PHE-ICTR meetings: Geneva 2016

Further Development of Spinal Tissue Radiotherapy Re-treatment Modelling, with inclusion of Hadrontherapy.

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Spinal cord re-treatments

- Sometimes re-treated in patients with recurrent thoracic, head and neck cancers/lymphomas
- More often re-treated for palliation of spinal bone metastases
- children and adults with primary spinal CNS malignancies.

OVERDOSAGE results in LIMB PARALYSIS/Loss of Bowel and Bladder control etc

Retreatment of primary brain CNS tumours can be clinically important [Amichetti et al 2011]

- Younger patients most often retreated, usually small volume low grade glioma recurrences 3-8 years after first radiotherapy.
- Treatment can be considered palliative but duration of second remission can exceed that of first remission.
- 5 year survivals reported in many series, around 25%.

Evidence for time dependent "Spinal Recovery"

- Many experiments in small animals…rats
- Only one data set in primates (K. Ang et al 2001)
- Human evidence from radiotherapy

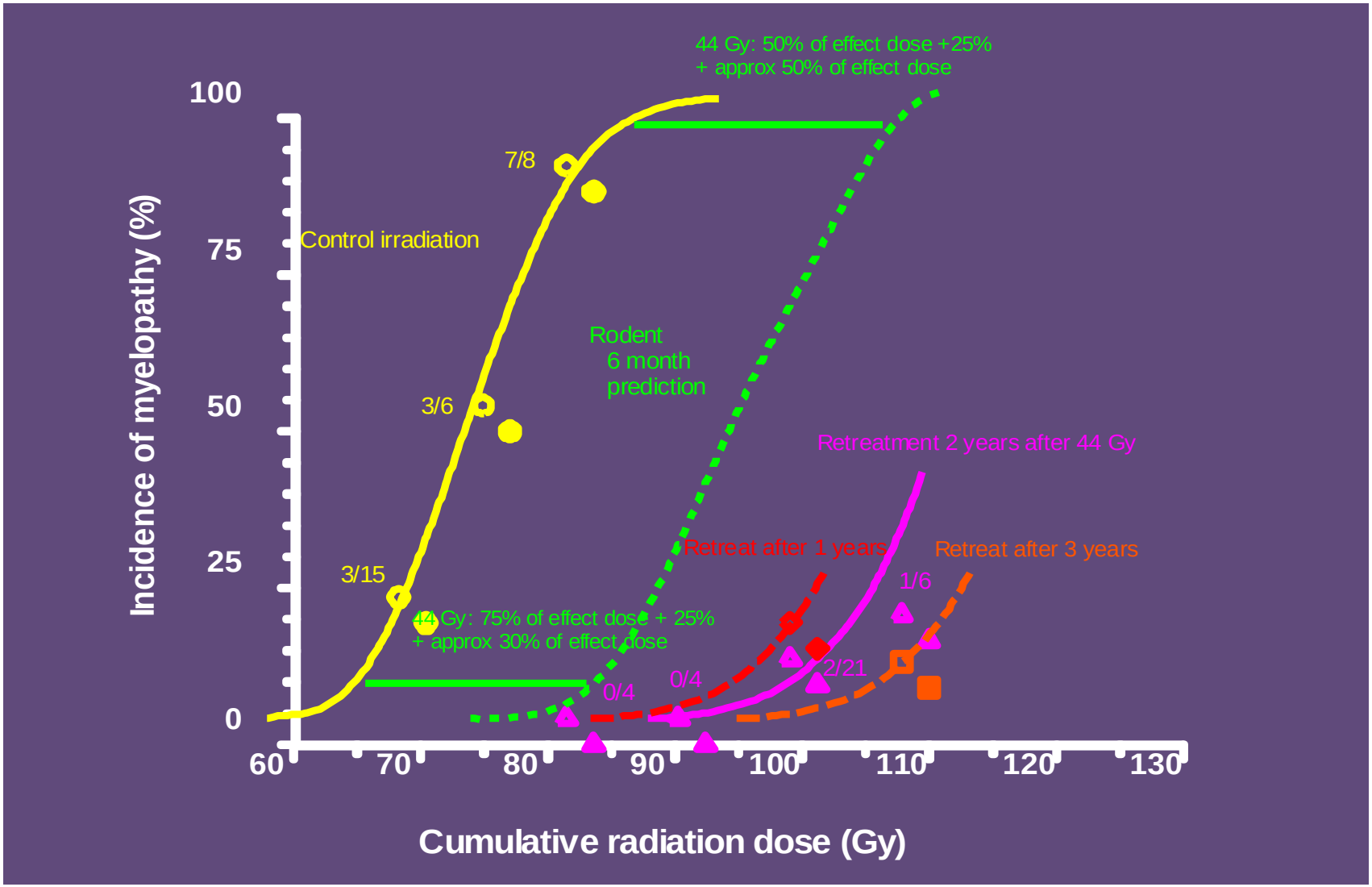
Model for estimation of re-treatment BED for 1-3 years between treatments:

