Clinical Significance of RBE Variations in Proton Therapy

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Introduction

Why RBE (relative biological effectiveness)?

- Prescriptions are based on dose (physics), not outcome (biology; tumor control probability (TCP) or normal tissue complication probability (NTCP))
- The dose in proton therapy is prescribed as Gy(RBE); RBE is a dose modifying factor
- Proton therapy is using a generic RBE of 1.1

Introduction

- The RBE is defined as the ratio of doses to reach the same level of effect when comparing two modalities
- RBE for TCP could potentially deduced from tumor control data
- RBE for NTCP is difficult to assess based on clinical data because photons generally deliver a more uniform dose to critical structures and the probability of radiation damage for a specified dose is sensitive to the volume of normal tissues irradiated
- The majority of laboratory data are on RBE for cell survival in vitro
Cells with higher repair capacity (low α/β) show higher RBE

\[ S(D) = e^{-\alpha D - \beta D^2} \]

RBE for cell survival – Endpoint dependency

Uncertainties due to α/β

Inter-patient variability on cell survival RBE can be substantial

“Links Fanconi Anemia/BRCA pathway defects to elevated proton RBE”

“Repair kinetics in HR-deficient cells were significantly delayed after proton irradiation, with elevated amounts of residual gH2AX foci”
**RBE for cell survival – Endpoint dependency**

**RBE relevant for NTCP:**

Effect of interest (organ level):
- early effects such as erythema
- late effects such as lung fibrosis, lung function, spinal cord injury, or necrosis

Typically measured other than cell survival (cellular level):
- Double-strand break induction
- Foci formation
- Chromosome aberrations
- Micronuclei formation
- Cell cycle disruption …

**RBE for cell survival – Dose dependency**

- Most experiments in vitro look at cell survival
- Precise measurements of cell survival below 2 Gy are sparse
- Prescription doses are typically 2 Gy/fraction
- There are only a few data points regarding dose dependency of RBE in vivo below 4 Gy for protons
Radiation is more effective when energy depositions are more concentrated in space.

\( R_{BE} = \frac{D_p}{D_p + \frac{a}{b} \times \text{LET}} \)

Where:
- \( D_p \) is the depth dose fraction.
- \( \frac{a}{b} \) is the LET ratio.
- \( \text{LET} \) is the linear energy transfer.

\( \text{LET} \) (keV/mm)

RBE (a/b) \( \times \) LET

Dose = Fluence [1/cm\(^2\)] × LET [keV/cm] / p [g/cm\(^3\)]

Entrance: ~1.1
Center: ~1.15
Distal edge: ~1.35
Distal fall-off: ~1.7

(values averaged over all cell lines and SOBPs for in vitro cell survival)

Healthy tissue

RBE = 1.1 is a conservative estimate!
RBE for cell survival

- RBE depends on LET
  - Increased effectiveness as a function of depth
  - RBE might be higher close to the 'target' edge (mainly in OAR)
  - Average RBE across a typical SOBP is, on average, about 1.1

- RBE depends on $\alpha/\beta$
  - RBE seems to be higher for tissues with a low $\alpha/\beta$ ratio (mainly OAR)
  - RBE values for endpoints other than cell survival are less well known.
  - The RBE for normal tissue response is unclear

- RBE depends on dose
  - RBE increases with decreasing dose
  - Indicates higher RBE for OAR
  - Measurements (in vitro and in vivo) typically do not provide high resolution below 2 Gy

Clinical evidence?

Correlation of toxicity and LET

Note:
All 119 cases had similar LET distributions
Only 4 with symptomatic treatment change
Only 1 symptomatic change correlated with LET

RBE increases with LET
LET is not the sole indicator
There is currently no clinical evidence for a correlation between areas of elevated LET (RBE) and toxicities.

Should we consider RBE for NTCP in treatment planning?

**RBE considerations in treatment planning**

Planning technique maximizing target conformity

<table>
<thead>
<tr>
<th>Dose x 1.1</th>
<th>LET</th>
<th>Dose x RBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.4 Gy(RBE)</td>
<td>2.52 keV/μm</td>
<td>6.1 Gy(RBE)</td>
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Planning technique minimizing maximum LET in the brainstem

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RBE considerations in treatment planning


Pencil beam scanning

Dose x RBE

Gy(RBE) 54

2.7

Pencil beam scanning

RBE considerations in treatment planning


CTV

Brainstem

Chiasm

Passive Scattering

Beam Scanning

RBE considerations in treatment planning

RBE considerations in treatment planning

Scanning reduces the OAR dose for RBE=LI but increases the OAR dose for variable RBE.

Uncertainties!!

Biological treatment planning using physics information

PLAN 1

IMPT

PLAN 2

Biological treatment planning using physics information

atypical meningioma

CTV overlaps with
- optic nerve
- chiasm
- brainstem
### Biological treatment planning using physics information

Scaling of LET x dose such that RBE = 1.1 in center of 5cm SOBP

- **physical dose**
- **LET x dose**

### Meningioma

Reference plan vs re-optimized

### Base-of-skull Chordoma

Reference plan vs re-optimized
SUMMARY

- Proton therapy uses a generic RBE of 1.1 because of substantial uncertainties in RBE as a function of dose, endpoint and LET.
- The RBE is potentially higher towards the distal end of an SOBP and for low α/β.
- The relevance of endpoints other than cell survival for defining clinical RBEs is unclear.
- For a given dose and organ, the RBE dependency on LET is monotone (reasonably linear).
- There is no evidence (yet) for a correlation between LET and toxicity or recurrence.
- RBE/LET optimization may improve treatment outcome.
- Inter-patient variability (biomarkers?) is not well understood.