The Clatterbridge Cancer Centre NHS
NHS Foundation Trust

Aspetto radiobiologico dell'ipofrazionamento

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- Navita Somaiah and John Yarnold, ICR, Sutton

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CONTENUTO

THE L-Q MODEL

CLASSICAL RADIOBIOLOGY – small good, large fractions bad

TUMOURS and α/β

NORMAL TISSUES and α/β

THERAPEUTIC RATIO and (hypo)fractionation – lung and prostate tumours

Do we really understand everything?
- LQ-VALIDITY : the gLQ alternative
- The success of SABR : expected?
- Hypoxia ?
- The SONG hypothesis: vascular damage at v. large fraction sizes

Take-home messages

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The radiation killing of tumor cells is described **most efficiently** by the **Linear-Quadratic (LQ)** equation. It defines the Poisson probability of escaping **two distinct** and **independent** lethal events, described by single-hit and double-hit kinetics.

Surving fraction SF $= \exp(-\alpha D) \times \exp(-\beta_{MAX} D^2)$
$= \exp(-\alpha D - \beta_{MAX} D^2)$

or

$$-\ln(SF)/D = \alpha + \beta_{MAX} D$$

(Don Chapman, Clatterbridge Radiobiology course)

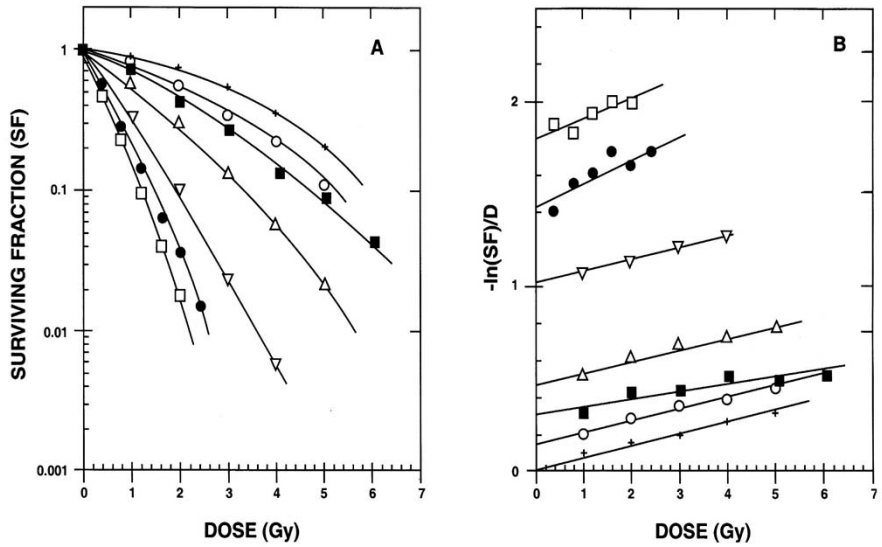
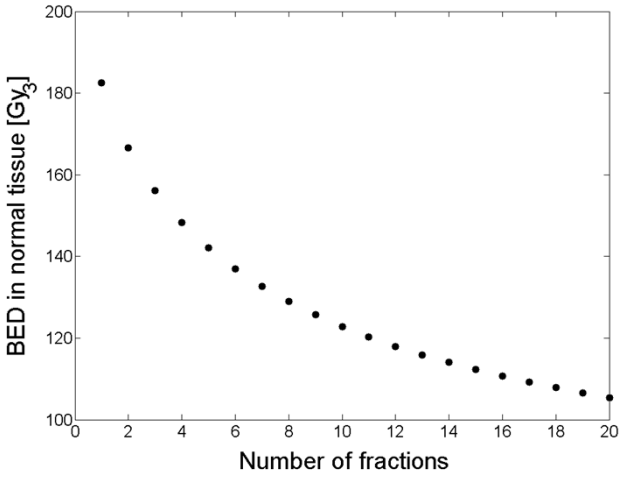


Figure 3. (a) Radiation survival curves for asynchronous populations of several human tumour lines. HT-29 (+), OVCAR10 (○), MCF7 (■), A2780 (△), HX142 (▽), HT-144 (●) and Mo59J (□). The data for the HX142 cell line are from Deacon *et al.* (1985); (b) survival data from figure 2a plotted as $-\ln SF/D$ versus dose.

