Curso de Radiobiología
UDELAR
Facultad de Ciencias
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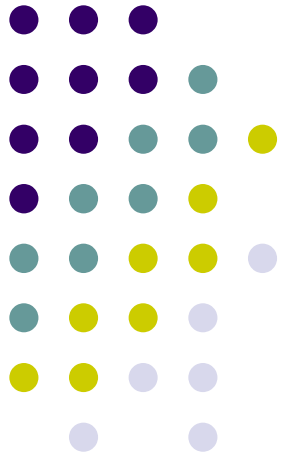


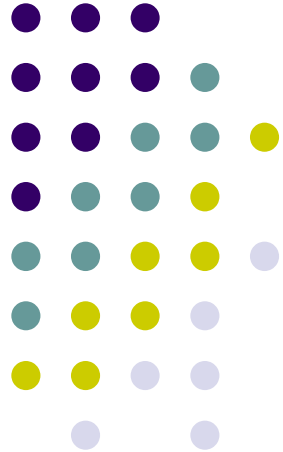
Radiobiología.

Aplicaciones en Radioterapia

Radiocirugía y Radioterapia Extracraneal Estereotáxica

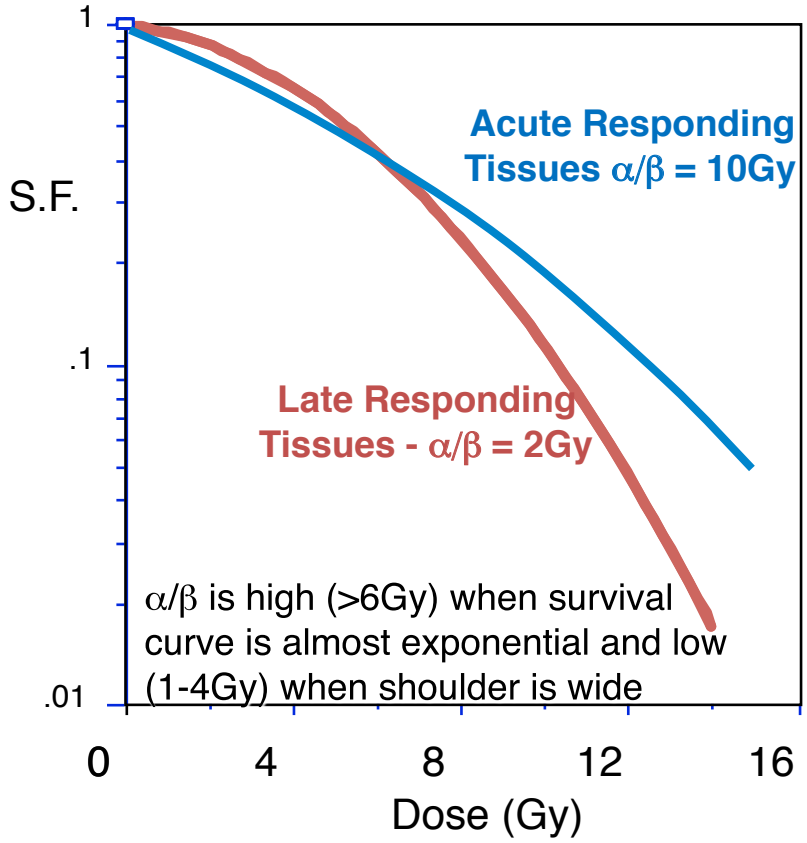
Bibliografía

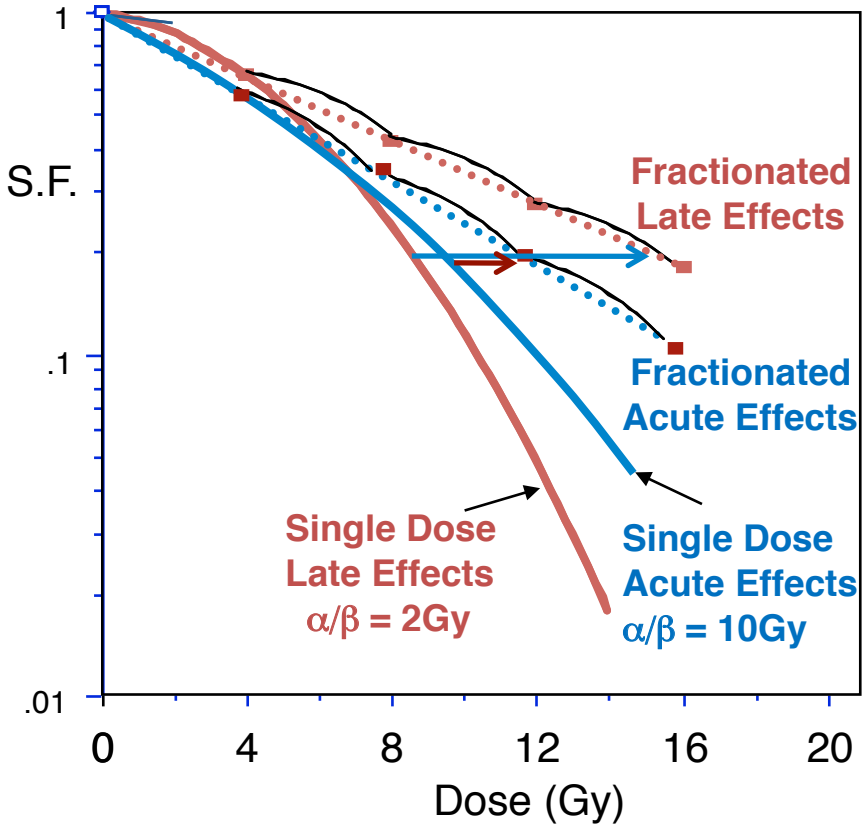
- Radiation Oncology For Medical Physicists. C.S. Sureka, C.Armpilia
- The Tumor Radiobiology of SRS and SBRT: Are More than the 5R's Involved? J. Brown et al. Int J Radiat Oncol Biol Phys. 2014 February 1; 88(2): 254–262
- Radiobiological Considerations for SRS and SBRT (from the perspective of a physicist). Kamil M. Yenice, PhD. University of Chicago



