ENLIGHT, UTRECHT 2016

Clinical Radiobiology of Proton and Ion beams

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Ultimate strength but intrinsic weakness – the example of Achilles, killed by the arrow of Paris

Particle therapy has Two Achilles heels

- **Physics** : positioning of dose; ionisation density [LET]
- **Biology** – How do different tumours and normal tissues (with different repair characteristics) cope with increased LET ?

The LQ model overview

- DNA level events: Base changes, SSB, DSB, short patch, long patch
- Cellular Response systems: Repair by multiple mechanisms, Mis-repair, un-repaired damage according to local complexity.
- These if sufficiently concentrated in a particular location on a chromosome or chromatid will lead to:
- Chromosomal and Chromatid level events: breakage at stressed points (radiation plus mechanical)
- Cellular response: attempted re-joining resulting in minimally some loss of heterozygosity; more severe and multiple breaks result in lethality.
- The number of lethal events per cell are expressed as α and β per unit dose and dose squared respectively.

Expressed in another way

α = Σ (unrepaired DNA damage $\Rightarrow$ lethal chromosomal injury events per cell)/dose

β= Σ (unrepaired DNA damage $\Rightarrow$ lethal chromosomal injury events per cell)/dose^2

The predominant mode of cell killing is via α-mediated damage: especially direct damage (less sensitive to oxygenation status), inferior repair mechanism operative (NHEJ) on strand breaks, highly susceptible to increased LET; no dose rate effect.

The lesser mode of cell killing is via β-mediated damage: especially indirect damage (more sensitive to oxygenation status or sensitising drugs), inter-track cooperation may occur, superior repair mechanism operative (NHEJ) on recombination and chromatid exchanges; less susceptible to increased LET; pronounced dose rate effect.

The Bethe Bloch equation

$$-\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \cdot \frac{n z^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2}{I \cdot (1-\beta^2)}\right) - \beta^2\right]$$

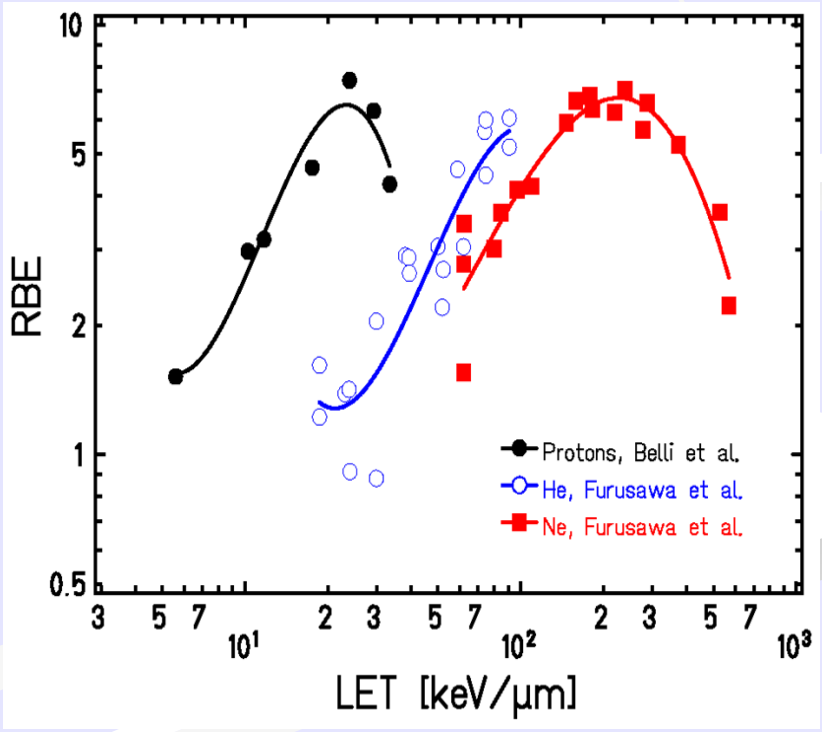
-dE/dx (Energy/cm)

= K (charge^2/velocity^2); proton charge=1, carbon=6

Protons are more efficient in increasing RBE with LET
Radial events - δ rays.

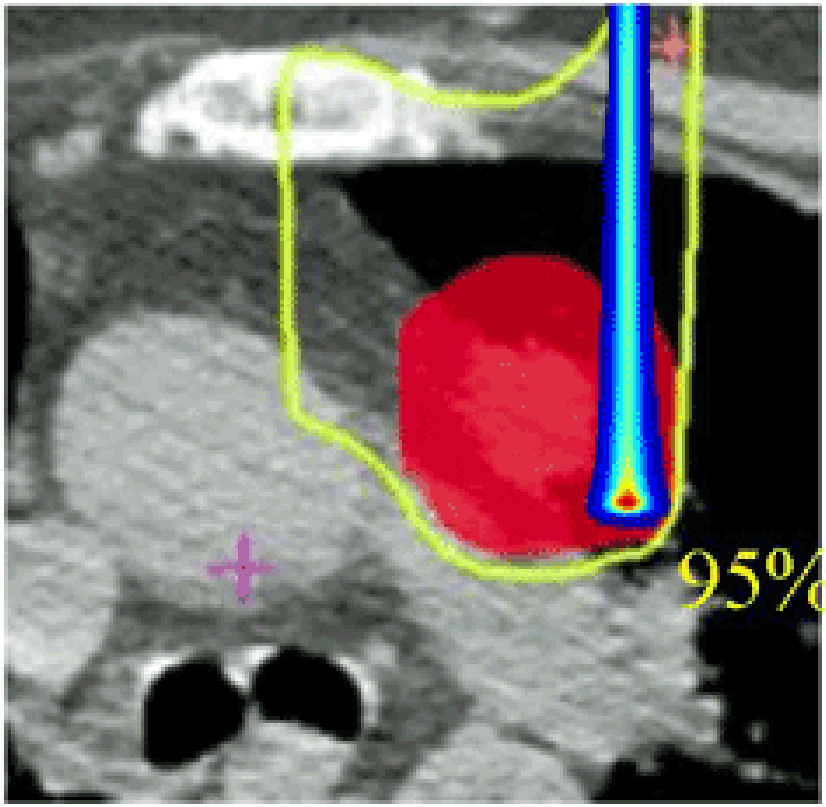
LET values in mid SOBP are mostly ~ 1.5-2 keV.μm^{-1}

LET values of 1.5-10 keV.μm^{-1} in clinical plans; especially if using scanned pencil beams/intensity modulated

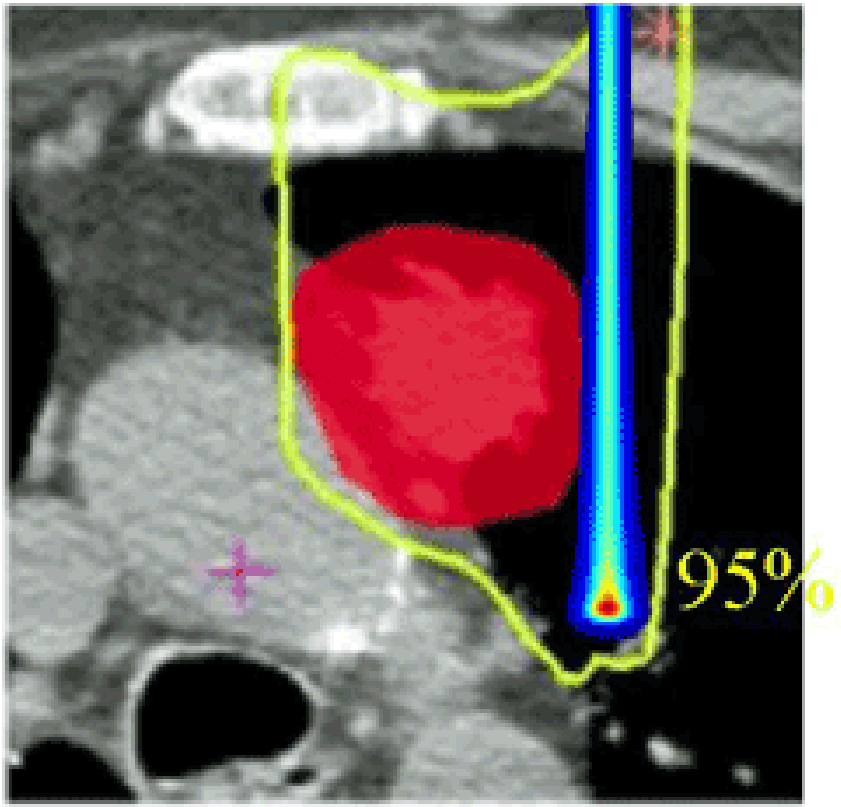


Issues 2: Range effects of breathing, 4D CT

exhale



inhale



Engelsman et al., IJROBP 64(5):1589-1595, 2006

Relative Biological Effect – ratio of doses for ISOEFFECT

$$RBE = \frac{Dose_{[LowLET]}}{Dose_{[HighLET]}}$$

The conventional radiation

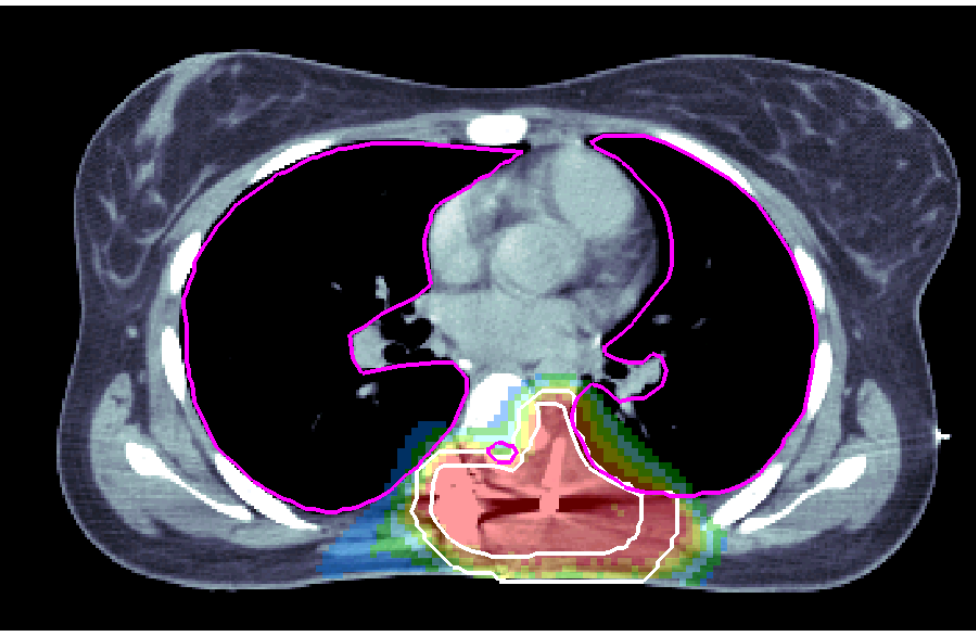
The particle radiation

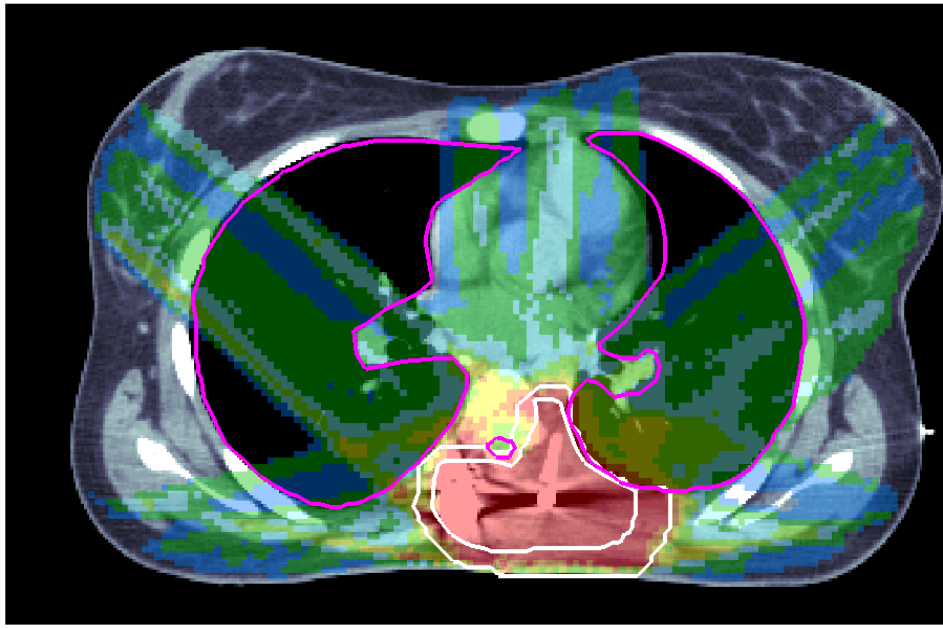
$$\text{Particle Dose to Patient} = \frac{Dose_{[Low\ LET]}}{RBE}$$

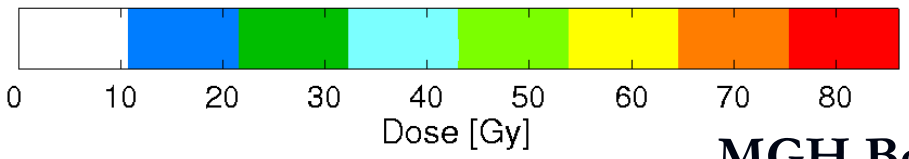
Paravertebral Epithelioid Sarcoma Intensity Modulated Protons (IMPT) vs. Intensity Modulated X-ray (IMXRT) 7 (field)

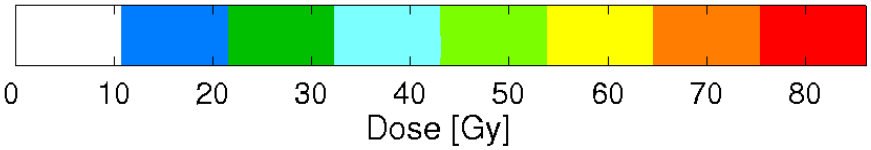
IMProtonT

IM X-ray RT









MGH Boston

What are the experimental findings/facts?

The great consultant detective, Sherlock Holmes, was inspired by the real-life figure of Joseph Bell, an Edinburgh surgeon at the who had taught the author Conan Doyle MD.

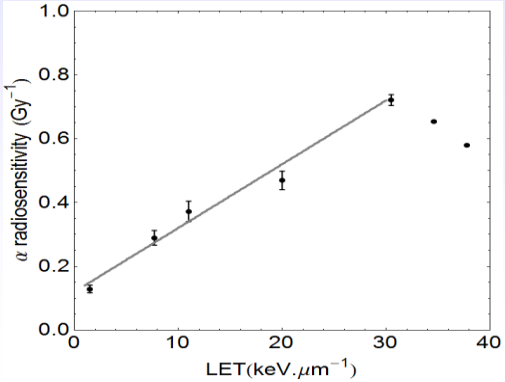
Bell was noted for drawing broad conclusions from minute observations, also Professor Sir Henry Littlejohn, Police Surgeon and Medical Officer of Health in Edinburgh. Deductive reasoning was used from detailed observations.

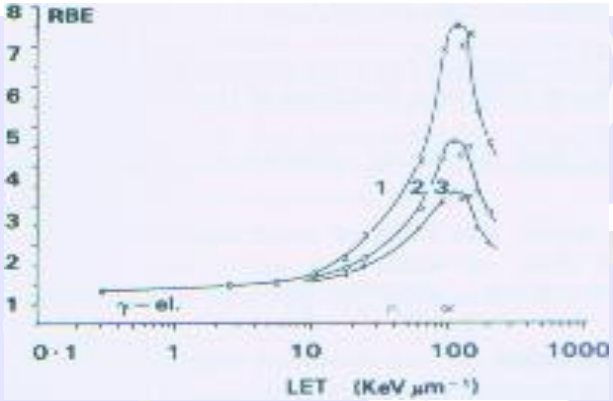
RBE depends on ……..

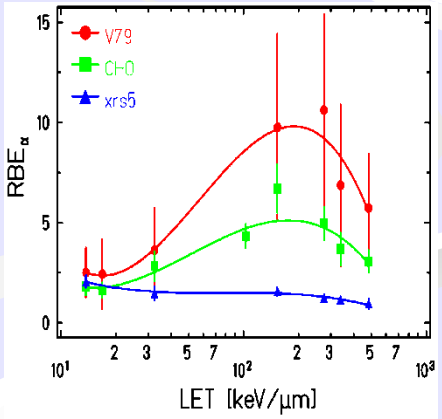
- **Particle Nuclear Charge [Z], Energy & Depth**
- Target **Volume** [mix of high LET Bragg peaks + low LET entry beams]
- **Dose** per treatment ...RBE varies inversely with dose.
- **Facility: neutron & γ-ray contamination**
- **Cell & Tissue type : slow growing and radiation repair proficient cells have highest RBEs, as in Normal Tissues.**

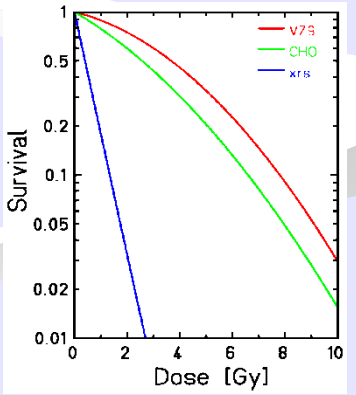
Any model of RBE must respect these six facts/phenomena

- RBE increases (LINEARLY) with LET until a maximum value LET_U is reached, followed by decreasing values.
- Increasing the radiation dose produces a **symmetrical** reduction in the LET-RBE relationship. The LET_U for each does not change with dose.
- It follows that RBE is inversely related to dose, but RBE magnitude depends upon the cell or tissue type.
- Systems with high radiosensitivity to the control radiation have a substantially lower RBE than cells which are more radioresistant to the control radiation.









Facts/phenomena II

- At any particular LET value on the overall LET-RBE plot, the relationship between RBE and dose varies between a maximum RBE (RBEmax) at near zero dose to a minimum value (RBEmin) at high dose.
- The magnitude of the RBE ceiling for each cell type is possibly independent of the ion species in some data sets, but again this needs to be determined by well-designed experiments using different ion beams.

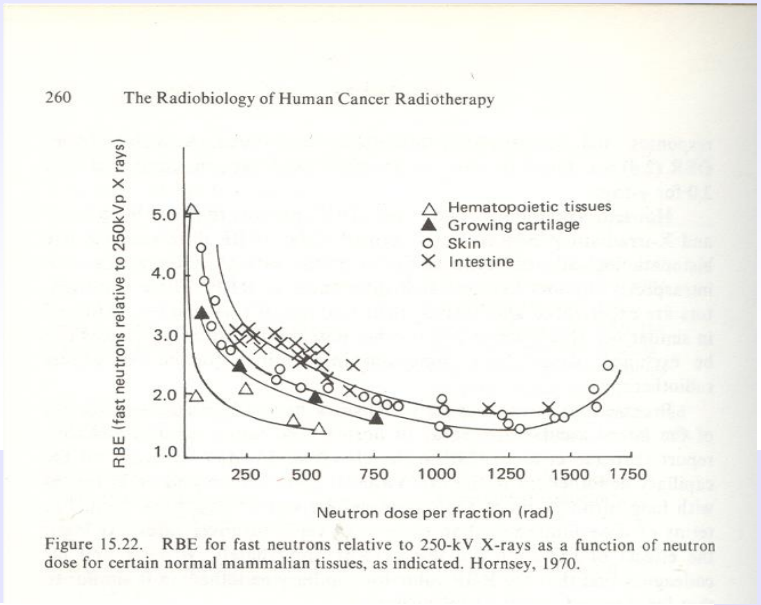
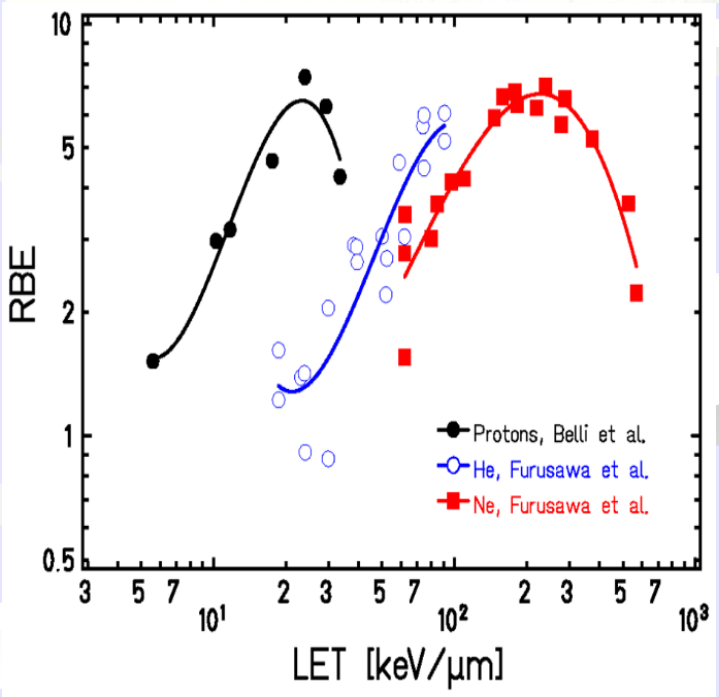
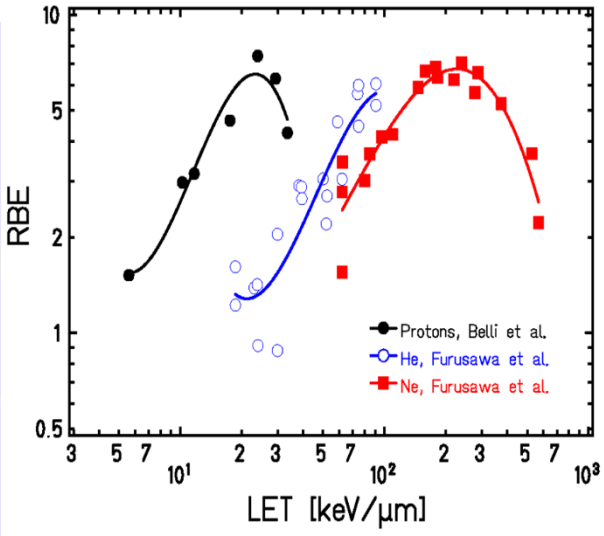


Figure 15.22. RBE for fast neutrons relative to 250-kV X-rays as a function of neutron dose for certain normal mammalian tissues, as indicated. Hornsey, 1970.

