Workshop on Current Challenges of Patient Re-irradiation

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Re-irradiation is now a real option – but how do we take it forward?

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Introduction

- **Re-treatment results can sometimes be as good as first line chemotherapy!**
- Brachytherapy and Particle therapy may be particularly suited for re-treatments ……..due to reduced irradiated volume, either as first or second treatment.
- Retreatment may refer not only to tumour recurrences but to tumours arising in a previously irradiated anatomical site, e.g. pelvis, thorax, head and neck.

Retreatment of CNS tumours is clinically useful in selected patients, although infrequently done in some hospitals [Amichetti et al 2011]

- Younger patients most often retreated, usually small low grade glioma recurrences 3-8 years after first radiotherapy
- Treatment can be considered palliative
- Duration of second remission can exceed that of first remission
- 5 year survivors reported in many series
- Cytoxic chemotherapy often given after first relapse or as part of management.

Importance of Patient Selection

- Risks of re-treatment should be lower than those of any other treatment policy.
- other treatment contraindicated
- Patient unsuitability for standard approaches
- Reasonable expectation of survival greater than 1 year.
- No significant clinical or radiological signs of late effects following first treatment course
- Formal consent procedures

Evidence for time dependent "Recovery"

- Many experiments in small animals…rats, mice, with short retreatment time interval possibilities
- Only one data set in primates (K. Ang et al 2001)
- Human evidence from radiotherapy

Estimations of re-treatment dose fractionation schedules - references

Changes in the retreatment radiation tolerance of the spinal cord with time after the initial treatment.
Int J Radiation Biology 2018 , Jun;94(6):515-531. TE Woolley, J Belmonte-Beitia, GF Calvo, JW Hopewell, EA Gaffney and B Jones.

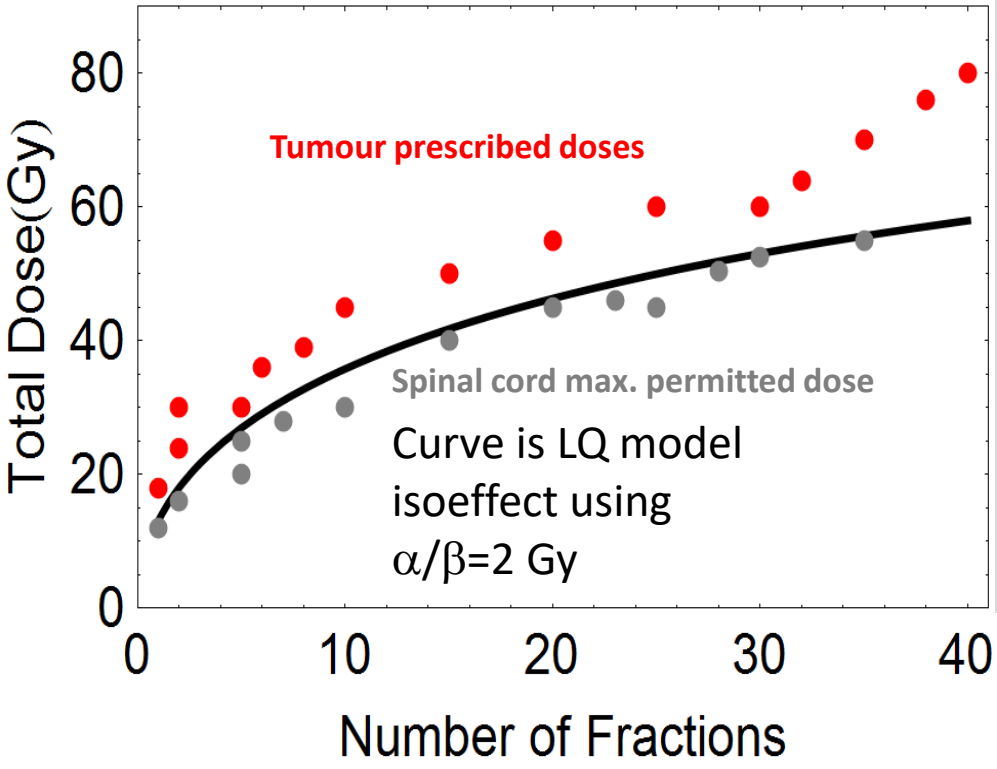
Based on two earlier articles:

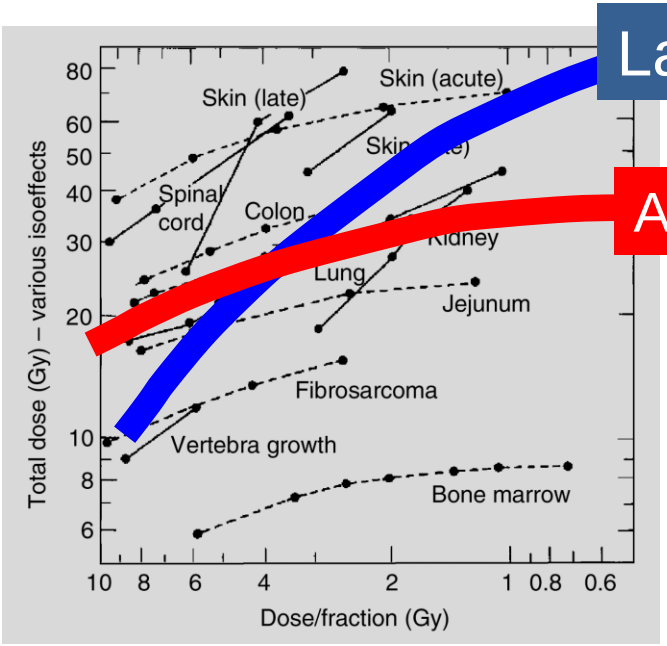
Jones B & Grant W. Retreatment of Central Nervous System tumours. Clinical Oncology, 26, 407-418, 2014.

Jones B & Hopewell JH. Alternative models for estimating the radiotherapy retreatment dose for the spinal cord. Int J Radiat Biol. 2014 Sep;90(9):731-41.

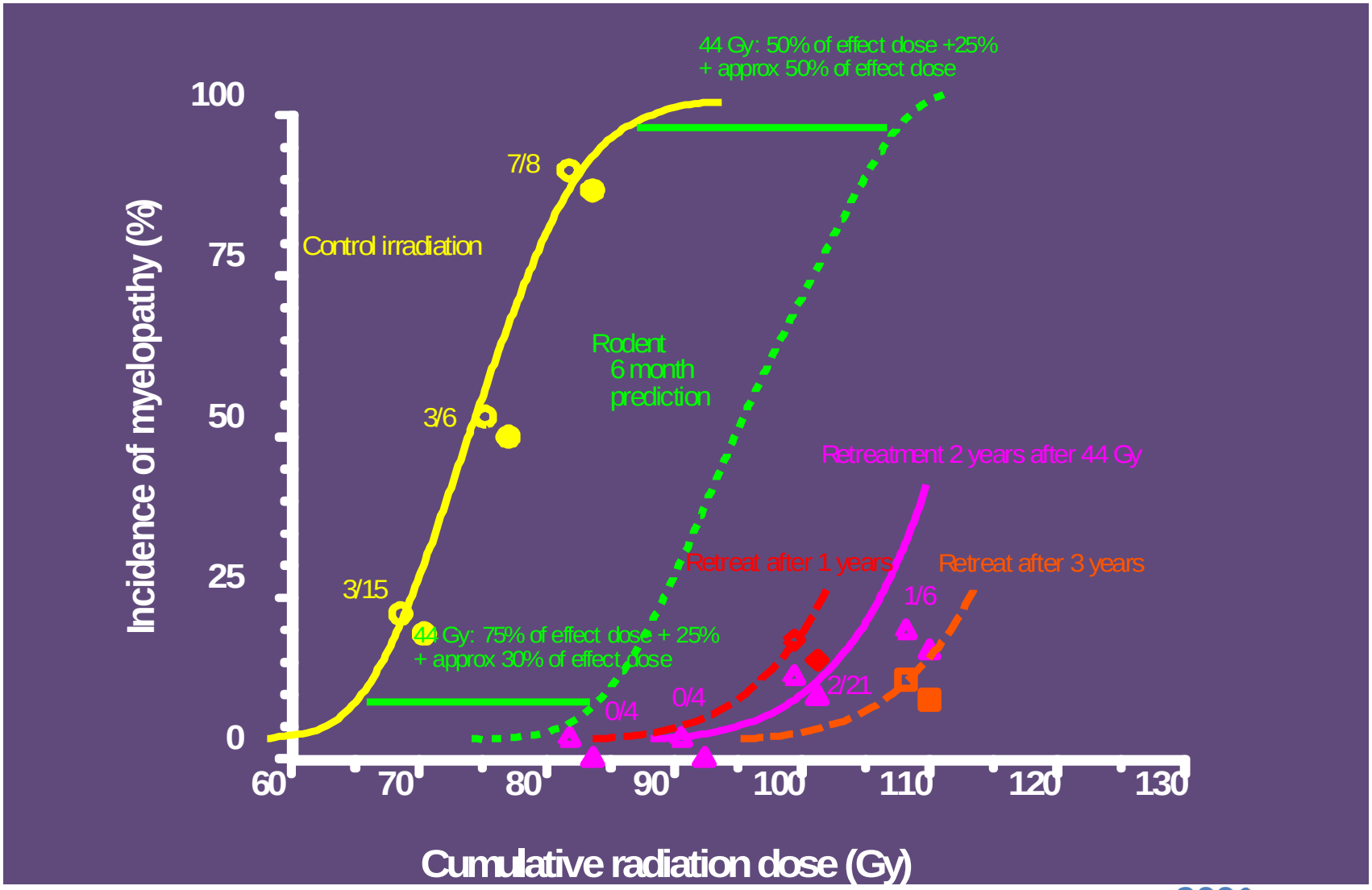
Many **clinical reviews** of re-treatment usefulness e.g. Clinical Oncology (R Coll Radiol), special edition 2018, e.g.
Re-irradiation in the **Brain**: Primary Gliomas. Ho ALK, Jena R. Clin Oncol 2018 Feb;30(2):124-136

Late reacting tissues (e.g. CNS with α/β=2 Gy) show greatest change in photon dose with dose per fraction, which will influence RBE numerator dose, so they have largest RBE`s. LQ model well isoeffect curve predicts





Dose-related incidence of radiation myelopathy in the Rhesus monkey: single and a repeated course irradiation of Ang et al 2001, compiled by John Hopewell.