- Jones B, Grant W. 2014. Retreatment of central nervous system tumours, Clinical Oncology 26:407-418.
- Jones B, Hopewell JW. 2014. Alternative models for estimating the radiotherapy retreatment dose for the spinal cord, Int J Radiat Biol 90:731-741.

Inferences from animal data

- Recovery starts after minimum time of 70 days
- Recovery kinetics may depend on initial dosage:
  1. rapid after higher doses,
  2. much slower after smaller doses
  (? following natural turnover time of the tissue)
- Similarity of human and monkey radio-tolerance, but need for conservatism, due to other factors that influence tolerance in human : surgery, chemotherapy, age etc.

Dose-related incidence of radiation myelopathy in the Rhesus monkey: single and a repeated course irradiation of Ang et al 2001



2001

The ‘BED – tolerance’ concept
where BED[tol] is the BED for a specified low incidence of myelitis
BED= n d (1+ d/(α/β))
n=number of fractions, d= dose per fraction

For the first treatment,

BED 1 (%) = BED[given]/BED [tolerance] x 100

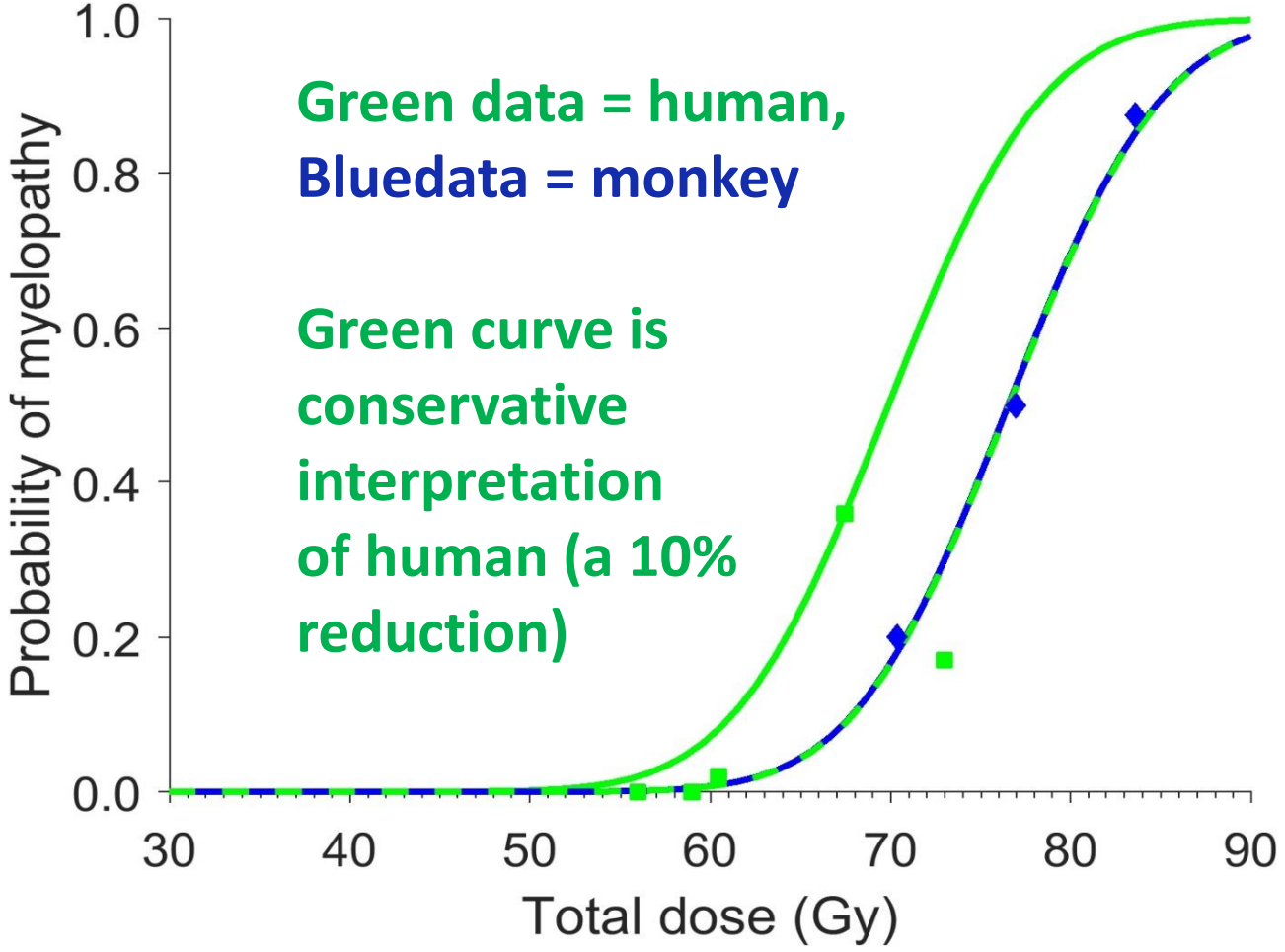
For the second treatment,

BED 2 (%) = BED[given]/BED [tolerance] x 100

These definitions may to a large extent overcome differences between species.