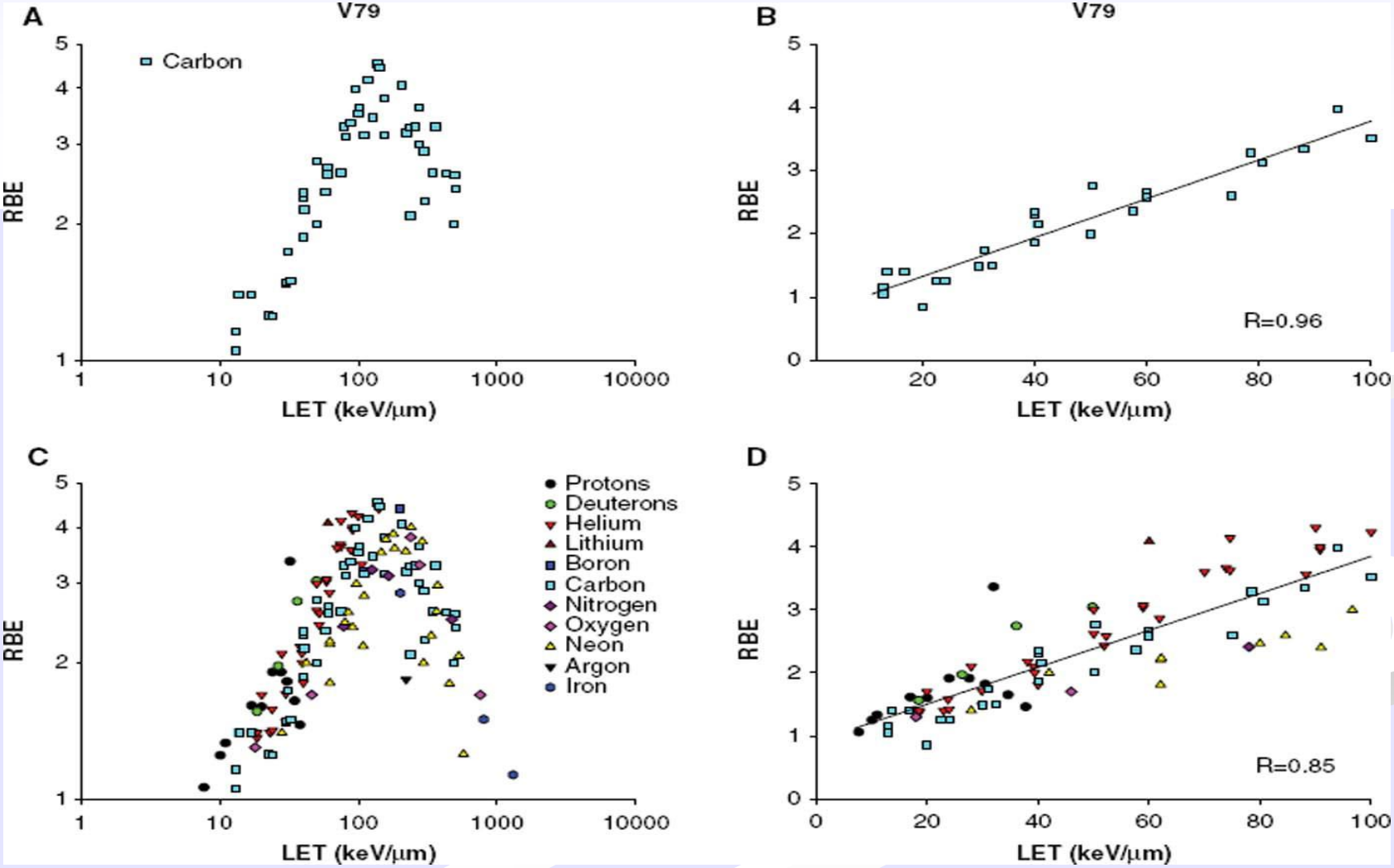


Lumping all ions together ?

- Some authors have taken ion data from separate laboratories to produce an overall LET-RBE curve. Data mining.
- But the LET-RBE turnover point positions (at a LET value of LET_U) for each ion species appears to be unique and dependent on the nuclear charge Z.
- Higher Z numbers have higher LET_U values. Effect is non-linear, with decreasing increments in LET_U as Z increases. The LET_U positions, with a few exceptions, have not been accurately determined owing to the paucity of data points.



Heterogenous Data Mining: Acta Oncol 2011, Sorensen, Overgaard and Bassler….V79 cells



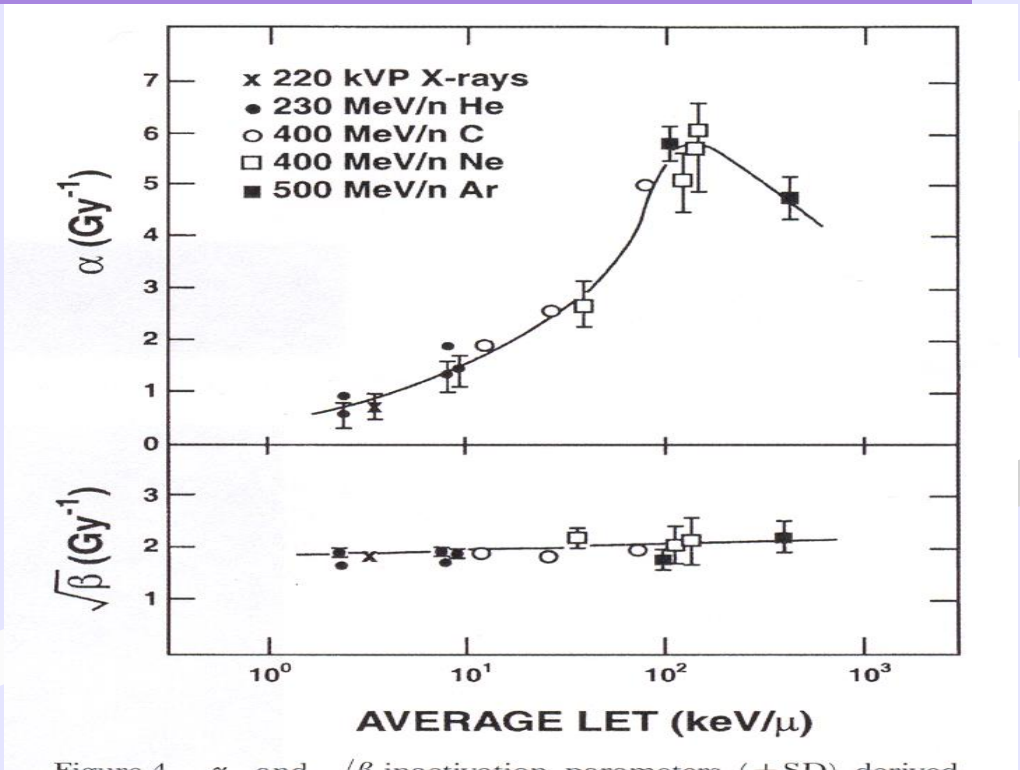
Does β parameter change with increasing LET ?

Since ratio $\sqrt{\beta_H}:\sqrt{\beta_L}$ is the RBE_{MIN} - at very high dose – then this ratio needs to be known if >1

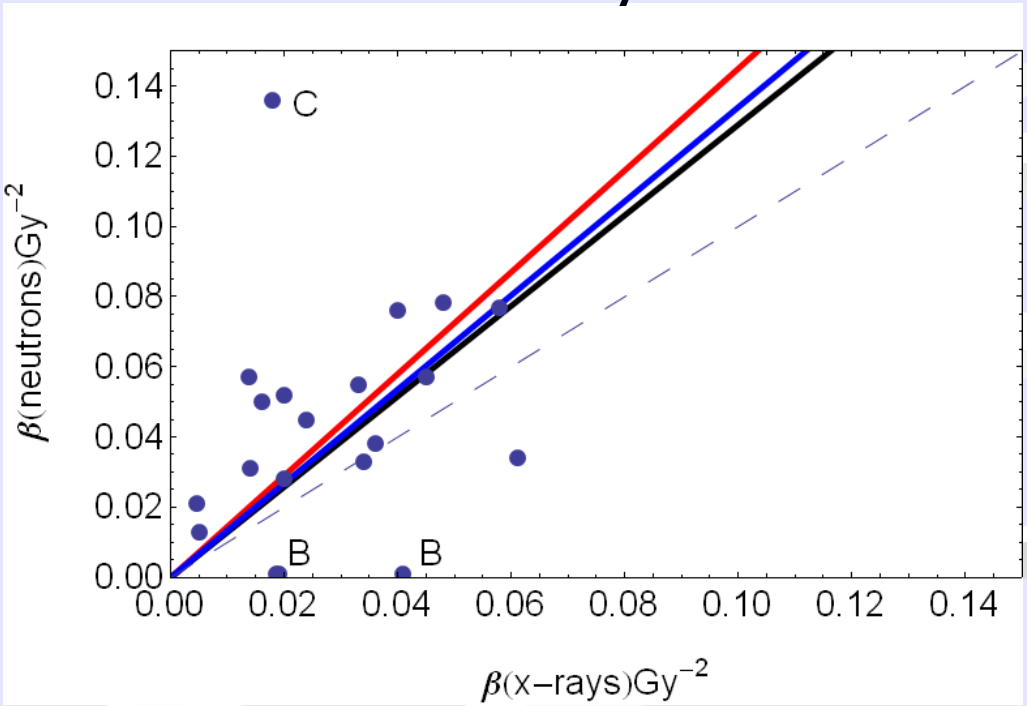
More research necessary to confirm if $RBE_{MIN}>1$ at range of high LET beam energies.

For each beam, each cell/tissue type would need to have this ratio estimated.

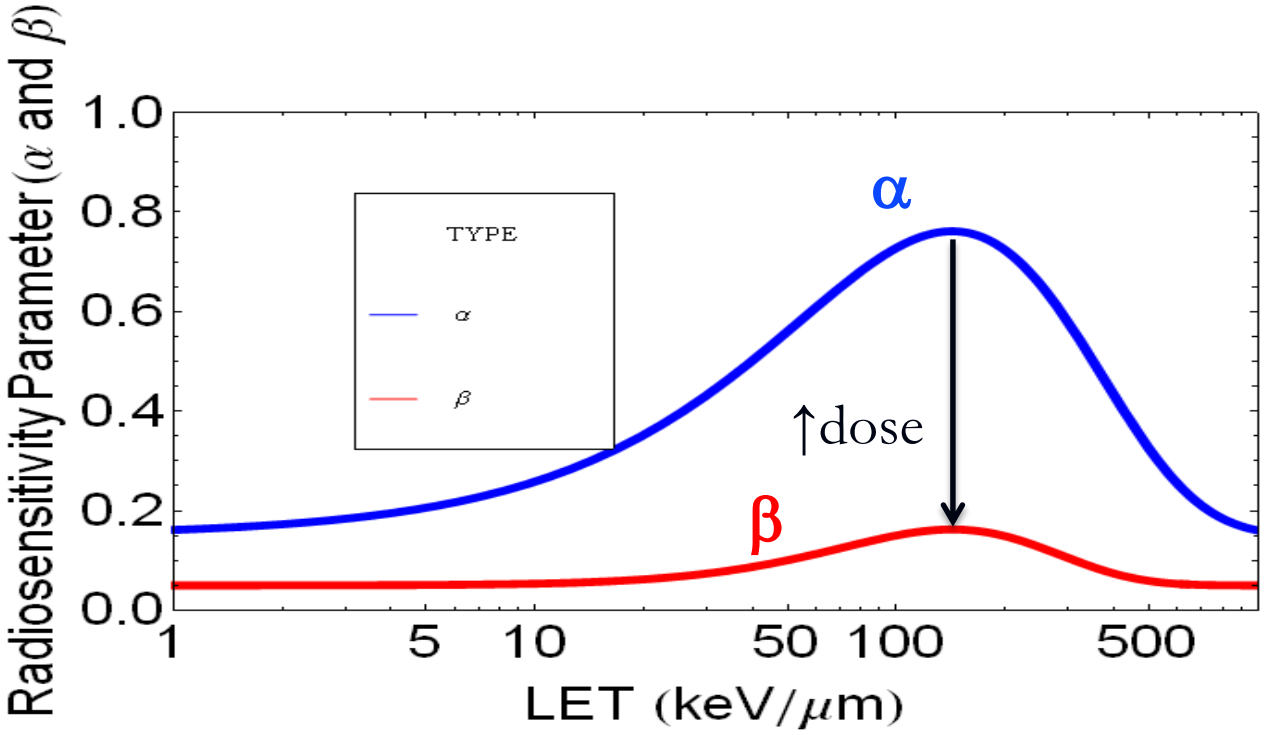
Chapman (IJRB 2003) measured $\sqrt{\beta}$, a larger number than β, and found no significant difference with increasing LET in CH V-79 in plateau phase.



β increases with LET [in the case of fast neutrons] in 23 human tumour cell lines. BUT the increase is small compared to α.
(Jones B. Brit J Radiology, 2009) using data of Britten and Warenius et al, Clatterbridge UK, show that α increases by 3.17 , √β increases by 1.59 for 60 MeV Neutrons compared with 4 MeV x-rays.



To build a model that includes above phenomena, assume the same turnover point for increment in α and β with LET, unique for each ionic Z number, in order to preserve symmetry of relationship when dose changes.



Increasing dose gives greater proportion of β-mediated damage (linked to dose^2)

Useful equations for high LET radiations

$$E = \alpha_H d_H + \beta_H d_H^{\,2} = \alpha_L d_L + \beta_L d_L^{\,2}$$

RBE is defined as $\mathbf{d_L/d_H}$

$$d_H \to 0, RBE_{MAX} = \frac{\alpha_H}{\alpha_L}$$

= the RBE at low dose

$$d_H \to \infty, RBE_{MIN} = \sqrt{\frac{\beta_H}{\beta_L}}$$

= the RBE at high dose

The RBE between RBEmax and RBEmin is given by solving the first equation for d_L, and then divide by d_H, so that

$$RBE = \frac{-k + \sqrt{k^2 + 4d_H k RBE_{\max} + 4d_H^{\,2} RBE_{\min}}}{2d_H}$$

Where *k* is the low LET α/β ratio

Jones, Carabe and Dale BJR 2006 – adapted for treatment interruption calculations

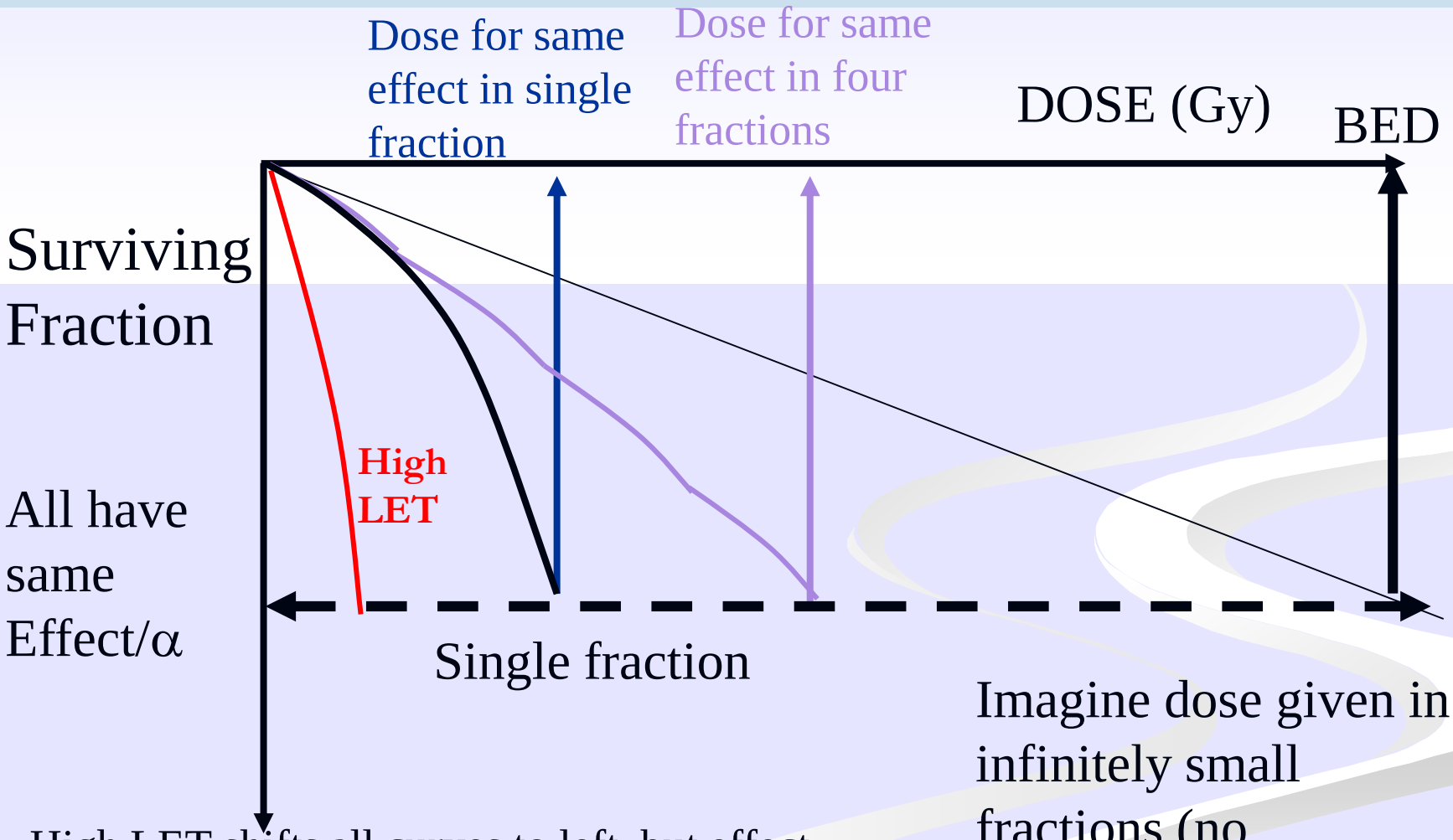
From previous definitions of RBE_{max} and RBE_{min} it is easy to show that

$$RBE_{\max} = \frac{\alpha_H}{\beta_H} \cdot \frac{RBE_{\min}^{\ 2}}{\left(\frac{\alpha_L}{\beta_L}\right)} = \frac{Q}{\left(\frac{\alpha_L}{\beta_L}\right)}$$

$$RBE_{\min} = \sqrt{\frac{\alpha_L}{\beta_L} \cdot \frac{RBE_{\max}}{\frac{\alpha_H}{\beta_H}}} = S\sqrt{\frac{\alpha_L}{\beta_L}}$$

Note: most LET-RBE models assume the first expression (RBE$\propto$1/(α/β) for the general RBE, but not the second expression; this may cause later difficulties for hypofractionated high LET RBE estimations.

How can we picture cell survival for high low and high LET radiations?



Biological Effective Dose
- how do we get there?
By definition of the "Log cell kill"=E

$$SF = e^{-\alpha d - \beta d^2},$$

$$SF^N = e^{-N(\alpha d + \beta d^2)},$$

$$-\ln(SF^N) = E = N(\alpha d + \beta d^2)$$

BED - The Concept

- **Represents total dose if given in smallest fraction size**

$$E = n(\alpha d + \beta d^2)$$

$$d \to 0, nd\alpha >> nd^2\beta$$

$$E \to nd\alpha$$

$$\frac{E}{\alpha} \to nd$$

$$BED = \frac{\mathrm{E}}{\alpha} = nd\left[1 + \frac{d}{\alpha / \beta}\right]$$

The Isoeffect equation – the same BED achieved in two different ways by varying dose per fraction and number of fractions

$$N_1.d_1(1+d_1/(\alpha/\beta)) = N_2.d_2(1+d_2/(\alpha/\beta))$$

IMPLICATIONS

- Can compare any two variants of dose and number of fractions that give same effect
- Used in assessing bio-effectiveness of different fractionation schedules
- Variants for dose rate, RBE, oxygen effect etc available.

Ref Jones et al

High LET Biological Effective Doses for iso-effective fractionation schedules

$$E = N(\alpha_H d_H + \beta_H d_H{}^2)$$

$$BED = \frac{E}{\alpha_L} = n\left(\frac{\alpha_H d_H}{\alpha_L} + \frac{\beta_H d_H{}^2}{\alpha_L}\right)$$

$$RBE_{MAX} = \frac{\alpha_H}{\alpha_L};$$

$$RBE_{MIN} = \sqrt{\frac{\beta_H}{\beta_L}},$$

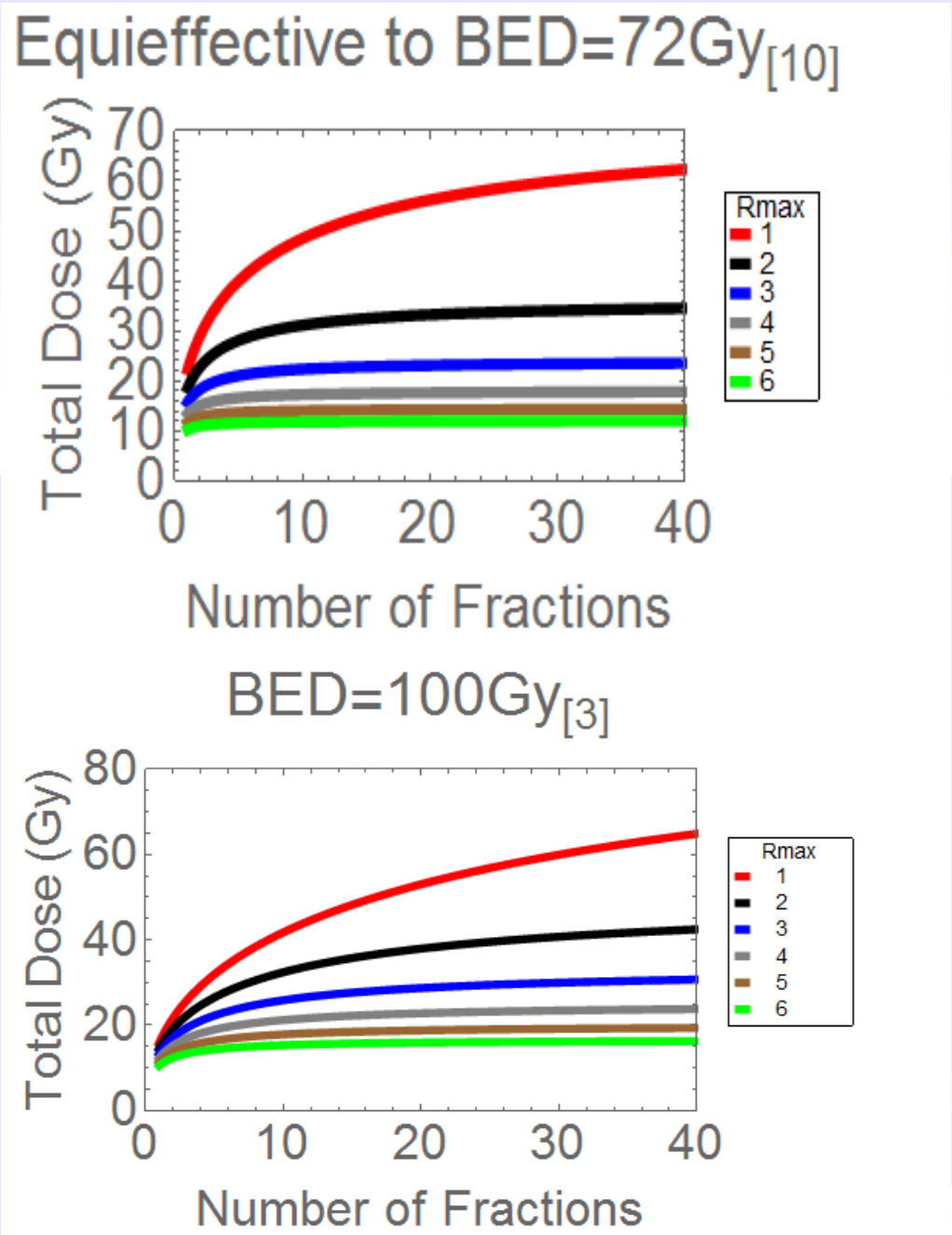
$$\therefore RBE_{MIN}{}^2.\beta_L = \beta_H$$

