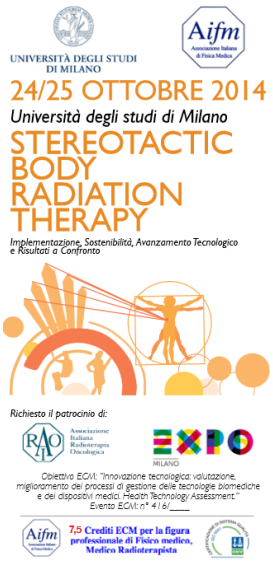


Radiobiologia:
High dose per fraction

Lidia Strigari
Laboratorio di Fisica Medica
e Sistemi Esperti

IRE
ISTITUTO NAZIONALE TUMORI
REGINA ELENA
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

SBRT

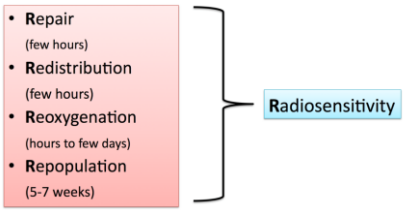
- Although SBRT constitutes a **potpourri** of technologies and techniques, including three-dimensional conformal, intensity modulation, image guidance, motion control, and stereotactic targeting, **the hallmark of SBRT is delivery of a potent, ablative or nearly ablative dose in oligofractions (i.e., five or fewer fractions).**

outline

- What is the biological basis of potent hypofractionation used in SRS and SBRT?
- Does LQ model work at high doses?
- What effect does occur increasingly at higher doses per fraction?
- Are “4Rs” of radiobiology still relevant to SRS/ SBRT regimens?

Radiobiology

Classical Radiobiology → Fractionation → 4Rs



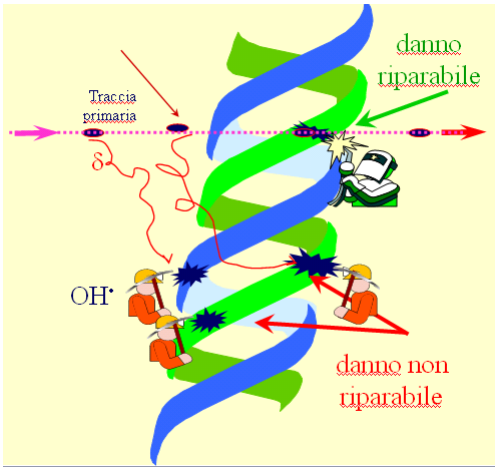
Cell survival curves and modeling

- Linear quadratic (LQ) model and modifications to LQ model to fit the data at high dose
- Vascular effects/endothelial cell damage at high dose
- Immune system effect
- Dose-rate effect ?

SBRT /SART 4Rs revisited

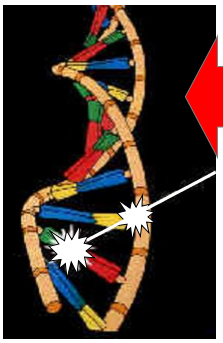
Il modello Lineare Quadratico

- Per semplicità è conveniente pensare che la radiazione in una cellula può produrre o un danno di tipo "A" o di tipo "B"

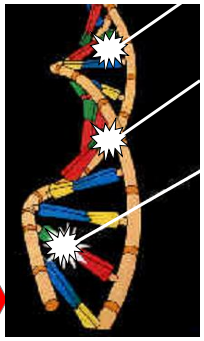


- Il danno di tipo "A" si ha quando un singolo evento disattiva due bersagli critici (es. due eliche del DNA);
- Il danno di tipo "B" è il danno prodotto su ogni singolo bersaglio da due eventi separati (es. ogni elica del DNA interrotta in punti diversi da due eventi separati).

Nel modello Lineare Quadratico

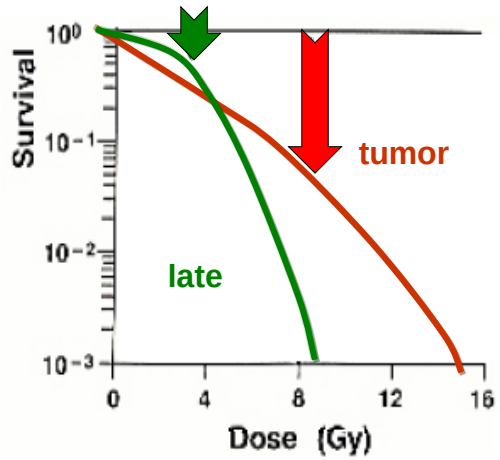


- Il danno di tipo "A" è rappresentato dal termine αD



- Il danno di tipo "B" è rappresentato dal termine βD^2

Differenze OARs e Tumore



maggiore vantaggio del frazionamento

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

David J. Brenner, PhD, DSc

Seminars in RADIATION ONCOLOGY
2008

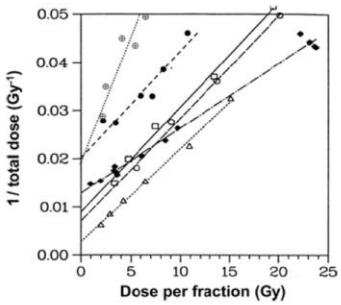


Figure 4 Isoeffect data for late response from 3 (□ ○ Δ) different regions of the rat spinal cord,[25] for acute skin reactions (◆) in mice,[26] and for early (●) and late (⊕) murine intestinal damage.[27] The data are plotted in a "reciprocal-dose F_c" form[26] such that, if they follow an LQ relationship, the points fall on a straight line.