2001

Percentage BED-Tolerance

- First Treatment

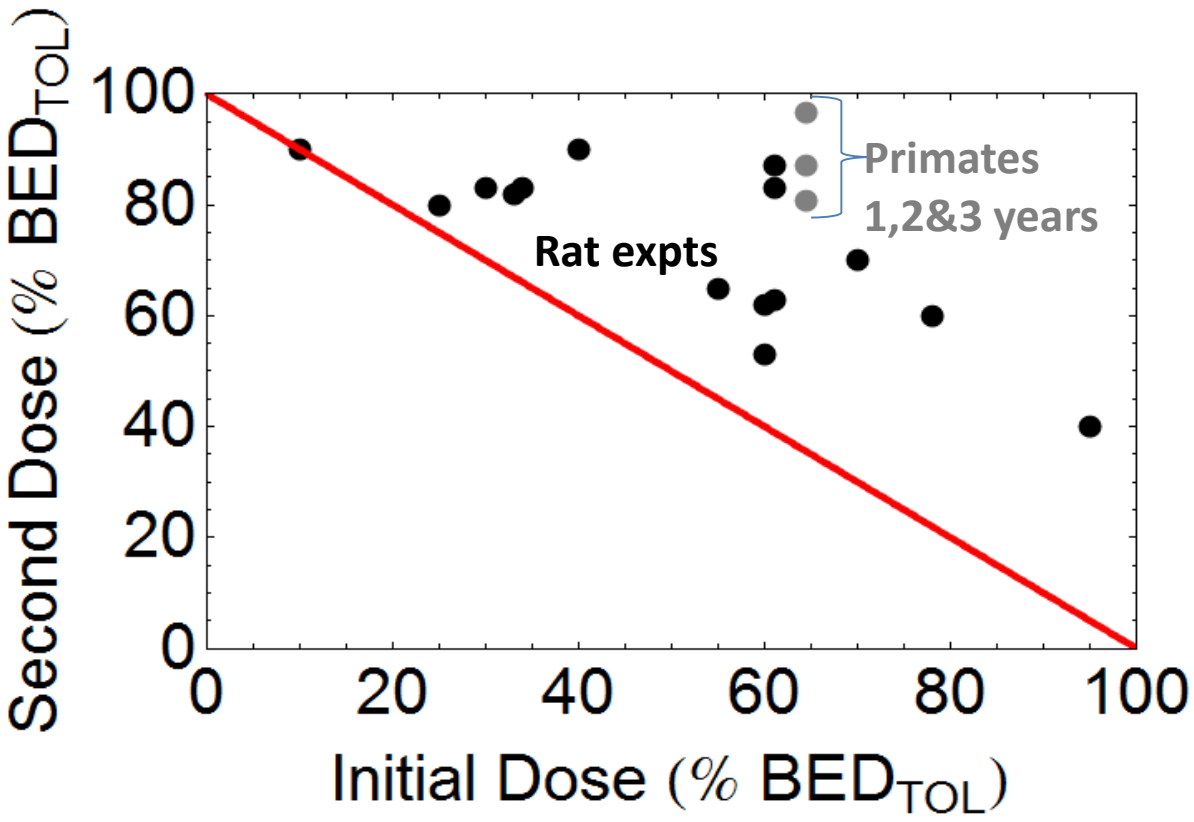
$$BED_1 = \frac{BED_{init}}{BED_{risk\%}} \times 100\% \,,$$

- Second Treatment

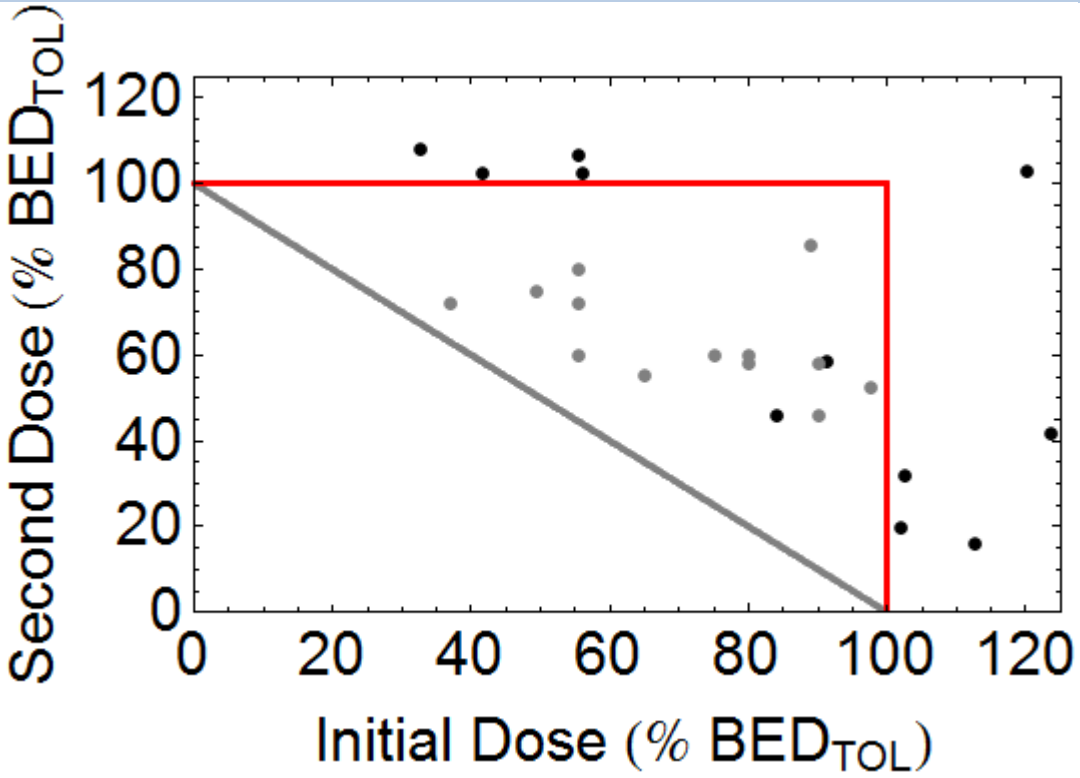
$$BED_2 = \frac{BED_{retreat}}{BED_{risk\%}} \times 100\% \,,$$

The risk is set at 1% (default), but may be changed according to clinical situation

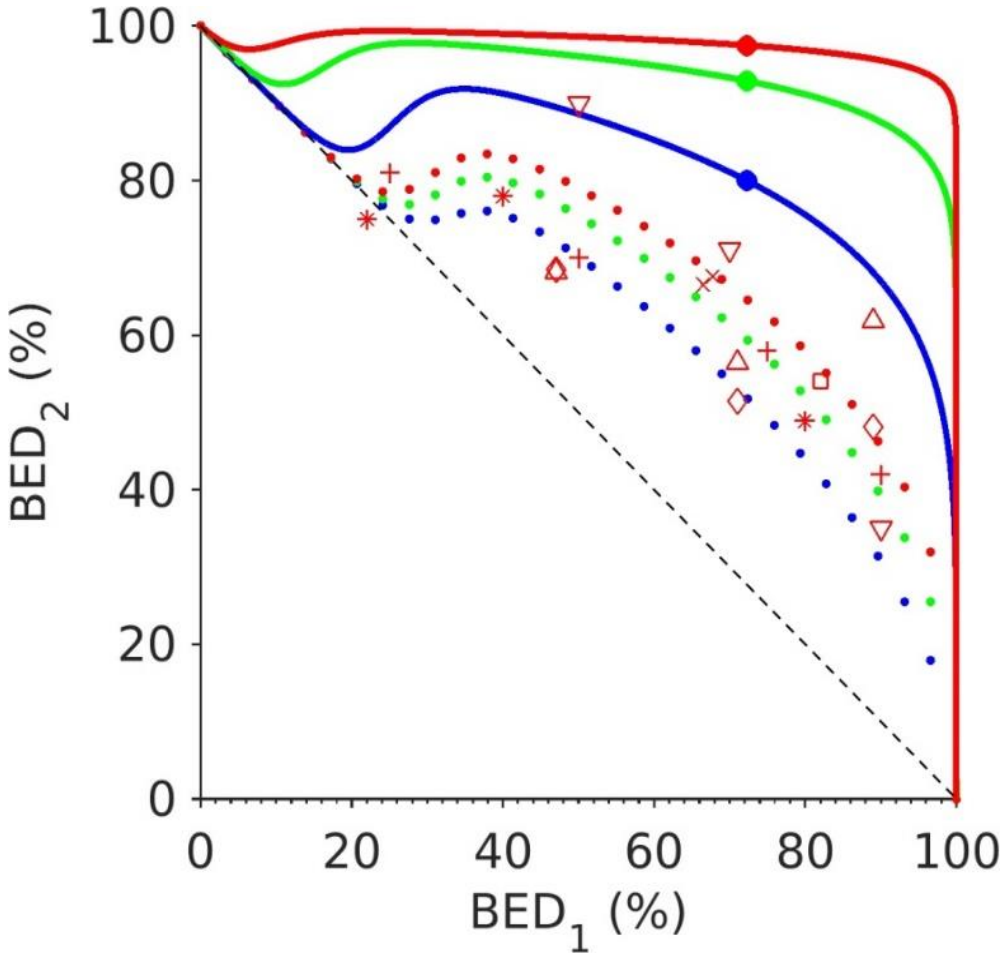
Biological Effective Dose (BED/BEDtol)% plots. Existing *in vivo* data above critical no recovery line



Clinical data sets (black points: Wong et al - myelitis; grey points Nieder et al – No myelitis, All data in agreement with model 1)



Re-treatment iso-effect curves grow ***upwards*** from the black hatched line of no recovery, with increasing time



3 year monkey
2 year monkey

1 year monkey

6 month rodent
5 month rodent
4 month rodent

Some special features

- Model incorporates all known data for white matter necrosis of spinal cord tissue in animals and also uses human myelitis dose-response curve data.
- Recovery rate depends on initial exposure and is rapid only after an initial priming BED1% of 35%.
- Flexibility for changing risk level due to adverse clinical factors

Original equation

- $BED_2 = 100\left(1 - \frac{BED_1}{100}\right)^{\frac{1}{r(t)+1}}$,

To extend for allowance of Lag time of 70 days and delayed recovery for 'lower BED' initial courses

New equation

- $BED_2 = 100\left(1 - \frac{BED_1}{100}\right)\left[1 + \left(\left(1 - \frac{BED_1}{100}\right)^{\frac{-r(t)}{r(t)+1}} - 1\right) f(BED_1, r(t))\right]$