Thence

$$BED = nd_H\left(RBE\max + \frac{RBE\min^2}{(\alpha/\beta)_L}\right)$$

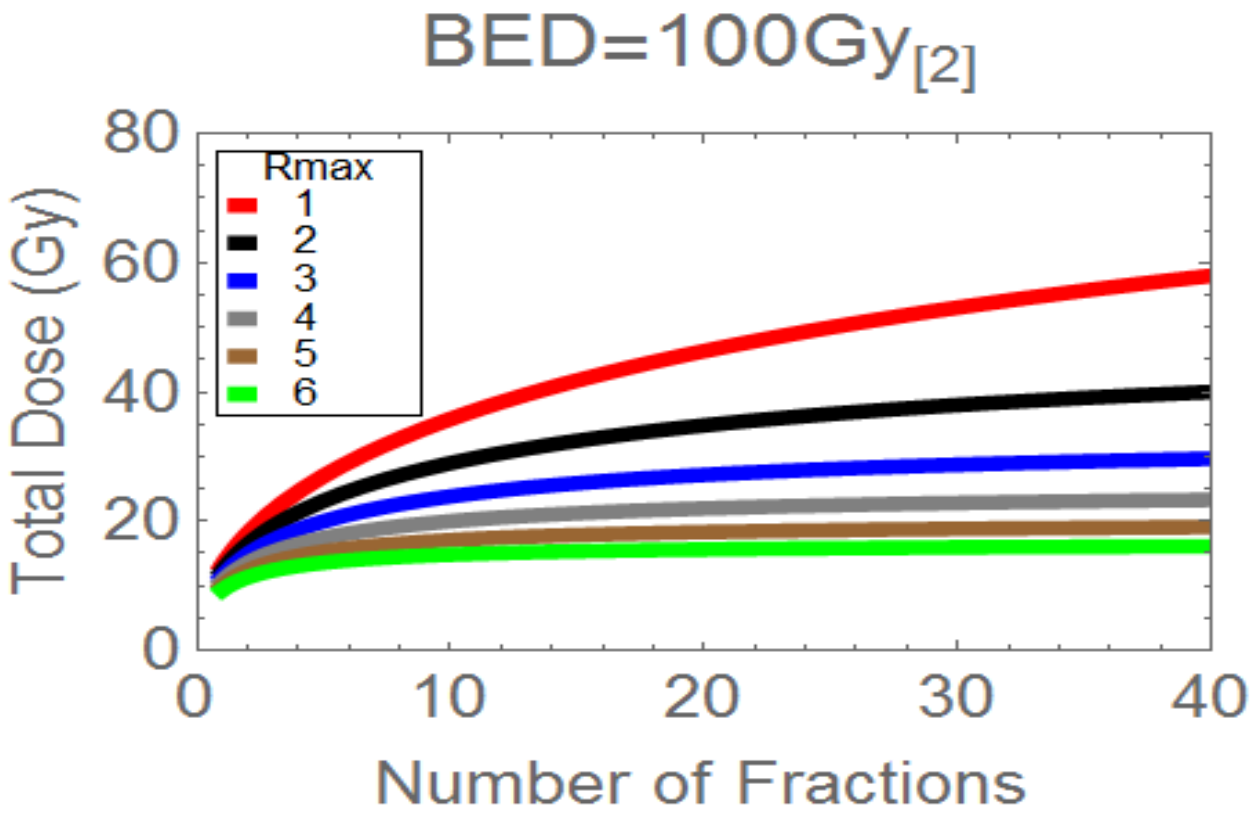
$$BED = nd_H\left(RBE\max + \frac{RBE\min^2}{(\alpha/\beta)_L}\right) - K_H(T - T_K)$$

- **the low LET α/β ratio is used**
- **RBEs act as multipliers**
- **RBE values will be between RBEmax and RBEmin depending on the precise dose per fraction**
- **K_H is daily high LET dose required to compensate for repopulation $\cong K_L/RBE_{max}$ low doses**
- **If a Japanese accelerator breaks down, a British equation can compensate for the delay in completion**

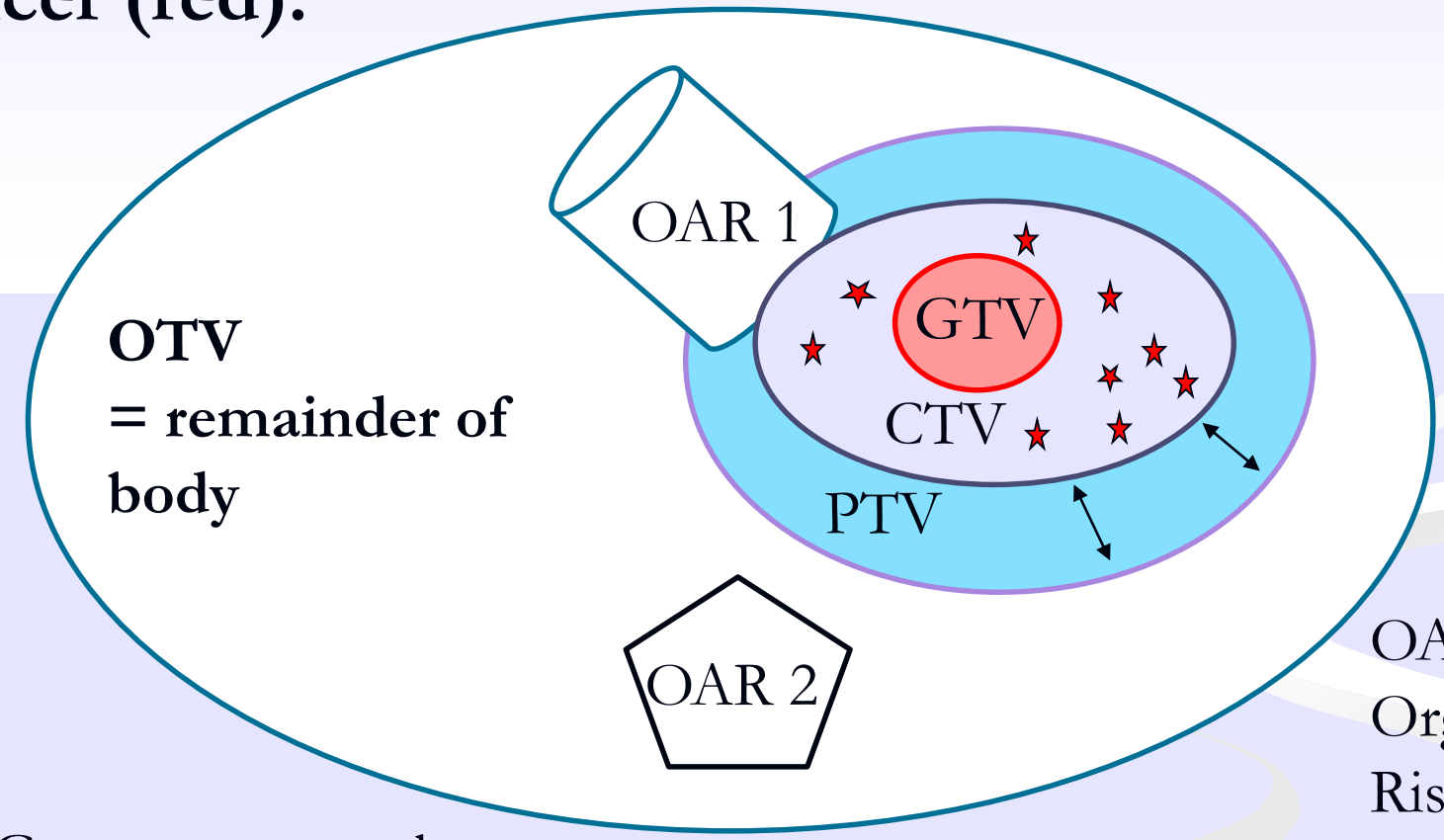


Isoeffective for 60 Gy in 30 fractions for α/β=10 Gy (rapidly growing cancers) and α/β=3 Gy (late reacting normal tissues

Isoeffective doses for spinal cord tolerance [50 Gy in 25 fractions for RBEmax=1] with α/β=2 Gy



International Commission on Radiation Units and Measurements (ICRU): Target Volumes around a cancer (red).



GTV Gross tumour volume

CTV Clinical target volume contains normal tissue

PTV Planning target volume contains normal tissue

OAR = Organs at Risk – within CTV, PTV and OTV

Important IF`s for charged hadrons when compared with megavoltage photons

IF: $RBE_{NT} > RBE_{Rx}$ in the normal tissue included to full dose (CTV+PTV), worse side effects could occur if these tissues are clinically important

IF: $RBE_{NT} > RBE_{Rx}$ outside the PTV, then the degree of tissue dose sparing achieved must exceed this difference, depending on the true tolerance level of the tissue of concern.

IF: $RBE_{CA} < RBE_{Rx}$, then cancer could be underdosed (applies mainly to tumours with high sensitivity to megavoltage x-rays).

- Legal dose requirements are ± 2% from accelerator ;
- Recommended ICRU dose variation across a PTV target is -5 to 7%.
- IF: RBE is incorrect by say 10, 30, 50% in some instances, then the above recommendations can be breached, and possibly seriously.

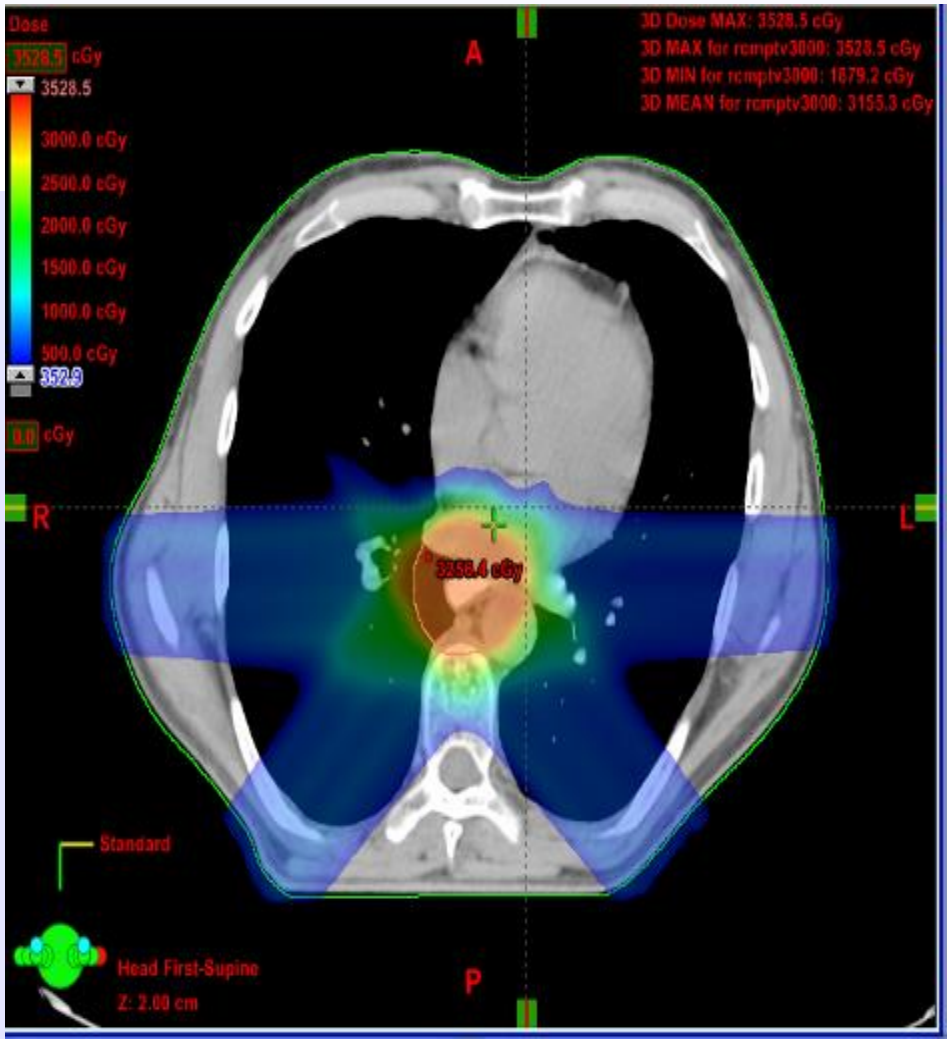
Dose Status	TCP (GTV,PTV)	PTV side effects	OTV side effects
GTV↑,PTV↑, OTV↓	Better	worse*	Better
GTV↑,PTV=, OTV↓	Better	equal**	Better
GTV=,PTV=, OTV↓	equal**	equal **	Better
GTV=,PTV↓, OTV↓	Worse	Better	Better

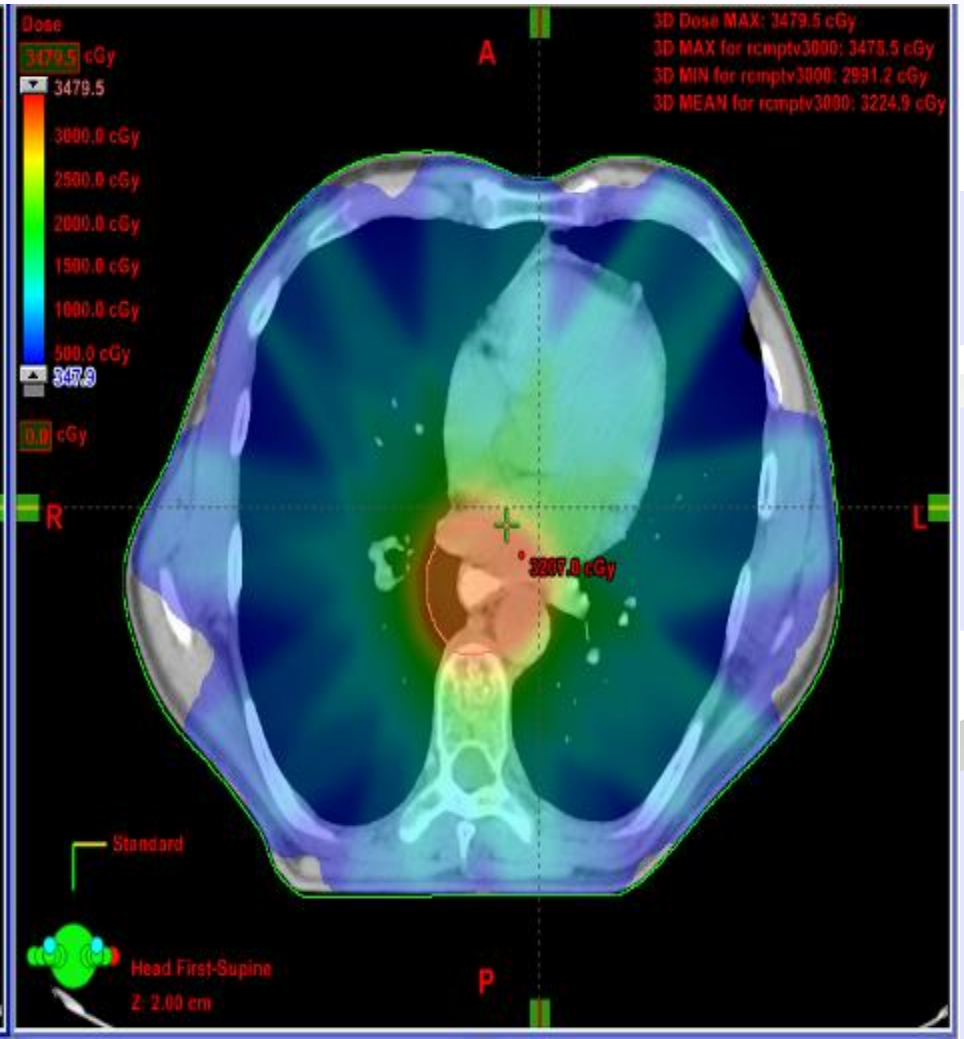
- Most European ion beam projects claim that increased RBE is an advantage for treatment of radioresistant tumours.
- This not necessarily true, since RBE is used in the prescription process to REDUCE DOSE, in an attempt to achieve an ISOEFFECT.

Therapeutic Success is more likely if:

1. if the RBE used is less than the tumour RBE, and
2. if the RBE used is greater than the normal tissue RBE.
3. Specific RBEs for tumour and NT should be used.

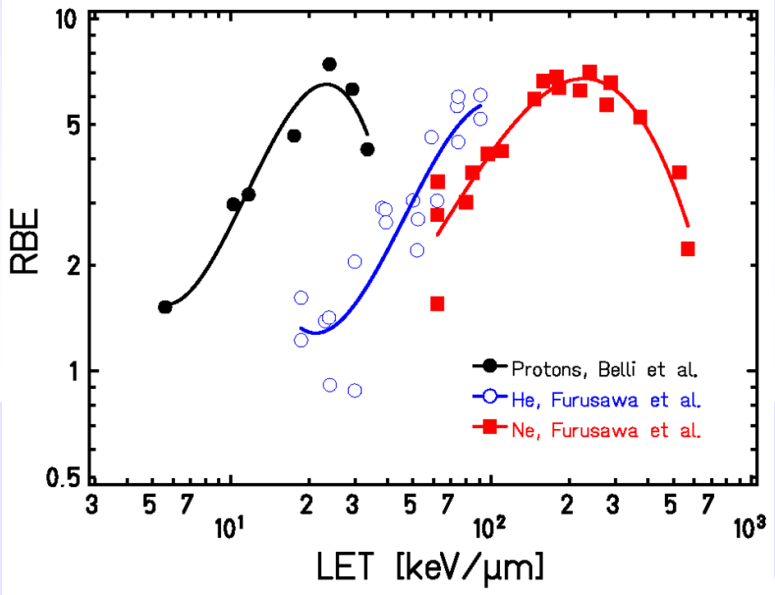
Esophageal radiotherapy dose distributions, chemotherapy is also used and sensitizes lung with acute and late serious effects (pneumonitis and fibrosis)

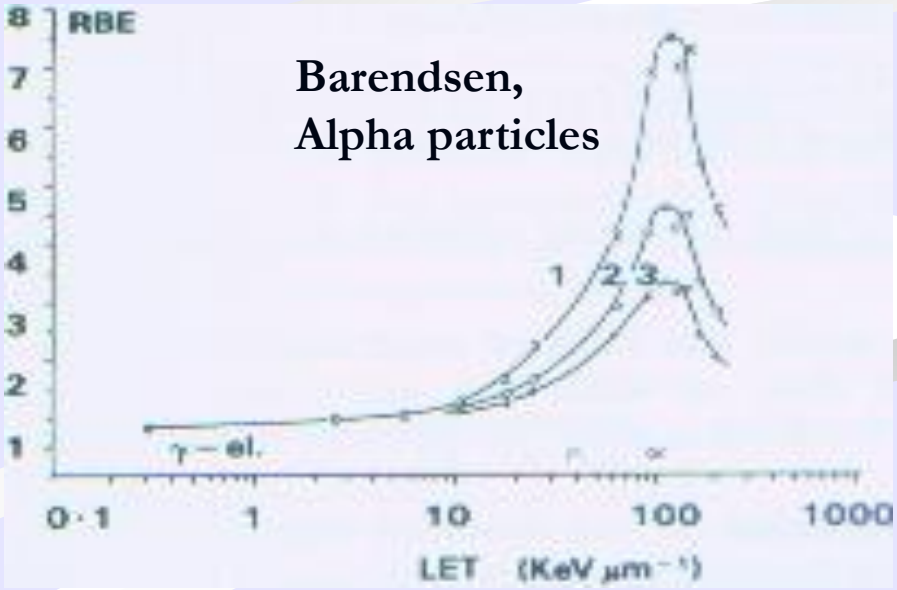




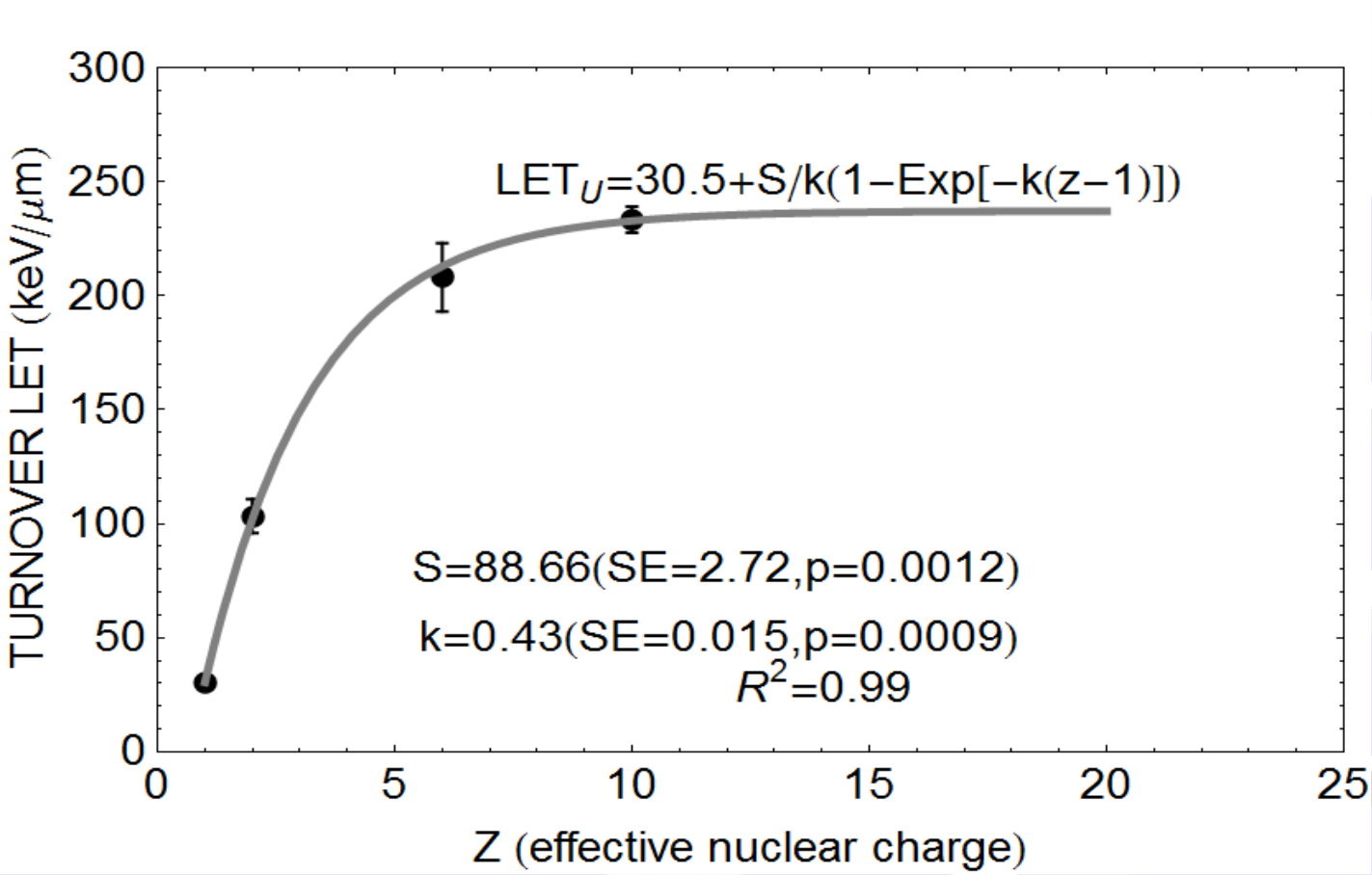
Relative Biological Effect - the facts

- 'Turnover points' depend on Z (nuclear charge) – protons are <u>more</u> efficient!
- RBE ↓ with increasing dose but with remarkable symmetry