In summary, LQ has the following useful properties for predicting isoeffect doses:

1. It is a mechanistic, biologically based model.
2. It has sufficiently few parameters to be practical.
3. Most other mechanistic models of cell killing predict the same fractionation dependencies as does LQ.
4. It has well-documented predictive properties for fractionation/dose-rate effects in the laboratory.
5. It is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction.
6. To date, there is no evidence of problems when LQ has been applied in the clinic.

Question 1: Is the LQ model appropriate to model high dose per fraction effects in **SBRT/SRS** ?

POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Colin G. Orton, Professor Emeritus, Wayne State University, Detroit: ortonc@comcast.net. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery

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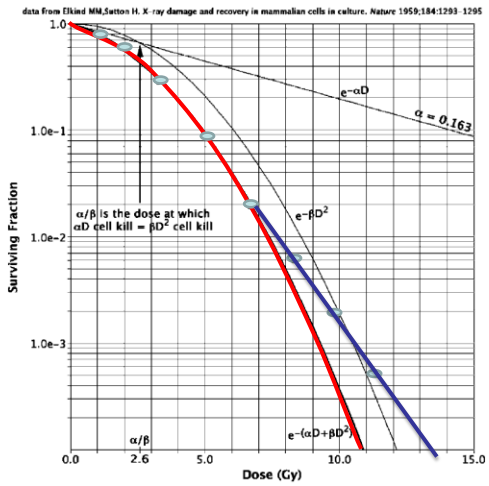
Colin G. Orton, Ph.D., Moderator

(Received 27 May 2009; accepted for publication 28 May 2009; published 1 July 2009)

[DOI: 10.1118/1.3157095]

Fowler J F 2008 **Linear quadratics is alive and well**: in regard to Park et al. (Int J Radiat Oncol Biol Phys 2008;70:847-852) *Int J Radiat Oncol Biol Phys.* **72** 957



Astrahan, Med. Phys. 2008

$$D_T = 2\alpha/\beta$$

$$\gamma = tg(@D_T)$$

On the log-linear plot, the LQ curve closely fits these experimental results for Chinese hamster **cells** in culture up to a dose of 6 Gy, but then continues to bend. The experimental results are observed to become linear at high dose.

$$BED_n(D) = D + \frac{D^2}{\alpha/\beta} \qquad D < D_T$$

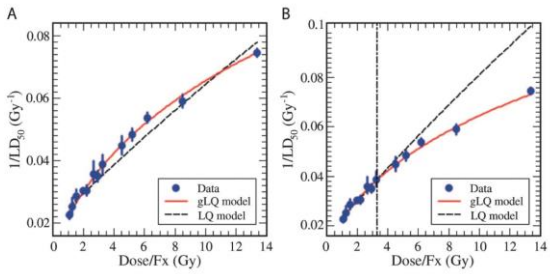
$$BED_n(D) = D_T + \frac{D_T^{\,2}}{\alpha/\beta} + \frac{\gamma}{\alpha}(D - D_T) \qquad D \geq D_T$$

LQ model tends to overestimate the effectiveness of cell killing by a single high dose

- The essential problem stems from ignoring the reduction of sublethal damage after conversion to lethal damage; therefore the pool size of the sublethals lesions which are available to be converted to lethal lesions with further irradiation is over estimated (*Wang JZ et al. Sci Transl Med. 2010*)

gLQ : α = 0.11/Gy, α/β=0.82 Gy gLQ: α = 0.10/Gy, α/β = 0.80 Gy

LQ: α=0.40/Gy, α/β= 16 Gy LQ: α = 0.15/Gy, α/β = 2.0 Gy



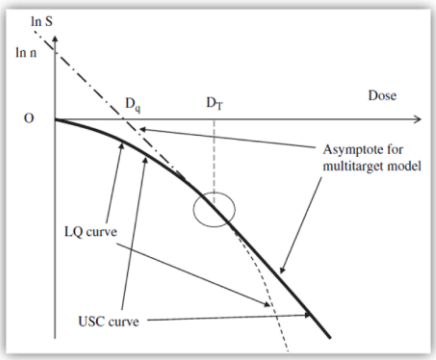
Universal Survival Curve *Park et al. 2008*

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

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

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

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



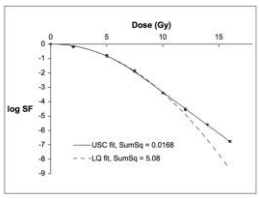
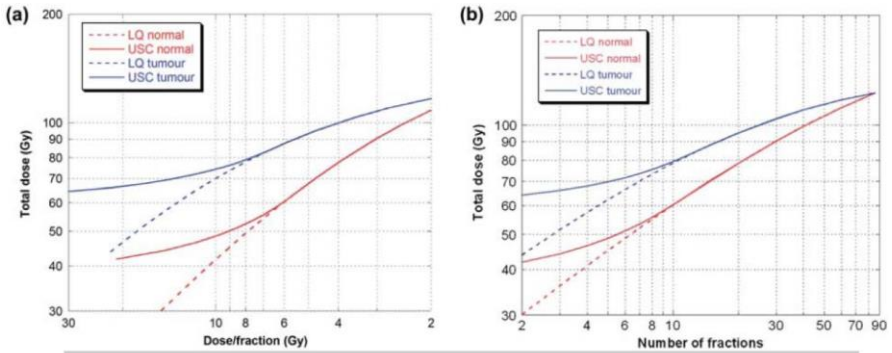


Fig. 4. Survival curve of H460 fitted with linear quadratic (LQ) model (using points ≤8 Gy) and with universal survival curve (USC) model. Fit over entire range drastically improved with USC model fit. If LQ model fit over entire dose range, sum of square improves compared with low-dose LQ model fit (sum of squares = 0.285) but still much inferior to USC model (data not shown). Details of generating this survival curve will be published separately.