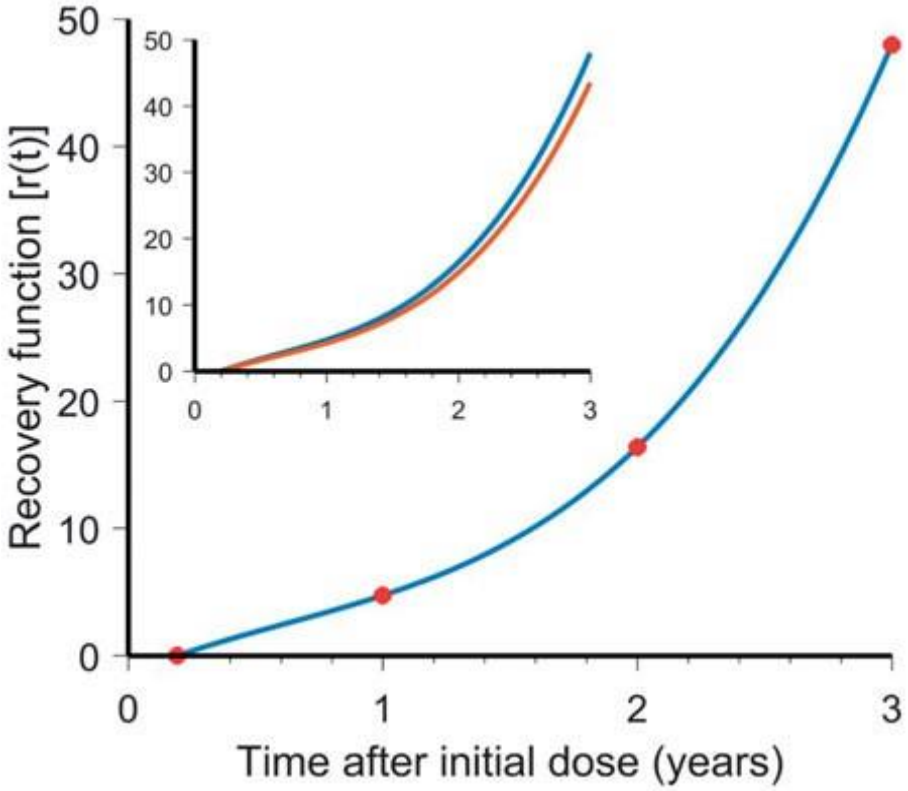
Where

$$f\left(BED_1, r(t)\right) = \frac{1}{2}\left[1 + \tanh\left[s_0\left(BED_1 - \frac{\overline{BED}}{1 + s_1 \cdot r(t)}\right)\right]\right]$$

Then, use Newton-Raphson procedure to determine r(t)

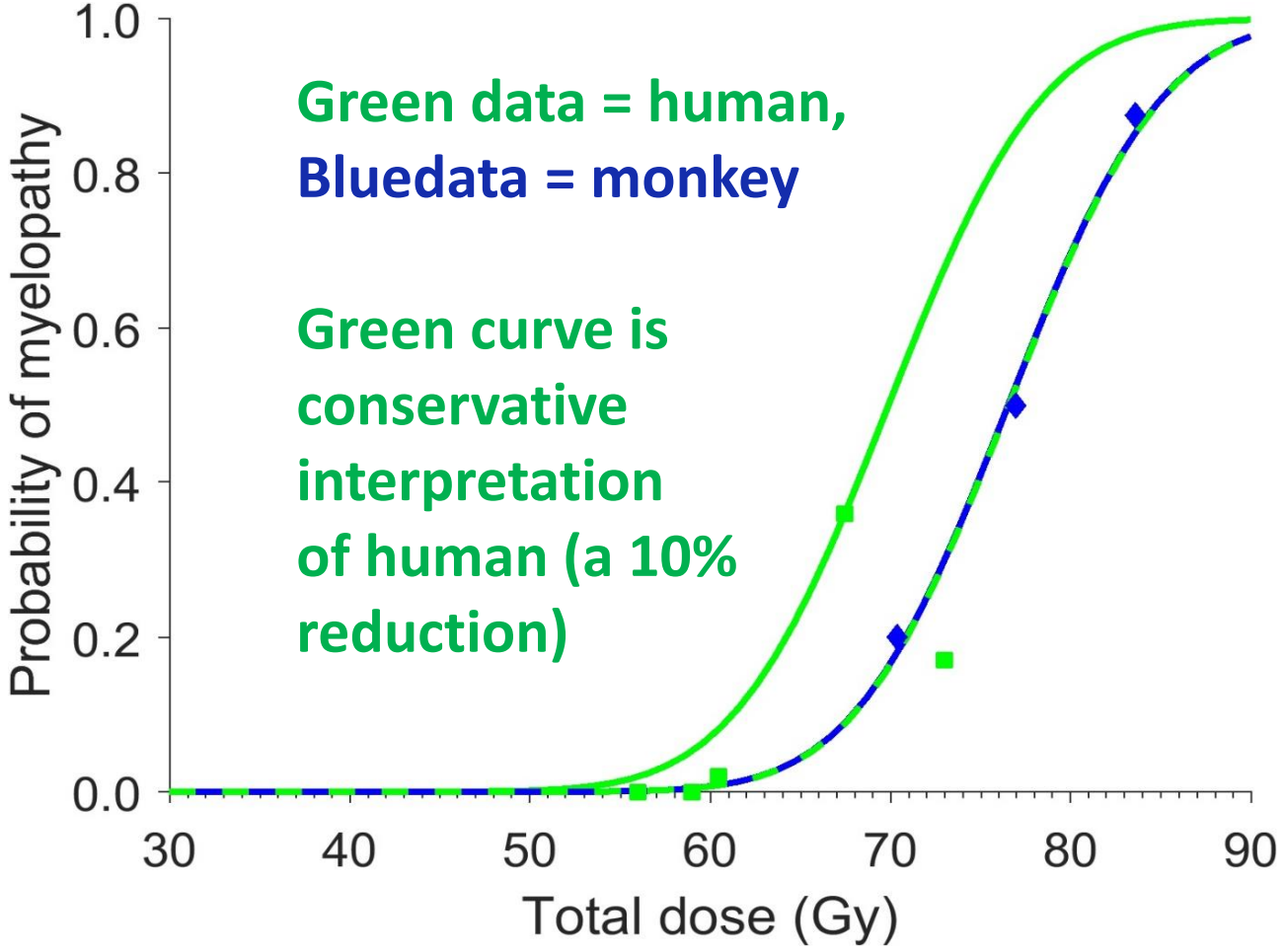
$$r(t) = \begin{cases} 0, & t \in [0, t_{IRO}] \\ a + bt + ct^2 + dt^3, & t \in [t_{IRO}, 3] \end{cases}$$

Fit of Recovery ‘time function’ r(t) to data of Ang etal.

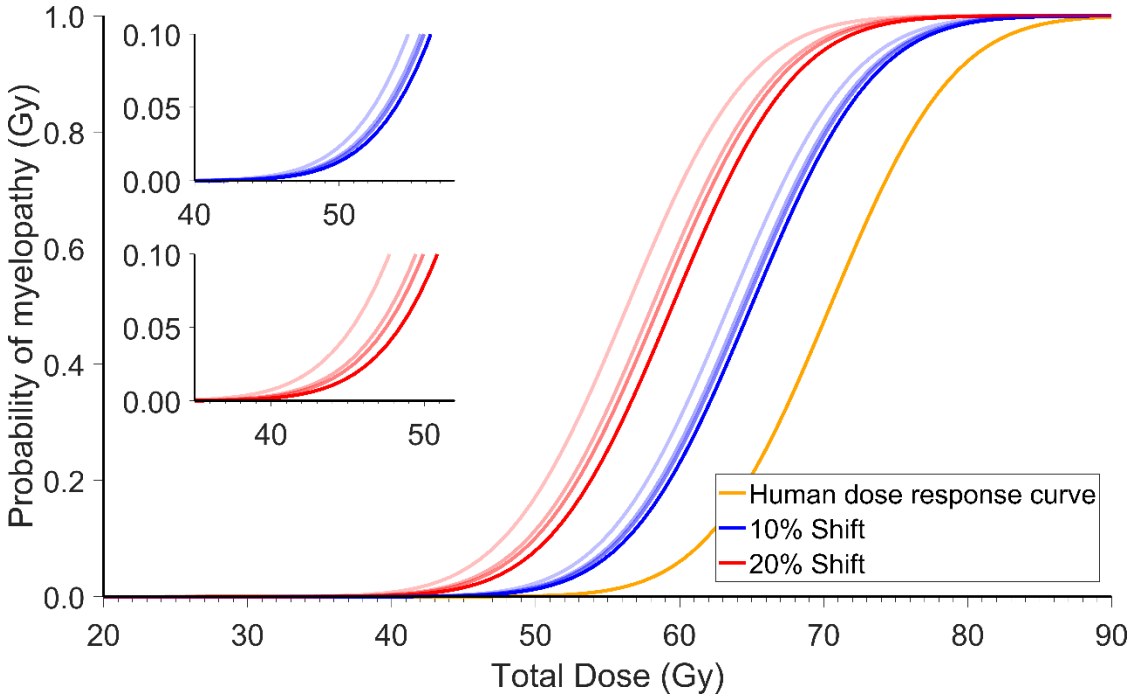


Main graph: fit for myelitis incidence of 1%.
Inset graph:
shows little change in r(t) between myelitis incidence of 1% and 0.01%.

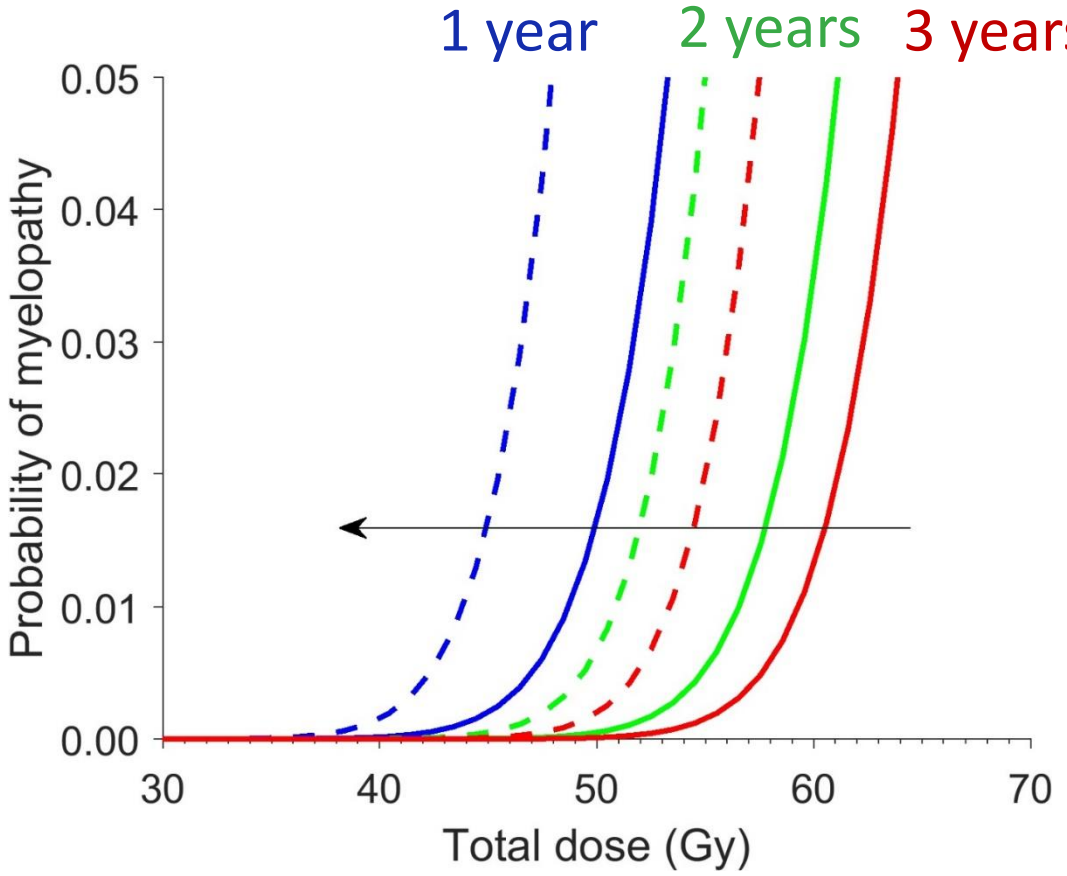
Human and rhesus monkey data from Ang and Hopewell



Introducing greater degrees of ‘conservatism’, for patients where tolerance is reduced (surgery chemotherapy, extremes of age, vasculopathies).