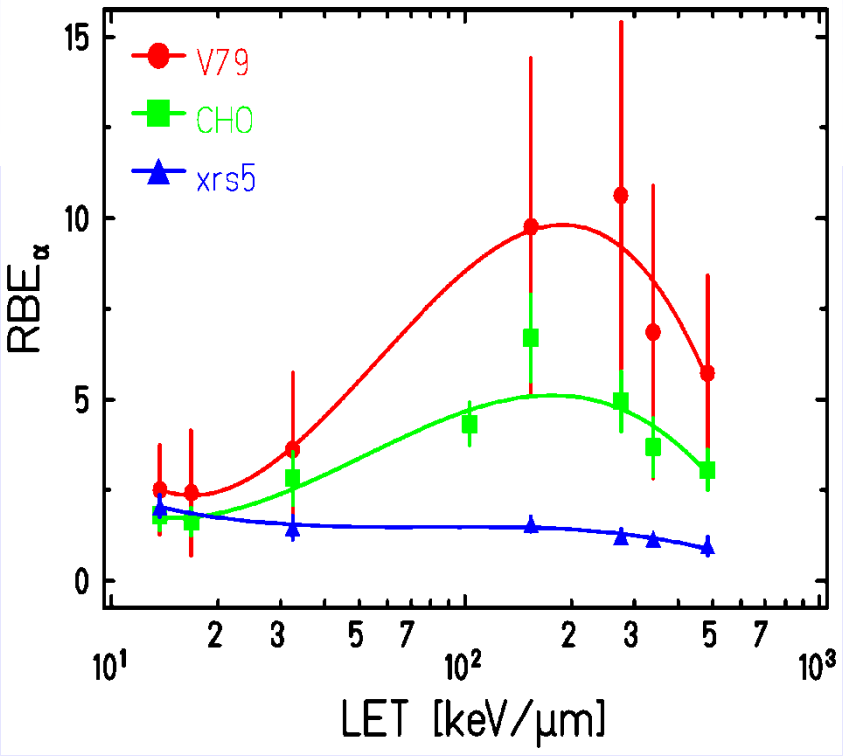


Estimating position of LET-RBE turnover point.

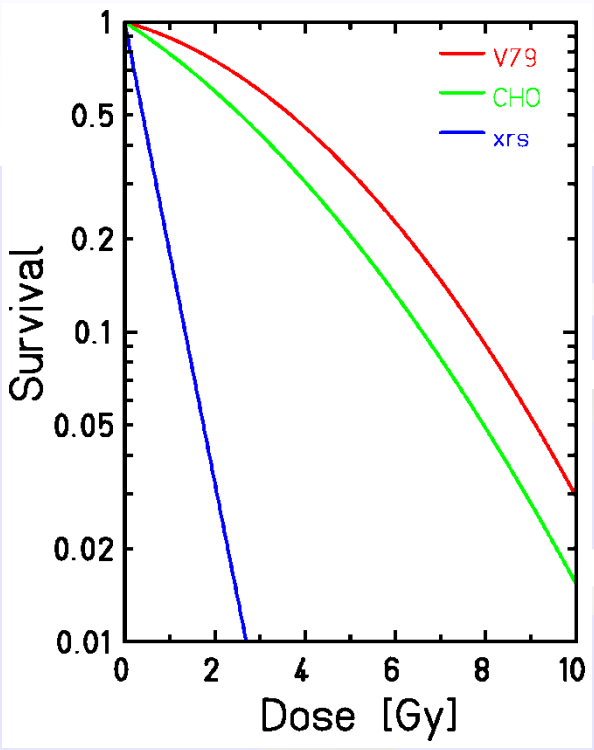


RBE depends on Cell Type (& probably repair capacity) – GSI data Weyrather et al 1999

Carbon ions



X-rays



Radioresistant cells (higher DNA repair capacity?) show higher RBEs

Biological effective dose (BED) dose required for a defined level of bio-effect if given in very small doses close to zero dose, where D=nd, and d is dose per fraction; [n is number of fractions]

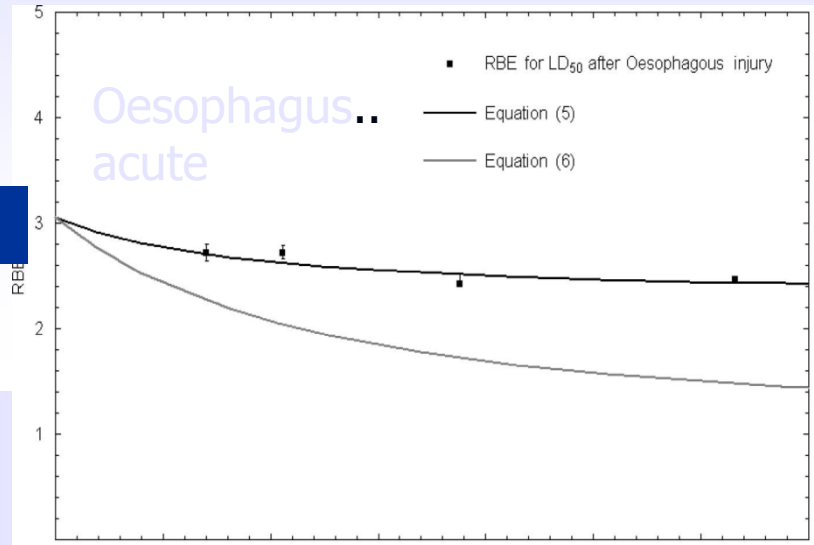
$$\boldsymbol{RBEmax = \frac{\alpha_H}{\alpha_L};\quad RBEmin = \sqrt{\beta_H}/\sqrt{\beta_L}}$$

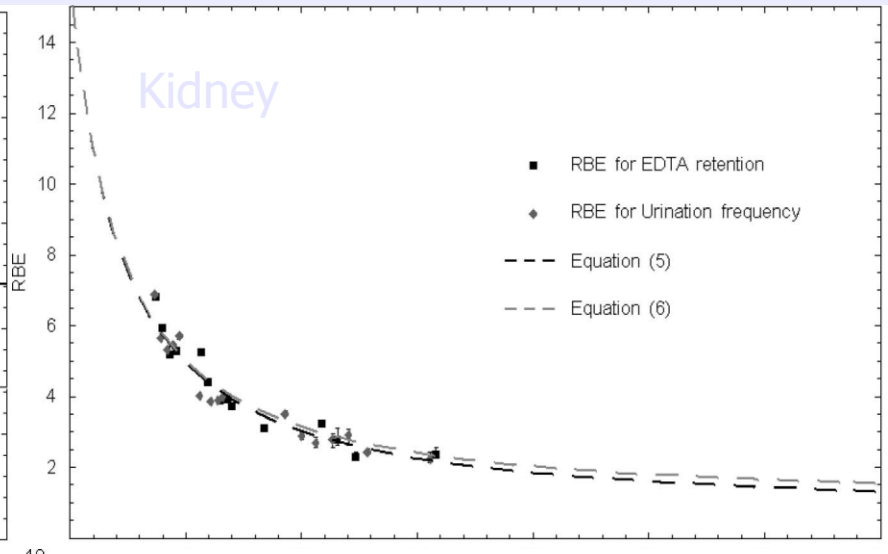
$$BED = D_L\left(1 + \frac{d_L}{\left(\frac{\alpha}{\beta}\right)_L}\right) = D_H\left(RBEmax + \frac{RBEmin^2 d_H}{\left(\frac{\alpha}{\beta}\right)_L}\right)$$

Standard clinical x-rays

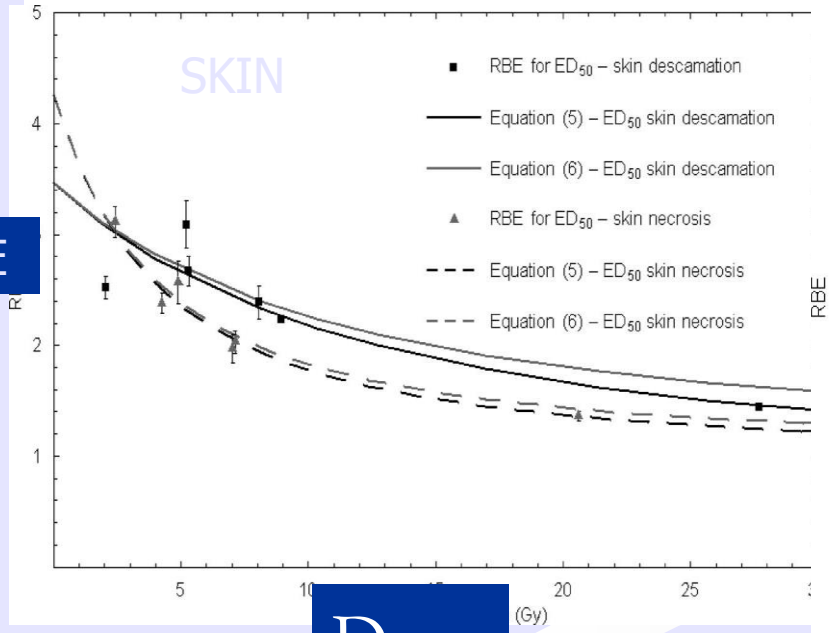
Protons or ions

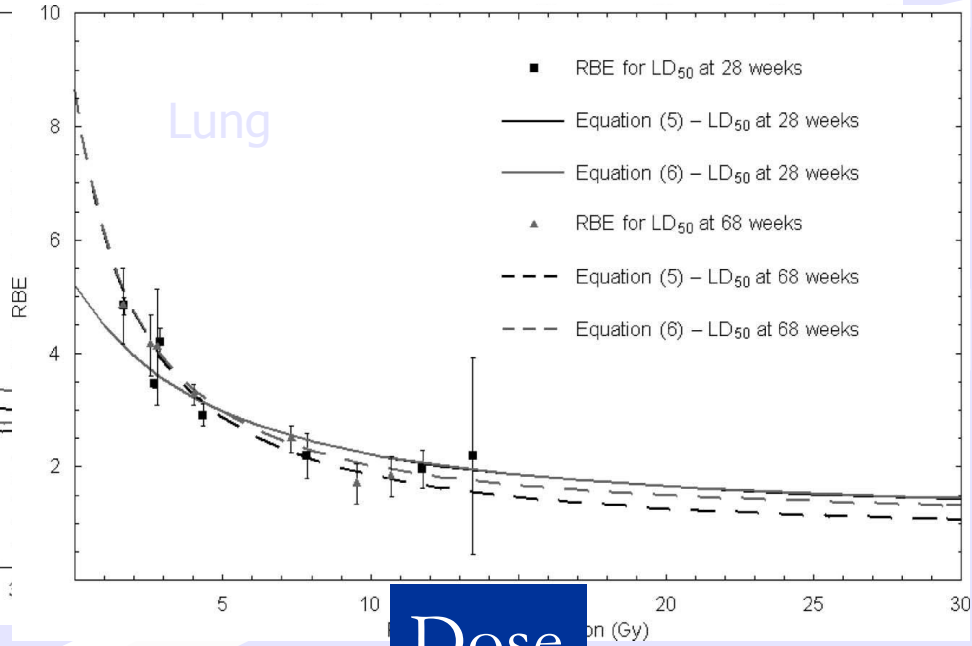
Examples of Hammersmith animal neutron experiments – Carabe-Fernandez et al IJRB 2007





RBE





RBE

Dose

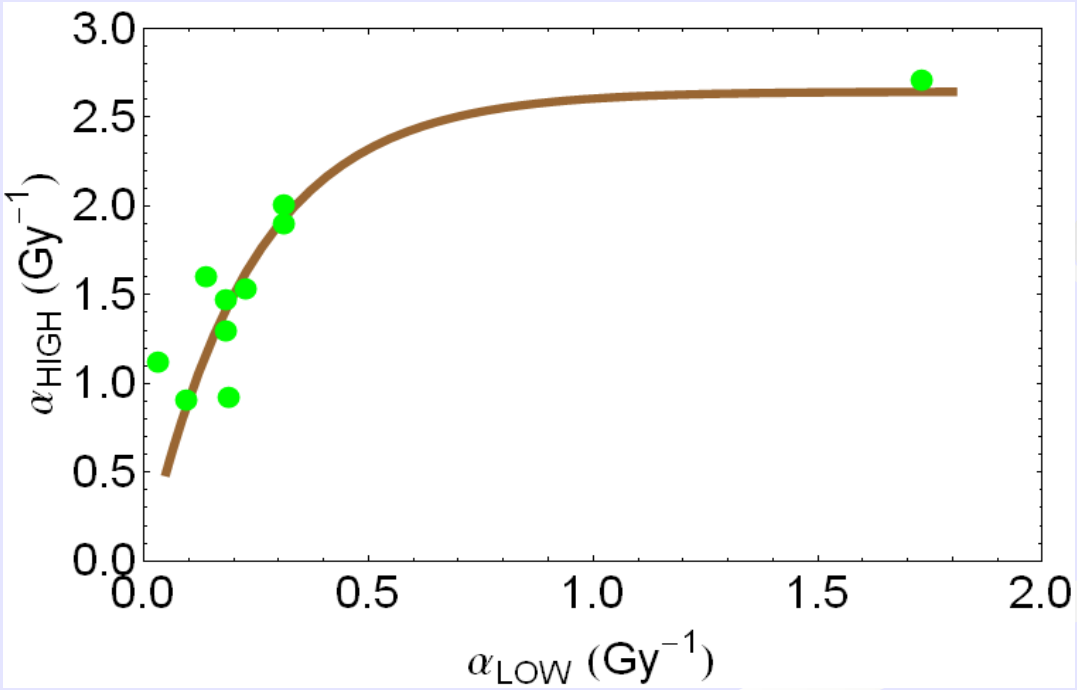
Dose

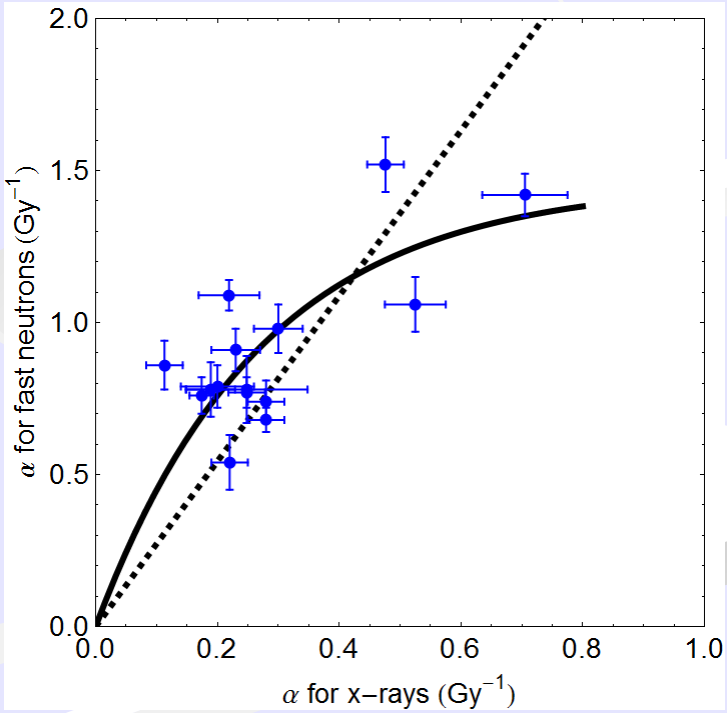
How does the α parameter change with increasing LET ?

α values at the LET-RBE turnover points

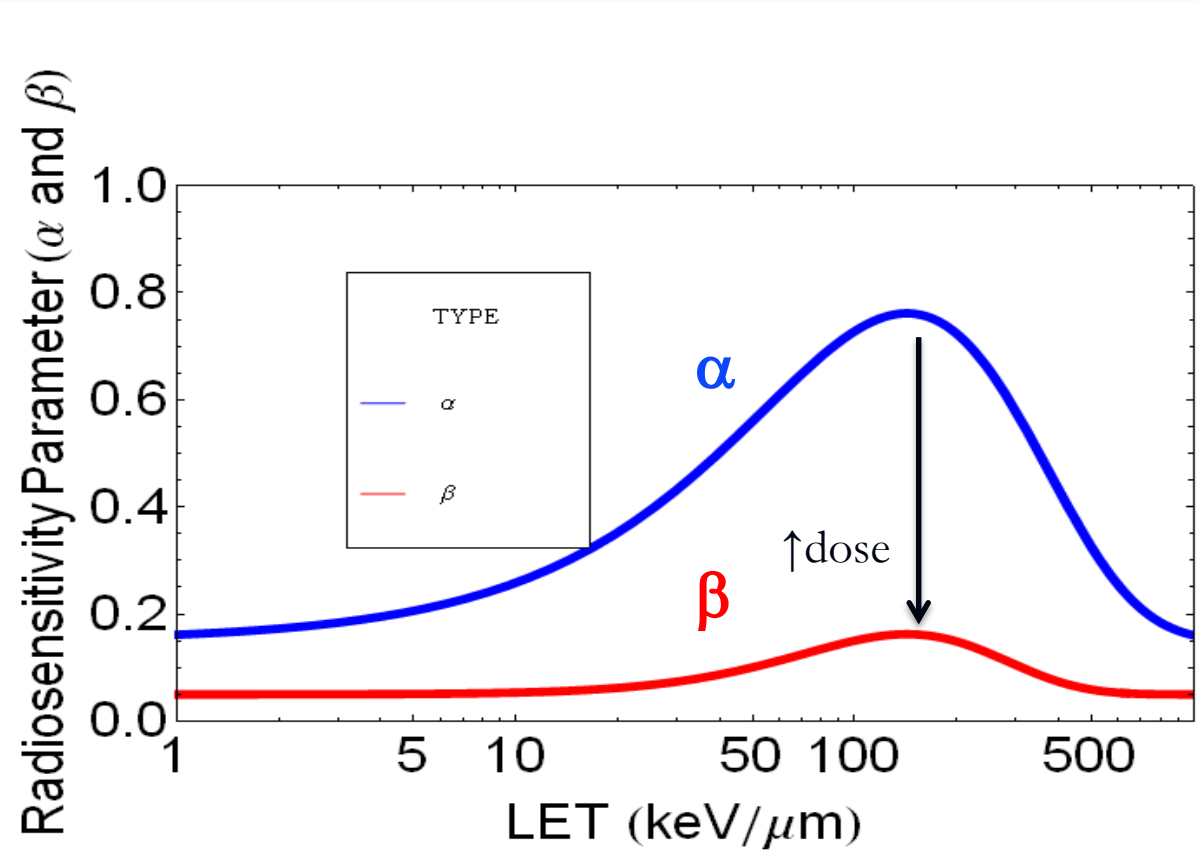
Fast Neutrons (Clatterbridge data)

Fitted by $\alpha_H = 11.1/4.2\,(1-\mathrm{Exp}[-4.2\,\alpha_L])$
$P<0.01$





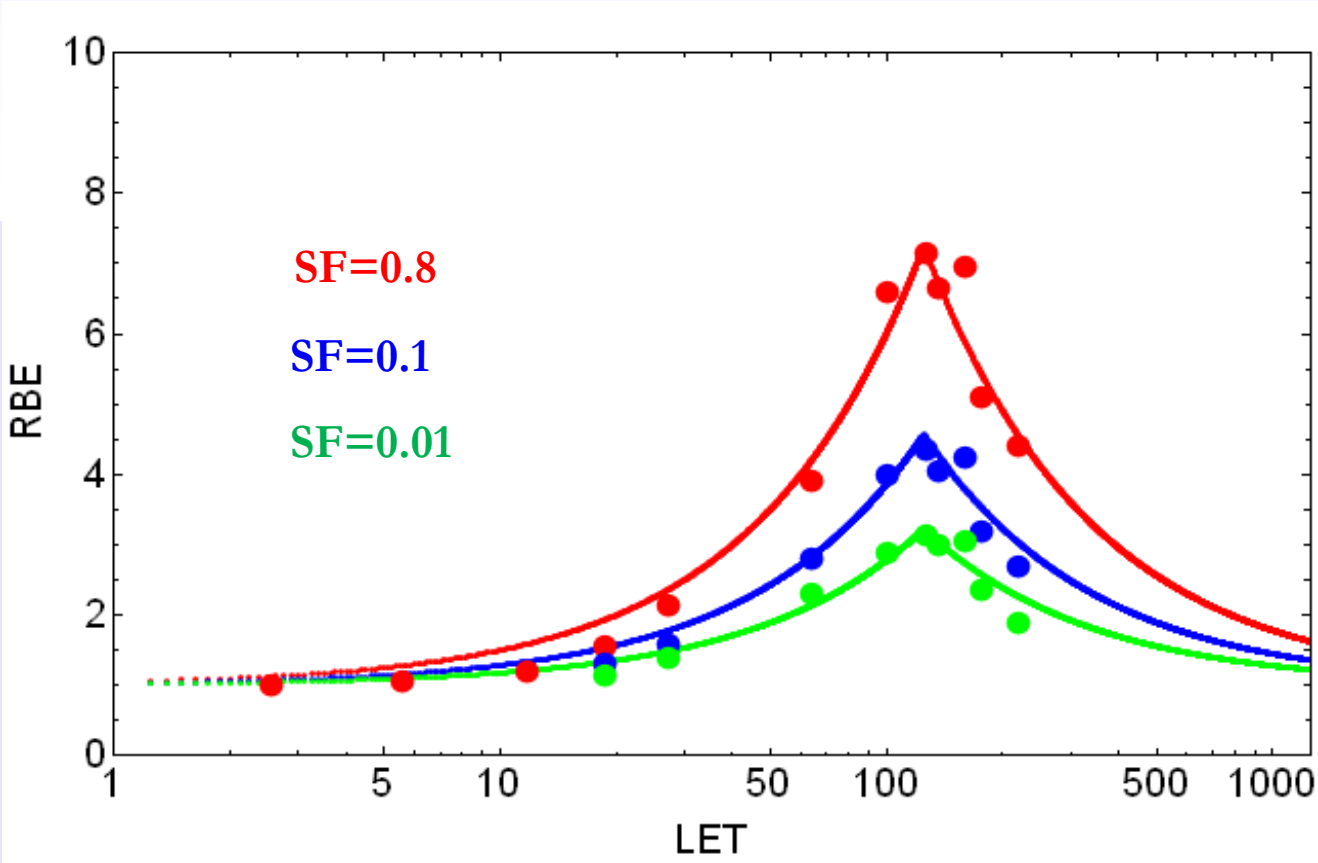
Assume same turnover point for increment in α and β with LET , in order to preserve symmetry of relationship when dose changes.



