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
Changes in the retreatment radiation tolerance of the spinal cord with time after the initial treatment.


**Based on two earlier articles:**


Many **clinical reviews** of re-treatment usefulness e.g. Clinical Oncology (R Coll Radiol), special edition 2018, e.g.

Late reacting tissues (e.g. CNS with $\alpha/\beta=2$ 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
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

\[ \text{BED}_2 = 100 \left( 1 - \frac{\text{BED}_1}{100} \right)^{\frac{1}{r(t)+1}}, \]

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

New equation

\[ \text{BED}_2 = 100 \left( 1 - \frac{\text{BED}_1}{100} \right) \left[ 1 + \left( \left( 1 - \frac{\text{BED}_1}{100} \right)^{\frac{-r(t)}{r(t)+1}} - 1 \right) f(\text{BED}_1, r(t)) \right] \]

Where

\[ f(\text{BED}_1, r(t)) = \frac{1}{2} \left[ 1 + \tanh \left( s_0 \left( \text{BED}_1 - \frac{\text{BED}}{1 + s_1 \cdot r(t)} \right) \right) \right] \]

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

\[ r(t) = \begin{cases} 
0, & t \in [0, \text{t}_{IRO}] \\
a + bt + ct^2 + dt^3, & t \in [\text{t}_{IRO}, 3] 
\end{cases} \]
Fit of Recovery ‘time function’ $r(t)$ to data of Ang et al.

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

Green data = human, Bluedata = monkey

Green curve is conservative interpretation of human (a 10% reduction)
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 .......... BED₁% is the (Given BED/Tolerance BED)%, also the risk level (or BED tolerance) and elapsed time.

• Output parameter is BED₂%, 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.
\[ \text{BED}_{\text{int}} \text{ (Gy)} = \text{BED}_2 \text{ (%) of } \text{BED}_{R\%} \text{ (Gy)} \]

\[ \text{BED}_{\text{ret}} \text{ (Gy)} = \text{BED}_2 \text{ (%) of } \text{BED}_{R\%} \text{ (Gy)} \]

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

- Nominal tolerated \( \text{BED}_{R\%} \) (Gy)
  
  (positive number)

- Initial total dose, \( D_{\text{int}} \) (Gy)

- Number of fractions, \( n \)
  
  (positive integer)

- Initial dose per fraction (Gy), \( d = D_{\text{int}}/n \)

- Percentage conservative factor, \( C \)
  
  (fixed)

- Number of retreatment fractions, \( n_r \)
  
  (positive integer)

- Tissue sensitivity, \( \alpha/\beta \) (Gy)
  
  (fixed)

- Number of years before next dose, \( t \)

- \( s_0 \)

- \( s_1 \)

- \( \text{BED} \)
1. Risk of myelopathy, $R$ (%)  
   (positive value, less than 100)

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

3. Initial total dose, $D_{init}$ (Gy)

4. Number of fractions, $n$  
   (positive integer)

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

6. Number of retreatment fractions, $n_r$  
   (positive integer)

7. Tissue sensitivity, $\alpha/\beta$ (Gy)  
   (fixed)

8. Percentage conservative factor, $C$

9. Number of years before next dose, $t$

10. $s_0$

11. $s_1$

12. $\overline{BED}$
For a myelitis risk of 0.1% (1 in 1000)

Each curve shows $\text{BED}_2(\%)$ 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.
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 $\alpha/\beta$. 
Relative Biological Effect – the ratio of ISOEFFECTIVE doses:

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

The conventional radiation – if \( \alpha/\beta \) 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.