The more conservative approach: -10% shifts for dashed lines



The GUI

- Input parameter……BED_1% is the

(Given BED/Tolerance BED)%, also the risk level (or BED tolerance) and elapsed time.

- Output parameter is BED_2%, which is

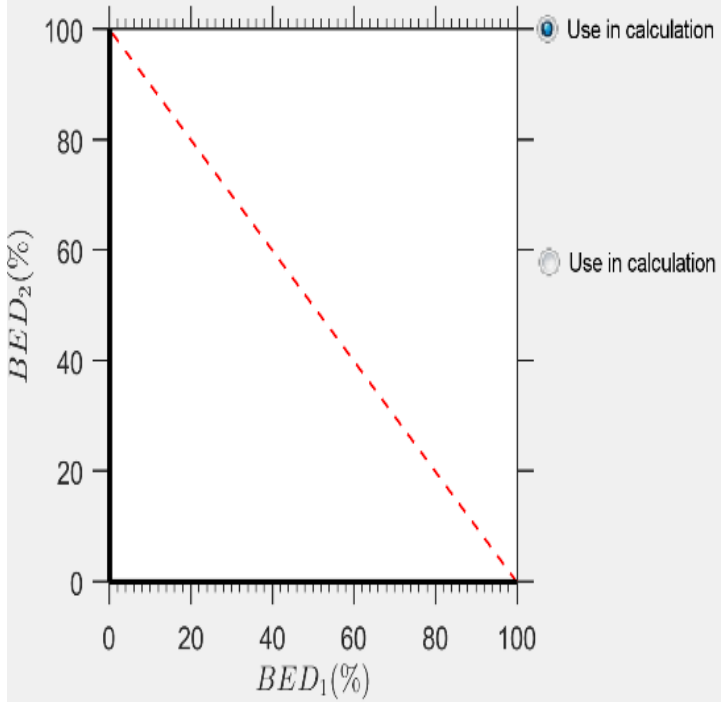
(allowable BED/Tolerance BED)%, and dose per fraction in a user set number of fractions.

Graphical User Interface (GUI) can be downloaded to facilitate estimates of **allowable** dose per fraction and number of fractions for the re-treatment. This should be regarded as a boundary value.

Allows changes in tolerance due to medical factors using

The percentage conservative factor: 0 to 20% shifts in dose response curves to the left.

Show rodent data



BED_{init} (Gy) = BED_1 (%) of $BED_{R\%}$ (Gy)

BED_{ret} (Gy) = BED_2 (%) of $BED_{R\%}$ (Gy)

= Retreatment dose per fraction (Gy), D_{ret}/n_r

1 Risk of myelopathy, R (%) (positive value, less than 100)

Nominal tolerated $BED_{R\%}$ (Gy) (positive number)

40 Initial total dose, D_{init} (Gy)

20 Number of fractions, n (positive integer)

Initial dose per fraction (Gy), $d = D_{init}/n$

20 Number of retreatment fractions, n_r (positive integer)

2 Tissue sensitivity, α/β (Gy) (fixed)

0.15 s_0

0.1 s_1

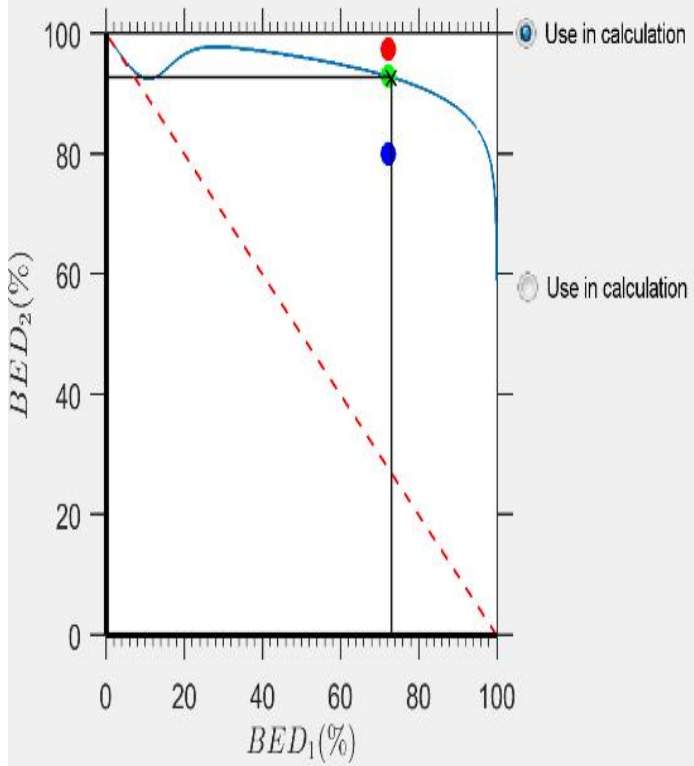
35 $\overline{BED}$

2 Number of years before next dose, t

0 Percentage conservative factor, C

Calculate

Show rodent data



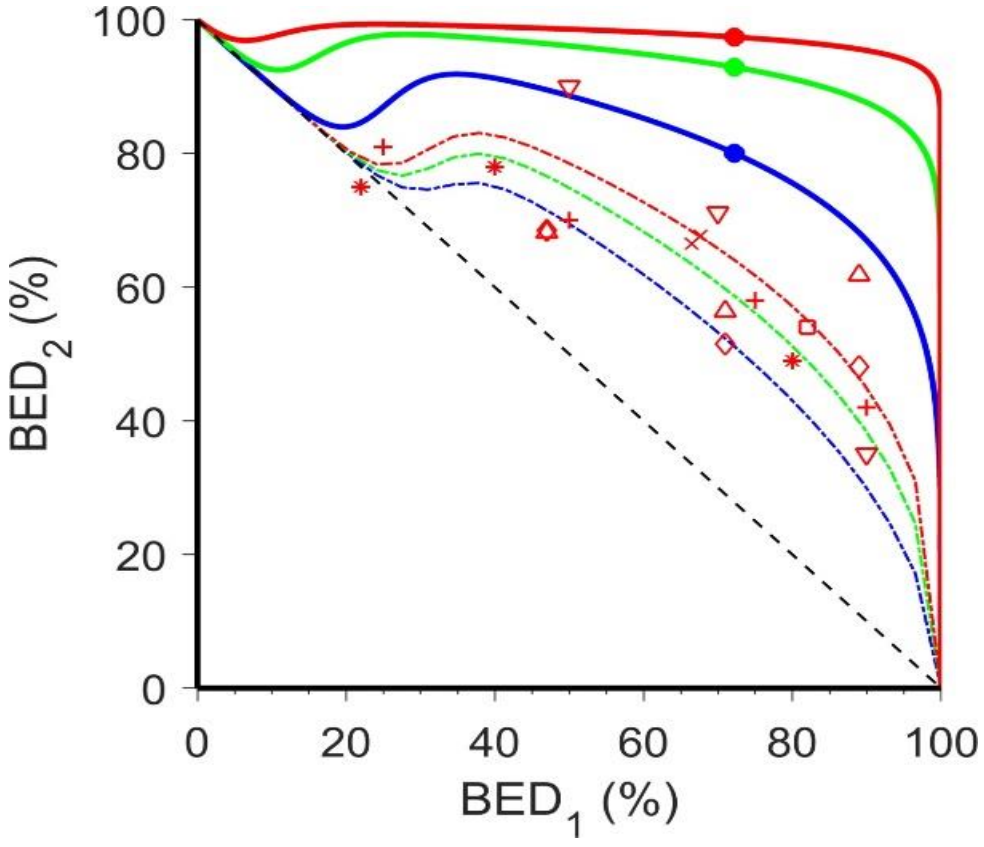
BED_{init} (Gy)	=	BED_1 (%)	of	$BED_{R\%}$ (Gy)
80		72.99		109.6

BED_{ret} (Gy)	=	BED_2 (%)	of	$BED_{R\%}$ (Gy)
101.66		92.75		109.6

2.34 = Retreatment dose per fraction (Gy), D_{rel}/n_r

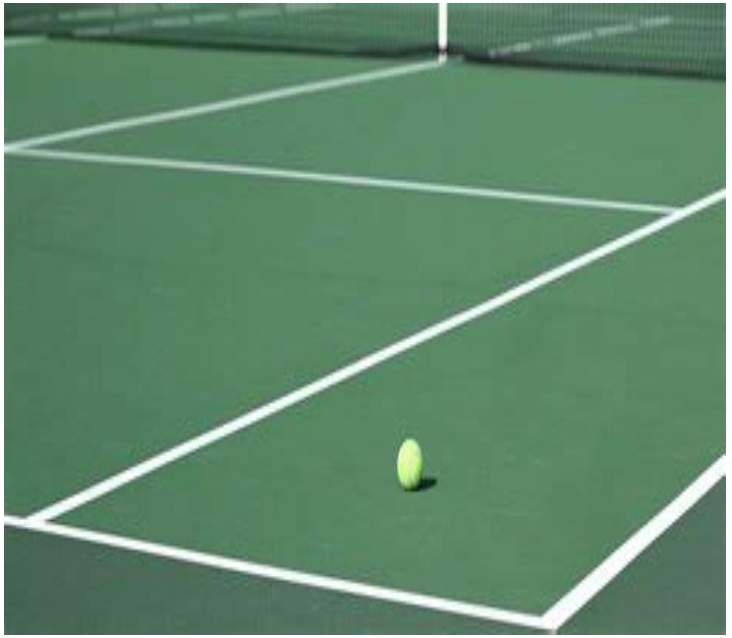
1	Risk of myelopathy, R (%) (positive value, less than 100)	0.15 s_0
109.6	Nominal tolerated $BED_{R\%}$ (Gy) (positive number)	0.1 s_1
40	Initial total dose, D_{init} (Gy)	35 $\overline{BED}$
20	Number of fractions, n (positive integer)	2 Number of years before next dose, t
2	Initial dose per fraction (Gy), $d = D_{init}/n$	0 Percentage conservative factor, C
20	Number of retreatment fractions, n_r (positive integer)	Calculate
2	Tissue sensitivity, α/β (Gy) (fixed)	