With increasing dose a greater proportion of damage is due to β curve (where damage proportional to dose squared)

Data of Barendsen (1968), monoenergetic alpha particles and deuterons only for three levels of dose [cell surviving fraction]

Oxford Model



Extra local energy provides efficiency up to LETU and inefficiency beyond it

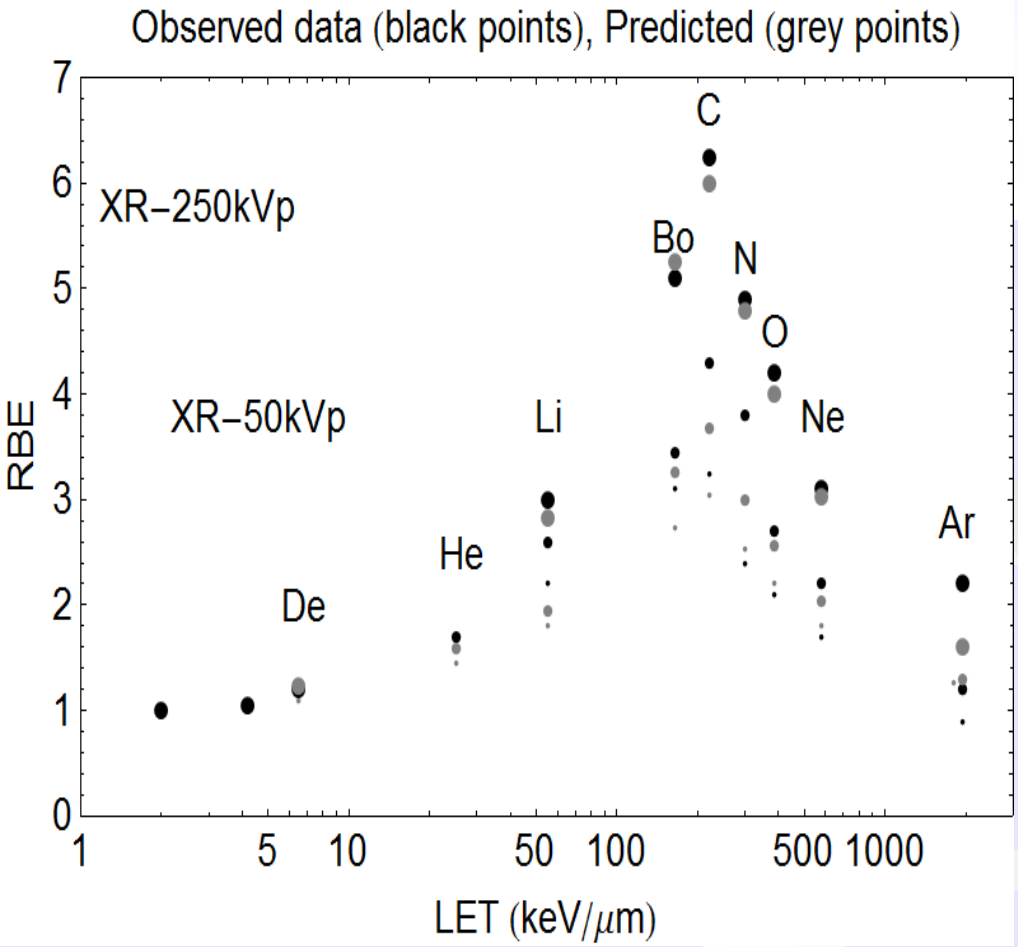
- For $LETx < LET_U$
- $\alpha_H = \alpha_L + \frac{LETx - LET_C}{LET_U - LETc} . (\alpha_U - \alpha_L)$

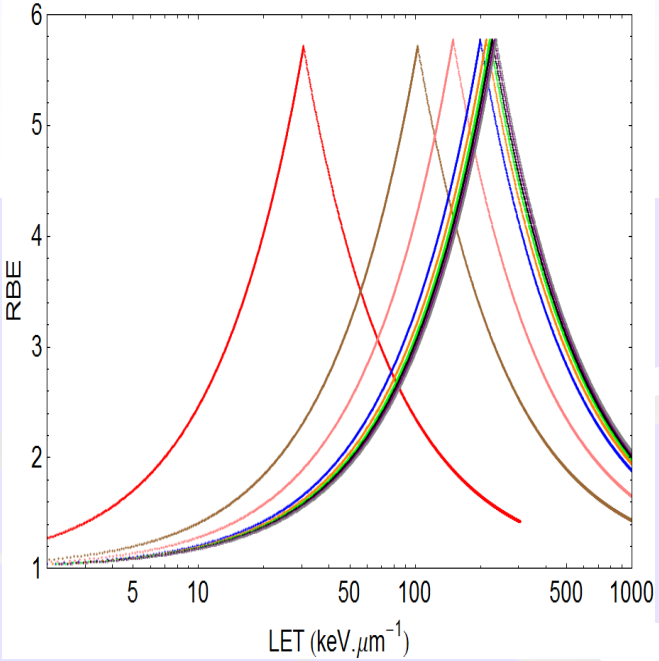
For $LETx > LET_U$:

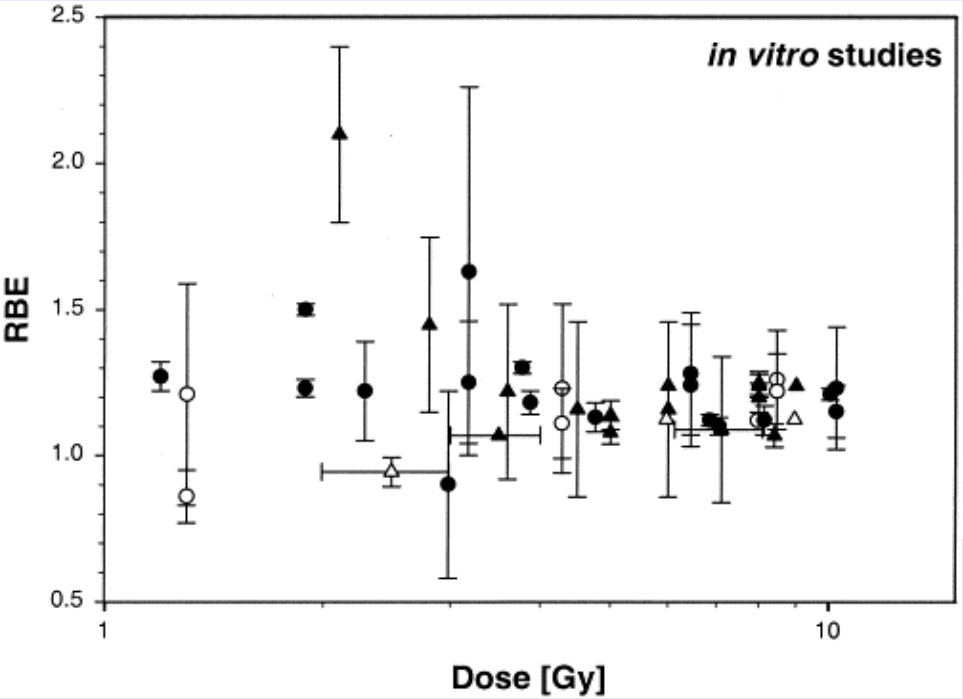
- $\alpha_H = \alpha_L + \left(1 - \frac{LETx - LET_U}{LET_x}\right) . (\alpha_U - \alpha_L)$

And similarly for β (i.e. $\beta_L, \beta_H, \beta_U$)

Reduced RBE with increasing dose – data of Todd (1967) modelled in Oxford





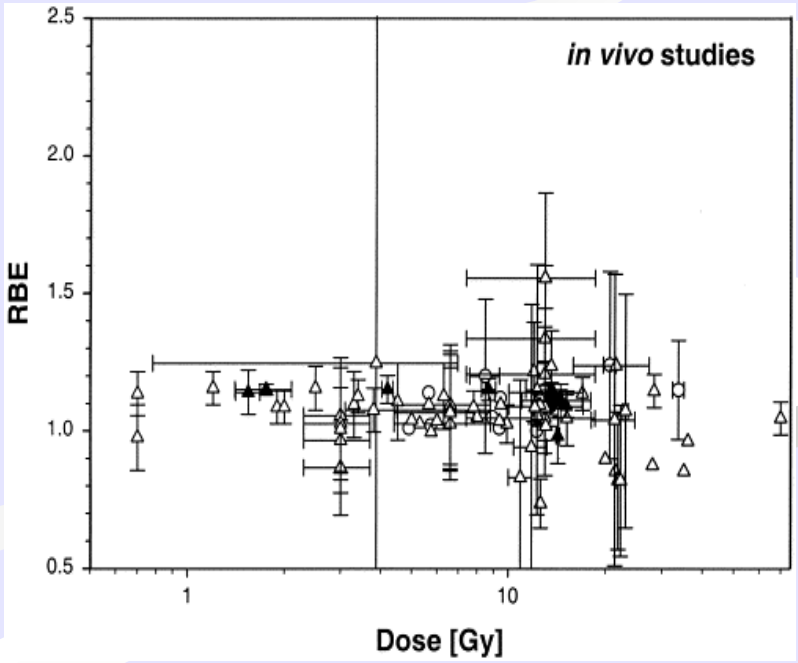


Boston review of proton RBE studies: Paganetti et al IJROBP 2002

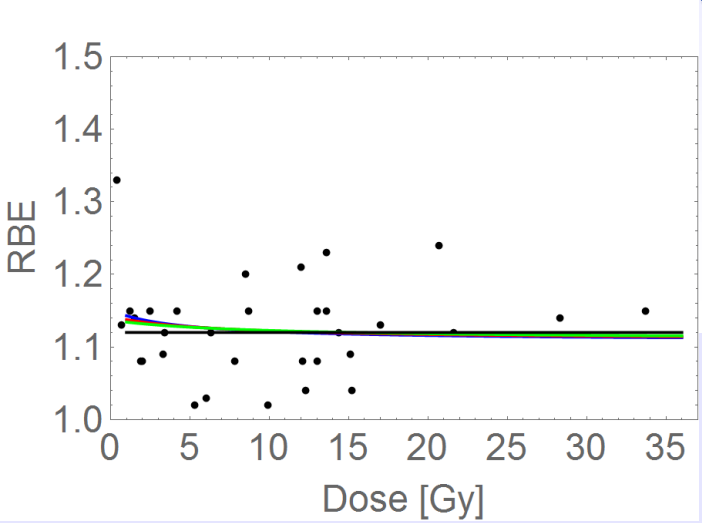
In vitro ? shows trend to higher RBE at low dose

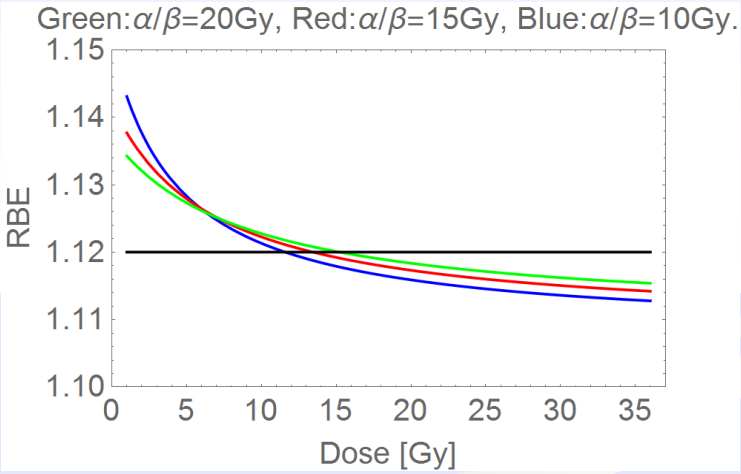
In vivo..mainly acute upper intestine assay

Experiments mostly used rapidly growing CHO, V79 [Hamster] cells and acute small intestine crypt assay, only three ‘late effect’ normal tissues tested only at 9-12 Gy per fraction (too high a dose to show effect)

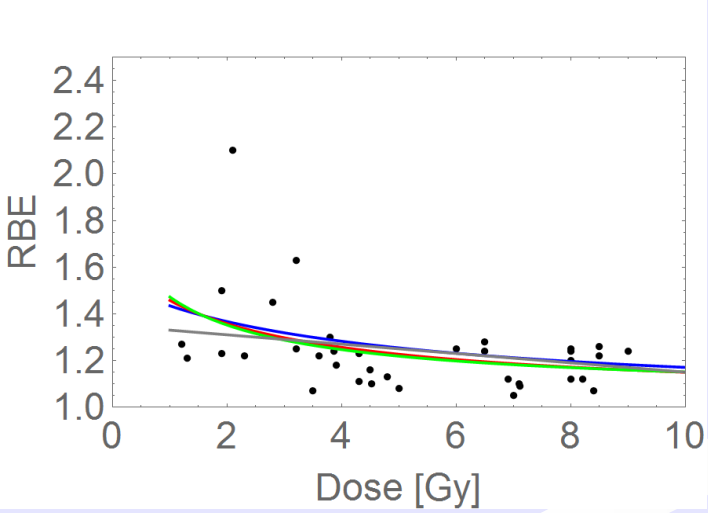


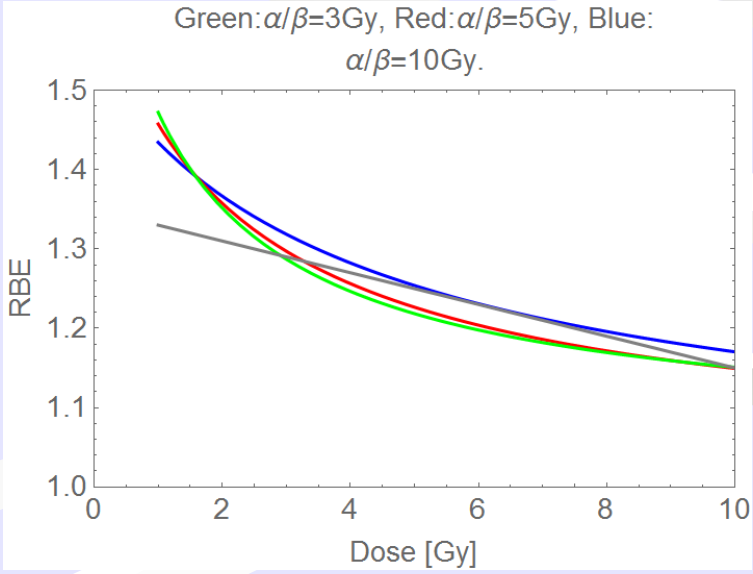
In vivo: Data in Paganetti et al 2003 Int J Radiat Oncol Biol Phys





In vitro



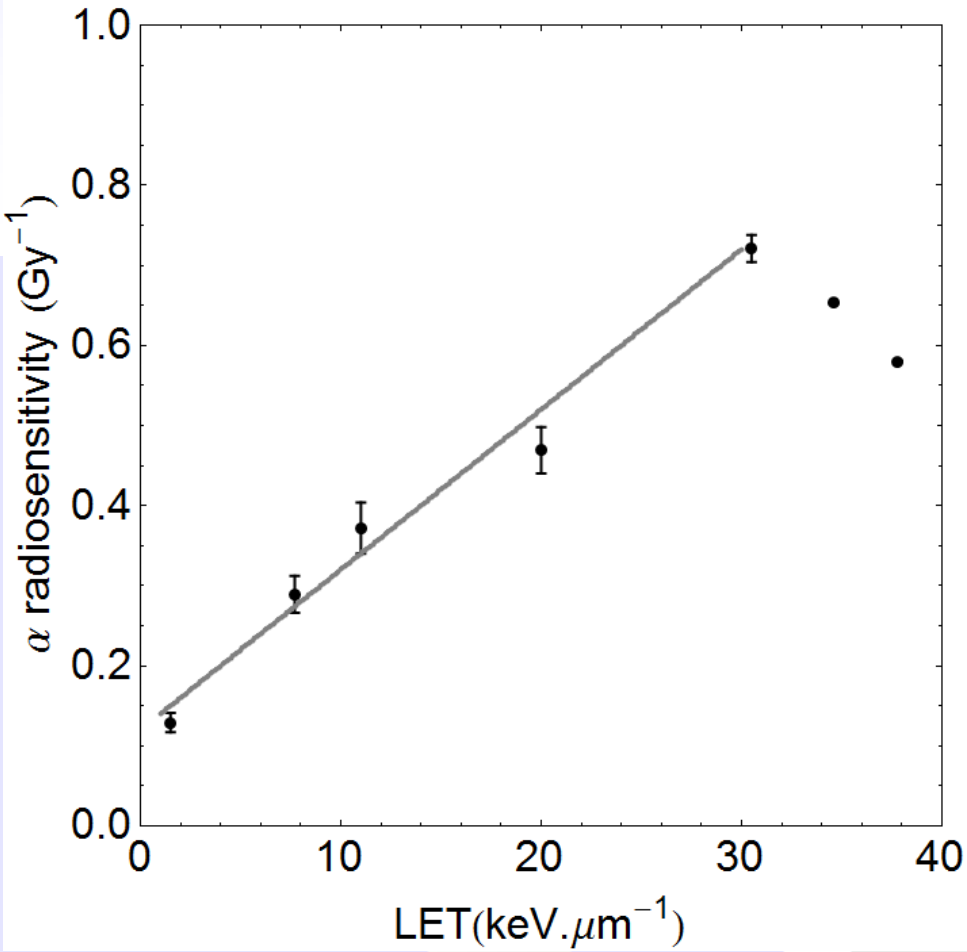


Critical analysis of the proton 1.1 RBE

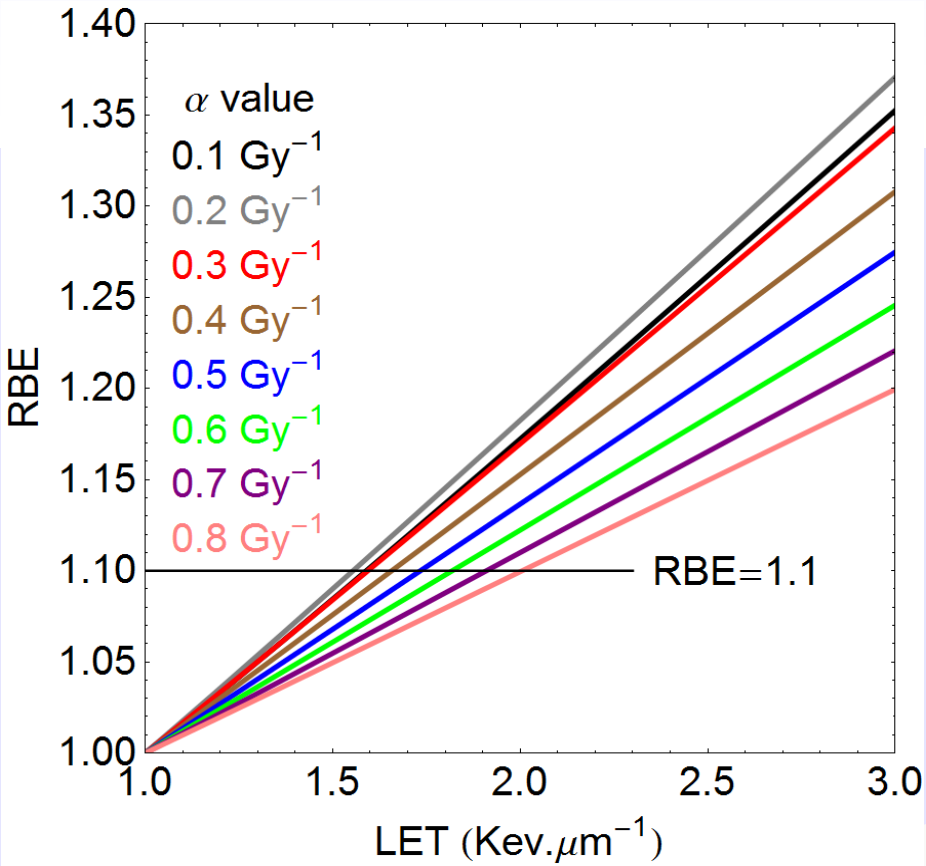
- Reasons why RBE must be a variable rather than constant.
- Criticism of experimental systems, including the control irradiation used and fitting approaches.
- Mid spread out Bragg peak assesments cannot fully reflect a clinical situation.