Kamil M. Yenice, PhD

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

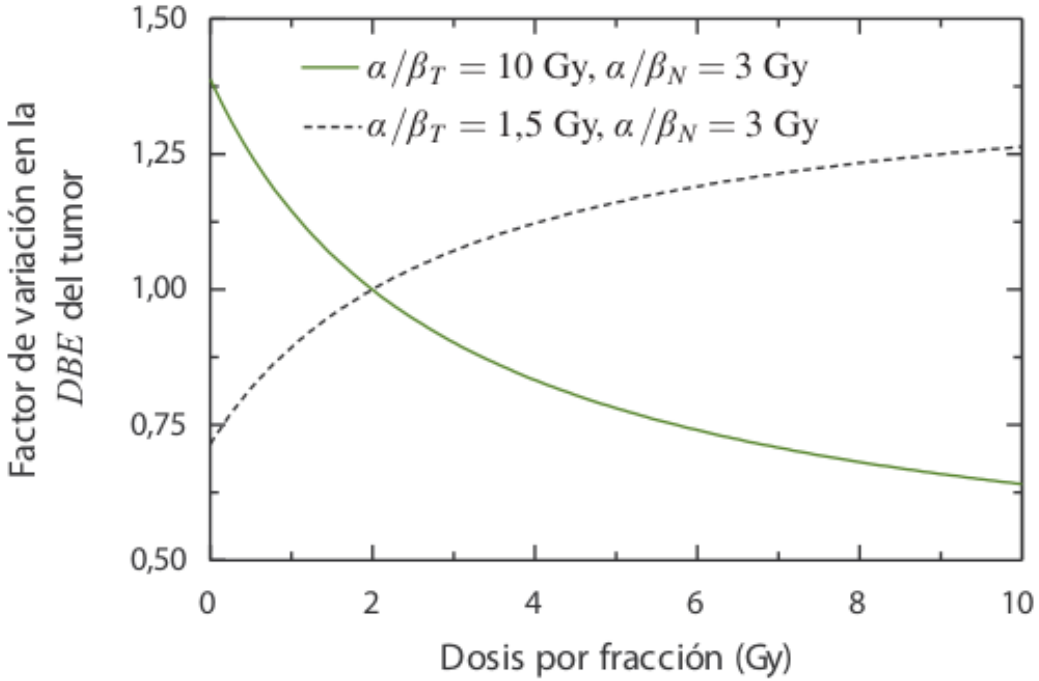
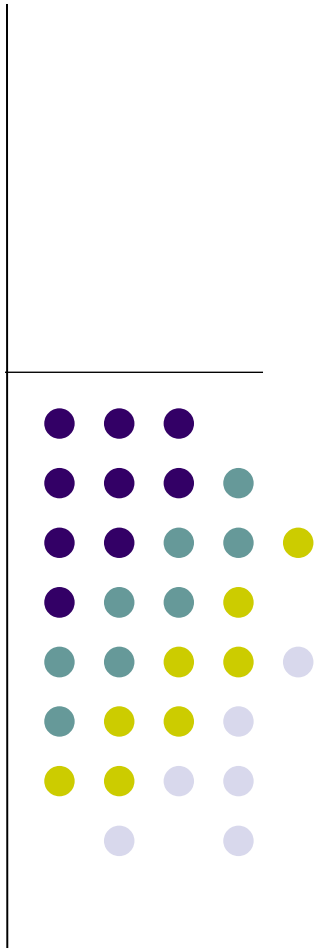
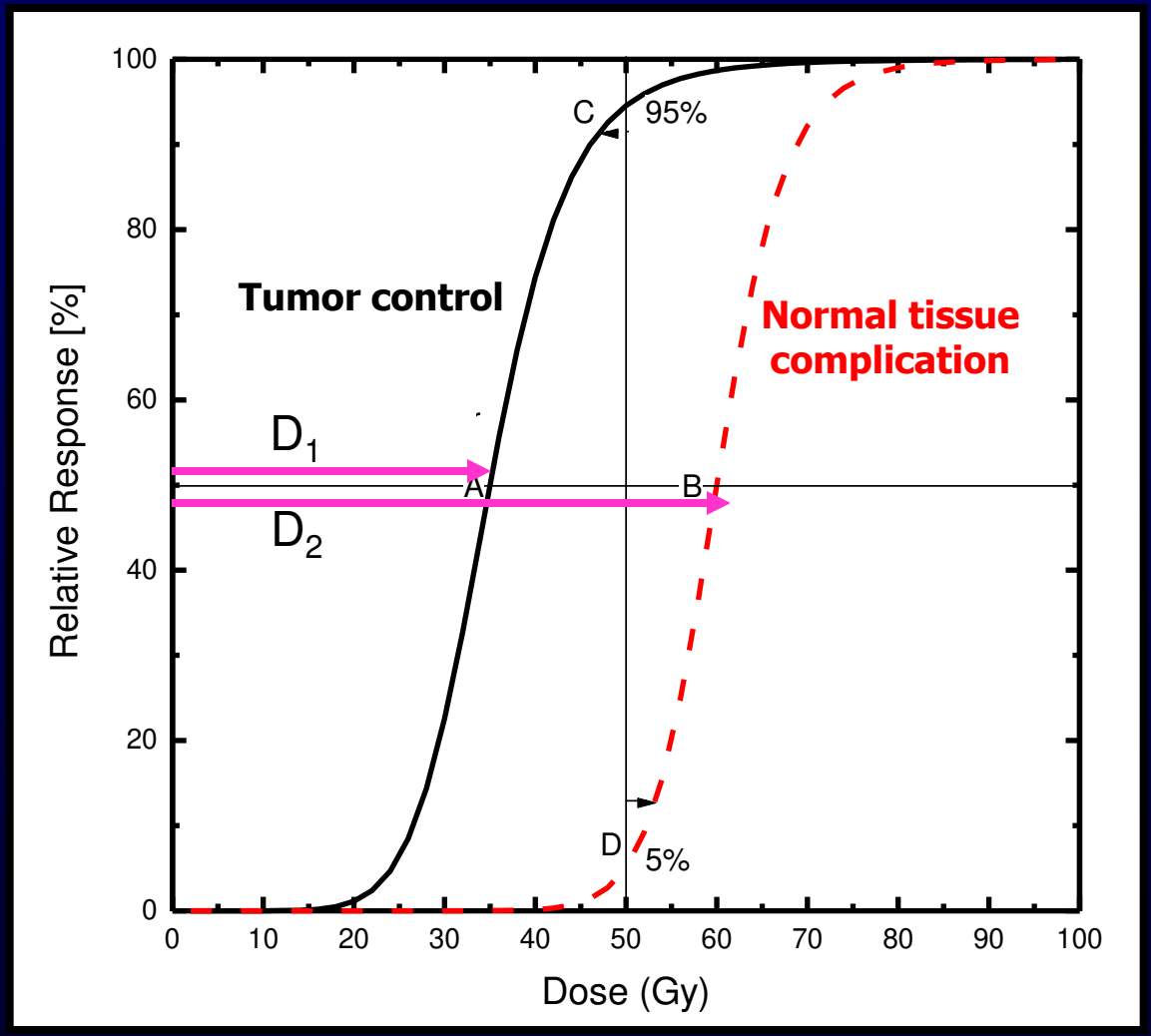