CNS α/β =2 Gy

Human and rhesus monkey data from Ang and Hopewell



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

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

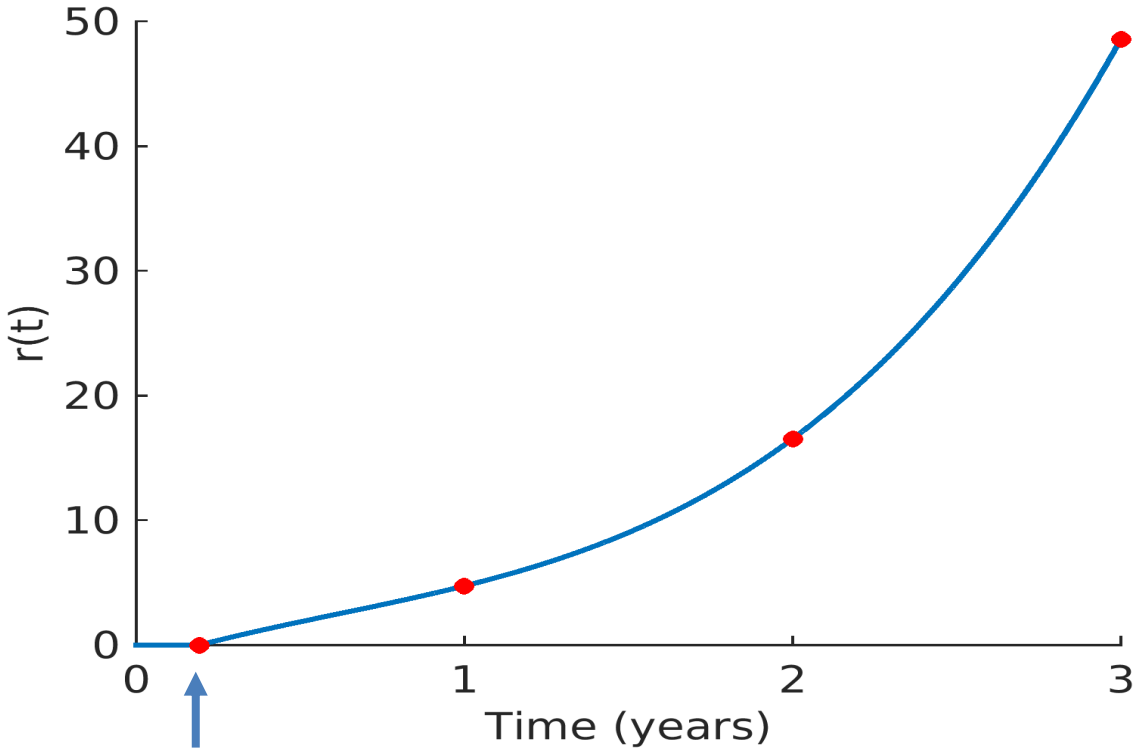
Where

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