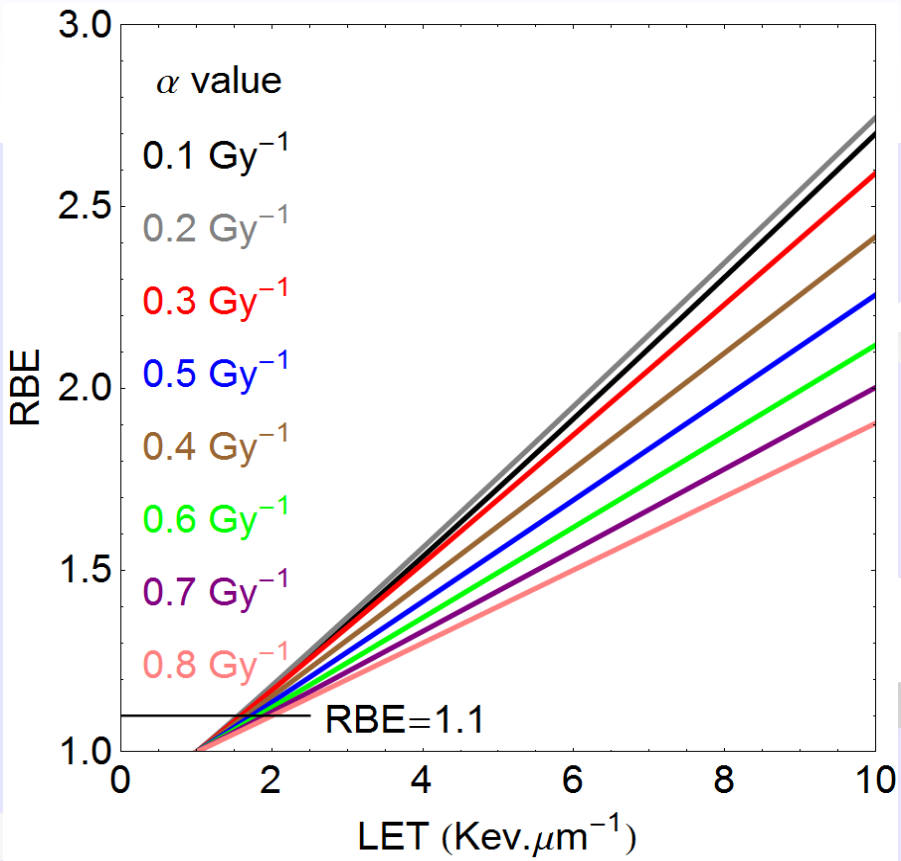
See Jones B:Why RBE must be a variable and not a constant in proton therapy. Brit J Radiology 2016

Data of Belli et al (protons)

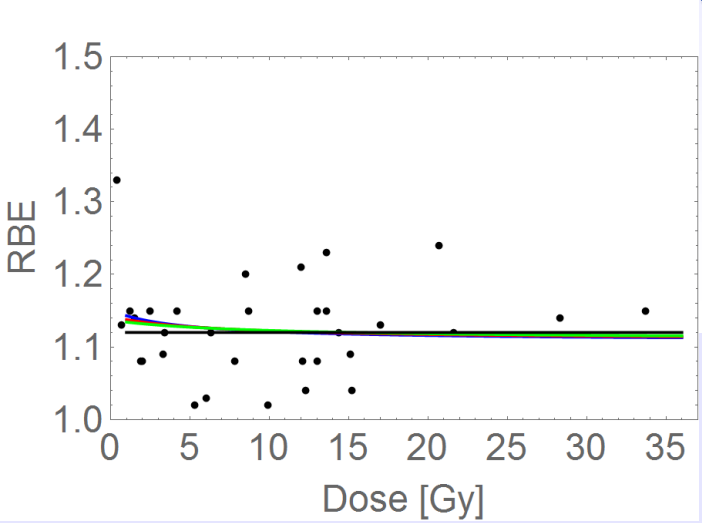


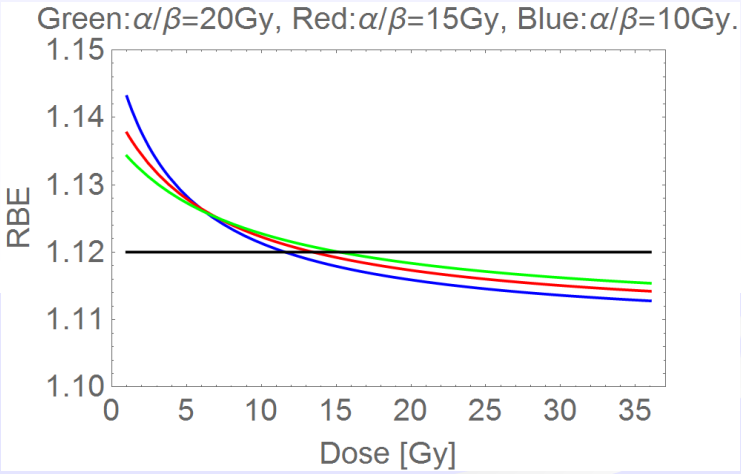
Proton RBE changes with LET for different low LET intrinsic radiosensitivities (α parameter)



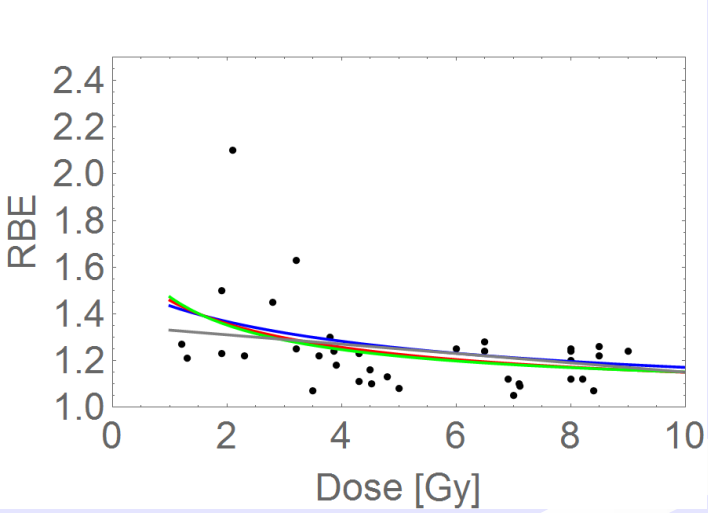


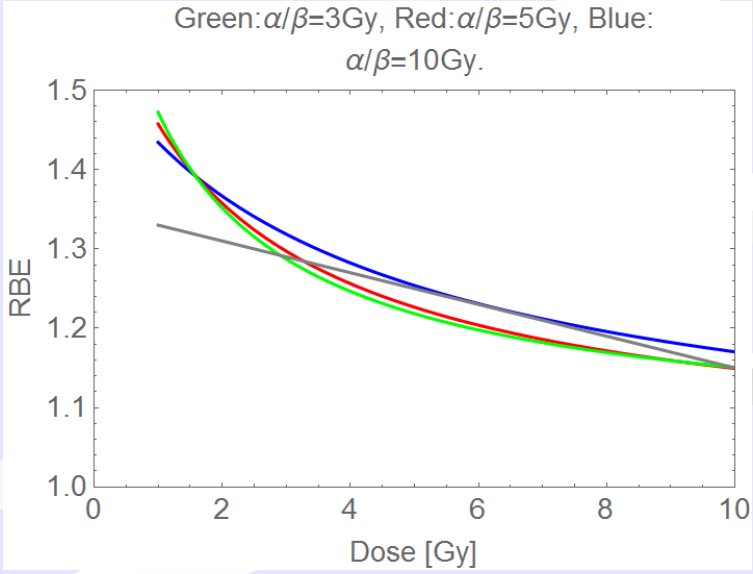
In vivo: Data in Paganetti et al 2003 Int J Radiat Oncol Biol Phys





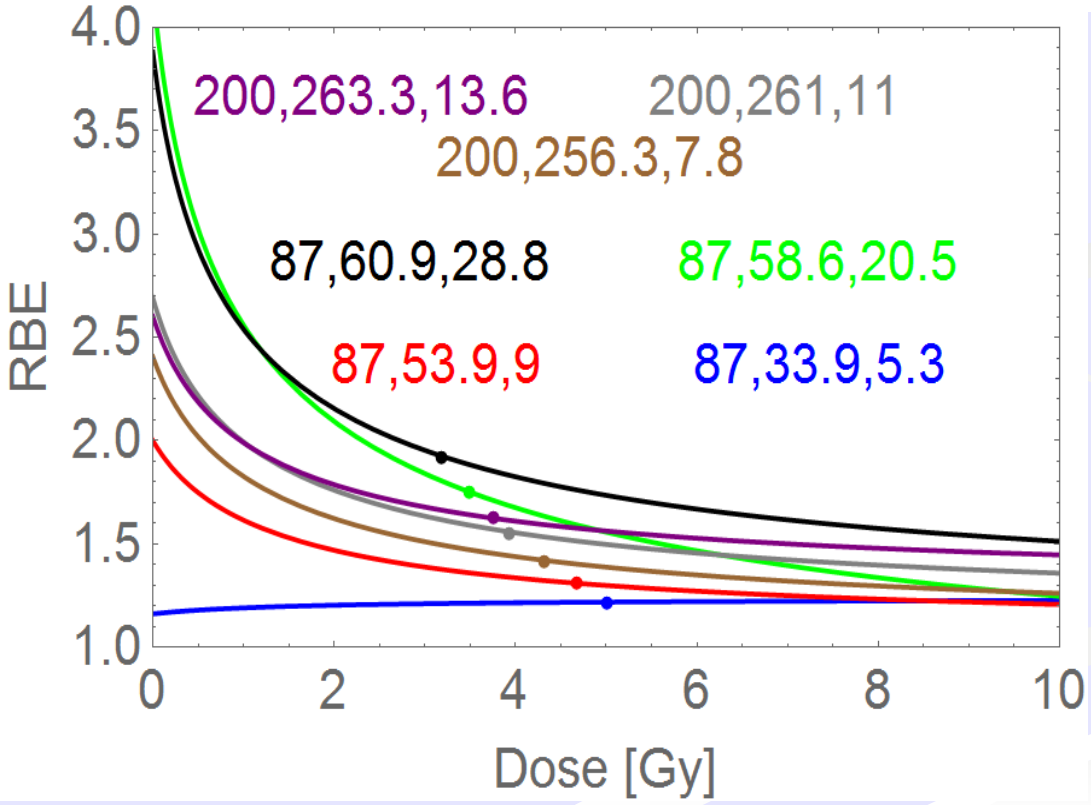
In vitro

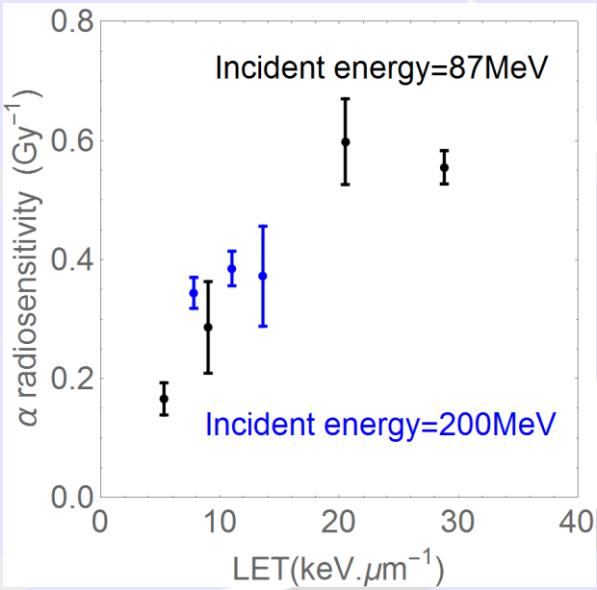


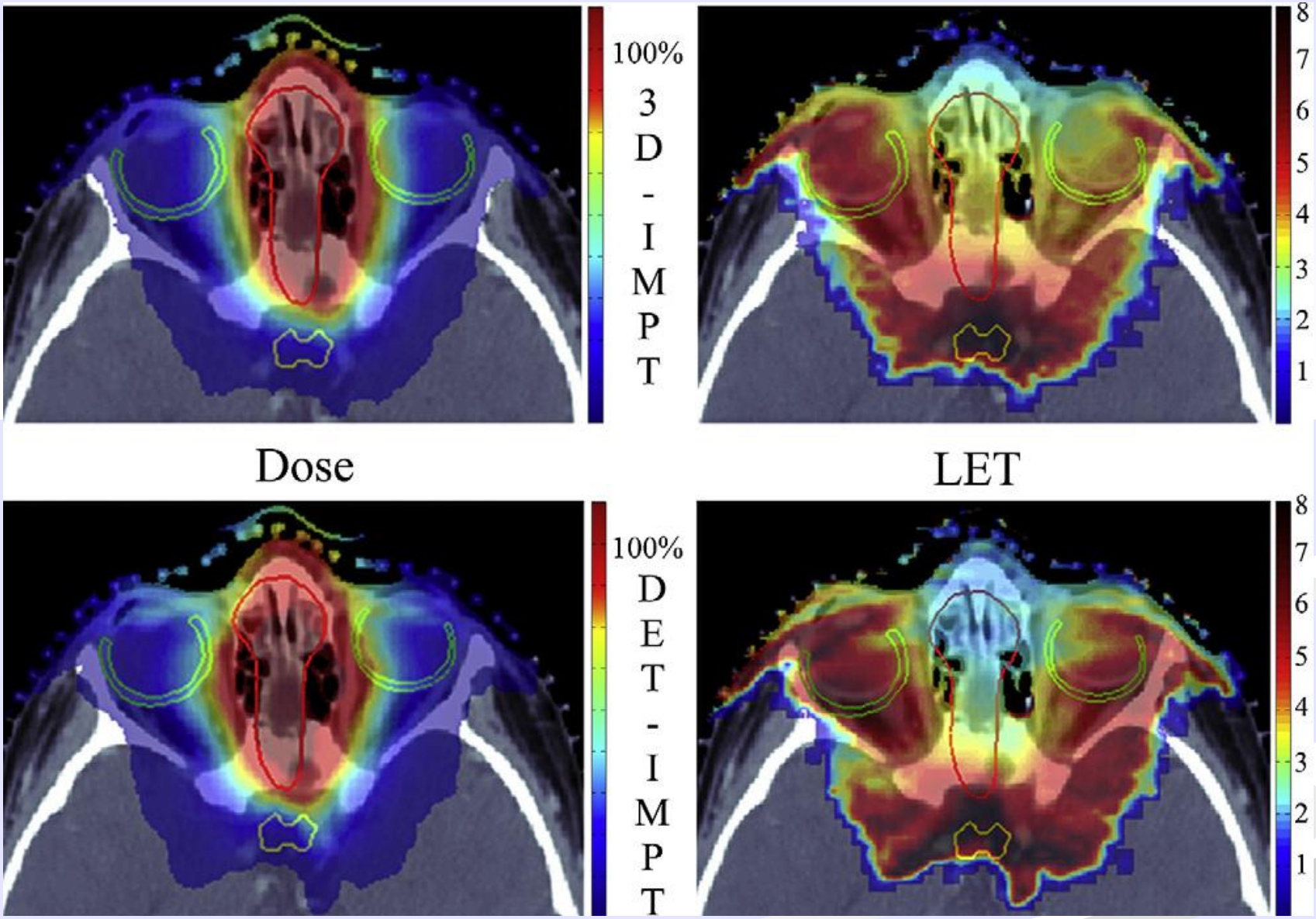


Take changes in α and β in data from Britten et al, Rad Research 179,21-28 [Bloomington, Indiana proton beam]

Code for numbers: incident energy (MeV), depth (mm) and LET KeV.μm^{-1}. Coloured points are published RBE for SF=0.1

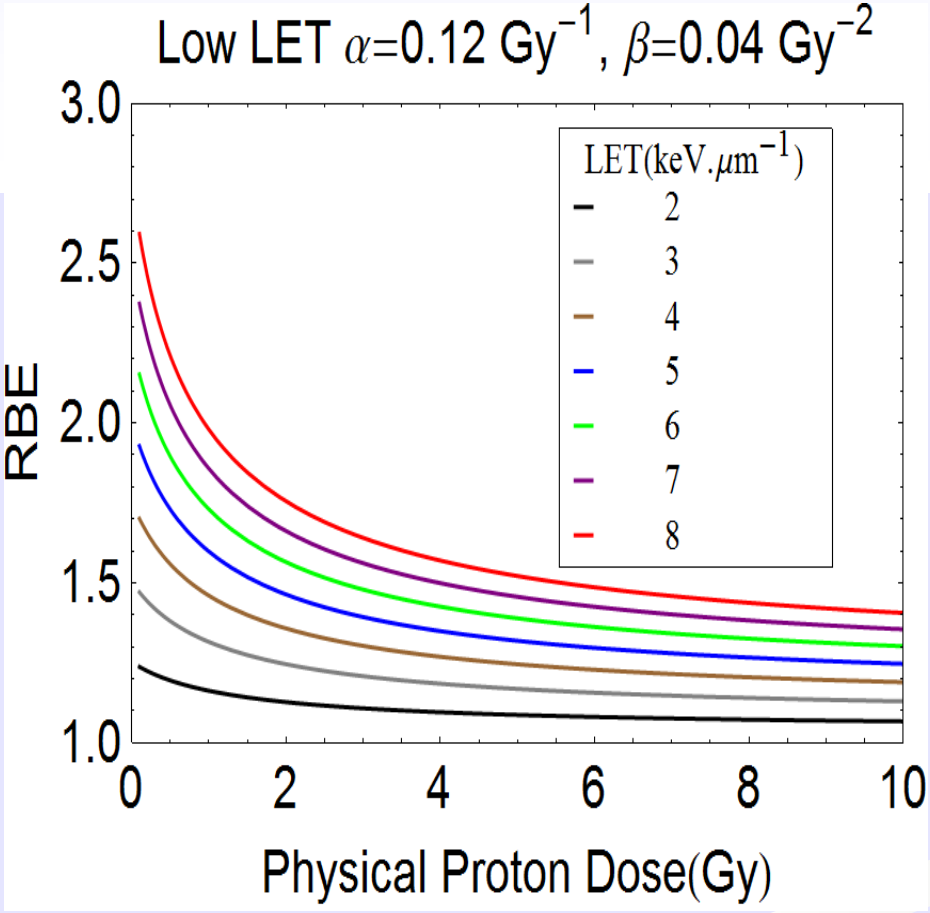


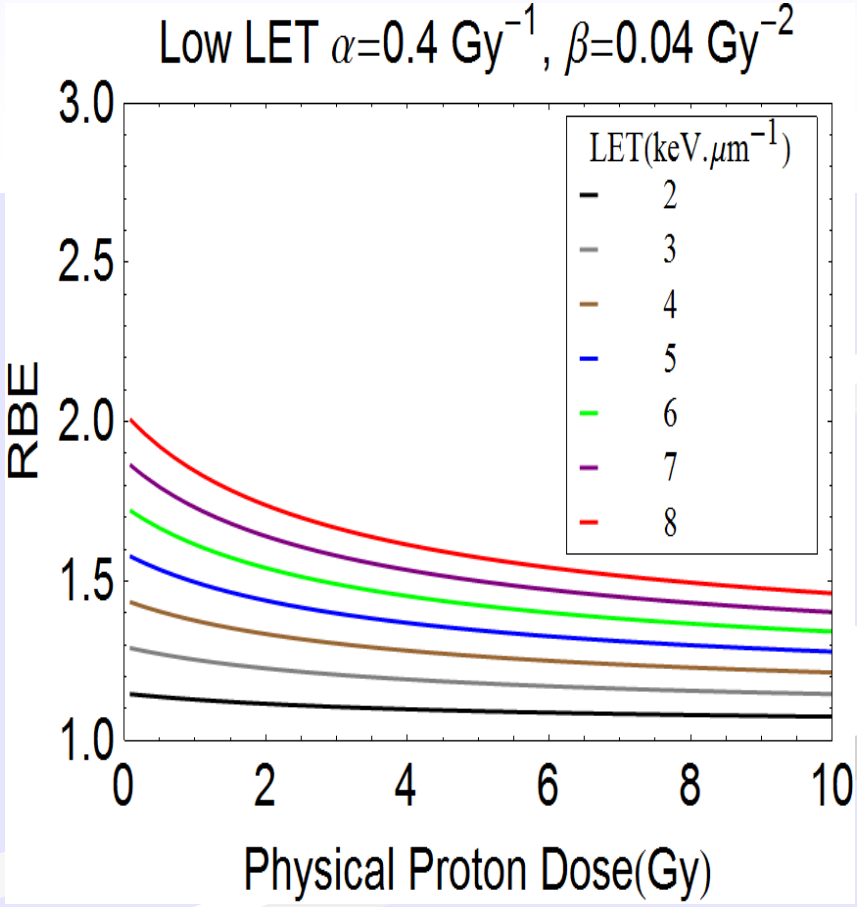




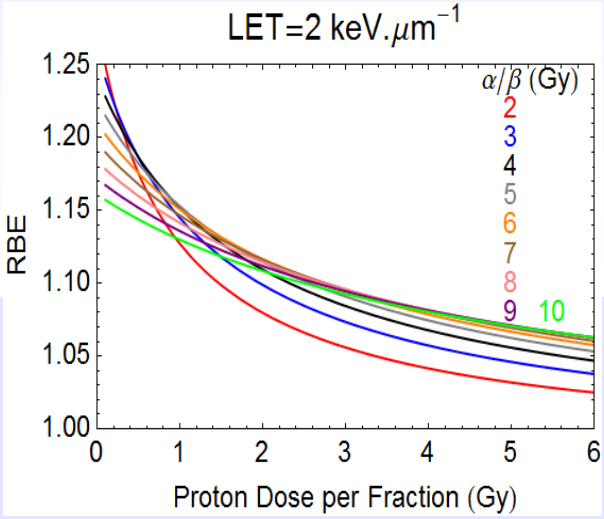
Grassburger, Trofimov, Lomax and Pagganetti: IJROBP 2011, 80: 1559-1566

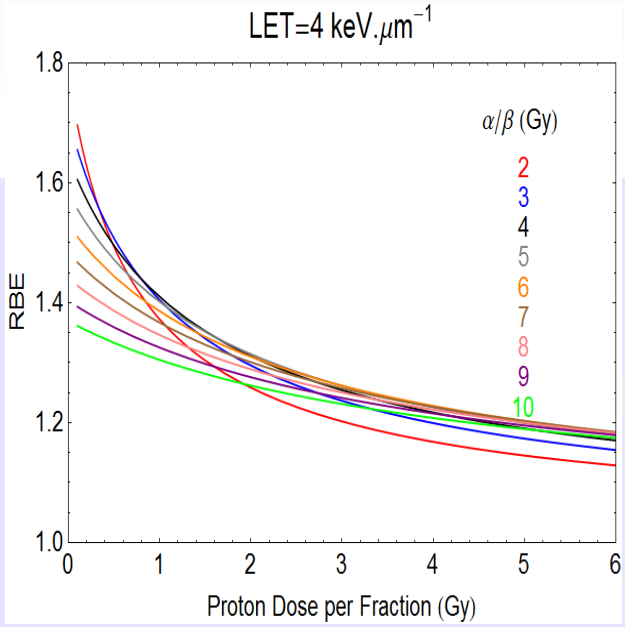
Proton RBE (bio-effectiveness) related to dose per treatment