Figura 12. Factor de variación de la DBE del tumor en función de la dosis por fracción cuando se mantiene fija la DBE de los efectos tardíos de los tejidos sanos (caracterizados por un valor de $\alpha/\beta_N = 3$ Gy) en dos situaciones diferentes: una, en el caso de tumores caracterizados por un valor de α/β alto ($\alpha/\beta_T = 10$ Gy) y la otra, para tumores con un valor de α/β bajo ($\alpha/\beta_T = 1{,}5$ Gy).



Therapeutic Ratio



Therapeutic dose ratio = D_2/D_1

- Want to maximize therapeutic ratio
  - i.e., separate curves
  - Parameters used to maximize the therapeutic ratio:
  - Time, fractionation, hyper-fractionation (greater sparing of late-responding normal tissue, radio-sensitizers, cytotoxic agents,),

Posibles razones que explican la eficacia de SRS/SBRT

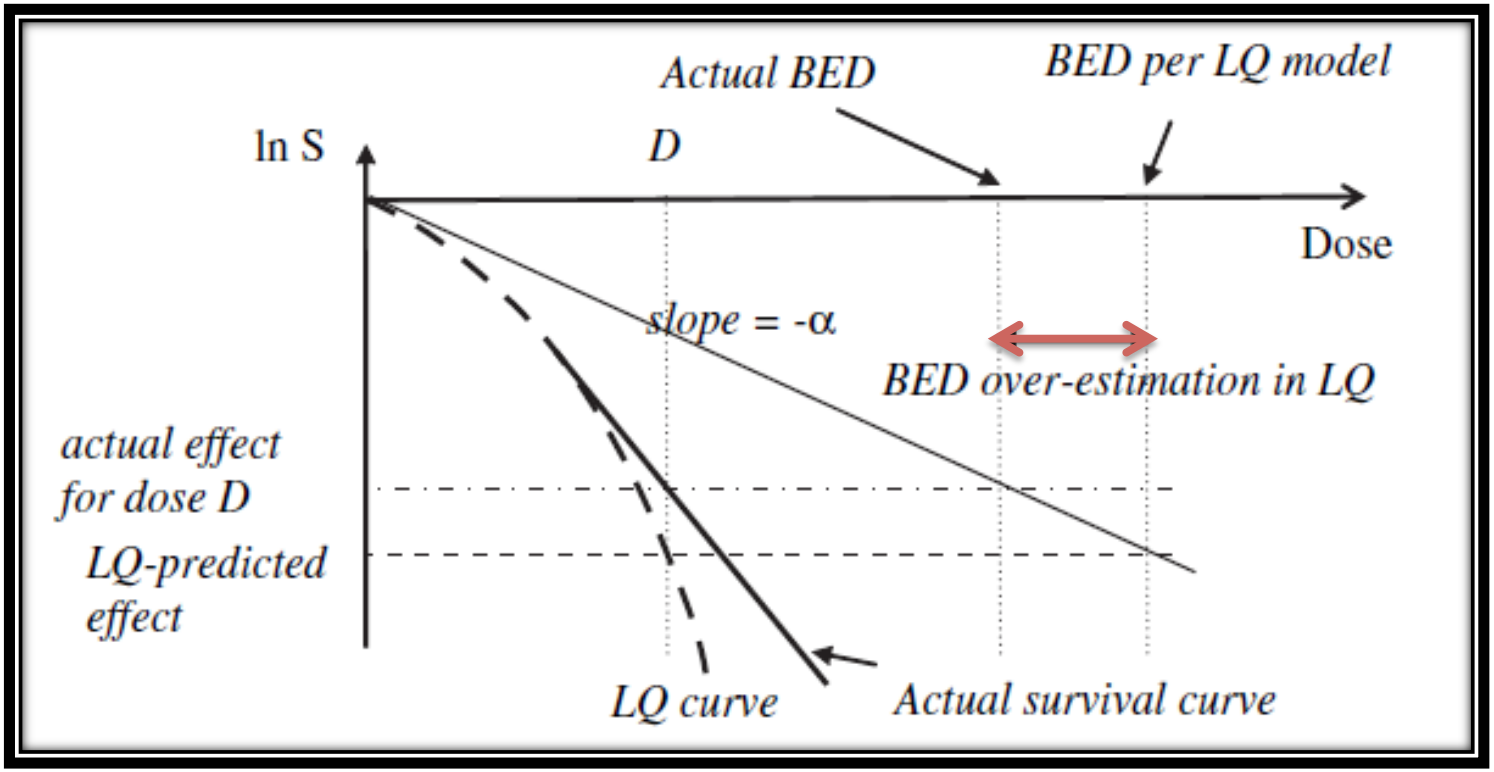
1. Advances in image guidance and dose delivery enable the delivery of large doses to tumors with much smaller volumes of normal tissue irradiated, thus overcoming the need in some situations to be concerned with normal tissue injury.