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

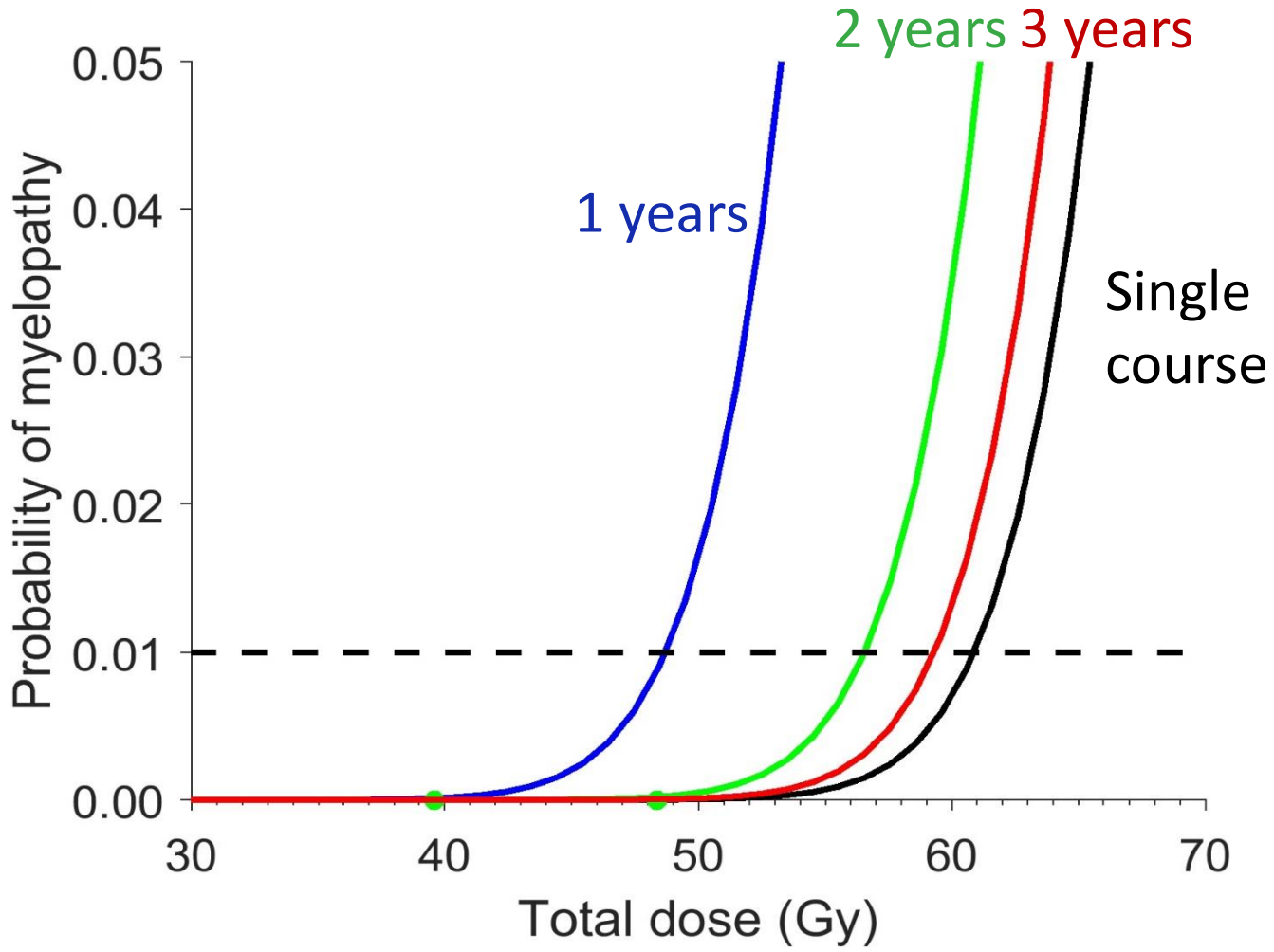
$$r(t) = \begin{cases} 0, & t \in [0, t_{IRO}] \\ a + bt + ct^2 + dt^3, & t \in [t_{IRO}, 3] \end{cases}$$

Fitting r(t), the recovery function, to primate data (Ang et al. 2001) , calculated from myelopathy probability set at p = 0.01.