$$D_{SBRT} = \alpha \cdot D_0 \cdot D_{CFRT} \cdot \left(1 + \frac{d_{CFRT}}{\alpha/\beta}\right) + n_{SBRT} \cdot D_q$$

$$D_{CFRT} = \frac{1}{\alpha \cdot D_0} \cdot \frac{D_{SBRT} - n_{SBRT} \cdot D_q}{\left(1 + \frac{d_{CFRT}}{\alpha/\beta}\right)}$$



Isoeffect curves for tumour and normal tissues, calculated with LQ and USC

For schedules with isoeffective tumour dose:
- -the cell survival in normal tissue outside the tumour will increase
- -the NTCP will decrease with more than 3 fractions

In general: a larger gain with the USC
In specific: USC predicts the largest gain compared to LQ models in volumes of OAR receiving less than full dose

Wennberg et al. 2013

VOLUME 24 · NUMBER 30 · OCTOBER 20 2006
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ranzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

- IU 70 patient phase II study
- 20 Gy X 3 for T1
  22 Gy X 3 for T2
- NO restriction on tumor location

Zone of the Proximal Bronchial Tree

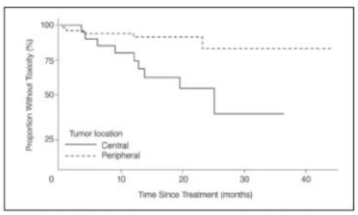
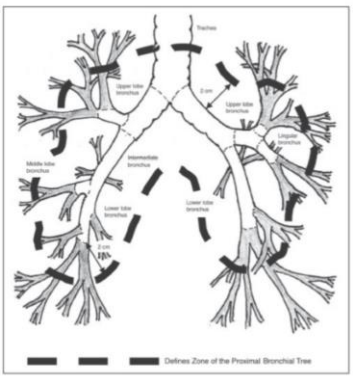


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.



ELSEVIER
Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 1, pp. 47–54, 2009

0360-3016/09/$–see front matter
doi:10.1016/j.ijrobp.2008.06.1939

NSCLC

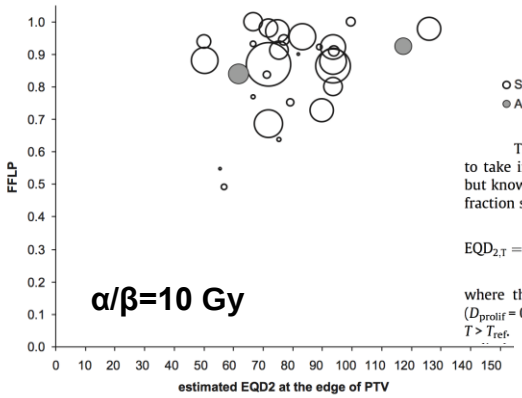
Local control rates were 89% and 62% at 36 months for >100 Gy and <100 Gy BED (p = 0.0001)

CLINICAL INVESTIGATION — Lung

DOSE–RESPONSE RELATIONSHIP FOR IMAGE-GUIDED STEREOTACTIC BODY RADIOTHERAPY OF PULMONARY TUMORS: RELEVANCE OF 4D DOSE CALCULATION

MATTHIAS GUCKENBERGER, M.D.,* JOERN WULF, M.D.,*† GERD MUELLER, M.D.,* THOMAS KRIEGER, M.SC.,* KURT BAIER, M.SC.,* MANUELA GABOR, M.S.,* ANNE RICHTER, M.SC.,* JUERGEN WILBERT, PH.D.,* AND MICHAEL FLENTJE, M.D.*

SBRT for stage I NSCLC



α/β=10 Gy

The EQD_2 was adjusted for overall treatment time ($EQD_{2,T}$) to take into account accelerated repopulation after 21 days [27], but knowing that these estimations may be less appropriate with fraction sizes over 10 Gy [28].

$$EQD_{2,T} = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta} - MAX(0, T - T_{ref}) \cdot D_{prolif}$$

where the second term is zero for $T \leqslant T_{ref}$ and equal to D_{prolif} (D_{prolif} = 0.6) multiplied by the number of days beyond T_{ref} for $T > T_{ref}$.

NSCLC

α/β=8.6 Gy

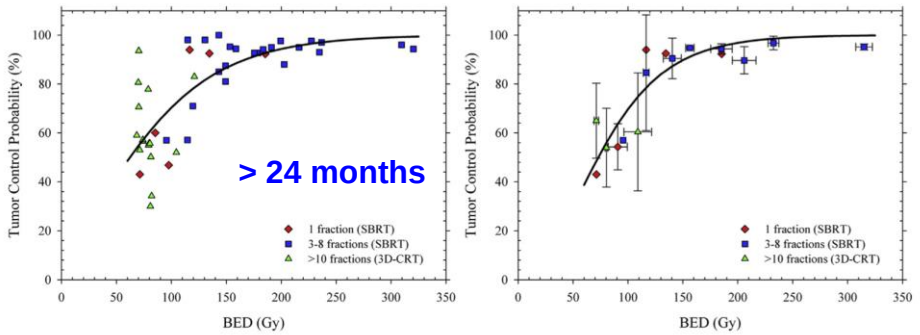
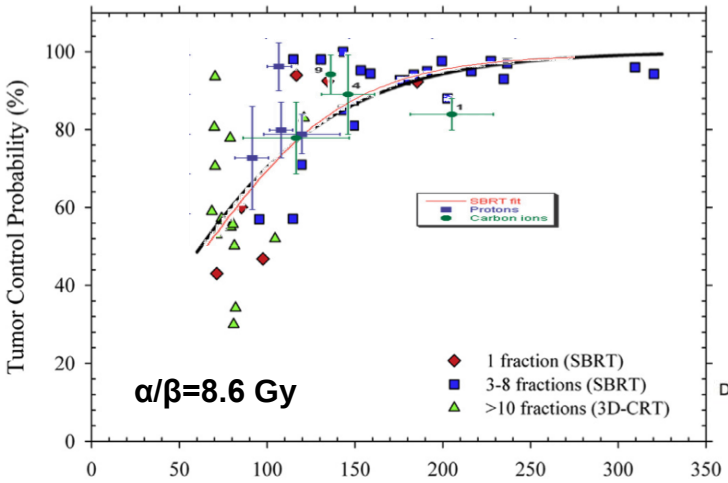