2. The LQ model may not accurately predict cell killing at high doses. It might be suggested that the model may over predict cell killing at high doses so the damage to late responding normal tissues (which have smaller α/β values and therefore a more "curvy" dose response curve) may be less than predicted by the model, thereby allowing bigger doses than predicted by the model to be used in practice.

3. There are anti-tumor effects of high radiation fractions that are not predicted by classical radiobiology including enhanced anti-tumor immunity and secondary effects deriving from injured vasculature.

4. Many tumors may not be hypoxic so there would be no benefit of reoxygenation between doses in a multi-fraction regime.

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.

Kamil M. Yenice, PhD

Universal Survival Curve

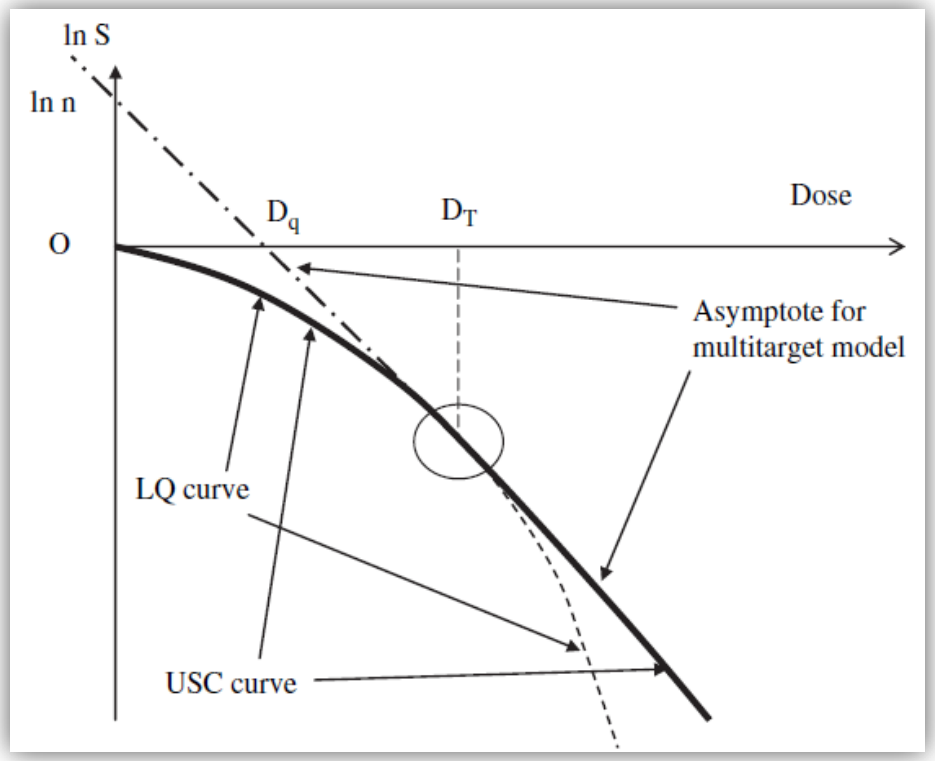
(Park et al IJROBP, Volume 70, Number 3, 2008)