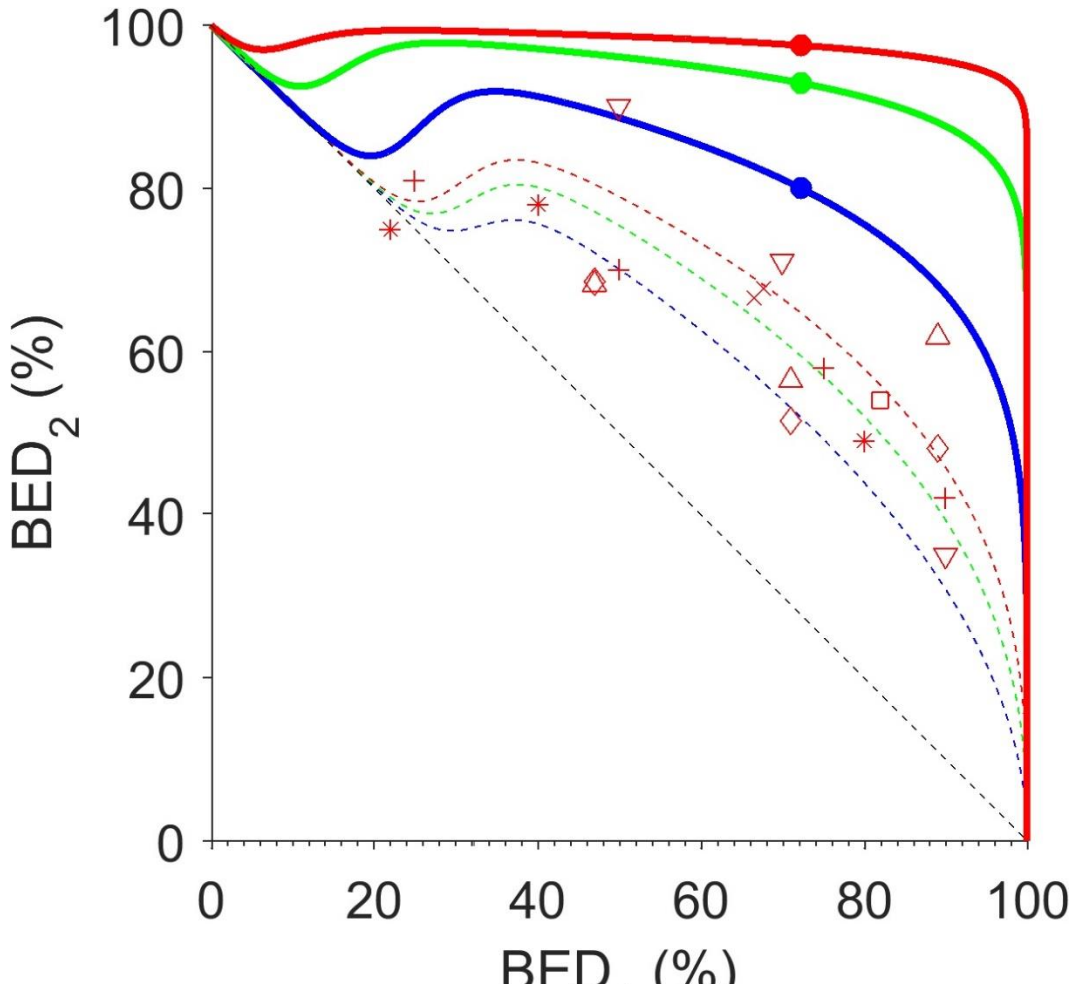


70 day recovery onset

Shift of myelitis probability curves with time compared with single course

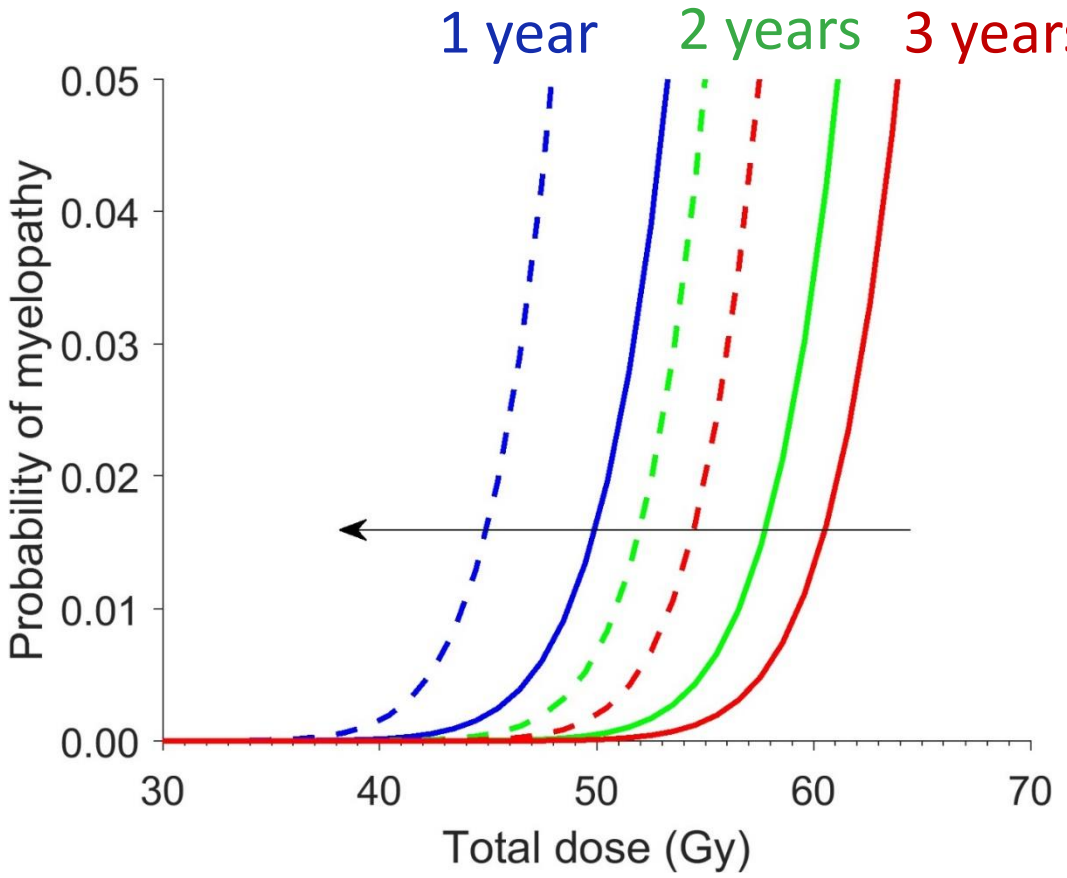


Predicted dependence between the initial and the re-irradiation doses expressed as a percentage of BED tolerance values. Dashed black, diagonal line corresponds to no recovery. Thick solid lines are fitted curves for 1, 2 and 3 years. Thin dashed lines are curves of times of 4, 5 and 6 months.