Biological effective dose (BED) in normal tissue $(\alpha/\beta)^{NT}$**= 3 Gy** under tumour iso-effect conditions $(\alpha/\beta)^{T}$ **= 10 Gy** for a reference scheme of 20× 2.75 Gy



***Classical Radiobiology*:**

Small fractions yield the highest 'therapeutic ratio'

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TUMOUR RESPONSE
and
(hypo)fractionation

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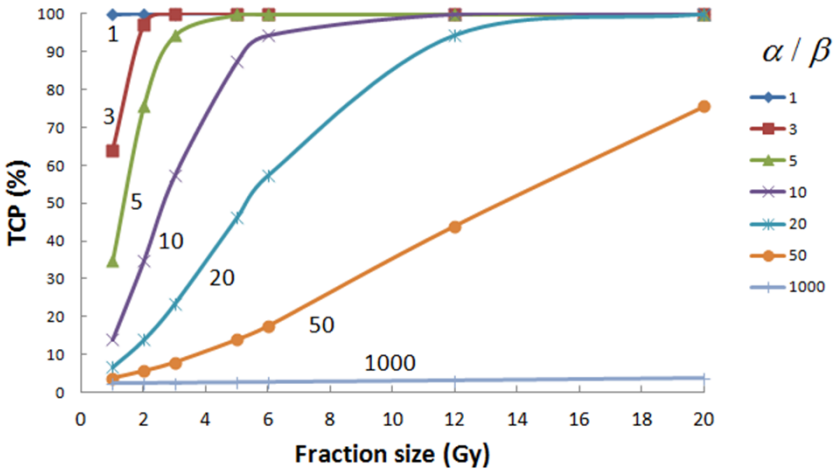
TCP vs d_{frac} at D_{tot} = 60 Gy for different α/β



Marsden TCP model:
no repopulation; 10^9 clonogens; α = 0.28 Gy^{-1} ; σ_α = 0.037 Gy^{-1}

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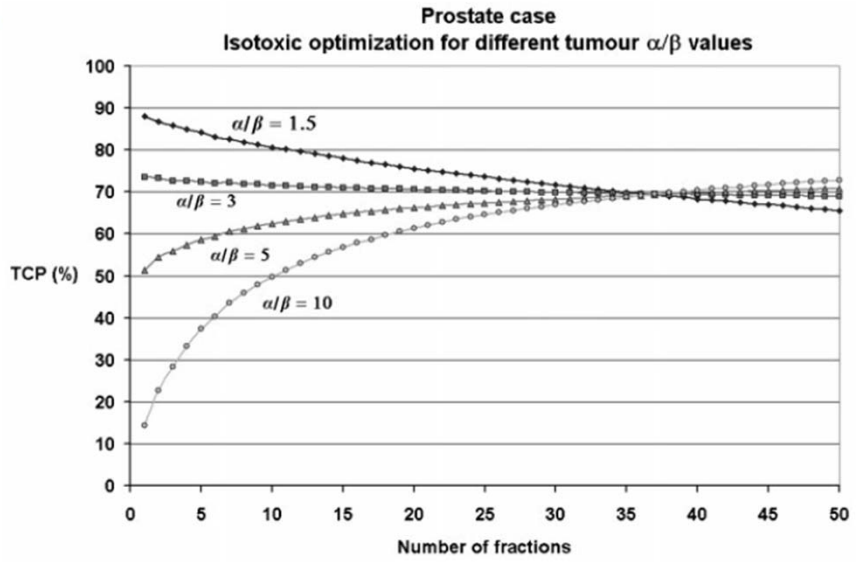

Tumour control probability (TCP) for the a prostate tumour for different numbers of fractions (1–50) for various tumour α/β, at constant normal tissue complication probability for rectal bleeding (4.3%) assuming α/β= 3 [computed using *BioSuite* Uzan & Nahum 2012]

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Breast tumours

- Breast cancer is as sensitive to fraction size as the dose-limiting normal tissues
- α/β ≈3 from trials done in the UK (J. Yarnold *et al*) and elsewhere.
- 40Gy/15F is 'gentler' than 50Gy/25F & non-inferior in terms of tumour control
- 5-fraction schedule of whole breast/chest wall RT is under test
- Identification of biomarkers of fractionation sensitivity is a priority

(with thanks to Dr. Navita Somaiah, Royal Marsden & ICR)

Prostate Radiotherapy Clinical/biological modelling results:

	Total	hypo#	α/β Ratio	95% CI
Mirabel	5969	3559	1.4 Gy	0.9-2.2
Proust-Lima	5093	1949	1.55 Gy	0.46-4.52

Fowler IJROBP 2001;50:1024; Brenner IJROBP 2002;52:6; Mirabel IROBP 2011; Proust-Lima IJROBP 2011;79:195-201

(with thanks to Dr. Isabel Syndikus, Clatterbridge)

Hyperfractionation (HFX) and prostate cancer

74Gy/ 2Gy (n=179) vs 79Gy/1.25Gy BID (n=151)