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

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

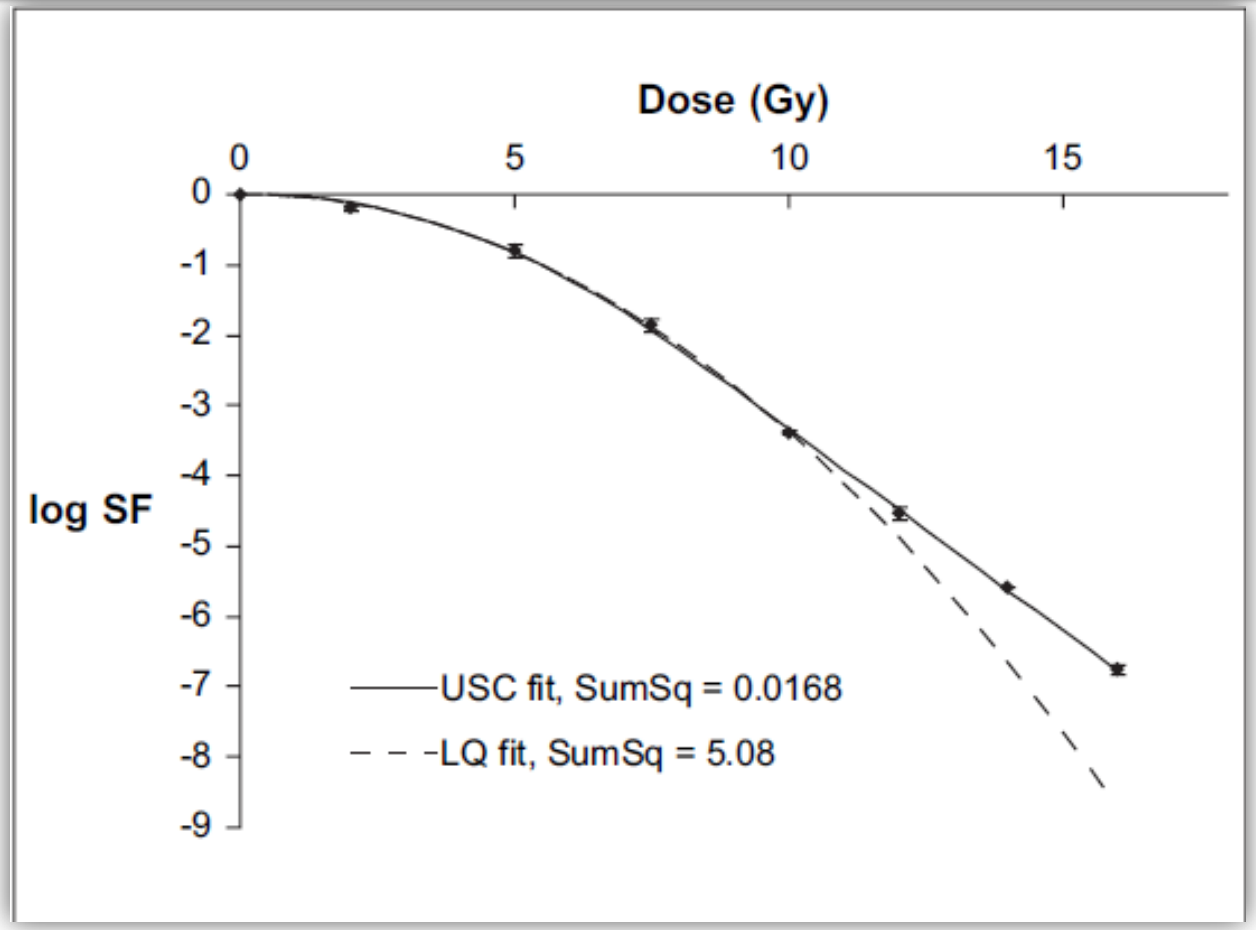
$$\ln S \approx -\frac{1}{D_0} d + \ln(\bar{n}) = -\frac{1}{D_0} d + \frac{D_q}{D_0}$$

