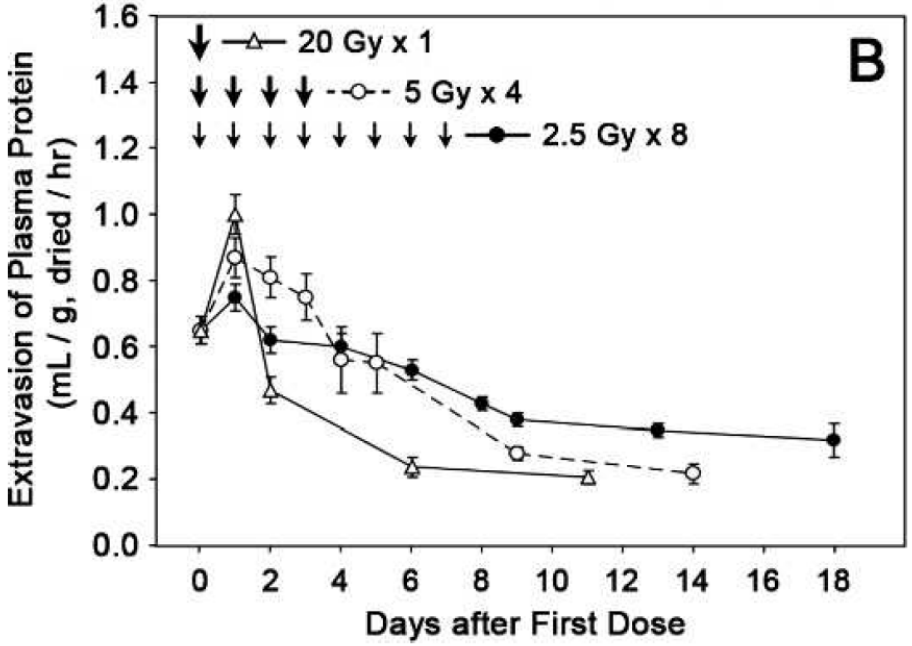
- X-rays
- Single exposure



Song CW, Levitt SH. Radiology 1971; 100:397–407



The rapid drop in the functional vascular volume after single dose 20 Gy irradiation was more substantial than that caused by 20 Gy given in 4 fractions



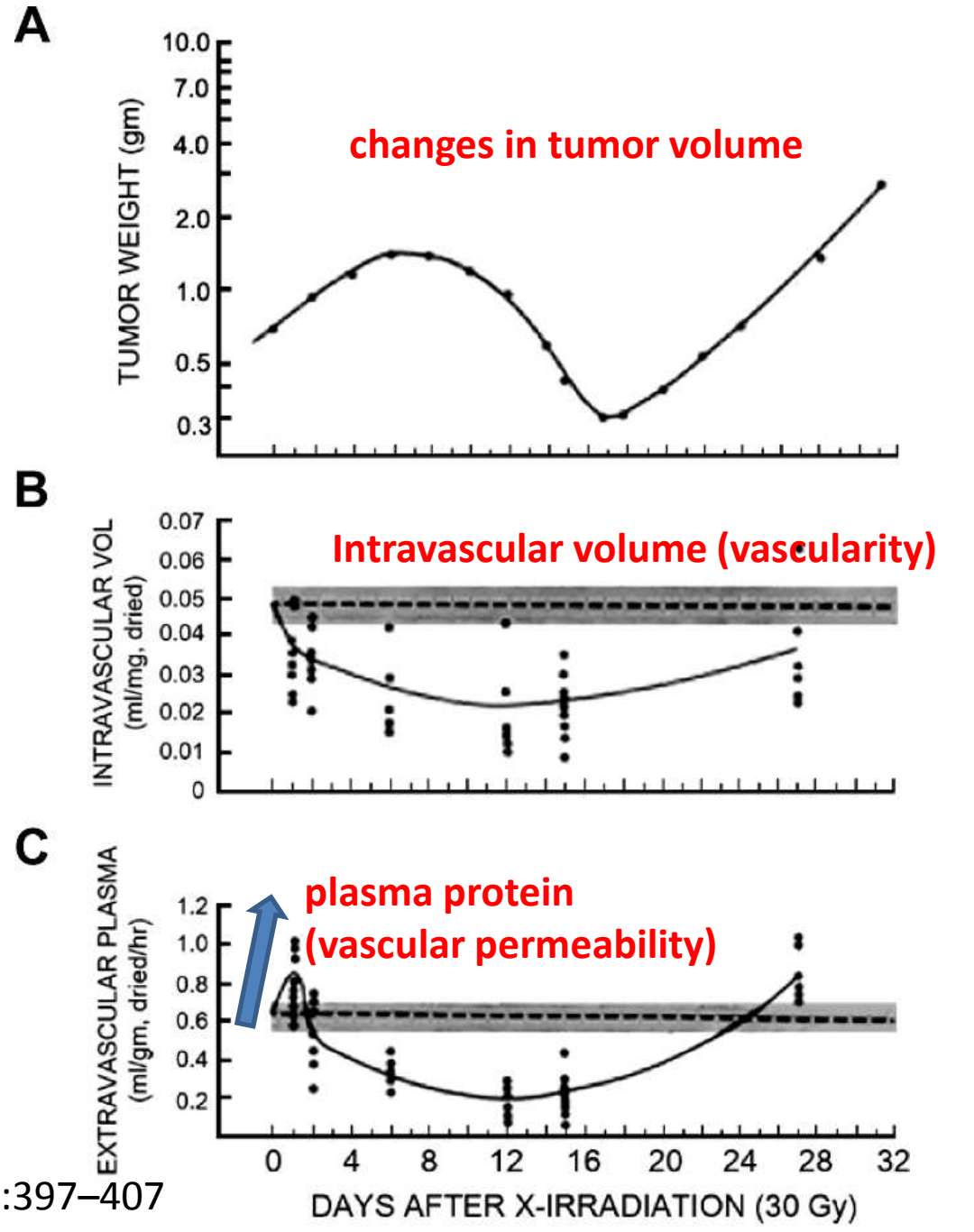
The extravasation of plasma protein (vascular permeability) increased significantly at 24 h after irradiation with 20 Gy