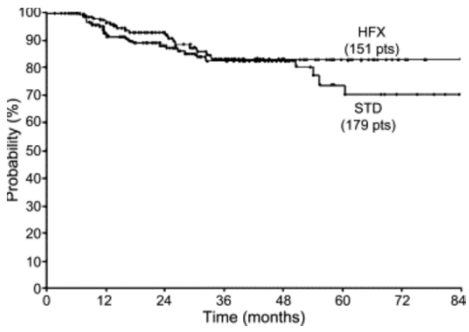
Non-randomised comparison

Pelvic or prostate only fields

No difference in PSA control

The 5-year actuarial biochemical control was 70.0 and 82.6% with STD and HFX (*P*=0.44).

Compatible with α /β ratio 8.3 (95%CI 0.75Gy - 16Gy)



Valdagni et al R&O 2005 ***75****:74-82; Bentzen,Ritter R&O 2005 76:1-3.*

GROUP A: lymphoma, myeloma, neuroblastoma
$\alpha = 0.79 \pm 0.25$ $\sqrt{\beta} = 0.241$ Gy^{-1} $\alpha/\beta = 13.6$

GROUP B: medulloblastoma, SCLC
$\alpha = 0.684 \pm 0.205$ $\sqrt{\beta} = 0.241$ Gy^{-1} $\alpha/\beta = 11.7$

GROUP C: breast, bladder, cervical carcinoma
$\alpha = 0.288 \pm 0.130$ $\sqrt{\beta} = 0.241$ Gy^{-1} $\alpha/\beta = 5.0$

GROUP D: pancreatic, colorectal, squamous lung cancer
$\alpha = 0.393 \pm 0.287$ $\sqrt{\beta} = 0.241$ Gy^{-1} $\alpha/\beta = 6.7$

GROUP E: melanoma, osteosarcoma, glioblastoma, renal carcinoma, prostate
$\alpha = 0.259 \pm 0.173$ $\sqrt{\beta} = 0.241$ Gy^{-1} $\alpha/\beta = 4.5$

(Don Chapman – Clatterbridge Radiobiology course)

NORMAL TISSUES
and
(Hypo)fractionation

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The (LQ-based) 'Withers' Isoeffect Formula (WIF) is frequently used to calculate **normal tissue (NT) iso-effect**:

WIF	WIF for normal tissue
$\frac{D_{\mathrm{new}}}{D_{\mathrm{ref}}} = \frac{\alpha/\beta + d_{\mathrm{ref}}}{\alpha/\beta + d_{\mathrm{new}}}$	$\frac{D^{\mathrm{NT}}_{\mathrm{new}}}{D^{\mathrm{NT}}_{\mathrm{ref}}} = \frac{(\alpha/\beta)^{\mathrm{NT}} + d^{\mathrm{NT}}_{\mathrm{ref}}}{(\alpha/\beta)^{\mathrm{NT}} + d^{\mathrm{NT}}_{\mathrm{new}}}$

Not obvious what the values for D^{NT} and d^{NT} should be …

In practice, the **tumour doses** D^{T} and d^{T} are used instead (!)

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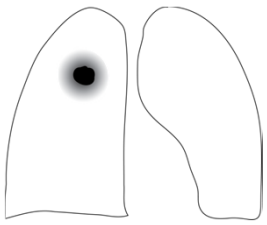
WIF is **valid if**:

- NT receives the same dose as the tumour dose **uniformly**
- NT response is solely determined by its **maximum dose** (100% serial organ) ≈ tumour dose
  - Early (animal) experiments on which the *low* $(\alpha/\beta)^{NT}$ and *high* $(\alpha/\beta)^{T}$ hypothesis was based fulfilled these conditions
  - **For all other situations, WIF as presently applied to NTs is wrong**

e.g. Lung



NTCP follows ≈ mean dose

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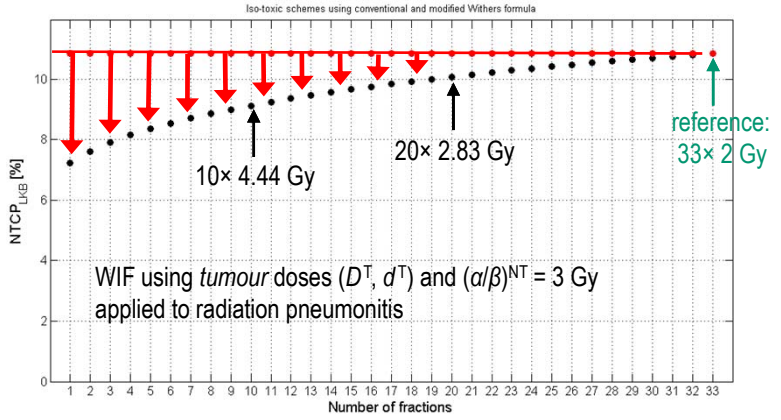
A demonstration of the invalidity of WIF