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



Universal Survival Curve

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



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

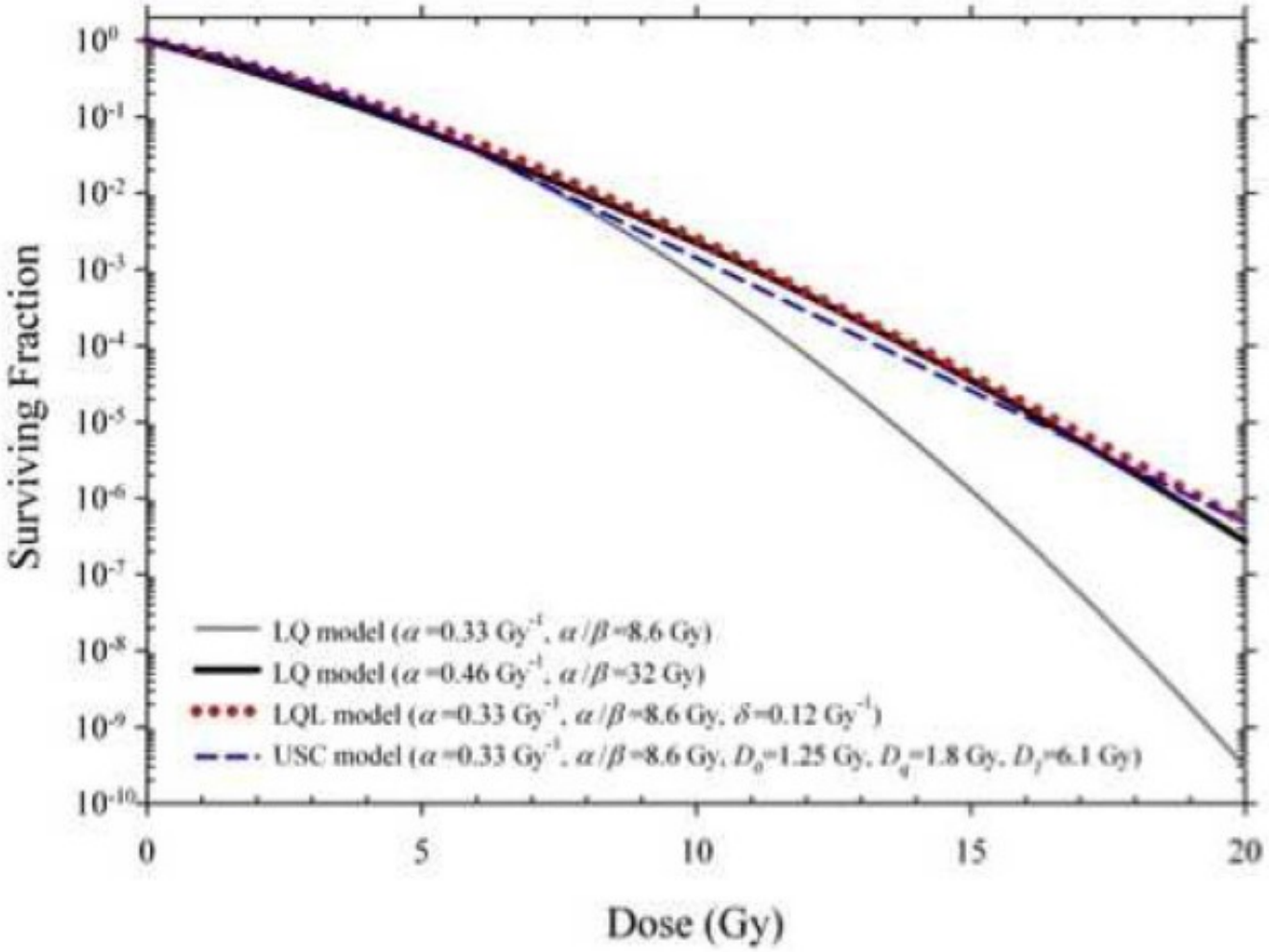


Figure 1. The perceived overprediction of cell killing at high doses by the LQ model is resolved by assuming a higher α/β value

Comparison of predictions of the Linear-Quadratic (LQ), Linear-Quadratic-Linear (LQL) (14, 22), and Universal Survival Curve (USC) (17) models. LQL and USC model predictions are similar assuming an α/β of 8.6 Gy..