For a myelitis risk of 0.1% (1 in 1000)



Each curve shows BED_2(%) increasing with time between treatments for 4, 5 and 6 months followed by 1, 2 and 3 years

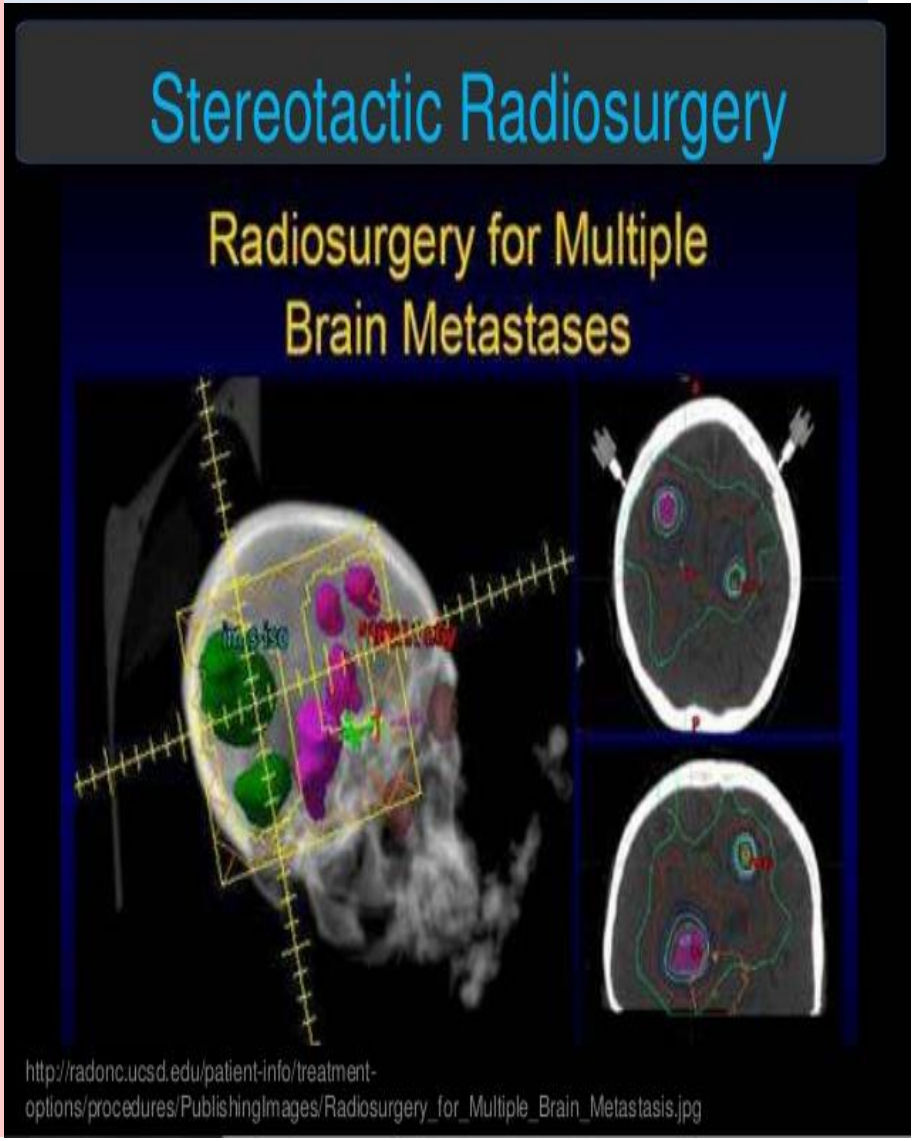
Tennis court boundary limits….the model gives an estimate of the boundary for the given risk estimate.



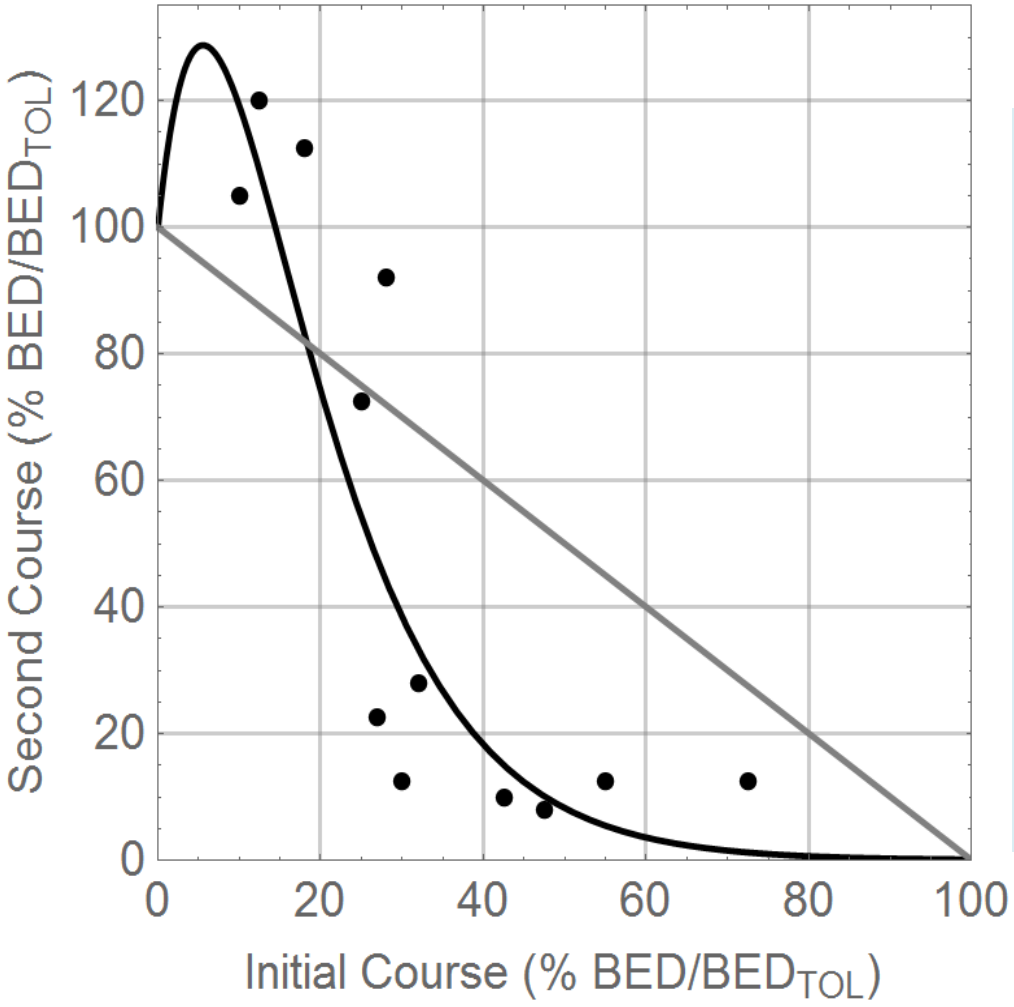
Important Caveats

Re-treatment situations that occur within 1-6 months: if the ‘first course’ BED is low.

- Example would be treatment of 3 metastases using GammaKnife or Linac; 2 months later a new metastasis arises in a region which has received a BED of 10 Gy $_{[2]}$. This dose should not be ignored in any further treatments.
- Or, long delays to complete an interrupted treatment course after only a few initial fractions given



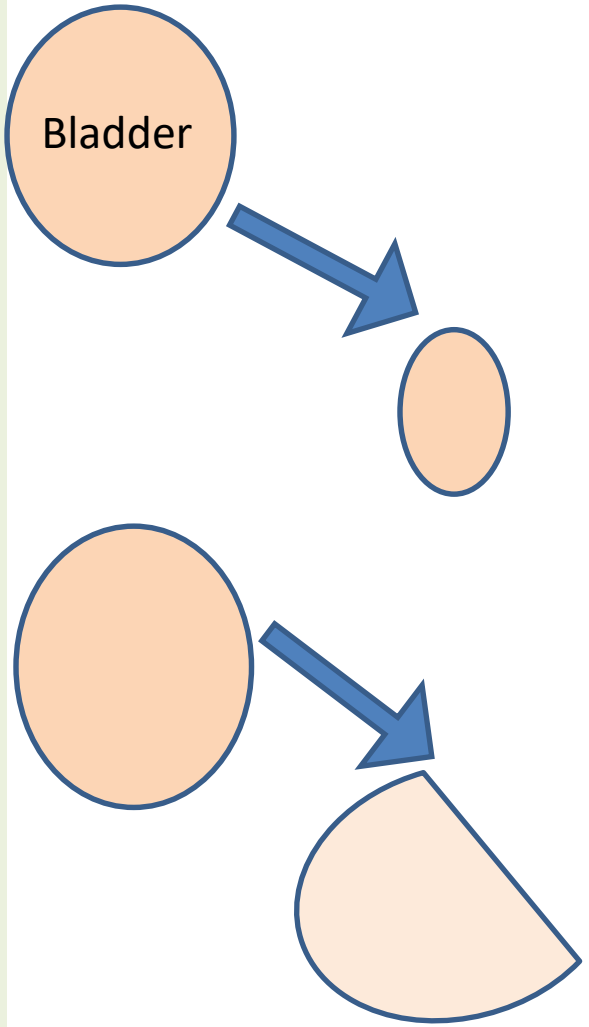
Different tissues – Whole Kidney



Data points of Fiona Stewart plotted as % BED/BED$_{TOL}$ of the first and second treatment courses, with null effect line in grey and the least-squares fitted curve in black.

Further caveats

- Large field irradiations to whole organs not relevant to sub-volume irradiation…e.g. urinary frequency inevitably worse with centripetal fibrotic shrinkage of bladder
- Small animal irradiators……may give useful data but they use low keV x-rays which inevitable have a higher LET and RBE….they will suggest a higher α/β.