– Conventional WIF yields **a decreasing NTCP** under NT 'iso-effect' conditions



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IOP PUBLISHING — PHYSICS IN MEDICINE AND BIOLOGY
Phys. Med. Biol. **58** (2013) 6897–6914 — doi:10.1088/0031-9155/58/19/6897

Fractionation in normal tissues: the $(\alpha/\beta)_{eff}$ concept can account for dose heterogeneity and volume effects

Aswin L Hoffmann[1] **and Alan E Nahum**[2]

[1] Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, 6201 BN Maastricht, The Netherlands
[2] Physics Department, Clatterbridge Cancer Centre, Bebington CH63 4 JY, UK

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WIF for normal tissue	WIF
$\frac{D^{\mathrm{NT}}_{\mathrm{new}}}{D^{\mathrm{NT}}_{\mathrm{ref}}} = \frac{(\alpha/\beta)^{\mathrm{NT}} + d^{\mathrm{NT}}_{\mathrm{ref}}}{(\alpha/\beta)^{\mathrm{NT}} + d^{\mathrm{NT}}_{\mathrm{new}}}$	$\frac{D^{\mathrm{T}}_{\mathrm{new}}}{D^{\mathrm{T}}_{\mathrm{ref}}} = \frac{(\alpha/\beta) + d^{\mathrm{T}}_{\mathrm{ref}}}{(\alpha/\beta) + d^{\mathrm{T}}_{\mathrm{new}}}$

– Left-hand expression should use the **NT dose distribution** instead of **tumour doses**
– Can $(\alpha/\beta)^{\mathrm{NT}}$ be replaced with an **"effective" value** which yields **exact NT iso-effect** whilst retaining the **tumour** dose in the WIF?

$$\frac{D^{\mathrm{NT}}_{\mathrm{new}}}{D^{\mathrm{NT}}_{\mathrm{ref}}} = \frac{(\alpha/\beta)^{\mathrm{NT}}_{\mathrm{eff}} + d^{\mathrm{T}}_{\mathrm{ref}}}{(\alpha/\beta)^{\mathrm{NT}}_{\mathrm{eff}} + d^{\mathrm{T}}_{\mathrm{new}}}$$

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Heterogeneous NT dose distribution:

Normal tissue with **'parallel'** architecture (n = 1):

- radiobiologically adjusted **mean dose** ($\mathrm{BED}_{\mathrm{mean}}$) correlates with NT response
- Equating $\mathrm{BED}_{\mathrm{mean}}$ doses of two fractionation schemes yields **gWIF** as ratio of physical NT **mean doses**:

$$\frac{\bar{D}^{\mathrm{NT}}_{\mathrm{new}}}{\bar{D}^{\mathrm{NT}}_{\mathrm{ref}}} = \frac{(\alpha/\beta)^{\mathrm{NT}}_{\mathrm{eff}} + d^{\mathrm{T}}_{\mathrm{ref}}}{(\alpha/\beta)^{\mathrm{NT}}_{\mathrm{eff}} + d^{\mathrm{T}}_{\mathrm{new}}}$$

where

$$(\alpha/\beta)^{\mathrm{NT}}_{\mathrm{eff}} = \frac{1}{1 + \left(\sigma^{\mathrm{NT}}_{\mathbf{d}_{\mathrm{ref}}} / \bar{d}^{\mathrm{NT}}_{\mathrm{ref}}\right)^2} \frac{d^{\mathrm{T}}_{\mathrm{ref}}}{\bar{d}^{\mathrm{NT}}_{\mathrm{ref}}} (\alpha/\beta)^{\mathrm{NT}}$$

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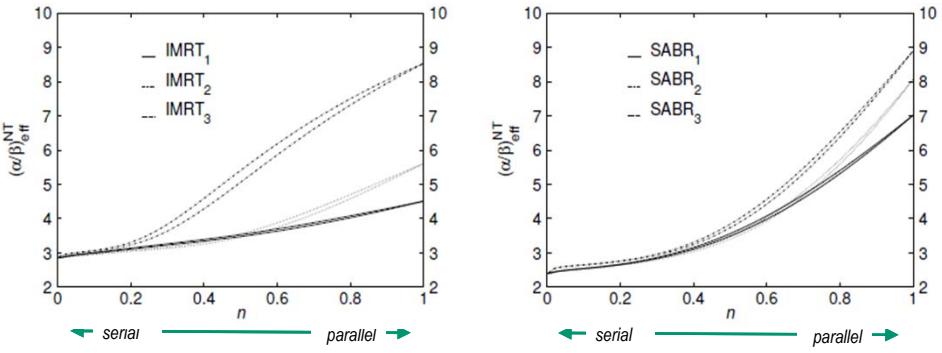
Arbitrary NT 'architecture'