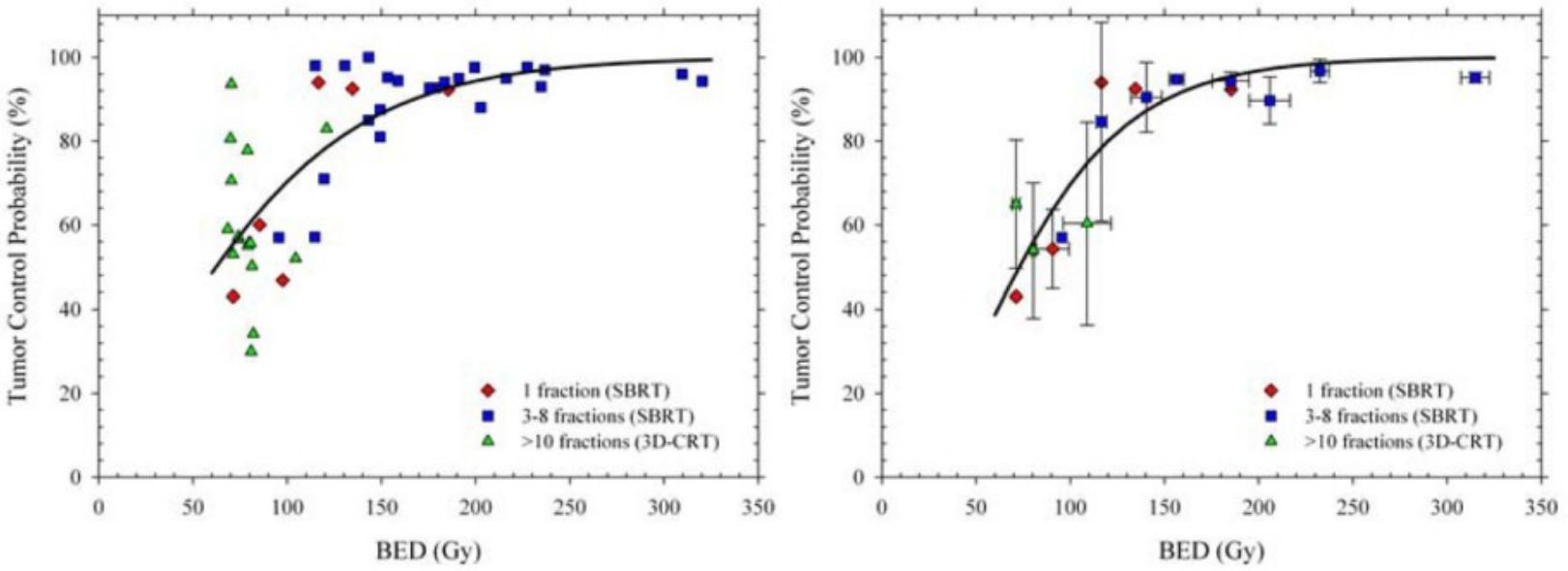


Figure 8. Tumor control probability (TCP) as a function of biologically effective dose (BED) for stage I NSCLC

Left panel: Symbols show local control rates (≥2 years) from a pooled analysis reported by Mehta *et al.* (27) with symbols distinguishing conventional and SBRT fractionations. Right panel: Weighted mean TCP probabilities calculated to compensate for the different numbers of patients in each study. Solid lines show LQ-based fits to the data which show that, within the limits of clinical data, the efficacy of single doses, a few SBRT fractions, and conventional radiotherapy produce the same overall TCP for the same BED. From (58) with permission.

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

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)

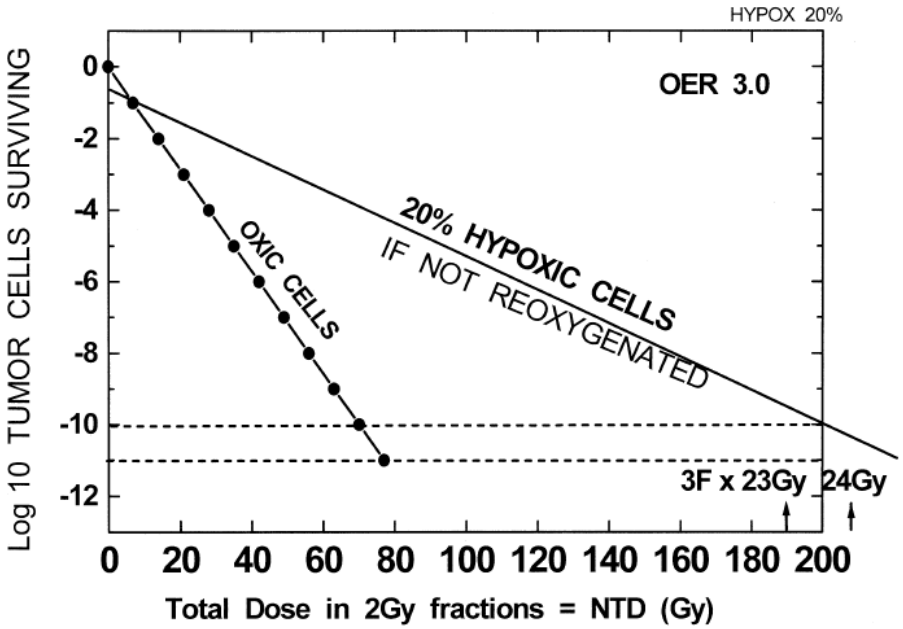
Phase II trials of SBRT for liver metastases