Relative Biological Effect – the ratio of ISOEFFECTIVE doses:

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

The conventional radiation – if α/β is small (for late tissue effects) this dose will change considerably with dose per fraction

The particle radiation – less sensitive to dose per fraction with increasing LET

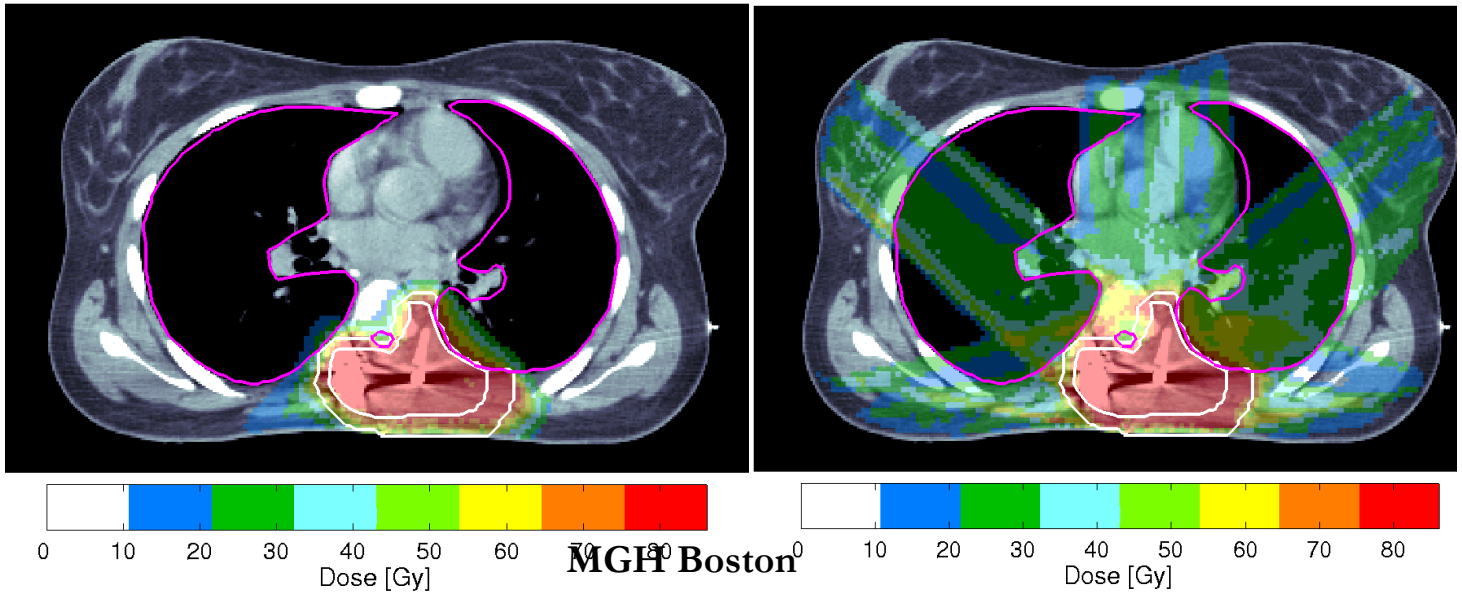
$$\text{Particle Dose to Patient} = \frac{Dose_{[Low\ LET]}}{RBE}$$

Paravertebral Epithelioid Sarcoma

Reduction in breast, lung cancer induction risk, cardiac sudden death and breathlessness on exertion; but if RBE incorrect and/or Bragg peaks misplaced there could be paralysis (spinal cord) and reduced tumour control

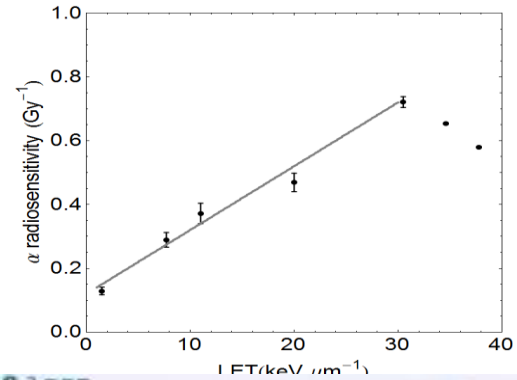
IMProtons

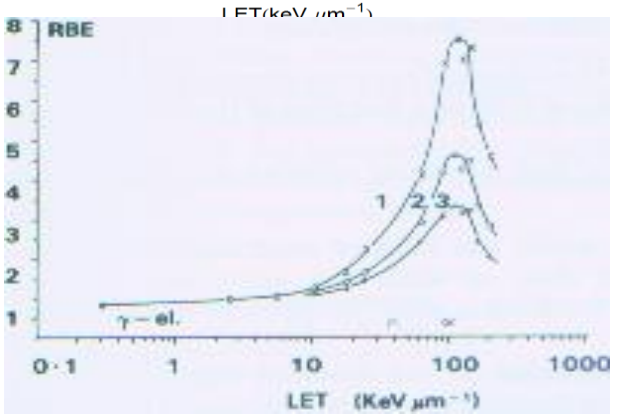
IM X-rays

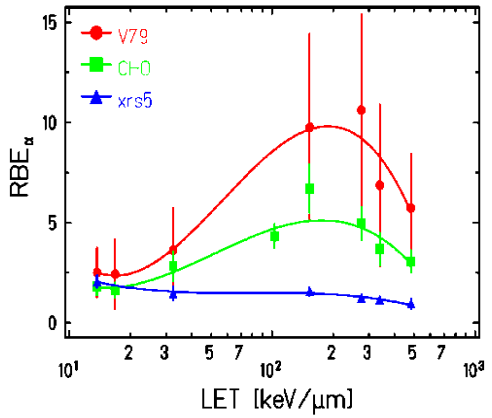


RBE model

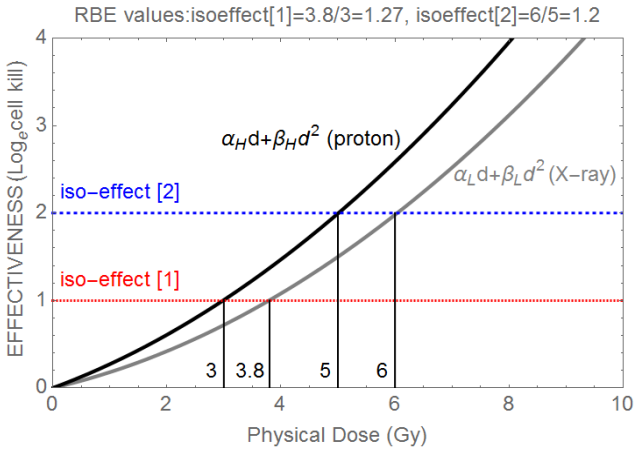
- Uses particle specific maximum LET efficiency point (LET_U).
- Scaling of increasing α_H and β_H with LET
- Incorporates saturation relationships between reference (control – low LET) radiation α and β and the maximum values at LET_U.
- These α_H and β_H values are used in LQ model and with BED concept.
- Results compatible with known phenomena regarding RBE in different bio-systems