Park, Griffin *et a*l. Radiat Res. 2012;177(3):311-27

Effects of 30 Gy radiation given in a single dose on the tumor size and vascular functions

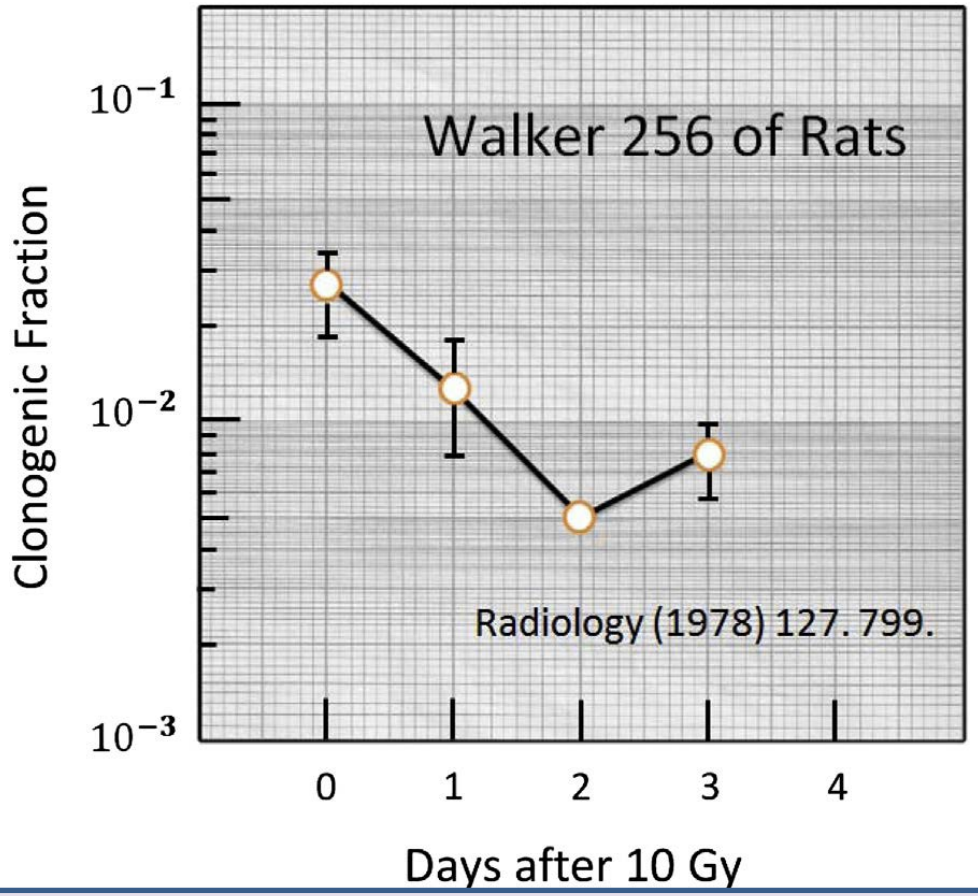
1. Death of endothelial cells
2. Collapse of the fragile tumor vessels
3. Increase in the interstitial fluid pressure caused by extravasation of plasma protein