Fig. 8. Tumor control probability (TCP) as a function of biologically effective dose (BED) for stage I non-small cell lung cancer. Left, symbols show local control rates (≥2 years) from a pooled analysis reported by Mehta et al (27) with symbols distinguishing conventional and stereotactic body radiation therapy (SBRT) fractionations. Right, weighted mean TCP probabilities calculated to compensate for the different numbers of patients in each study. Solid lines show linear quadratic-based fits to the data showing that within the limits of clinical data, the efficacy of single doses, a few SBRT fractions, and conventional radiation therapy produce the same overall TCP for the same BED. From (58) with permission. 3D-CRT = 3-dimensional conformal radiation therapy.

NSCLC



Stage I NSCLC

- Proton data from LLUMC, HIBMC, NCCE, University of Tsukuba (10-22 fr)
- Carbon ion data from NIRS (hypofractionation trial)

Durante, *Br. J. Radiol.* 2013

Tumour responses to radiotherapy

Non-uniform response of tumour cells to radiotherapy

- Intrinsic radiosensitivity
  Radiosensitisers
- Hypoxic fraction
- Non-local dose effects
- **Dose rate effect**

Vascular effect
Endothelium

Bystander Responses
Response observed in cells which are not directly traversed by radiation

<5 frs

Models

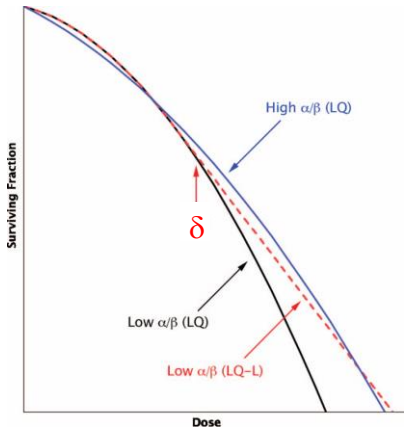
LQ

$$S_0(d) = \exp\left[-d(\alpha_0 + \beta_0 d)\right]$$

$$S_h(d) = \exp\left[-d(\alpha_h + \beta_h d)\right]$$

$$\alpha_h = \frac{\alpha_0}{OER_\alpha}$$

$$\beta_h = \frac{\beta_0}{OER_\beta^{\,2}}$$



LQ-L

$$S_0(d) = \exp\left[-d(\alpha_0 + G(\lambda T)\cdot \beta_0 d)\right]$$

$$S_h(d) = \exp\left[-d(\alpha_h + G(\lambda T)\cdot \beta_h d)\right]$$

$$G(\lambda) = 2\frac{\lambda T + \exp(-\lambda T) - 1}{(\lambda T)^2}$$

$$\lambda = \lambda_0 + \delta \cdot \dot{d}$$

$$\alpha_h = \frac{\alpha_0}{OER_\alpha}$$

$$\beta_h = \frac{\beta_0}{OER_\beta^{\,2}}$$

$$R(\Delta t) = 2^{\frac{\Delta t}{T_{eff}}}$$

$$B = f(d,n)$$

Guerrero M et al. 2004

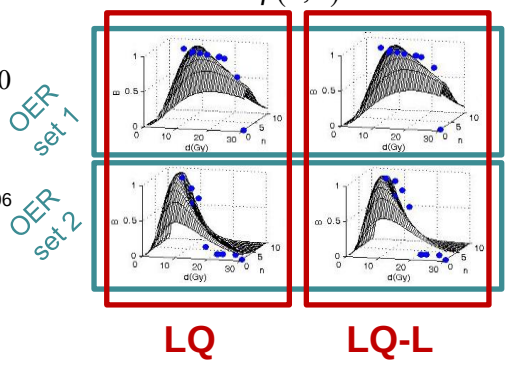
Parameters

N_0, η, T_{eff} , α_0, β_0

α_h, β_h Nahum et al. 2003

Carlson et al. 2006

$$B = f(d,n)$$



LQ **LQ-L**

TABLE I. Schedules of stereotactic hypofractionated radiotherapy on stage I NSCLC with experimental LC3.

Authors	Year	# pat.	# fr.	d (Gy)	p.i. (%)	Δt (days)	LC3 (%)
Nyman *et al.*	2005	45	3	15	100	2	80
Nagata *et al.*	2005	45	4	12	100	4	97
Zimmerman *et al.*	2006	43	3	12.5	60	1	88
Baumann *et al.*[a]	2006	138	3.03	13.39	65	2.5	85
Fritz *et al.*	2007	40	1	30	100	0	81
Koto *et al.*[a]	2007	31	4.07	11.6	100	2	63
Baumann *et al.*	2009	57	3	15	67	2	92
Fakiris *et al.*[a]	2009	35	3	21.03	80	2.5	88.1
Kopek *et al.*[a]	2009	88	3	17.2	100	2.5	89
Mirri *et al.*	2009	40	5	8	95	2	72
Baba *et al.*[b]	2010	85	4	12	100	2.5	81
Baba *et al.*[b]	2010	37	4	13	100	2.5	74
Haasbeek *et al.*[a,b]	2010	193	4.85	12.37	80	1	89
Ricardi *et al.*[b]	2010	62	3	15	80	2	87.8
Matsuo *et al.*[b]	2011	101	4	12	100	3	86.8
Timmermann *et al.*[b]	2011	55	3	18	90	2.5	97.6

Note: abbreviations: d = dose/fraction; #pat. = number of patients; #fr = number of fractions; p.i. = prescription isodose; Δt = time between fractions; LC3 = local control at 3 yr. In the studies marked with 'a' multiple doses per fraction and fraction numbers were used, patient group-averaged values have therefore been calculated and listed in the table. 'b' indicates the validation set.