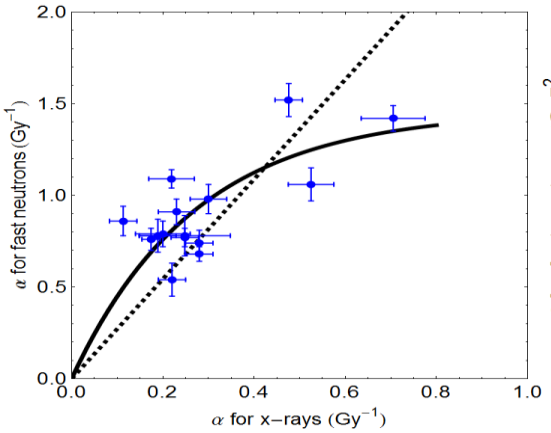


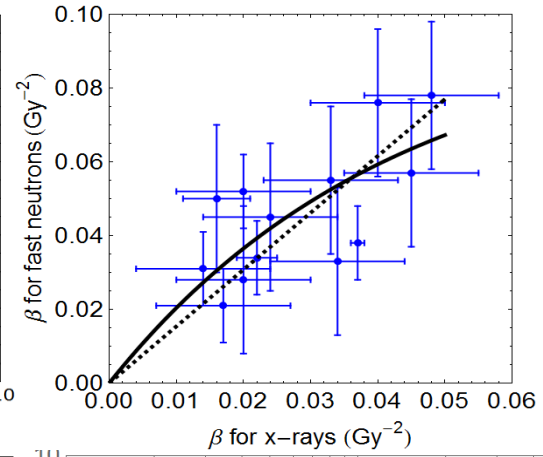


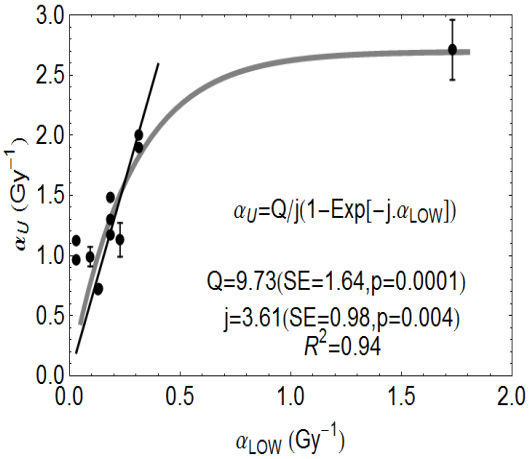


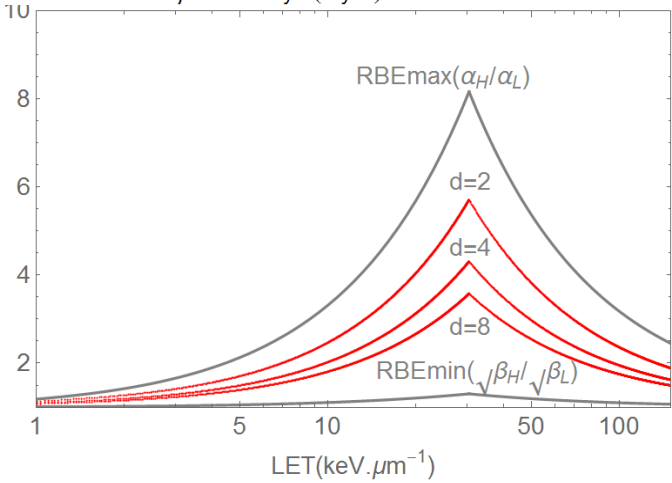
RBE Model





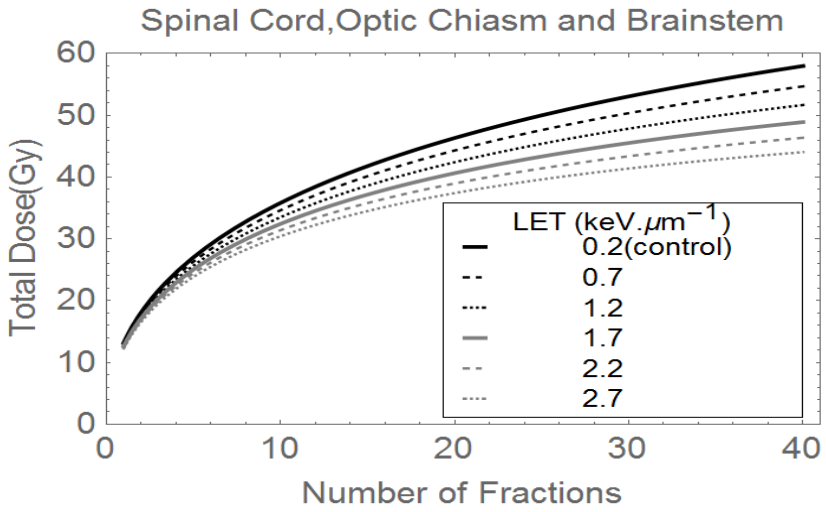


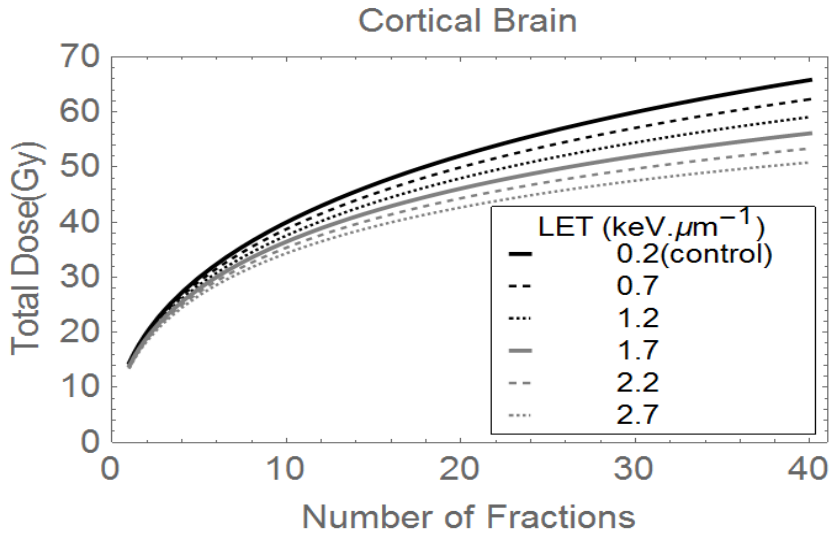




Uses separate increases in α and β with LET, rather than fixed multiple of α/β as in some other systems. Also included saturation effects to be more realistic (Jones 2016, 2017, 201)

Some modelled RBE and dose fractionation estimates using methods in Jones B, 2015: Cancers (Basel), but with control LET=0.22 keV.μm^{-1}





For α/β=2 Gy
White matter
Conventional Tolerance 50 Gy in 25#

Cortical Brain (Grey Matter) Conventional Tolerance 60 Gy in 30#

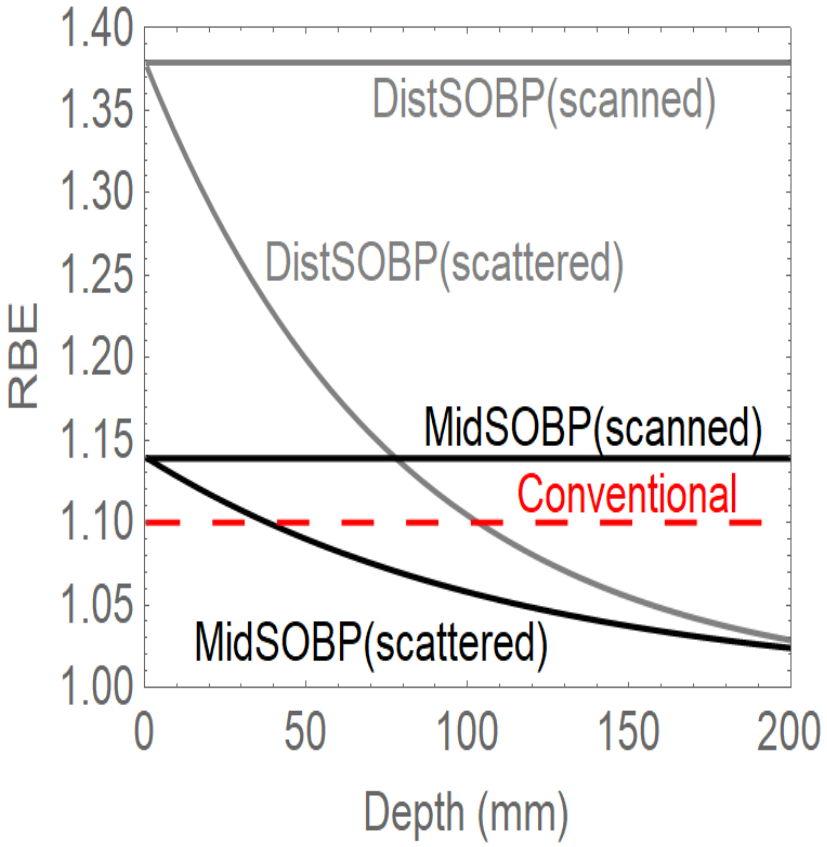
α/β=2 Gy: Central Nervous System [Jones B, Acta Oncol 2017, supplementary secion]

Dose (Gy)	LET=1	LET=1.25	LET=1.5	LET=1.75	LET=2.0	LET=4.0	LET=8.0
d=1.25	1.10 (1.08, 1.11)	1.12 (1.08, 1.14)	1.15 (1.13, 1.18)	1.18 (1.16, 1.21)	1.21 (1.18, 1.24)	1.42 (1.37, 1.48)	1.80 (1.7, 1.9)
d=1.5	1.09 (1.07, 1.10)	1.11 (1.10, 1.13)	1.14 (1.12, 1.16)	1.17 (1.14, 1.19)	1.19 (1.16,1.22)	1.38 (1.33,1.44)	1.72 (1.63, 1.82)
d=1.8	1.08 (1.07, 1.09)	1.10 (1.09, 1.12)	1.13 (1.11, 1.15)	1.15 (1.13, 1.17)	1.17 (1.15, 1.20)	1.35 (1.30, 1.40)	1.66 (1.57, 1.75)
d=2	1.07 (1.06, 1.09)	1.10 (1.08, 1.11)	1.12 (1.10, 1.14)	1.14 (1.12,1.16)	1.16 (1.14, 1.19)	1.33 (1.28, 1.38)	1.62 (1.53, 1.71)
d=2.5	1.06 (1.05, 1.08)	1.08 (1.07, 1.10)	1.10 (1.09, 1.12)	1.12 (1.10, 1.15)	1.14 (1.12, 1.17)	1.29 (1.24, 1.34)	1.54 (1.46, 1.64)
d=3	1.06 (1.05, 1.07)	1.07 (1.06, 1.09)	1.09 (1.07, 1.11)	1.11 (1.09, 1.13)	1.13 (1.10, 1.15)	1.25 (1.21, 1.31)	1.48 (1.41, 1.58)
d=5	1.04 (1.03, 1.05)	1.05 (1.04, 1.07)	1.06 (1.05, 10.8)	1.08 (1.06, 1.10)	1.09 (1.07, 1.11)	1.18 (1.14, 1.23)	1.35 (1.28, 1.44)
d=10	1.02 (1.01, 1.03)	1.03 (1.02, 10.5)	1.04 (1.03, 1.06)	1.05 (1.03, 1.07)	1.05 (1.04, 1.08)	1.11 (1.08, 1.12)	1.22 (1.15, 1.31)
d=12.5	1.02 (1.01, 1.03)	1.03 (1.02, 1.04)	1.03 (1.02, 1.05)	1.04 (1.02, 1.06)	1.05 (1.03, 1.07)	1.10 (1.06, 1.15)	1.19 (1.12, 1.28)

RBE changes with method of beam delivery: ***passive scattering*** *or* ***scanned beams***

Actively **Scanned** pencil beams: Data of Britten et al (Radiation Research 2013), Bloomington USA
Passively scattered beams: Data of Megnin-Chanet (Calugaru et al Int J Radiat Oncol Biol & Physics, 2011), Orsay, Paris.
Both used two different cell lines for targets at 4 and 20 cm depth, given same dose and LET profile

Variation in RBE (Relative Biological Effectiveness) with depth and delivery systems (pre-scattered versus scanned pencil beams).



Modelled Bloomington USA and Orsay, Paris, results.

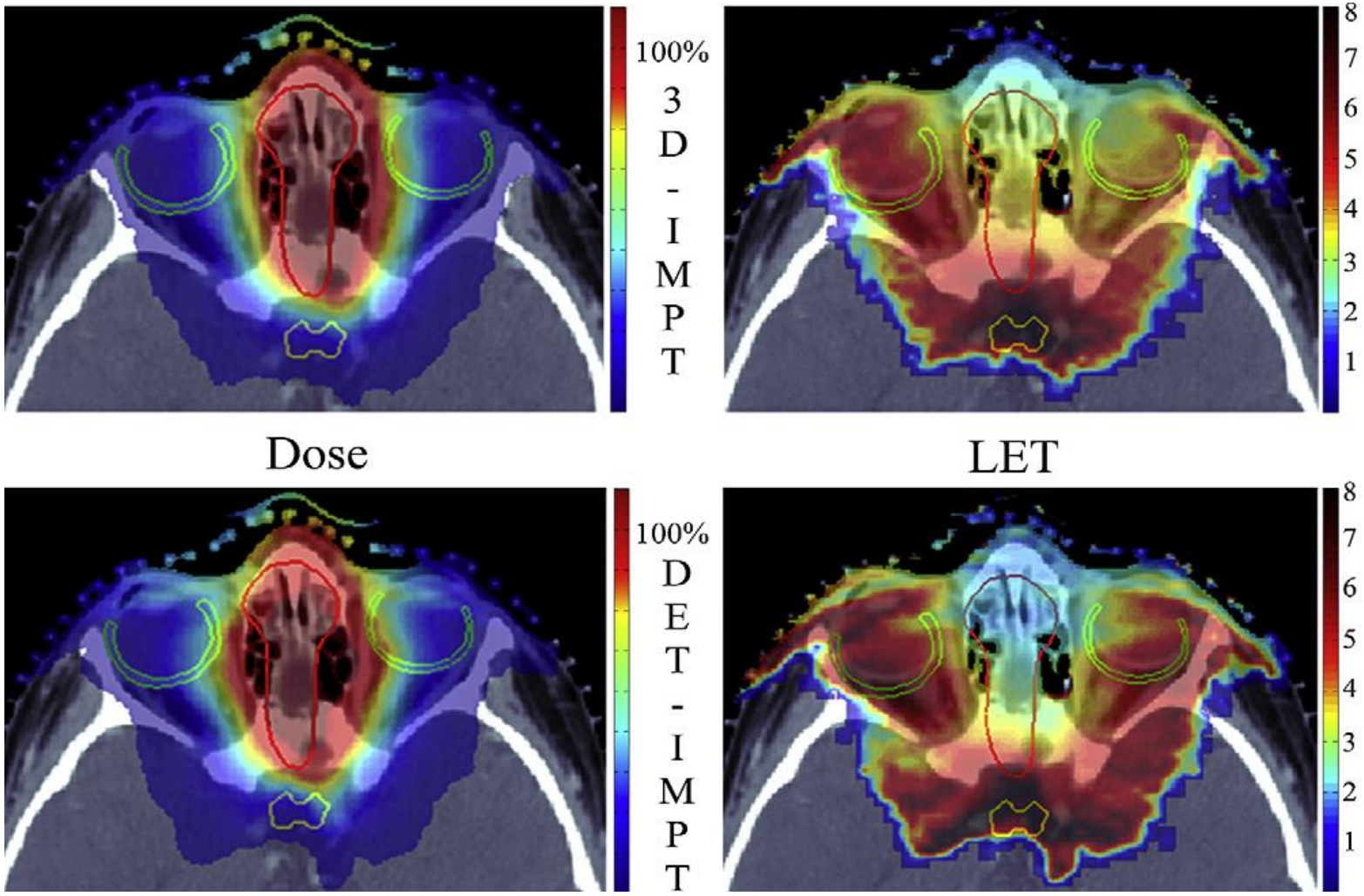
Working Hypothesis : inter-track distances are stable for scanned beams, but increase with depth for pre-scattered beams due to 'inverse square law' effects.