How $(\alpha/\beta)^{NT}_{eff}$ varies with volume parameter *n*



'Intrinsic' $(\alpha/\beta)^{NT} = 3$ Gy

- We see here how fractionation sensitivity depends on both normal tissue 'architecture' (via *n*) **and** dose heterogeneity (via the DVH).
- Rate of increase with *n* is **greate**r for the **more conformal** plans

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THE OVERALL PICTURE:

How the Therapeutic Ratio varies with the number of fractions.

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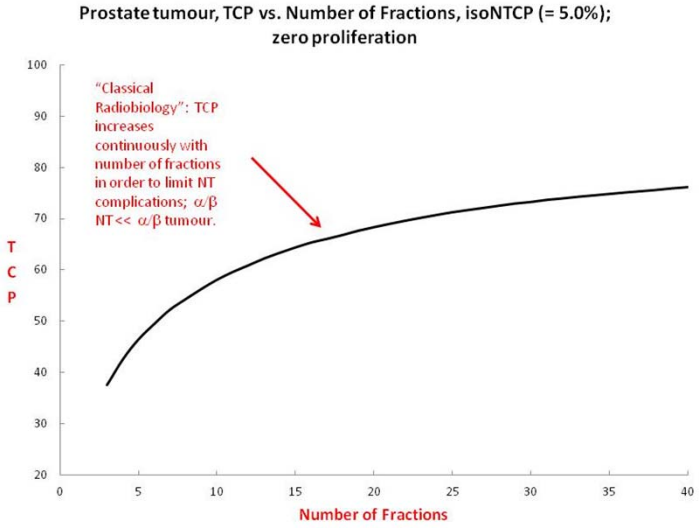

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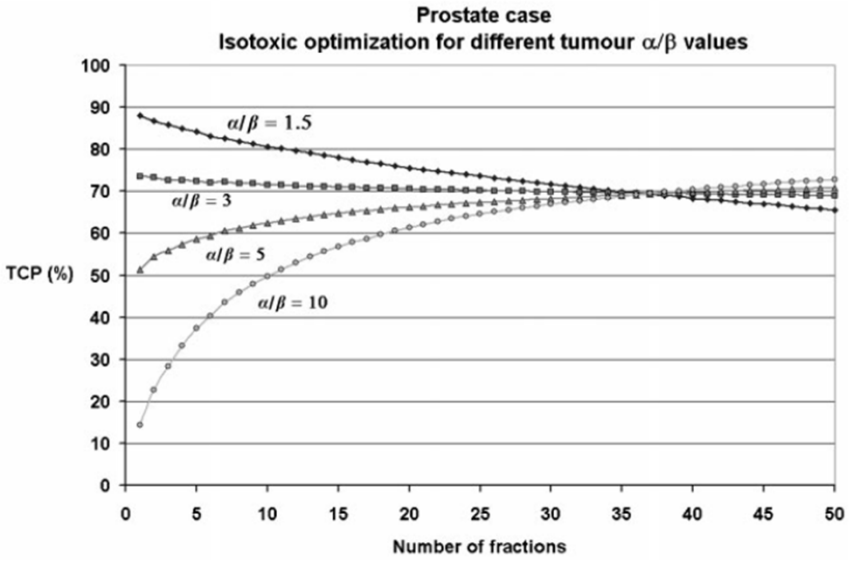

Tumour control probability (TCP) for a prostate tumour for various fraction numbers (1–50) and for different tumour α/β, for the same normal tissue complication probability for rectal bleeding (4.3%) assuming α/β= 3.