TABLE III. Log-likelihood and AIC calculated using the validation set for different models (LQLM and LQM), OER parameter set, and fractions of hypoxic cells (η_h).

		LQM		LQLM	
η_h	Parameter	OER set 1	OER set 2	OER set 1	OER set 2
0.05	L	−588.1	−582.4	−589.8	−582.6
	AIC	−6.8	−6.7	−6.8	−6.7
0.10	L	−557.7	−554.9	−558.6	−554.8
	AIC	−6.6	−6.6	−6.7	−6.6
0.15	L	−545.6 (*)	−546.6(*)	−546.0(*)	−546.3(*)
	AIC	−6.6 (*)	−6.6(*)	−6.6(*)	−6.6(*)
0.50	L	−575.1	−600.8	−564.4	−596.4
	AIC	−6.7	−6.8	−6.7	−6.8
0.00	L	−1038.2		−1038.2	
	AIC	−12.9		−12.9	

Strigari et al. 2012

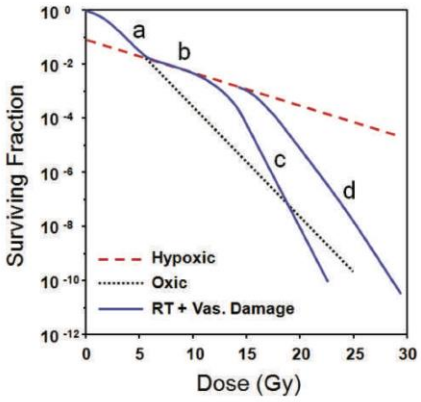
RADIATION RESEARCH 177, 311–327 (2012)
0033-7587/12 $15.00

DOI: 10.1667/RR2773.1

REVIEW

Radiation-Induced Vascular Damage in Tumors: Implications of Vascular Damage in Ablative Hypofractionated Radiotherapy (SBRT and SRS)

Heon Joo Park,[a,b] Robert J. Griffin,[c] Susanta Hui,[a] Seymour H. Levitt[a,d] and Chang W. Song[a,1]



- For D < 5Gy oxic cells die
- For D > 5Gy hypoxic cells death dominates
- For D >10 Gy Vascular damage at high doses produces secondary cell killing, **suggests that radiation doses induce vascular damage leading to indirect tumor cell death**.

Tumour responses to radiotherapy

Non-uniform response of tumour cells to radiotherapy

Intrinsic radiosensitivity
Radiosensitisers

Hyp[illegible]ion

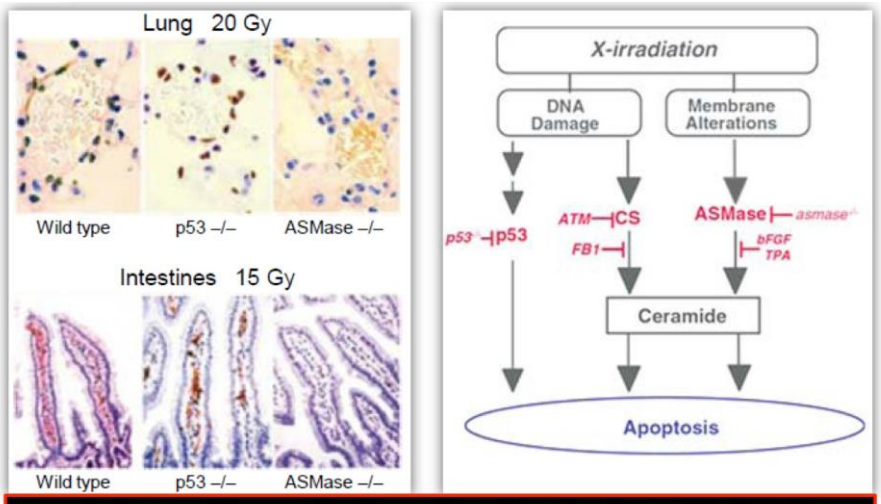
Non-local dose effects

Dose rate effect

Vascular effect
Endothelium

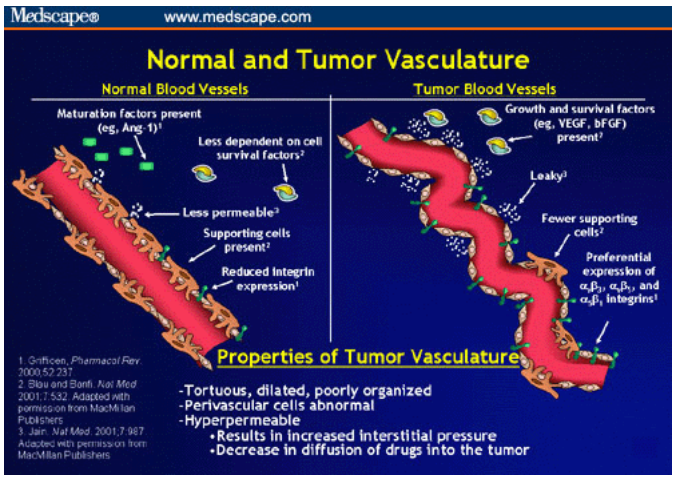
Bystander Responses
Response observed in cells which are not directly traversed by radiation