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.
RBE model

• Uses particle specific maximum LET efficiency point (LET$_U$).
• Scaling of increasing $\alpha_H$ and $\beta_H$ with LET
• Incorporates saturation relationships between reference (control – low LET) radiation $\alpha$ and $\beta$ and the maximum values at LET$_U$.
• These $\alpha_H$ and $\beta_H$ 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 $\alpha$ and $\beta$ with LET, rather than fixed multiple of $\alpha/\beta$ 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 $\alpha/\beta=2$ 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 section]

<table>
<thead>
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<th>Dose (Gy)</th>
<th>LET=1</th>
<th>LET=1.25</th>
<th>LET=1.5</th>
<th>LET=1.75</th>
<th>LET=2.0</th>
<th>LET=4.0</th>
<th>LET=8.0</th>
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<td>d=1.25</td>
<td>1.10 (1.08, 1.11)</td>
<td>1.12 (1.08, 1.14)</td>
<td>1.15 (1.13, 1.18)</td>
<td>1.18 (1.16, 1.21)</td>
<td>1.21 (1.18, 1.24)</td>
<td>1.42 (1.37, 1.48)</td>
<td>1.80 (1.7, 1.9)</td>
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<tr>
<td>d=1.5</td>
<td>1.09 (1.07, 1.10)</td>
<td>1.11 (1.10, 1.13)</td>
<td>1.14 (1.12, 1.16)</td>
<td>1.17 (1.14, 1.19)</td>
<td>1.19 (1.16, 1.22)</td>
<td>1.38 (1.33, 1.44)</td>
<td>1.72 (1.63, 1.82)</td>
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<td>1.10 (1.09, 1.12)</td>
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<td>1.15 (1.13, 1.17)</td>
<td>1.17 (1.15, 1.20)</td>
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<td>1.14 (1.12, 1.16)</td>
<td>1.16 (1.14, 1.19)</td>
<td>1.33 (1.28, 1.38)</td>
<td>1.62 (1.53, 1.71)</td>
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<td>1.12 (1.10, 1.15)</td>
<td>1.14 (1.12, 1.17)</td>
<td>1.29 (1.24, 1.34)</td>
<td>1.54 (1.46, 1.64)</td>
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<td>1.09 (1.07, 1.11)</td>
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<td>1.13 (1.10, 1.15)</td>
<td>1.25 (1.21, 1.31)</td>
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<td>1.35 (1.28, 1.44)</td>
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<td>1.22 (1.15, 1.31)</td>
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<td>1.04 (1.02, 1.06)</td>
<td>1.05 (1.03, 1.07)</td>
<td>1.10 (1.06, 1.15)</td>
<td>1.19 (1.12, 1.28)</td>
</tr>
</tbody>
</table>
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


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.
35% of prescribed dose in optic chiasm, but LET ~ 7.5 keV.μm⁻¹
BED with dose sparing + LET

Rx: 70 Gy/35#; LET(keV/μm⁻¹)

Three Tolerance levels

CNS BED (Gy²)

Degree of NT sparing (%)
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 → N=23 fractions  
   Total Dose 36.8 Gy

(b) LET = 5 keV.μm⁻¹  RBE=1.47 → N=16 fractions  
   Total Dose 25.6 Gy

**Caveat**: For ‘generic’ RBE= 1.1 → 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] → High Risk
Two proton therapy courses, 2 years apart, no adverse histories

First: \( N=30, \, d=1.3 \text{ Gy (physical dose)} \)

If \( \text{LET}=3, \, \text{RBE}=1.32, \, \text{BED}=95.7 \text{ Gy} \) \(^{[2]}\), equiv. photon dose=1.72 Gy
If \( \text{LET}=1.5, \, \text{RBE}=1.15, \, \text{BED}=78.38 \text{ Gy} \) \(^{[2]}\), equiv. photon dose=1.5 Gy

*Note for \( \text{LET}>3.5 \) this would have exceeded tolerance*

*If second course also treated in 30 fractions:*
Re-treatment schedules: max permissible doses are:
If \( \text{LET}=3, \quad \rightarrow \quad N=29 \# \text{ of 1.3 Gy} \)
If \( \text{LET}=1.5, \quad \rightarrow \quad N=35 \# \), so 30\# of 1.3 Gy permissible.

*Caveat:*
If \( \text{RBE}=1.1 \), then \( N=38 \# \); with 30\# near tolerance limit for \( \text{LET}=3 \), so for actual \( \text{LET}>3 \) 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