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Variable fraction number : TCP at (iso)NTCP = 10% (non-small-cell lung tumours)

Patient #1

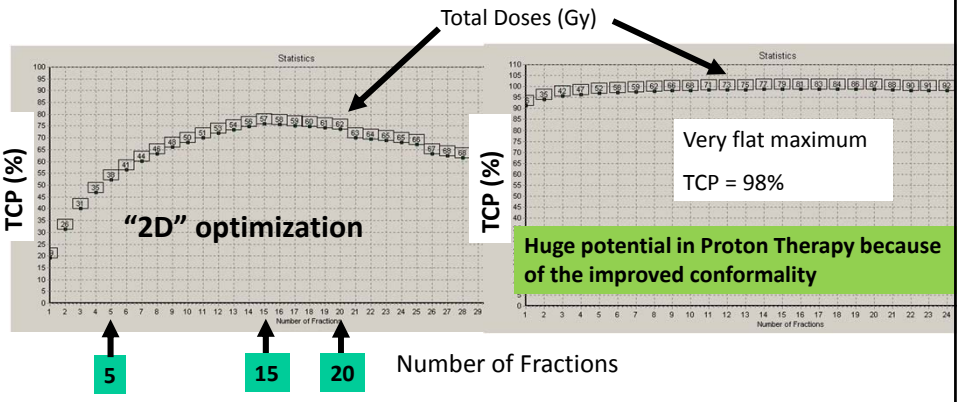
For (CCO) standard protocol, 55 Gy in 20 fracs.

TCP = 48% NTCP = 6.6%

Patient #9 - **Smaller** normal-lung volume irradiated

For 55 Gy in 20 fracs.

TCP = 50.4% NTCP = **4.3%**



Computed using *BioSuite* (Uzan and Nahum *BJR* 2012)

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What could possibly spoil this beautiful picture?

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Can we really predict what happens at very large fractions?

- The validity of the LQ model has been questioned; it appears to **over-predict** of local control rates for the extremely hypo-fractionated SBRT/SABR of early-stage NSC lung tumours (e.g. Timmerman *et al*).
- Modifications/alternatives to LQ proposed by Wang and others (see below)
- David Brenner (NY), Martin Brown (Stanford) and others 'defend' the LQ model, saying it explains the success of SBRT/SABR regimens perfectly well!
- Chang Song *et al* (Minneapolis) claim that there is **vascular damage** at large fraction sizes and this explains why SABR regimens can eliminate hypoxic clonogens (evidence for these?)
- **If you're not confused by now then you haven't been paying attention!**

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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

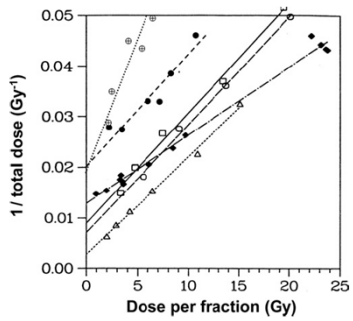

Figure 4 Isoeffect data for late response from 3 (□ ○ Δ) different regions of the rat spinal cord,[25] for acute skin reactions (♦) in mice,[26] and for early (●) and late (⊕) murine intestinal damage.[27] The data are plotted in a "reciprocal-dose F_e" form[26] such that, if they follow an LQ relationship,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

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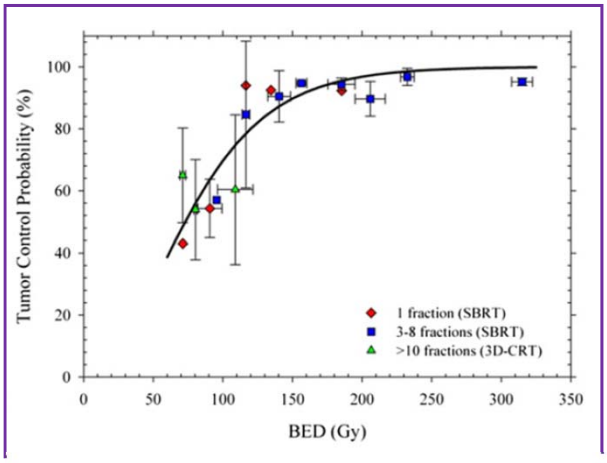


Tumor control probability (TCP) as a function of biological effective dose (BED) for stage I non-small cell lung cancer.

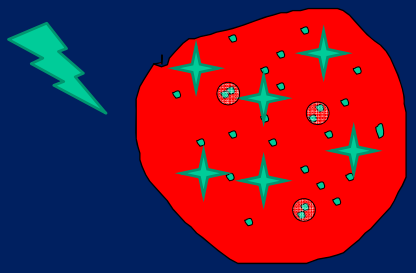
Dose Escalation, Not "New Biology," Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer

J. Martin Brown, PhD,* David J. Brenner, PhD,† and David J. Carlson, PhD‡

Int J Radiation Oncol Biol Phys, Vol. 85, No. 5, pp. 1159–1160, 2013

1) No indications that CFRT and SBRT produce different tumour control when adjusted for BED
2) no difference in Tumour Control with single/multifraction SBRT
3**) higher TCP explained by higher tumour BEDs**