Subcutaneous Walker 256 carcinoma in the leg of Sprague–Dawley rats



Song CW, Levitt SH. Radiology 1971; 100:397–407

SBRT: **Indirect vascular effects**



Assay of clonogenic cell fraction after 10 Gy

"Attributed the decrease in viability of tumor cells over 2 days after irradiation with a single dose of 10 Gy to **indirect cell death** due to vascular damage".

Clement JJ, Takanka N, Song CW. Radiology 1978;127:799-803.

Indirect effects: **Anti-tumor immunity**

- The idea that SBRT may turn the tumor into an '**immunogenic hub**': Priming systemic immune response
  - release of high mobility group protein B1 (HMGB1)
- Clinical evidence SBRT contributes to an antitumor immunologic at a distant site[1]
- Demonstrated for pre-clinical[2]
  - Discussed fractionated RT but >2.5 Gy fractions[3]
- Only SBRT studies to date, and comparison with conventional fractionated RT difficult
  - little is known on whether different dose/fractionation regimens impact anti-tumor immune response[4]
- 'Systems Biology' approach to radiation response

1 Postow *et al*. N Engl J Med 2012;366:925-931
2 Matsumura *et al*. J Immunol 2008;181:3099-3107
3 Dewan *et al*. Clin Cancer Res 2009;15:5379-5388
4 Demaria and Formenti. Front Oncol. 2012 Oct 26;2:153

Indirect effects: **Cancer stem cells**

- Solid cancers are organized hierarchically and contain a small population of self-renewing cancer stem cells
  - Cancer stem cells are considered radioresistant[1]
  - Give rise to the bulk of relapse
- Cancer stem cells identified in perivascular niche
  - Tumor endothelial cells supply factors that maintain state of self-renewing cancer stem cells[2]
- SBRT destroying endothelial cells may inadvertently eradicate cancer stem cells
  - Potential explanation of SBRT killing above LQ prediction