This will change the averaged LET per voxel of interest.

LET 'Density' = LET × Fluence

(Energy/distance × N/Area)

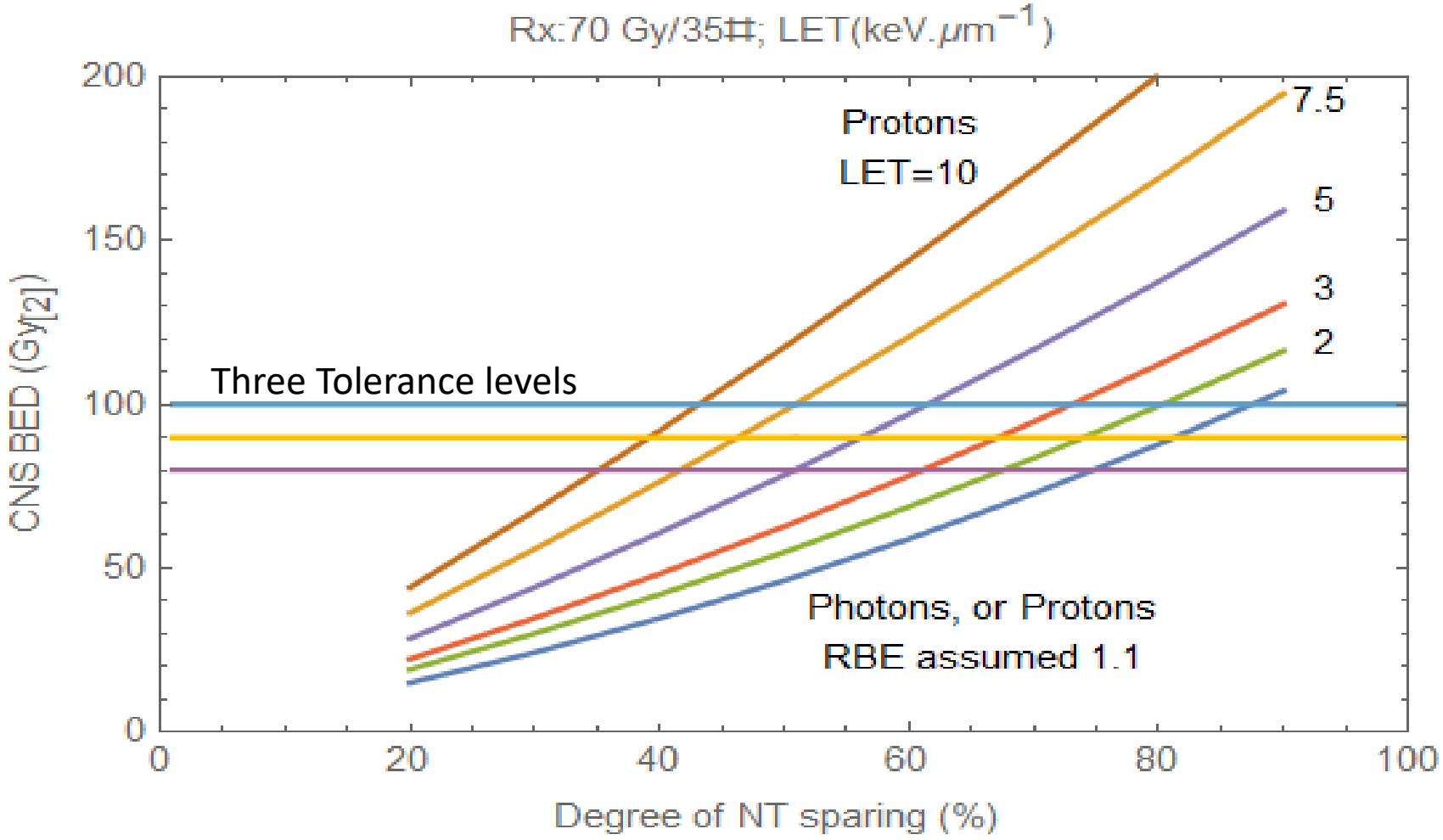
or Total Energy per unit volume.



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

35% of prescribed dose in optic chiasm, but LET ~ 7.5 keV.μm^{-1}

BED with dose sparing + LET



Some re-treatment examples

First treatment: Photons to 47.5 Gy in 30 fractions; with no adverse features

Second treatment (Protons), 18 months later,
with two different LET possibilities using 1.6 Gy protons/# (physical dose)

(a) LET= 1.5 keV.μm^{-1} RBE=1.14 $\rightarrow$ N=23 fractions
Total Dose 36.8 Gy

(b) LET= 5 keV.μm^{-1} RBE=1.47 $\rightarrow$ N=16 fractions
Total Dose 25.6 Gy

Caveat: **For 'generic' RBE= 1.1 $\rightarrow$ N=24 #, Tot.Dose=38.4 Gy**

But if LET actually=5 then BED=122 Gy $_{[2]}$, which far exceeds tolerance of 100 Gy $_{[2]}$ $\rightarrow$ High Risk

Two proton therapy courses, 2 years apart, no adverse histories

First: N=30, d=1.3 Gy (physical dose)

If LET=3, RBE=1.32, BED=95.7 Gy $_{[2]}$, equiv. photon dose=1.72 Gy
If LET=1.5, RBE=1.15, BED=78.38 Gy $_{[2]}$, equiv. photon dose=1.5 Gy
Note for LET>3.5 this would have exceeded tolerance

If second course also treated in 30 fractions:
Re-treatment schedules: max permissible doses are:
If LET=3, $\rightarrow$ N= 29# of 1.3 Gy
If LET=1.5, $\rightarrow$ N=35 # , so 30# of 1.3 Gy permissible.
Caveat:
If RBE=1.1, then N=38#; with 30# near tolerance limit for LET=3, so for actual LET>3 there is **high risk**

In principle, the following approach can be used in these difficult clinical situations

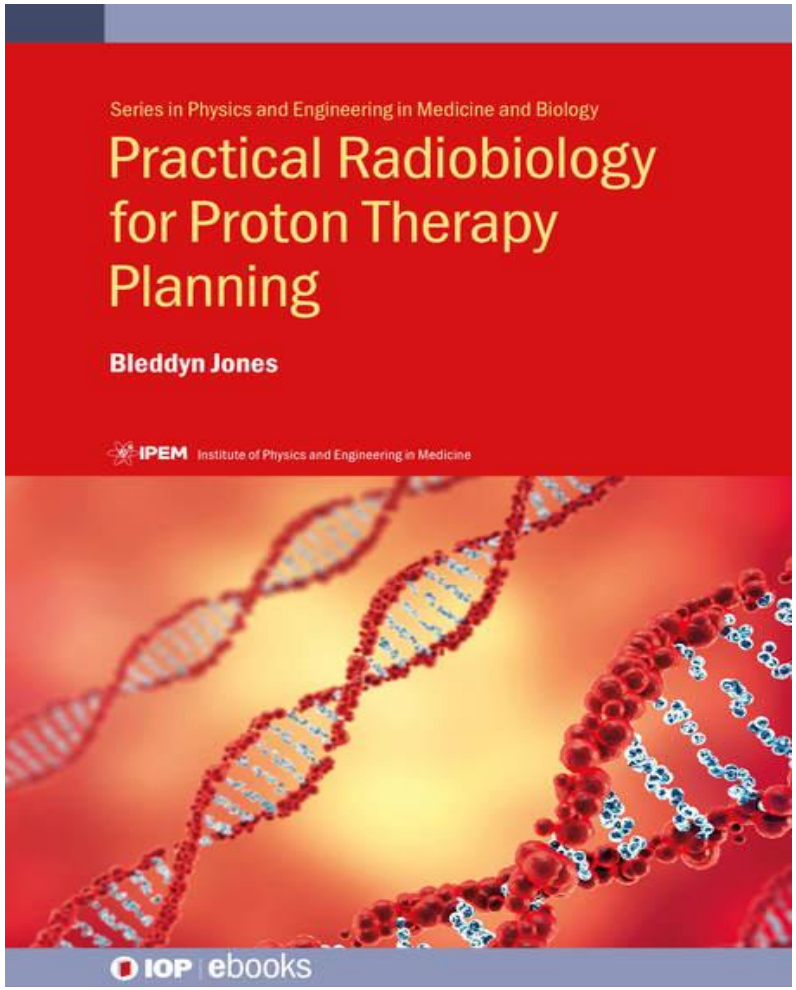
- Estimate first course BED:
- If protons – use LET and dose per fraction→ RBE.
- Use RBE to convert proton dose to equivalent photon dose which can be used in the retreatment GUI
- Use ‘conservative factor’ as appropriate for medical history…..5-20% reduction in tolerance BED.
- The estimated BED allowed for re-treatment is used with the intended proton dose per fraction, modified by the RBE according to the operative LET, to provide a max permissible number of fractions.
- The clinician must finally decide if a lower number of fractions is used.

What is required to improve re-treatment confidence?

- More experiments after low dose priming and higher doses, at 1, 2, 3 years? Difficult experiments in primates. Cost and ethical restrictions
- National or International data bases and analysis of similar groups of patients
- More precise allowances for chemotherapy effects, local surgery/pressure effects/trauma, age, medical conditions etc. required.

Some references

- Woolley TE, et al Int J Radiat Biol. 2018 Jun;94(6):515-531. *The GUI is available in this paper*
- Jones B, Acta Oncol. 2017 Nov;56(11):1374-1378. *Gives estimated Proton RBE values*
- Jones B, McMahon SJ, Prise KM. Clinical Oncology (R Coll Radiol). 2018 May;30(5):285-292. *Scanned beam RBE`s discussed.*



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