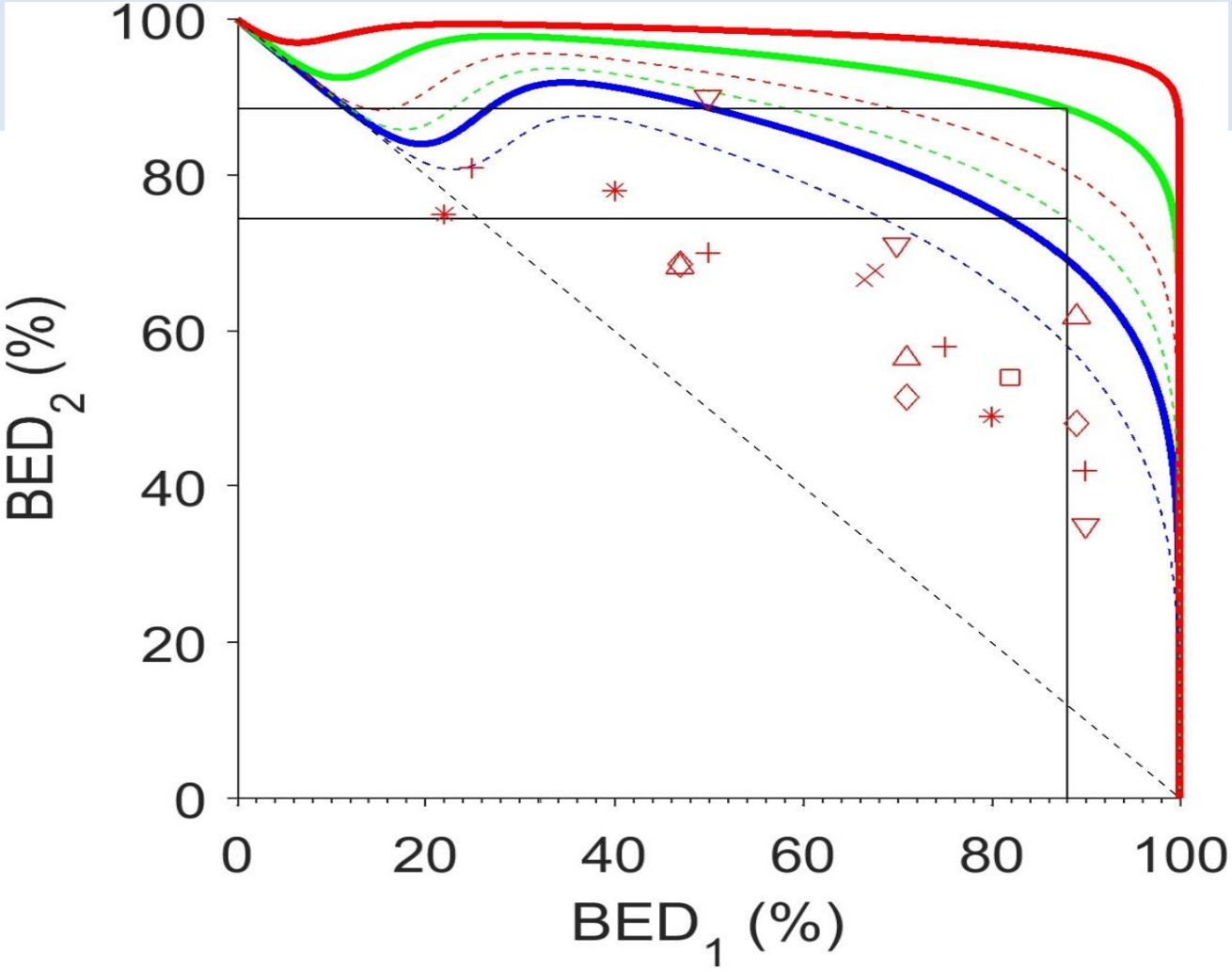


Animal data
solid dots - primates of Ang et al (2001)
Blue 1 year,
Green 2 years,
Red 3 years
after 44 Gy in 20 #
Other symbols = rodent data sets of Wong et al, Morris et al, Van der Kogel et al