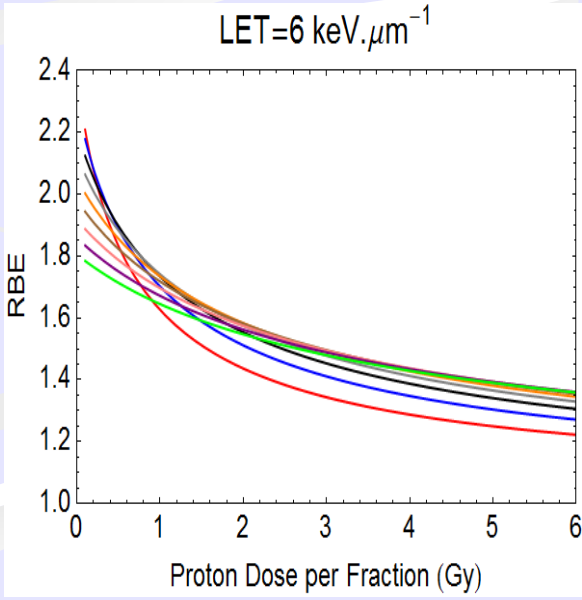




RBE and dose per fraction with LET for different α/β ratios





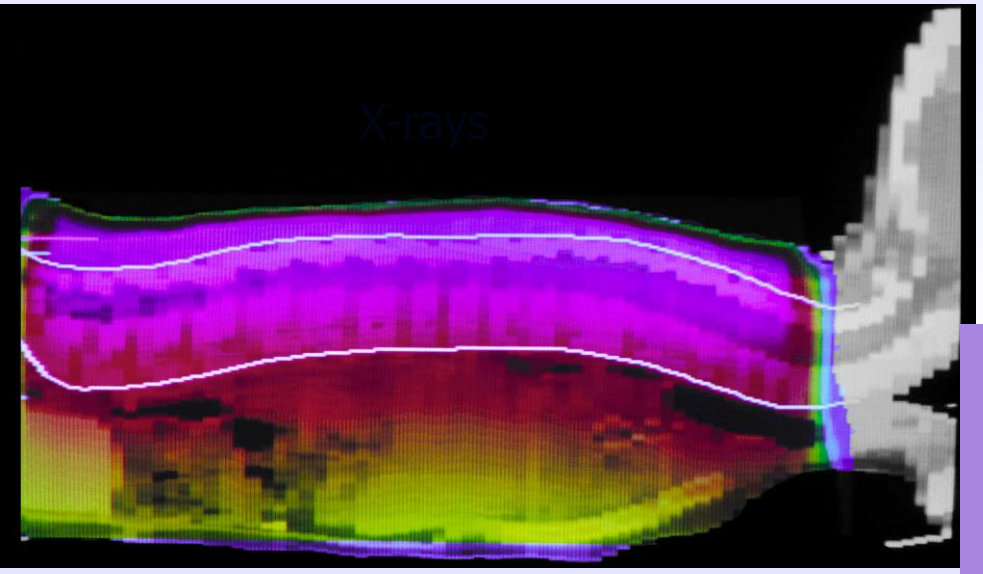


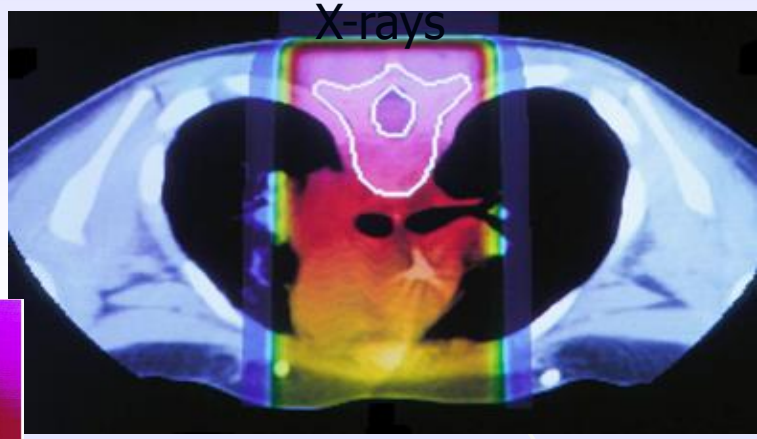
Compensating dose and LET placement errors on 3/15 fractions for 50% dose reduction and LET changes

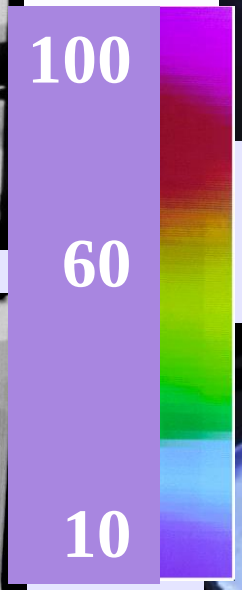
	SCC α=0.35, β=0.04	PROSTATE α=0.18, β=0.035
At LET=45	α_U=2.035 α_H=0.662 RBEmax=1.89α_U=0.0555 β_H=0.0429 RBEmin=1.035	α_U=1.402 α_H=0.406 RBEmax=2.25α_U=0.045 β_H=0.037 RBEmin=1.027
At LET=15	α_H=0.454 Rmax=1.297 β_H=0.041 RBEmin=1.012	α_H=0.255 Rmax=1.419 β_H=0.0359 RBEmin=1.0128
At LET=53	α_H=0.780 RBEmax=2.051 β_H=0.434 RBEmin=1.04	α_H=0.447 RBEmax=2.482 β_H=0.0372 RBEmin=1.031

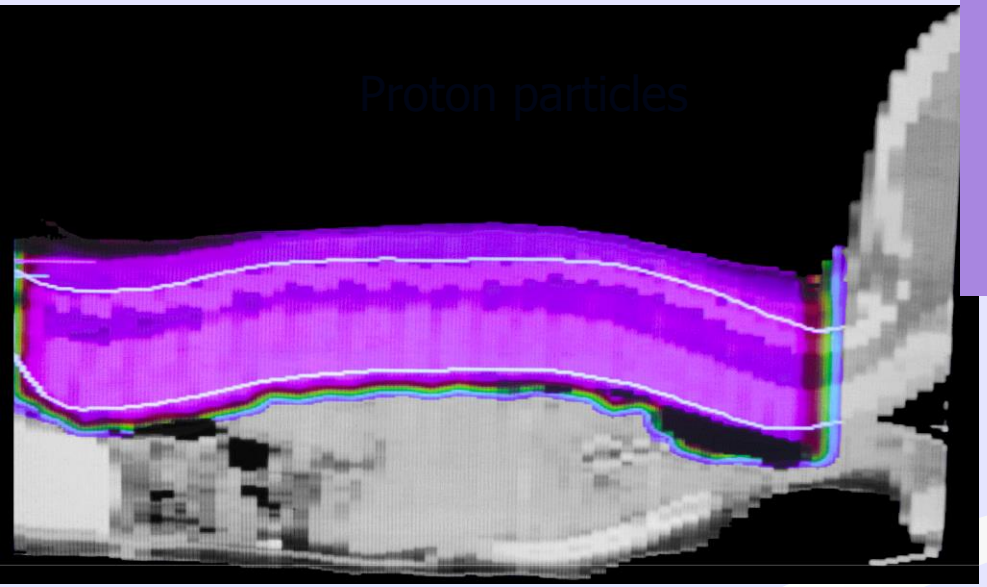
	SCC, Dose/# 1.867 Gy	Prostate, Dose/# 2.33 Gy
Intended BED	59.375 Gy $_3$	95.765 Gy $_{8.75}$
Given BED to 50% of tumour in 3#	3.855 Gy $_3$	5.780 Gy $_{8.75}$
Deficit BED for compensation in remaining 12 #	55.488 Gy $_3$	89.985 Gy $_{8.75}$
Compensatory dose per fraction to under-dosed region for remaining 12 #	2.01 Gy	2.50 Gy

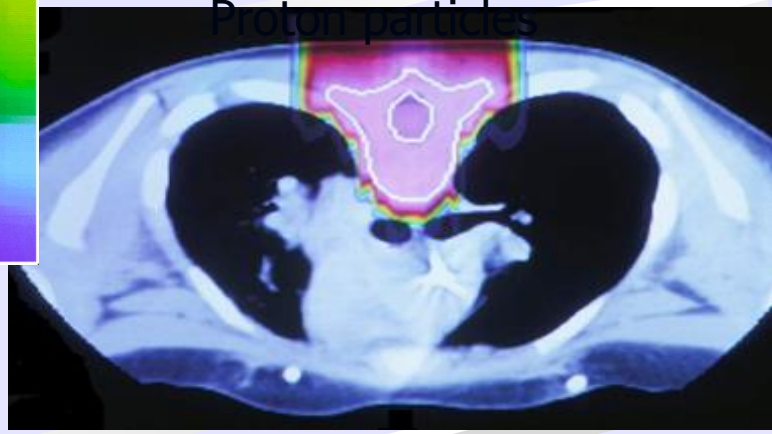
Medulloblstoma in a child

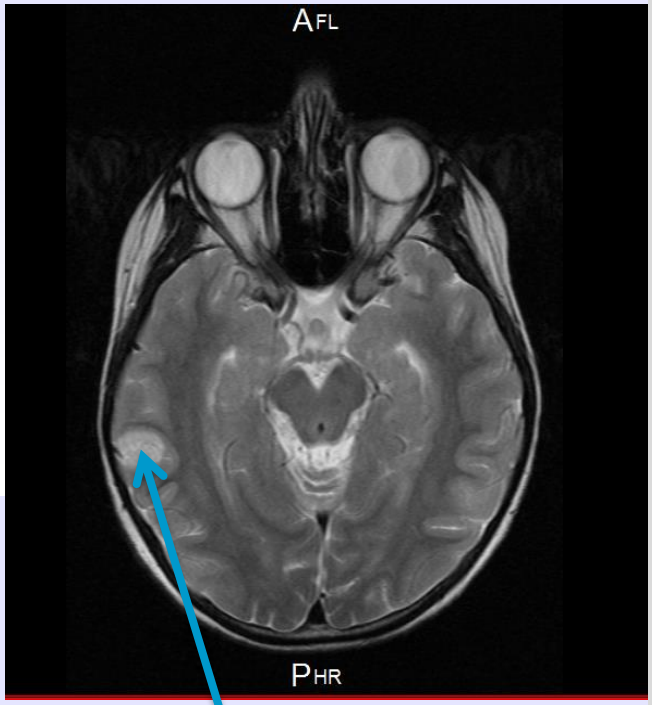












Recurrent medulloblastoma

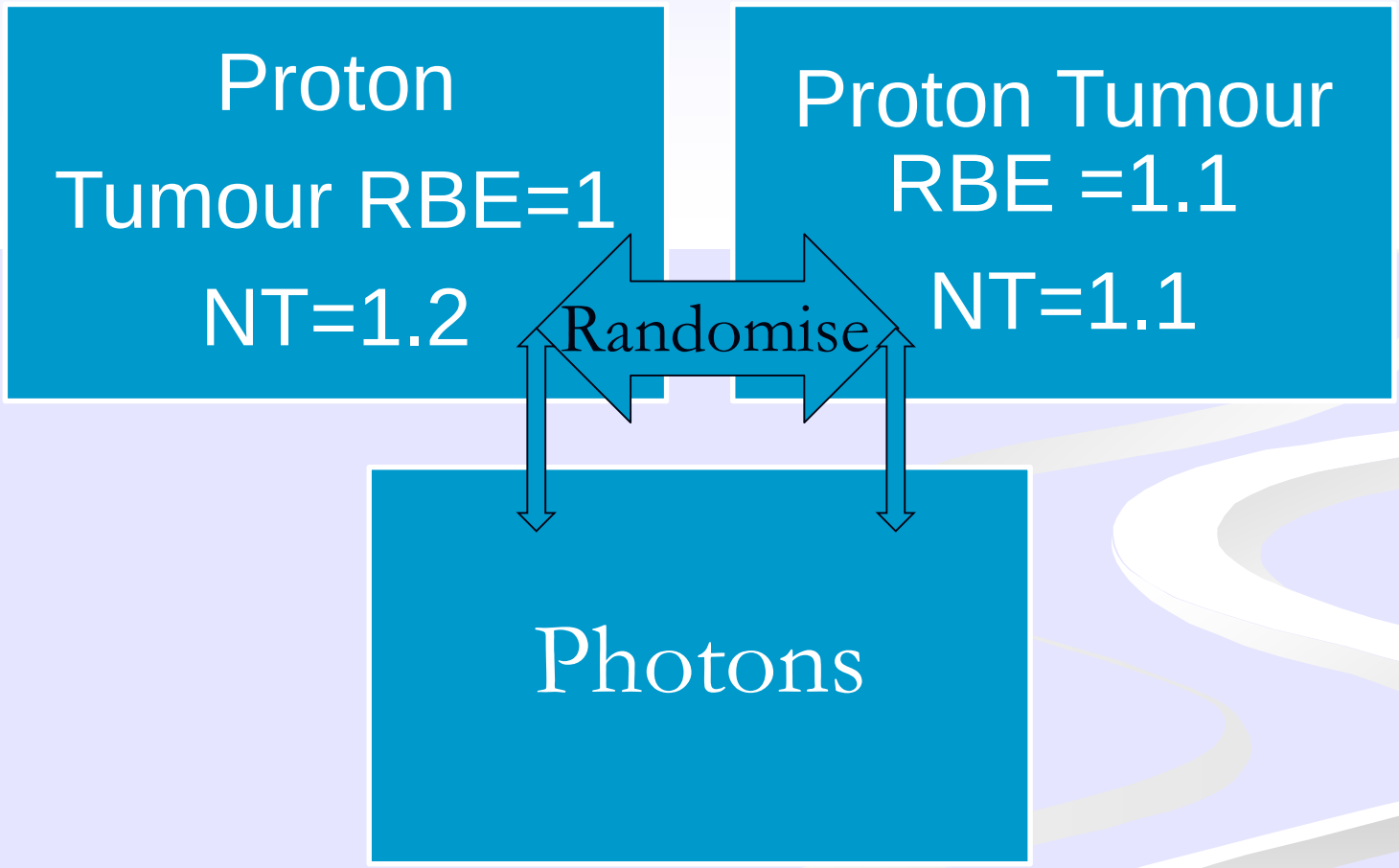
Relative risks of spinal recurrence after protons for medulloblastoma and ependymoma are 1.7 & 2.0 (2 publications).

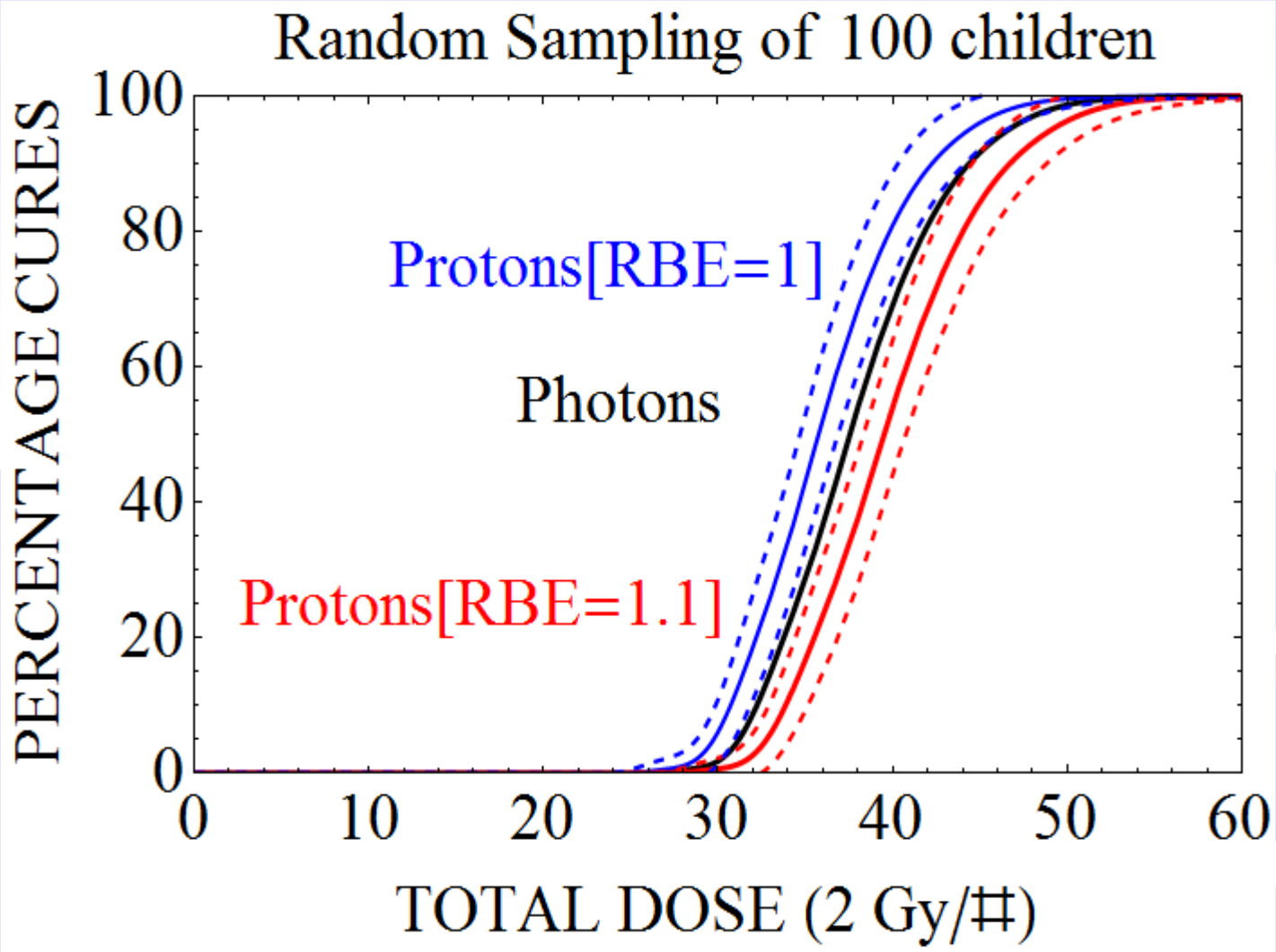
Is this partly due to incorrect RBE in highly radiosensitive childhood tumours ($\alpha/\beta=28$) and /or deliberate under-dosing with x-rays (to avoid side effects) being followed by protons [illogical].

Boston estimate of tumour RBE ~ 1.06, Oxford 1.03-1.06 …….causing underdosage (if RBE of 1.1 used).

RBE in Brain and Spinal tissue ($\alpha/\beta=2$) may be 1.2 or more, not 1.1. So, what is effective dose?

Proposed trial in 'radiosensitive' tumours of childhood where expected RBE<1.1

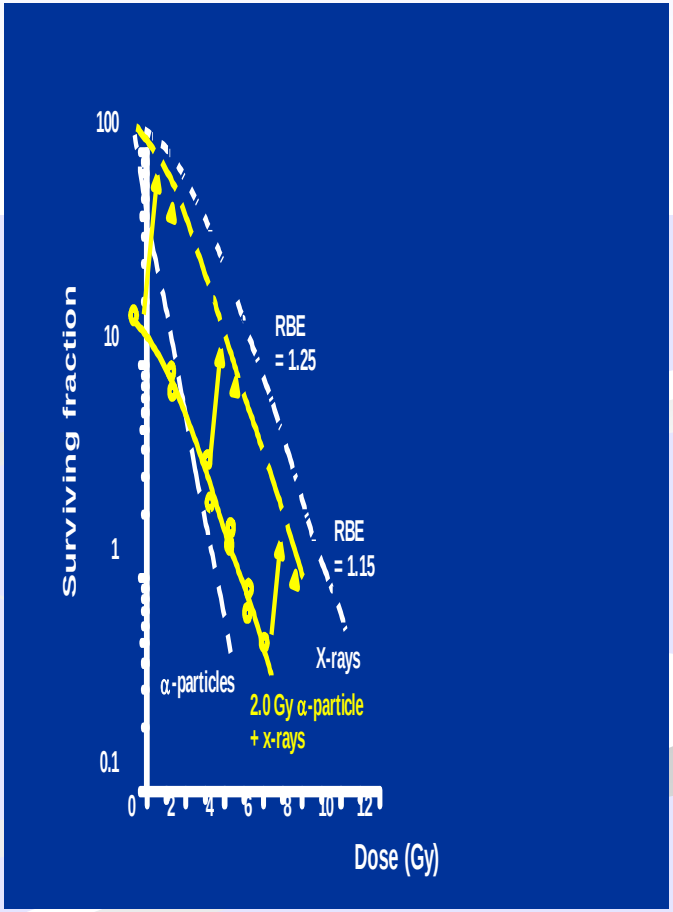




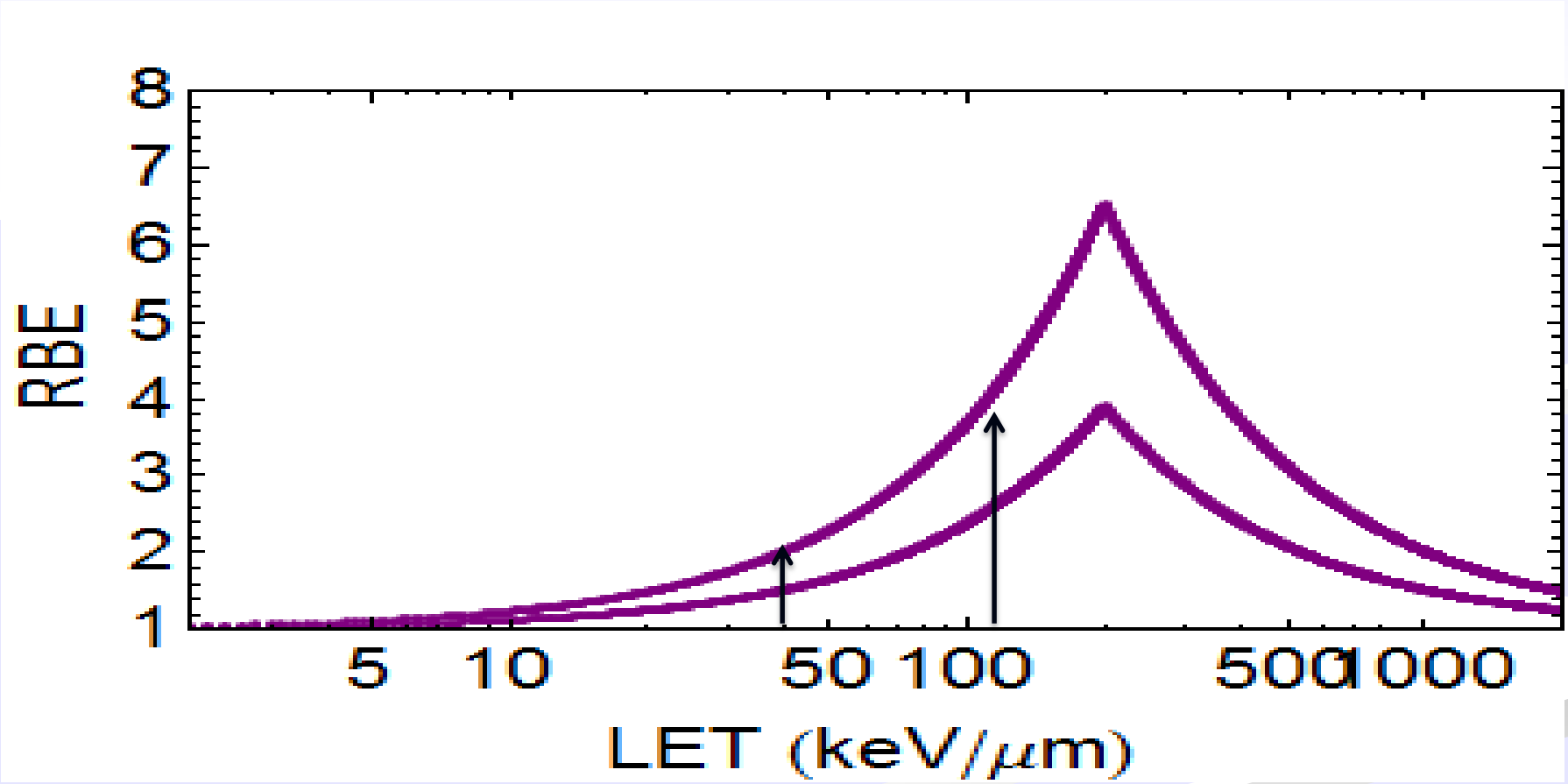
Around 100 in each arm, randomly allocated, sufficient for statistical significance $p<0.05$. [medulloblasotma, PNETs, rhabdomyosarcomas, high grade ependymomas]

data sets on mixed fields

- Cells exposed to X-rays then given a series of neutron or Alpha particle doses regard the X-ray dose as equivalent to the higher LET radiation giving the same surviving fraction.
- If the cells exposed to neutrons or Alpha particles followed by X-rays the resulting survival is higher than would be obtained if first dose had been an iso-effective X-ray dose. It is lower than what would be expected if the two radiations acted independently.
- Results imply an interaction between low and high LET mixed radiation. McNally et al.