1. Pajonk *et al. Stem Cells*. 2010; 28(4): 639–648

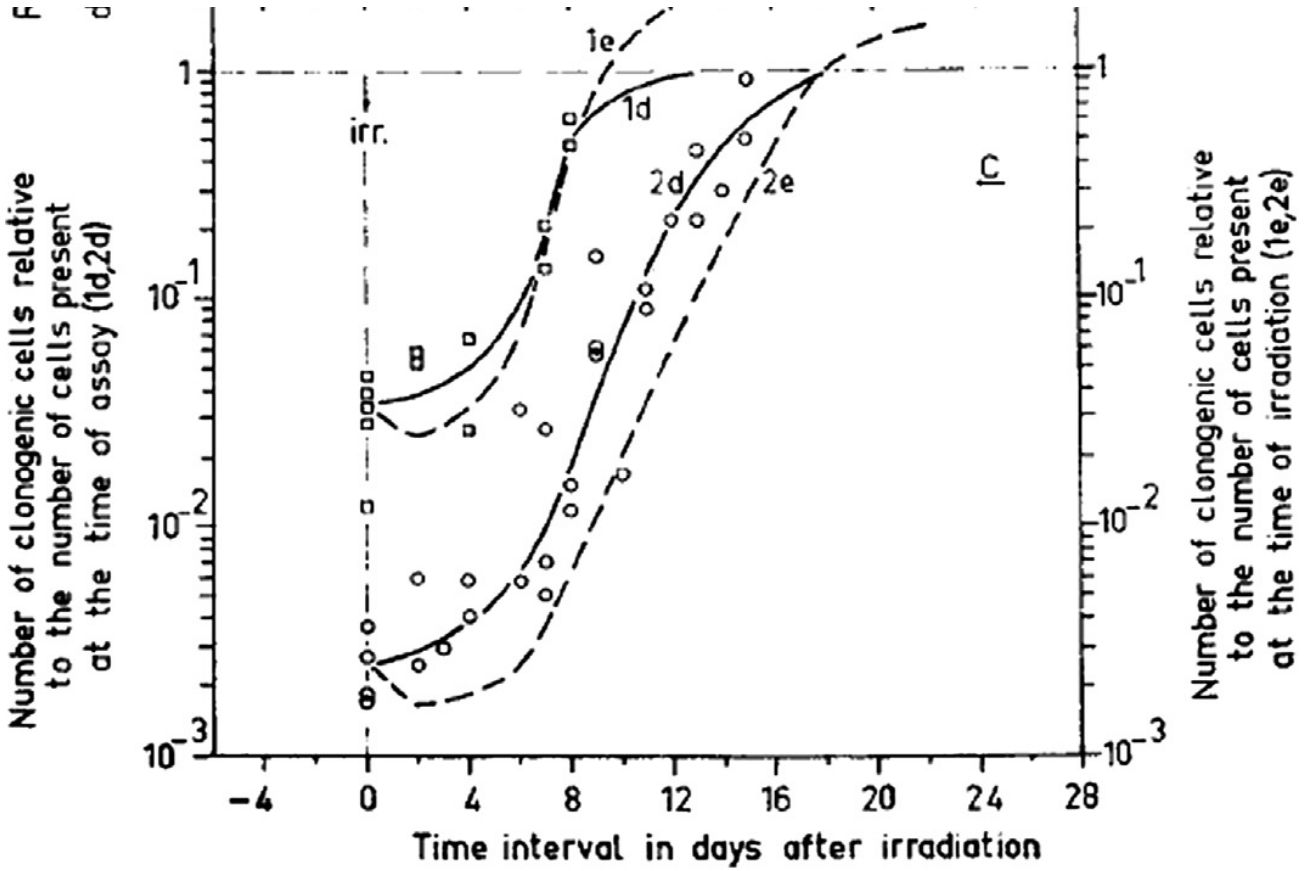
2. Charles and Holland *Cell Cycle* 2010; 9:3012–3021

Some evidence that
hypoxia and reoxygenation are important,

some evidence of some indirect effects
…….but not conclusive

…..evidence of non-indirect effects

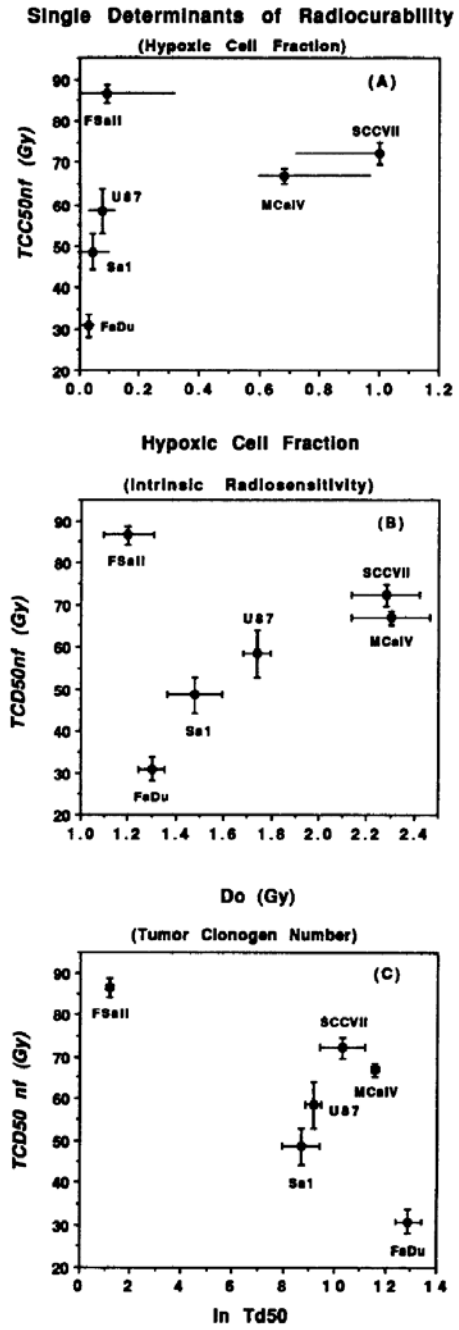
SBRT **10 and 20 Gy**: No indirect effect