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%

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

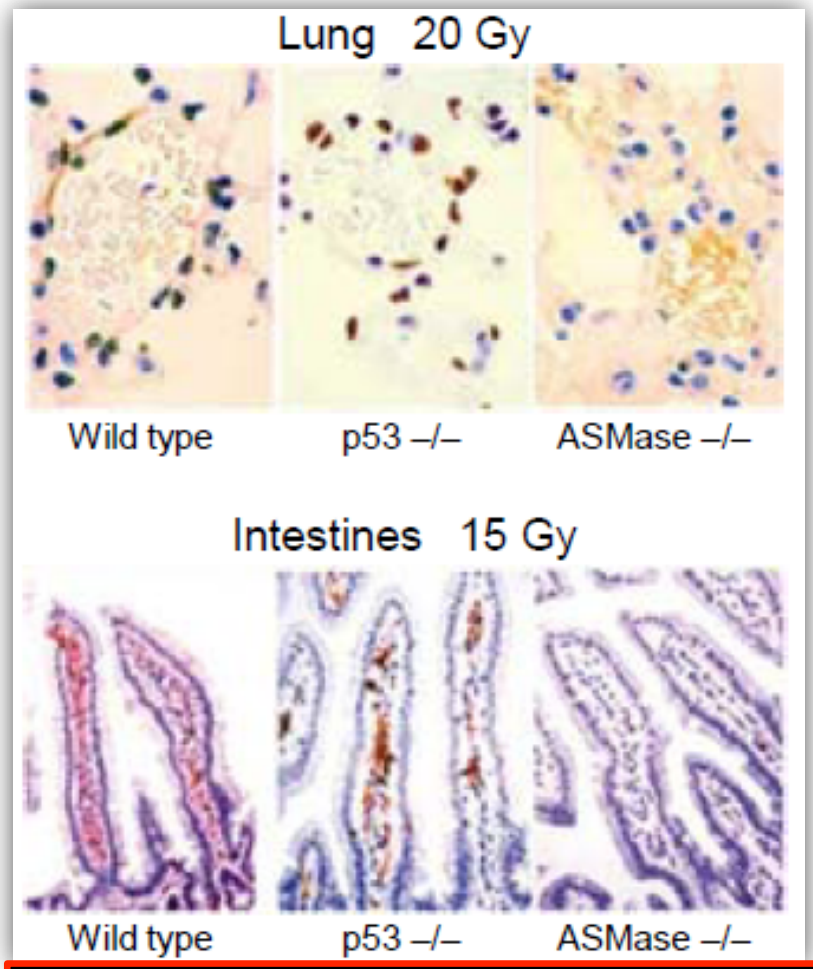
Brown et al 2010 IJROBP: V 78, pp 323-327

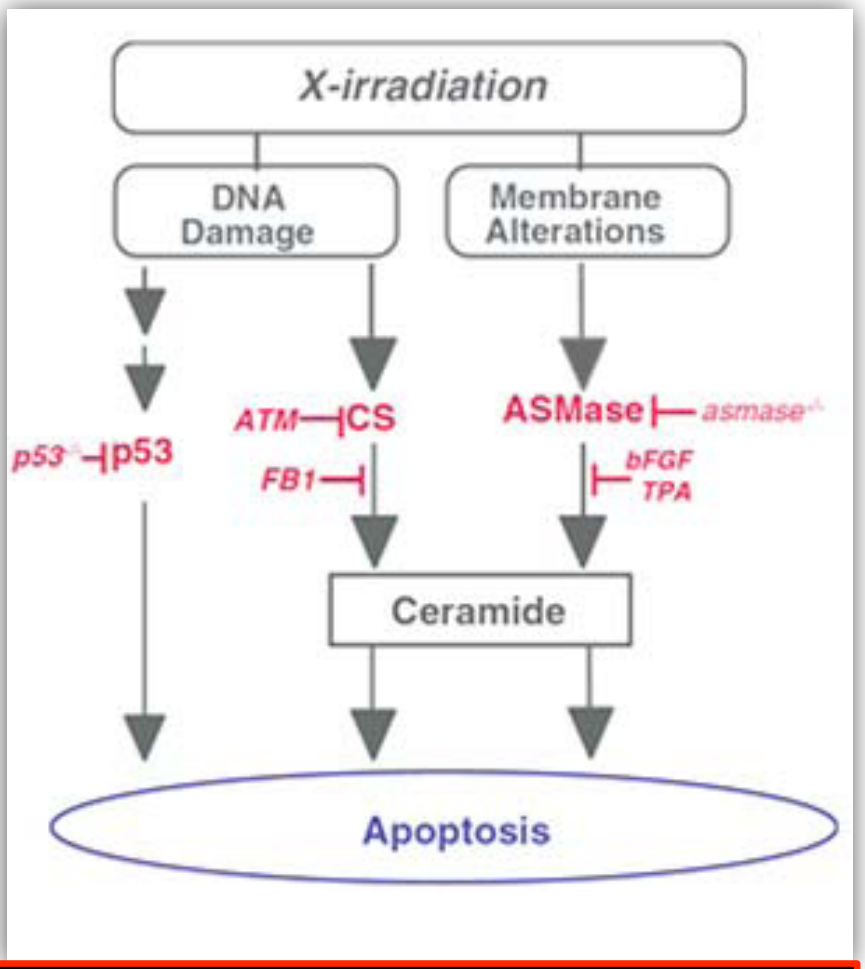


Fowler et al 2004 IJROBP V60, pp1241-1256

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!

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

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