Two types of events can lead to reproductive cell death:



Tumour

Type A: "single hit" – no repair possible: αD

Type B: "2 sub-lethal hits" in same nucleus within a given time: βD^2

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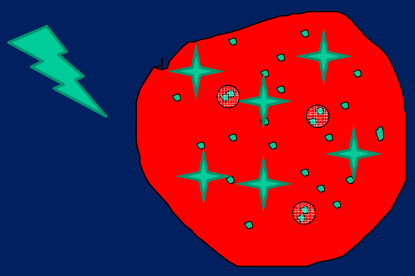

Tumour

But the "single hit" events will successively reduce the 'pool' of sub-lethal hits, and hence reduce the amount of 'β cell-killing' as the dose increases!

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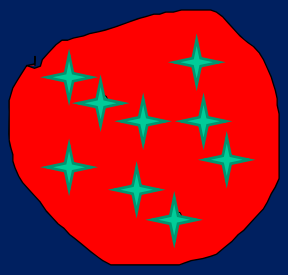
Several hours later:



Tumour

Type A: "single hit" – no repair possible: αD

Type B: 'sub-lethal' lesions either converted into (a reduced number of) lethal ones or repaired (after approx. 6 hours): G x βD^2

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A Generalized Linear-Quadratic Model for Radiosurgery, Stereotactic Body Radiation Therapy, and High–Dose Rate Brachytherapy

Sci Transl Med **2**, 39ra48 (2010);
DOI: 10.1126/scitranslmed.3000864

Jian Z. Wang,[1]* Zhibin Huang,[1] Simon S. Lo,[1] William T. C. Yuh,[2] Nina A. Mayr[1†]

(Published 7 July 2010; Volume 2 Issue 39 39ra48)

$$\begin{cases} S = \exp(-\alpha D - \beta G D^2) \\ G = \dfrac{2}{D^2}\displaystyle\int_0^t I(w)dw \int_0^w I(v)dv \exp\left[-\mu(w-v) - \int_v^w \beta_2 I(s)ds\right] \end{cases}$$

The major difference from the LQ model is the reduction term $\exp[-\int_w^t \beta_2 I(s)ds]$ of sublethal lesions.

Assuming the dose rate is constant, $I(t) = I_0$,

$$\begin{cases} S = \exp(-\alpha D - \beta G D^2) \\ G = \dfrac{2}{\varepsilon^2 T^2}[\varepsilon T - 1 + \exp(-\varepsilon T)] \end{cases}$$

where $\varepsilon = \mu + \beta_2 I_0$.

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Wang *et al* 2010

Sci Transl Med **2**, 39ra48 (2010);
DOI: 10.1126/scitranslmed.3000864

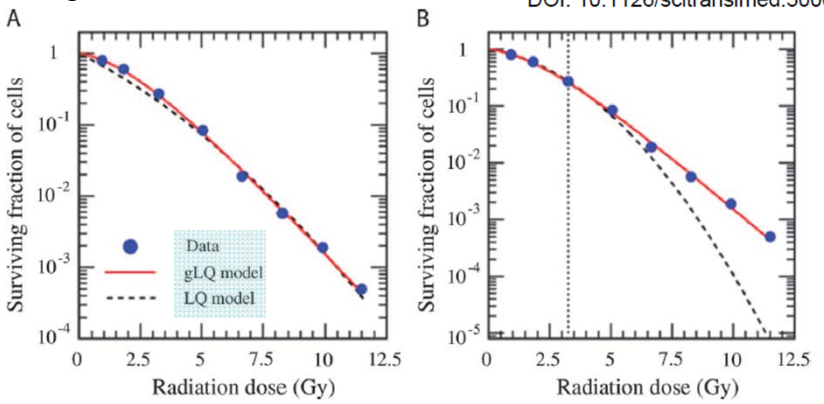

Fig. 1. Dose-response curve of radiation effects on Chinese hamster ovary cells. Both the conventional LQ (dashed curves) and the gLQ (solid curves) models were used to fit the experimental data. (**A**) Full dose range (0 to 11.5 Gy). (**B**) Low-dose data (≤3.25 Gy, as indicated by the vertical dotted line). The curves above 3.25 Gy in (B) represent the model predictions based on low-dose data. Experimental data are the same in both plots and are from (*46*). Details regarding this analysis are available in the Supplementary Material.