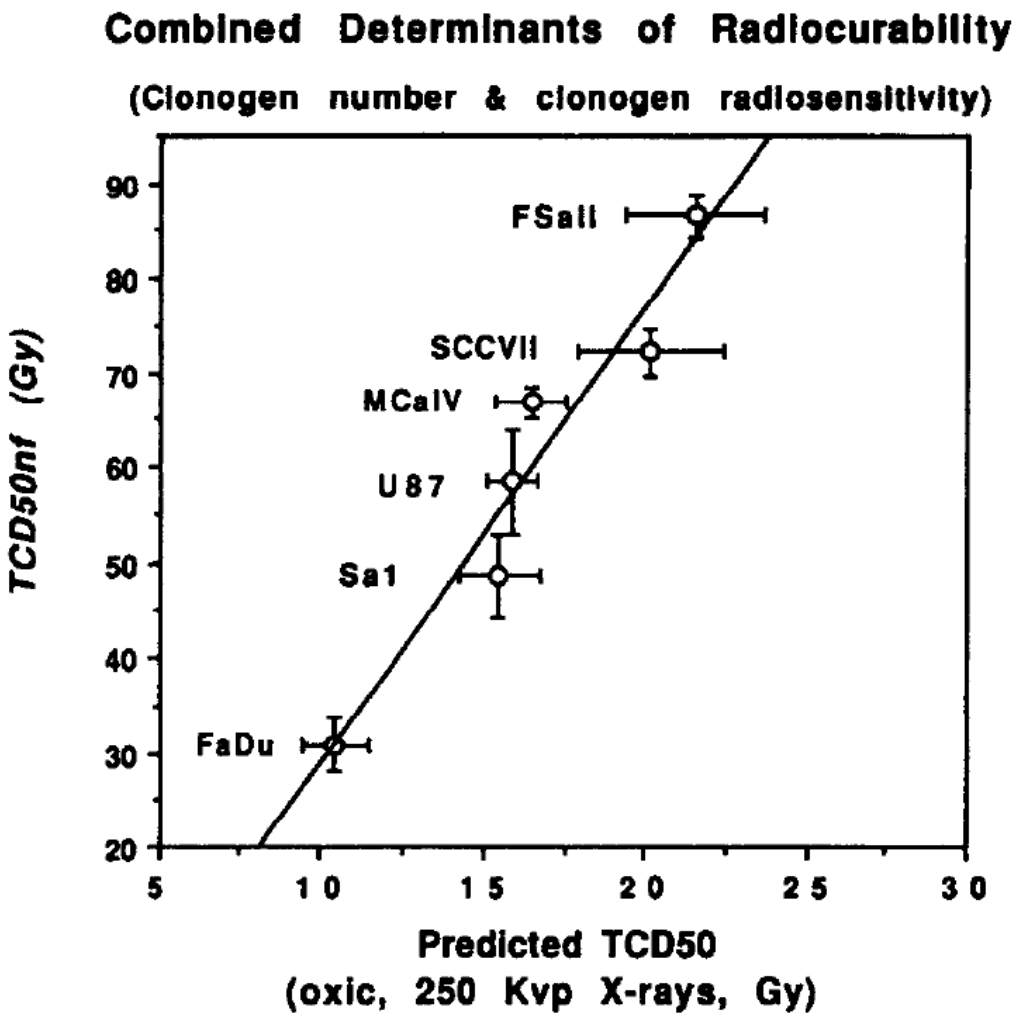


"…..no evidence of this increasing cell kill as a function of time after irradiation" - **ergo** no indirect effects

Barendsen and Broerse, *Eur J Cancer* 1969;**5**:373-391.