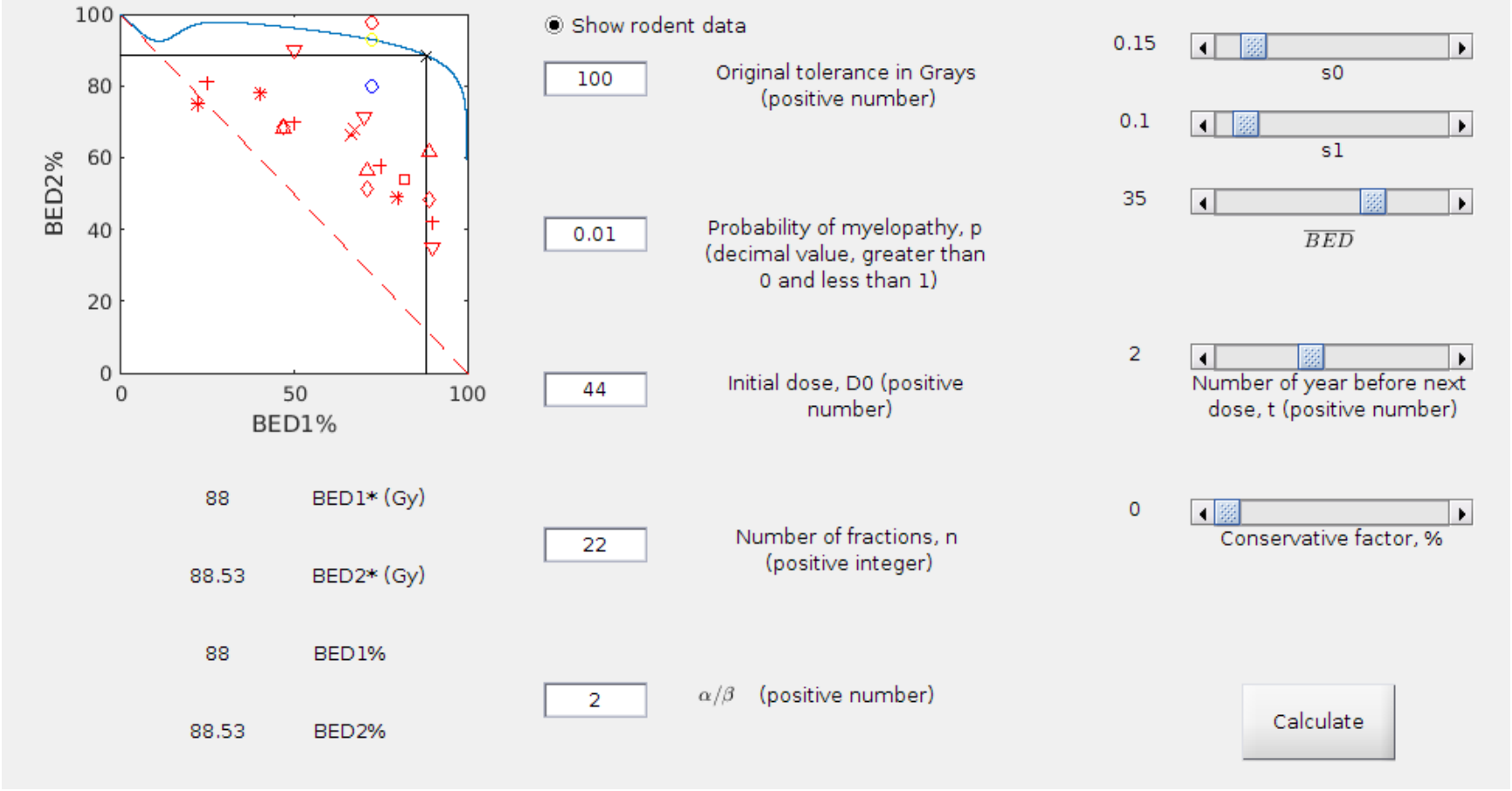
The more conservative approach: -10% shifts for dashed lines



Fits for different values of the recovery function as solid curves for one year (blue), two years (green) and three years (red). Dashed curves contain 10% conservative reduction for each year.



. Graphical User Interface (GUI)



Estimated proton & carbon ion re-treatment dose per fraction (d) and total doses (TD) 2 years after previous photon dose of 54 Gy in 28 to cortical brain (tolerance 60 Gy in 30 fractions).

Number of fractions	Proton dose estimates (Gy)	Carbon ion estimates (Gy)
10	d = 3.17 TD = 31.7	d = 1.47 TD = 14.7
25	d = 1.70 TD = 42.5	d = 0.68 TD = 17
30	d = 1.48 TD = 44.4	d = 0.58 TD = 17.4

Assumptions: Available tolerance= 81.53% of tolerance BED at 2 years proton RBEmax=1.4, RBEmin=1.05; carbon ion RBEmax=5, RBEmin=1.5 CNS α/β=2 Gy.

The estimated maximum photon retreatment dose would be 54 Gy in 28 fractions. In clinical practice more cautious doses are advised.

Future requirements

- More experiments after lower and higher initial doses? Is it possible to do these?
- National or International clinical data base and analysis?
- With allowances for: chemotherapy/surgery/age/other medical conditions etc.

Summary

- New model allows estimation of re-treatment doses between two courses of radiation from 70 days to 3 years or more after the initial course.
- It can also be adapted for hadrontherapy with knowledge of particle, energy, LET, RBE etc.
- It could be used cautiously in clinical practice by choosing doses lower than predicted.
- Predictions for Retreatment for Brain can be considered by experienced Radiation Oncologists.

People



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