<5 frs



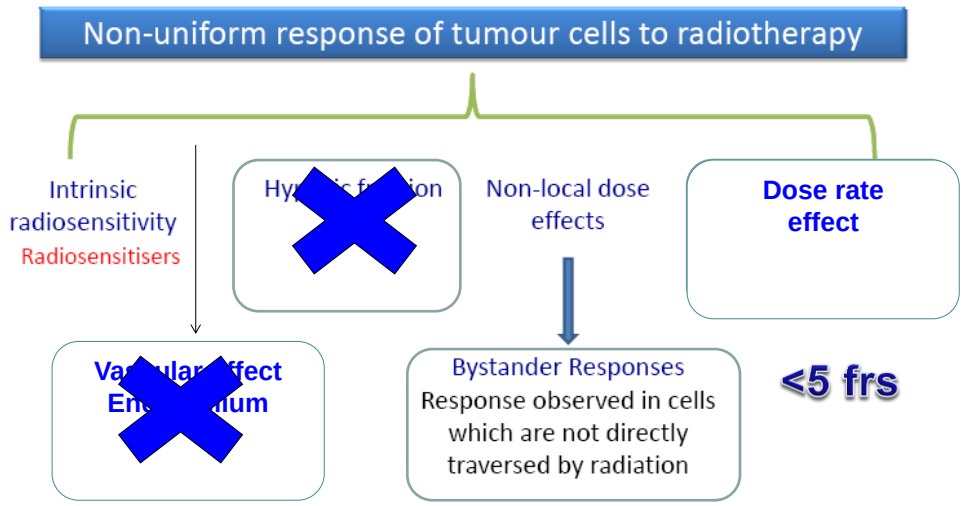
HYPOTHESIS: Ceramide mediated Endothelial Apoptosis causes indirect cell kill at >10Gy!

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



- vasculature associated with tumors is not normal
- The blood vessels in a tumor bed, generally speaking, are tortuous, dilated, and poorly organized
- The surrounding pericytes are abnormal. They tend to be hyperpermeable and leaky

Tumour responses to radiotherapy



The oncologist's prospective

Most reports on abscopal effects refer to antitumor consequences outside the radiation field

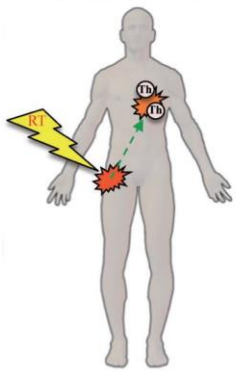
Multiple mechanisms have been proposed to cause the abscopal effects, such as:

- **the systemic secretion of specific cytokines and chemokines,**
- **a systemic immune response against local tumor antigens released**
- **local inflammation that can lead to a distant effect.**

In any case, the hypothesis that the abscopal effect is immune-mediated is becoming stronger

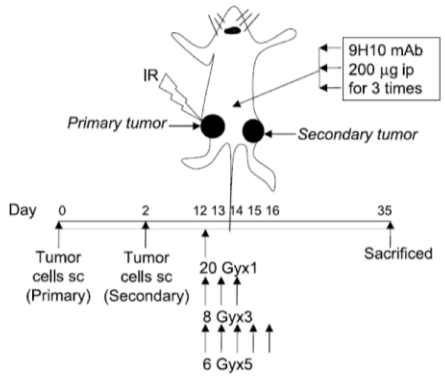
Sologuren et al., 2014

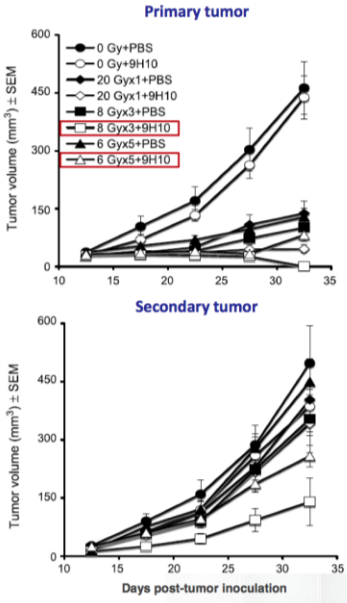
Distal areas to the primary tumor (metastasis)



Anti-tumor T-cell response

Animal model

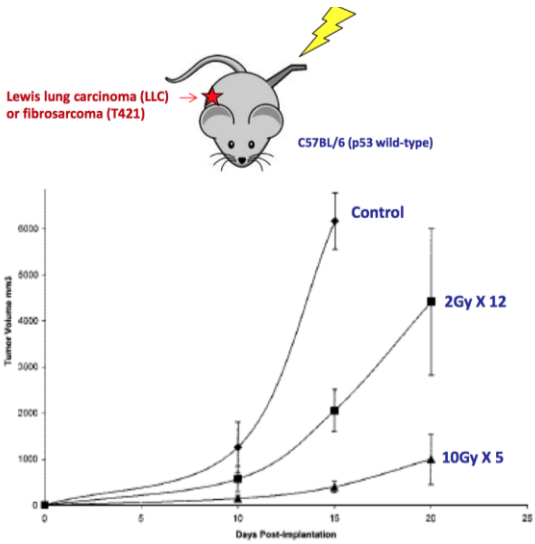




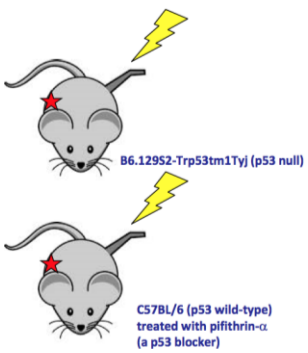
Only fractionated, and not RT administered as a single high dose, induced an immune-mediated abscopal effect in a secondary tumor when combined with anti-CTLA-4 antibody.