Pre-clinical
No SBRT indirect effects



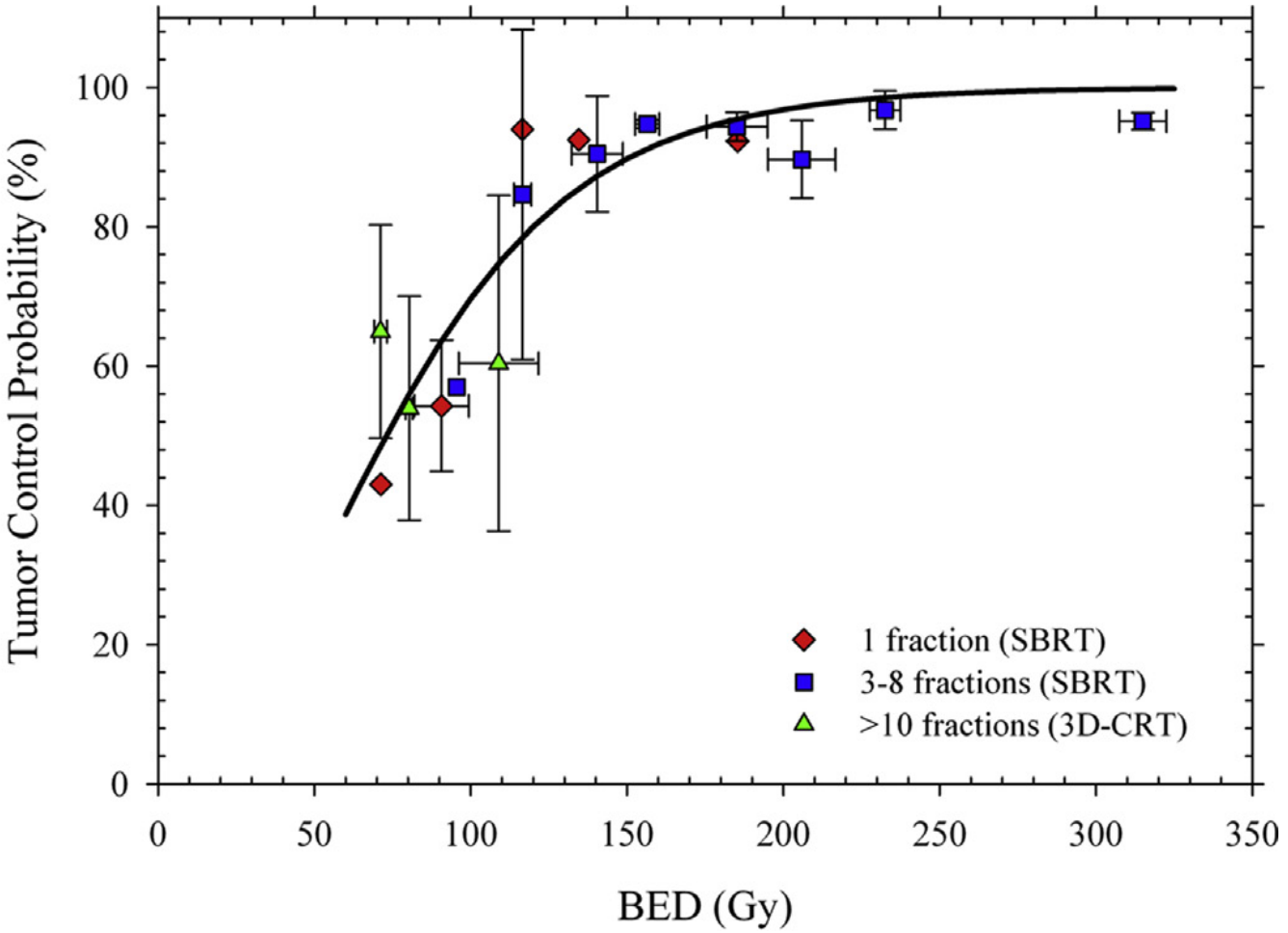


Gerwick *et al. Int J Radiat Oncol Biol Phys*. 1994 30;29(1):57-66.

Brown, Carlson and Brenner,
Int J Radiat Oncol Biol Phys. 2014 Feb 1;88(2):254-6

Clinical – NSCLS

No SBRT indirect effects



"….the efficacy of single doses, a few SBRT fractions, and conventional radiation therapy produce the same overall TCP for the same BED".

Conclusions

- High-dose fraction (HDF) SBRT
  - Not well-described by LQ
  - Disconnect between LQ model and HDF SBRT
  - Vascular effects after HDF SBRT
  - Potential of immune effects by HDF SBRT
  - Potential for stem cells eradicated by HDF SBRT
- Modest dose SBRT experimental evidence tends to indicates LQ model is sufficient
  - no indirect SBRT killing – suggests no disconnect
- 4 R's of radiobiology
  - Re-oxgyenation most relevant
  - Neovascularization may be important