It may involve further processes, integrating neutron spectrum on this type of plot; with dose related changes in the plot



Textbook statements

- Leading textbooks such as Hall and Gaccia, maintain that all ions have max efficiency around 100-120 keV.μm^{-1}, and claim this is relevant to DNA dimensions.

This claim ignores the important radial distribution of δ-rays around a particle track, which will be unique for each ion and proportional to Z, the atomic charge.

Are there significant differences in LET_U positions for different ionic Z numbers?

Ion and data source	Cell type	Estimated LET_U ($keV.\mu m^{-1}$) (mean, standard error)
C ions, (Weyrather et al, GSI, Darmstadt, Germany)	CHO	145.81±9.88
	V-79	159.05±3.95
	Combined CHO+V-79 data	152.43±4.29
Helium, (Barendsen, Netherlands)	Human T cells	124.24±0.56

The locations of the combined C ion and Helium data are significantly different ((Mann-Whitney $p=0.028$, t-test $p<0.0001$).

Furusawa et al data (Japan). Estimated turnover point (LET_U) positions

	V-79 cells	HSG cells	T cells
carbon ions	151.6 (n=24)	108.8 (n=21)	No LET_U
neon ions	177.59 (n=18)	127.92 (n=21)	119.24 (n=9)

Problem areas: beam 'quality' parameters

- LET: energy lost per unti length of medium by a charged particle. (as e.g. 1 keV.μm^{-1}, or 1.602 J/m)
- Variants of LET: L_{Δ}, where Δ refers to max limit of energy (e.g. L_{100} would consider only energies below 100 keV.μm^{-1}).
- LET as total energy loss (L_{∞}). This reflects 'stopping power' in the medium, and so includes its density, so with units expressed as MeV.cm^2.g^{-1}, or J m^2 kg^{-1}.

Problem areas: beam 'quality' parameters

- When there are different energies in a beam, a LET spectrum can be used, calculated as either 'track average' or as 'absorbed dose average' (or energy average) LET.
- In microdsmetry, the unsatisfactory aspects of 'average LET', is often overcome by graphical presentations of LET plotted against dose fraction per log LET interval.
- **Lineal Energy (*y*)** takes account of stochastic energy deposition (LET does not); $y=\varepsilon/d_{av}$, where ε is energy imparted in a volume with d_{av} being the mean chord length in the volume.

Problem areas: beam 'quality' parameters

- To account for δ-rays ejected from tracks, which are radially distributed and responsible for most bio-effects and ionisations collected by detectors, Katz(1970) proposed use of:

  $Z^{*2}.\beta^{-2}$,

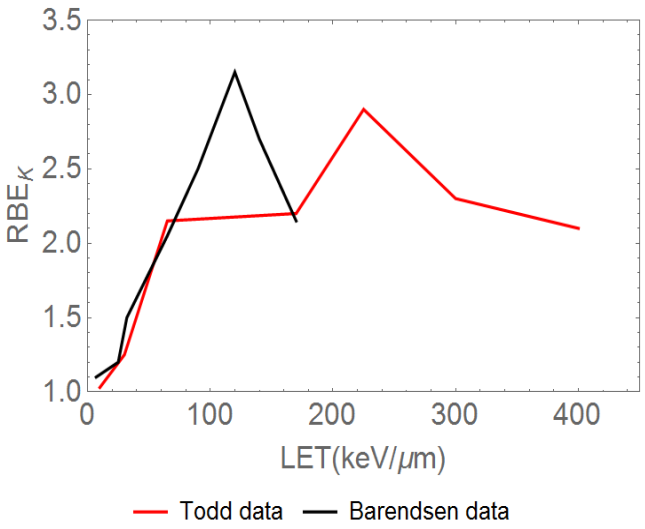
[Z^*= effective nuclear charge of atomic nucleus of atomic charge Z]

[β is the relativistic velocity (v/c)]

As fully stripped ions slow down they pick up electrons so Z^* becomes less than Z.

Comparison of two 'quality' and two RBE parameters, alpha (Todd), alpha and deuterons (Barendsen)

Out[30]=



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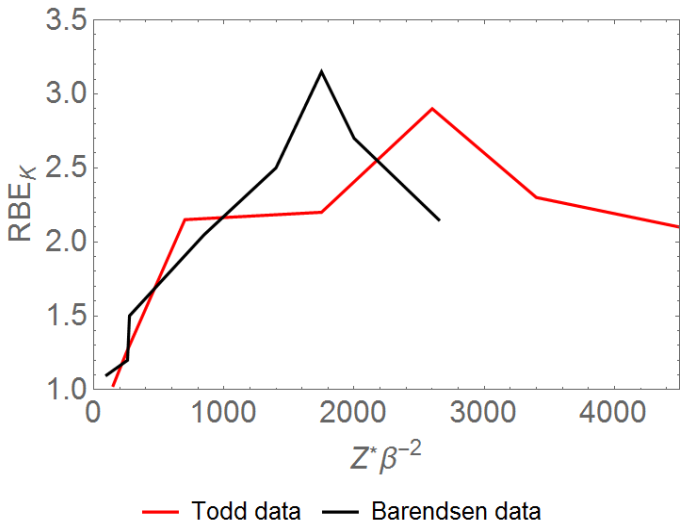

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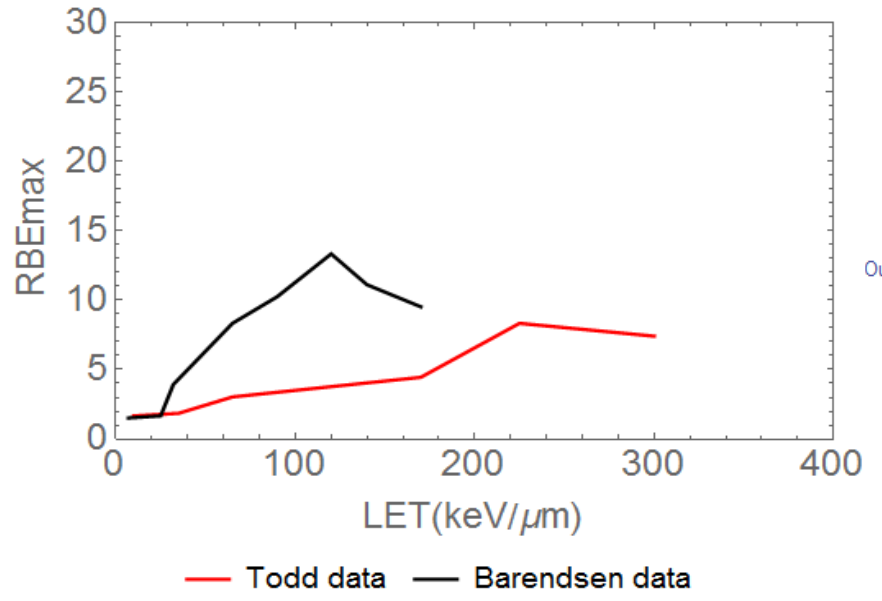

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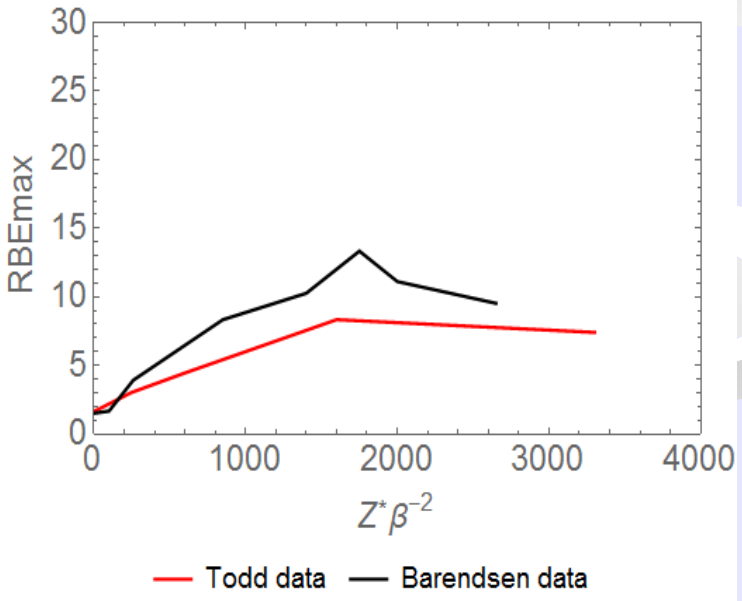
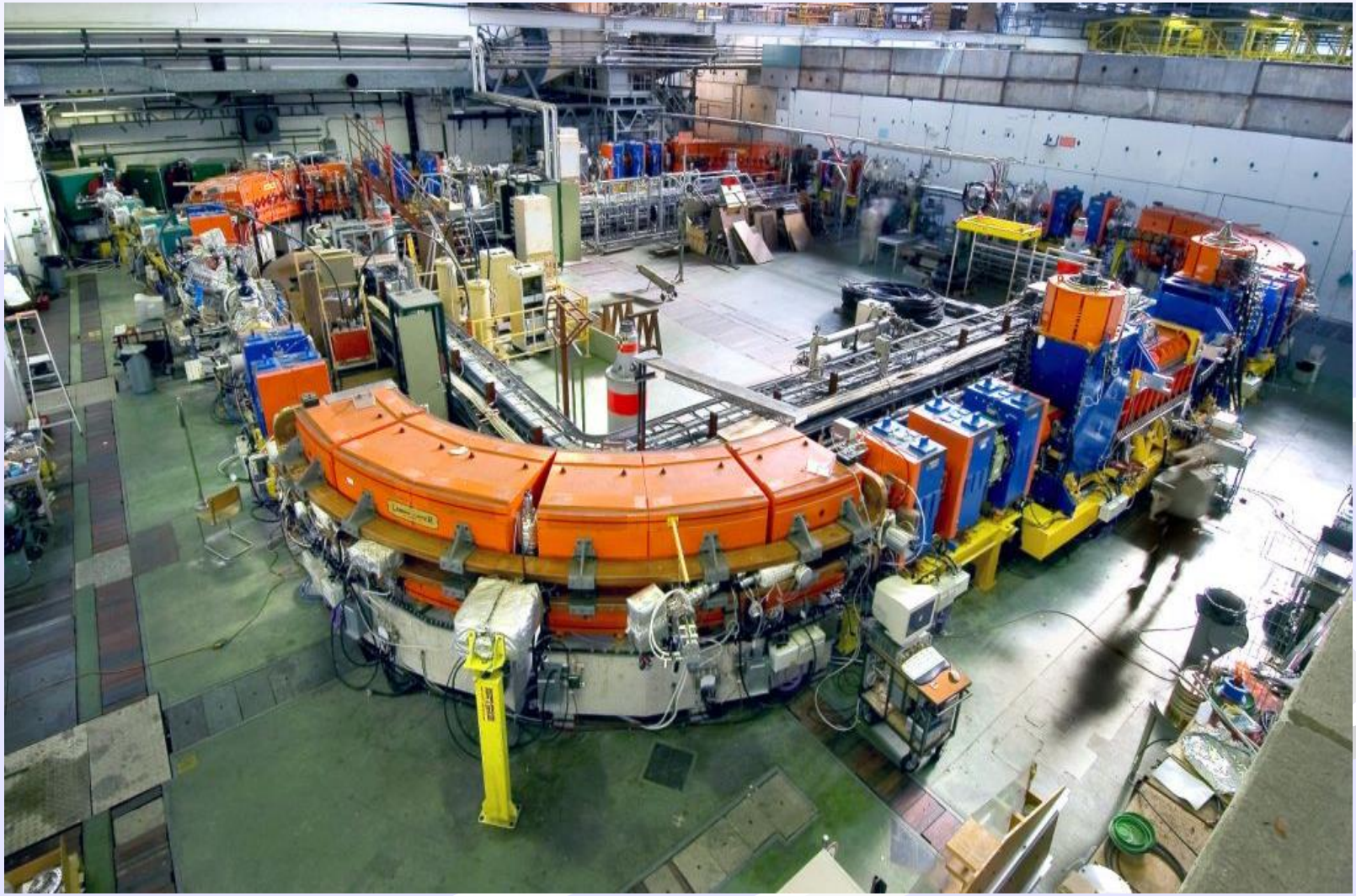


Two possibly unexpected outcomes were found as charge changed

- Goodhead et al. Int J Radiation Biology, 61, 611-624, 1992
- Folkard et al 69, Int J Radiation Biology, 729-738, 1996

For LET above ~ 30 keV.μm^{-1}, singly charged particles are more effective at inactivating cells than doubly-charged particles of the same LET…. this difference can be understood in terms of the radial dose distributions around the primary ion track.

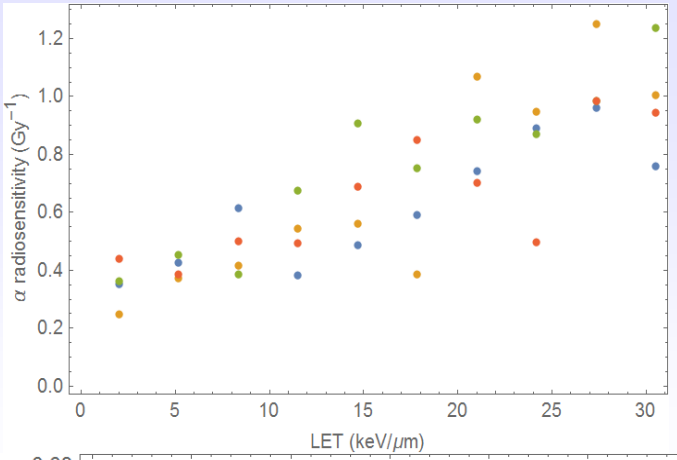
Proposed Biomedical Research Facility using existing LEIR Synchroton

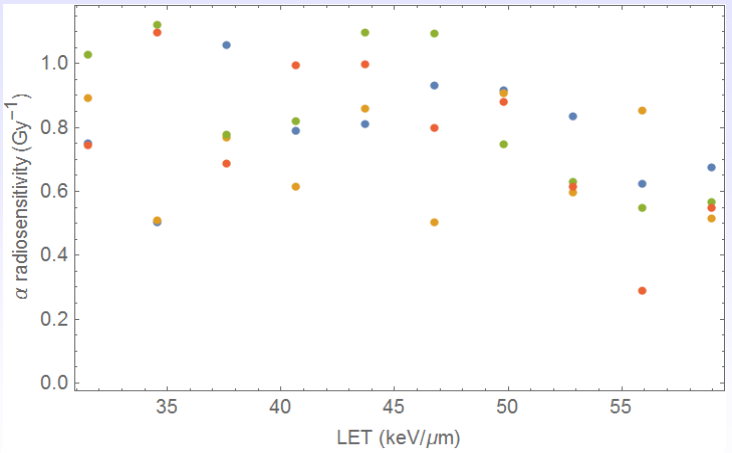


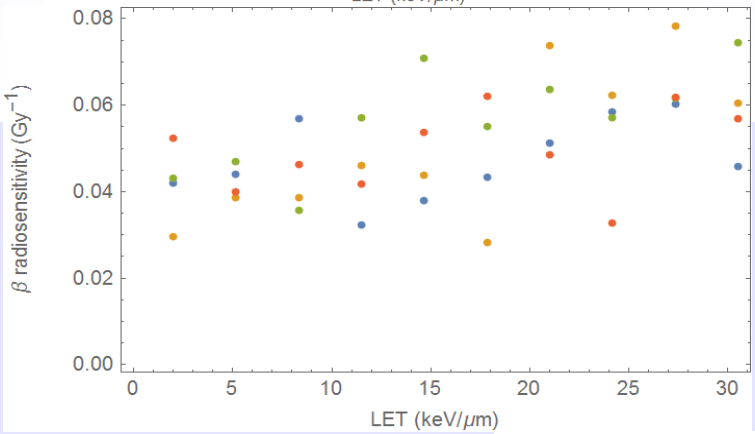
Example of a single *Mathematica* (Wolfram, USA) simulation of experiments to determine LET_U for protons, using variations in cellular radiosensitivities in cell survival assays.

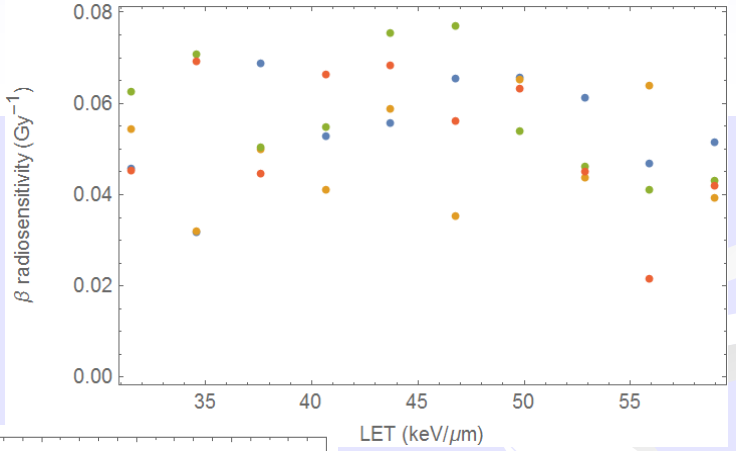
Here 20 RBE data points are used. The expected LET_U is assumed to be 30.5 keV.μm^{-1}.

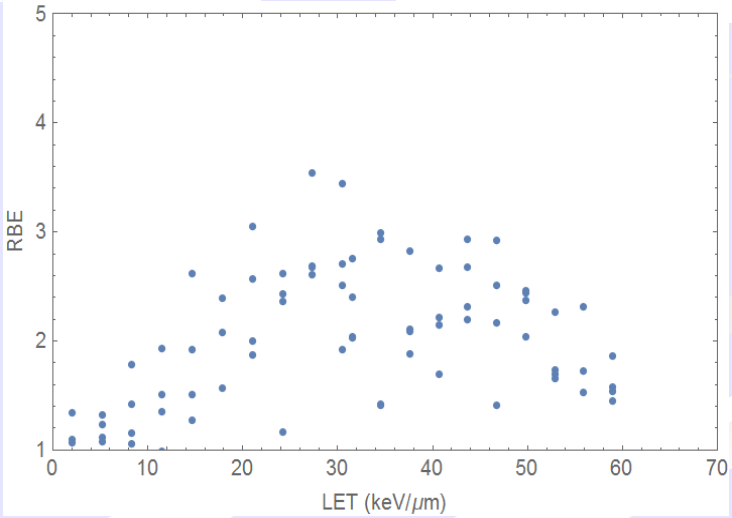
The LET_U value is obtained by obtaining the intersection point of the two upward and downward data linear regression fits.

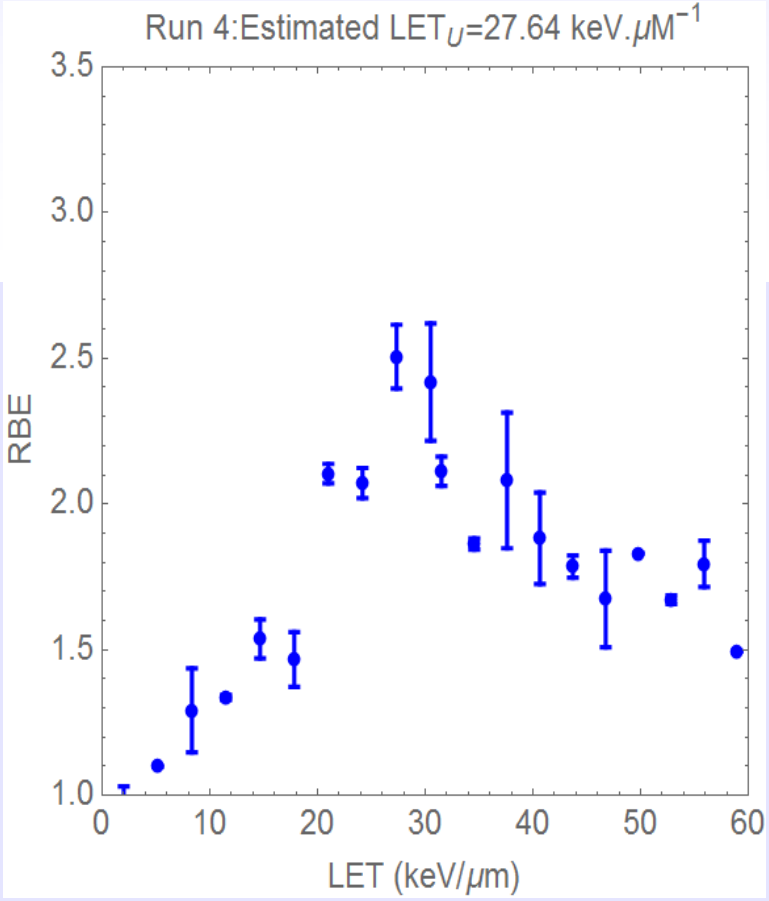

α radiosensitivity (Gy^{-1})
LET (keV/μm)


α radiosensitivity (Gy^{-1})
LET (keV/μm)


β radiosensitivity (Gy^{-1})
LET (keV/μm)


β radiosensitivity (Gy^{-1})
LET (keV/μm)


RBE
LET (keV/μm)



Four repeated simulations, using seeded random sampling, provides LET_U values of 29.6; 32.06; 33.73 and 27.64, [Mean =30.75±1.34 (SEM)] when there are 20 LET-RBE data points (N=20). This is a good result for medical purposes, but if N=16 the estimate falls to 29.96±1.24, and if N=12 the estimate is 31.5±1.92.

From geometrical considerations, an experimental LET_U result of 28.8 or 31.8 keV.μm^{-1} instead of the assumed correct 30.5 would lead to a 5% error in RBE estimation. Then, using the BED equation

$$BED = nd_H\left(RBE_{max} + \frac{RBE_{min}.d_H}{\left(\alpha/\beta\right)_L}\right)$$

If LET_U=25 (BED error is 6.16%) and 26 (BED error=4.79%) for a neurological effect. [Generally severe late complications rise by 1-2% per unit BED].

Also, compared with standard use of RBE=1.1, then if LET ~ 9 keV.μm^{-1}, the calculated and normally given dose (normalised to 100%) are: 80.21% for use of the correct LET_U, and 76.92% for an incorrect LET_U of 27 keV.μm^{-1}.