Dewan et al., 2009

Animal model



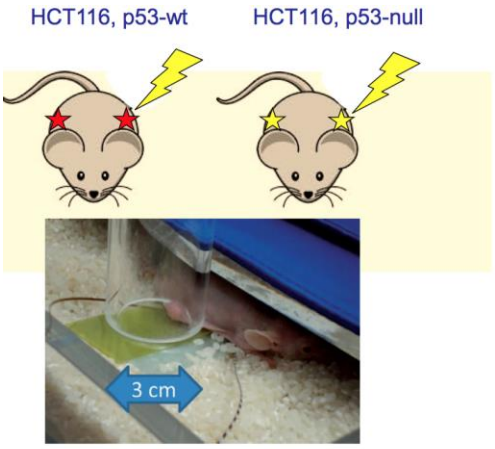
The abscopal effect is dose dependent and not tumor-specific



These data implicate p53 as a key mediator of the radiation-induced abscopal effect

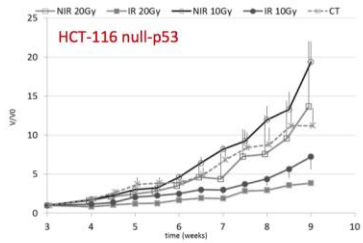
Camphausen et al., 2011

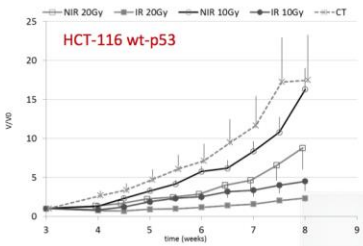
IRE experience



When tumours reached a volume of 0.2 cm³, irradiation was performed, under strict dose monitoring, with a dedicated mobile accelerator designed for intra-Operative-RT (IORT). A dose of 10 or 20 Gy delivered by a 10 MeV electron beam, was delivered to a tumour established in one side flank (IR groups), leaving the other non-irradiated (NIR groups).

Strigari et al., 2014





Our results suggest that the interplay between radiation dose and p53 status plays a critical role in the RT-induced bystander effects

Tumour responses to radiotherapy

Non-uniform response of tumour cells to radiotherapy

Intrinsic radiosensitivity
Radiosensitisers

Hy[illegible]ion

Non-local dose effects

Dose rate effect

Vas[illegible]lar [illegible]ffect
End[illegible]um

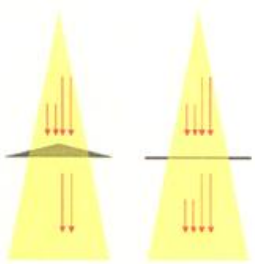
Bystander Responses
Respons[illegible]d in cells which [illegible]directly traver[illegible]d by [illegible]diation

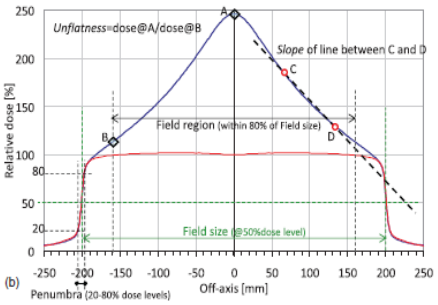
<5 frs

VMAT

FFF vs FF: beam hardening

- FFF ha una più bassa energia media
- 10FFF → 8

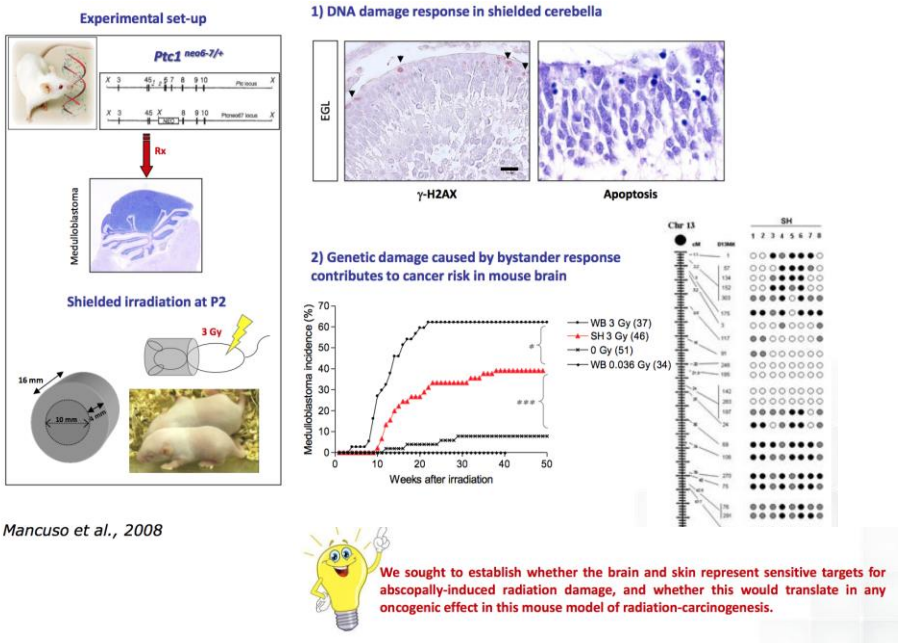




- Dose rate → 24 Gy/min

Ref.	Cells	E (MV)	Dose rate (Gy/min)	Modulated beam	Effect
Sørensen et al. RO 2011	HN FaDu V79	6FFF 6X	5, 10, 30	No	No
Loshe *et al.*RO 2011	Gliomas T98G (mut-p53) U87MG	10FFF 10X	0.02, 4, 24	No	Yes at D≥10 Gy
King *et al.*PMB 2013	PCa DU 145, NSCLC H460	6FFF 6X	3, 11	Yes (bolus)	No
Verbakel et al. AO 2013	Lung SW1573 ; gliom T98 (Mut-p53); astroc D348	6/10 FFF/X	4, 8	Yes (IMRT)	No
Karan *et al.* PMB 2013	cervix SiHa; NSCLC H460; V79	6/10 FFF/X	3, 10	No	No
Bewes et al. 2008	melanoma MM576; NSCLC H460	6FFF 6X	1.2, 5	Yes	Dose rate effect on protracted delivery