gLQ: α = 0.10 Gy^{-1}, α/β = 0.80 Gy; LQ: α = 0.15 Gy^{-1}, α/β = 2.0 Gy

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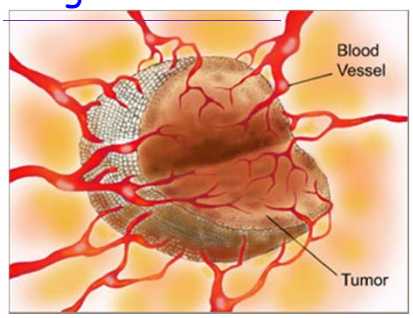
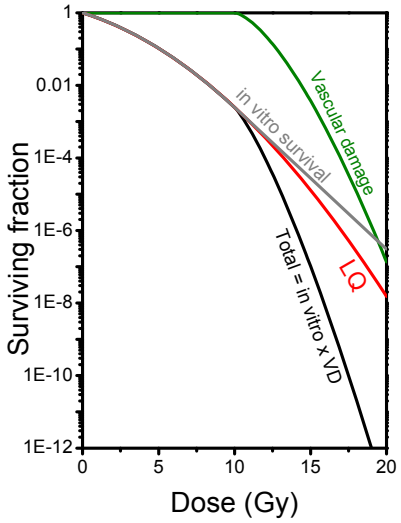
Target- vasculature



- High doses of radiation cause damage to the vasculature of the target (Song *et al*)
- The total effect of radiation will be a combination of the cytotoxic effect on the cells and the effect on the vasculature.



Courtesy of Giovanna Gagliardi and Iuliana-Toma Dasu

Summary

'Classical radiobiology' (i.e. Hyperfactionation) still valid for 'serial' NTs and non-proliferating tumours with high α/β (ever-decreasing number of cases!)

Parallel NTs can have a high $(\alpha/\beta)_{eff}$ due to the 'mean dose effect' e.g. lung (Hoffmann & Nahum 2013)

Low tumour α/β (breast, prostate) offers a lot of scope for large fraction sizes.

However, even where indicated theoretically, hypofractionation could jeopardize clonogen re-oxygenation between fractions.

The LQ model at large fraction sizes is under a lot of pressure at present; the gLQ model (Wang) appears to fit cell-survival data better.

The SABR experience ought to be a lesson on proceeding cautiously towards optimum prescriptions (total dose, fraction size).

Highly conformal modalities such as Protons could be made more cost-effective through moving towards larger fraction sizes

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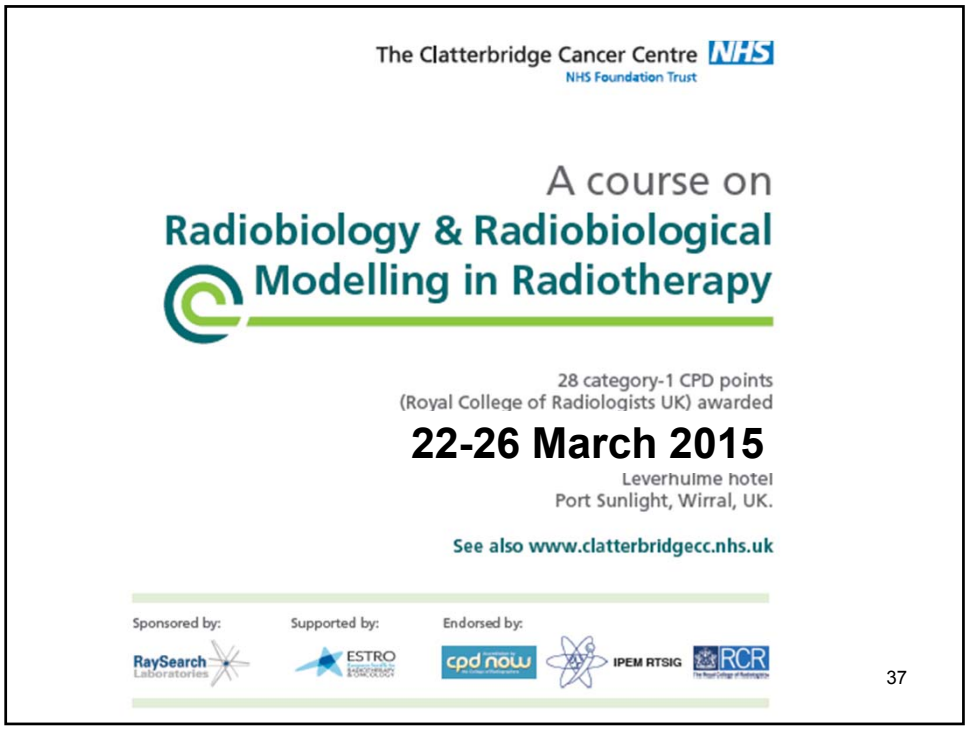

Vi ringrazio per l'attenzione

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