In vivo bystander effect: carcinogenic potential



Mancuso et al., 2008

SBRT /SART 4Rs revisited

- Reoxygenation

When tumors are treated with SRS/SBRT the intra-tumor 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**

Adaptive RT – Liver

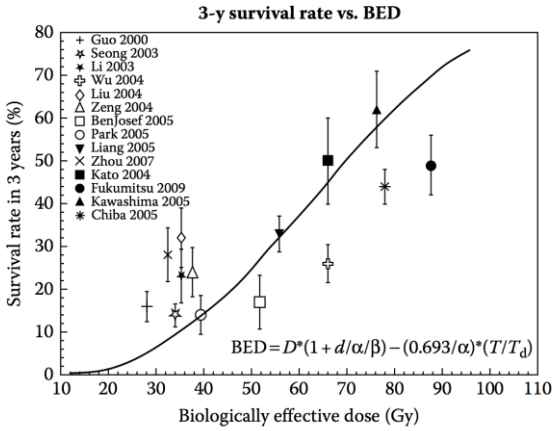
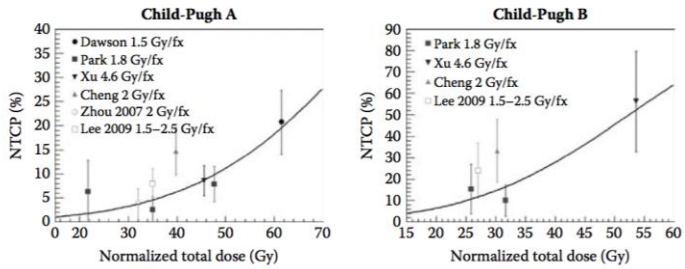


FIGURE 20.1 Three-year overall survival rate as a function of biologically effective dose (BED) for primary liver tumors. BED and the curve were calculated using the model described by Tai, A., et al. (2008). Note that in the studies by Wu, D. H., et al. (2004), Liu et al. (2004), and Zeng, Z. C., et al. (2004) the follow-up time was recorded from the beginning of diagnosis, whereas in other studies it was recorded from the start of treatment.

Adaptive RT – Liver



Normal tissue complication probability (NTCP) data plotted as a function of normalized total dose (NTD) from he CC) patients of Child-Pugh A (left panel) and Child-Pugh B (right panel). NTD was calculated by $\left(\frac{\alpha/\beta+d+f\times N}{\alpha/\beta+d_{ref}+f\times N_{ref}}\right)D(d)$, w ctions and f is a fitting parameter (0.156 and 0 for Child-Pugh A and B, respectively; Tai 2009). The subscript refers to t scheme at which the Lyman model parameters were derived. (Adapted from Tai, A., B. Erickson, and X. A. Li. 2009. *Int J* 83–9. With permission.)

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Original Article

Is Biochemical Relapse-free Survival After Profoundly Hypofractionated Radiotherapy Consistent with Current Radiobiological Models?

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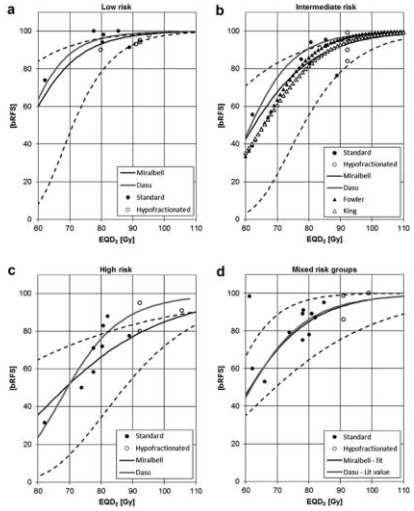

Fig 1. Biochemical relapse-free survival against EQD_2 for low-, intermediate- and high-risk patients and for mixed-risk groups (a, b, c and d, respectively). Data points show the result of trials of standard and moderate hypofractionation (●) and profound hypofractionation (○). Solid lines show published model fits, with the exception of the Miralbell model for mixed-risk group data, which is fitted to the data in (d). Dotted lines show 95% confidence intervals for the Miralbell fit.

Recommendations, thorax and abdomen region

	Absorbed dose recommendations	EQD2/BED/NTCP recommendations	Prob.curve
Heart/cardiac mort Heart/pericarditis.	Yes, new data needed	NTCP α/β=3Gy	RS LKB
Lung /RP	Yes, new data keep coming	MLD, EQD2 (SBRT open)	Function of MD + clin/risk factors + genetic
Esophagus/acute	Yes, but limited evidence	Mean dose	
Ribs/fracture	Yes,but few data	LQ	Logistic - D_{2cm3} V_{30}
Chest wall/pain	Yes, but few data		
Liver/RILD	Yes	Primary,and metastatic EQD2 α/β=2Gy (SBRT open)	Function of MD + clin/risk factors
Spine/myelitis	Yes, but few data	EQD2 α/β=3Gy	Function of EQD2

Conclusion

- Extreme hypofractionated RT (SBRT/SABR) seems to be capable of overcoming hypoxic radioprotection through mechanisms other than directly killing tumor cells via DNA damage.
- Important mechanisms for cell inactivation has been hypothesized to become important at doses >10 Gy
  - Vascular effects occurs increasingly at higher doses per fraction
  - Immunological effect
  - Bystander effect