Clinical considerations of RBE in proton therapy

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Why do we need the RBE concept in clinical proton therapy?
• When using different modalities one has to consider the difference in biological effectiveness because prescriptions are based on dose (physics), not outcome (biology; tumor control probability (TCP) or normal tissue complication probability (NTCP)).

• We do not have proton specific dose-response curves (such as Quantec for photons) and as proton doses are more heterogeneous in organs at risk, it might be more realistic to rely on photon doses translated into equivalent uniform doses responses.
The current clinical practice is the use of an RBE = 1.1
What can we expect in terms of RBE variations in patients?

Why do we need the RBE concept in clinical proton therapy?
The RBE is expected to decrease with increasing dose

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

\[ RBE \approx 1.6 \]

\[ RBE \approx 1.3 \]

\[ RBE[L,d_H,(\alpha/\beta)_L] = \sqrt{\left((\alpha/\beta)_L\right)^2 + 4(\alpha/\beta)_L RBE_{max} d_H + 4 RBE_{min}^2 d_H^2 - (\alpha/\beta)_L} / 2d_H \]
Prescription doses are typically 2Gy/fraction. Precise measurements of cell survival below 2 Gy are sparse.

There are only a few data points regarding dose dependency of RBE in vivo below 4 Gy!
The RBE is expected to decrease with increasing $\alpha/\beta$

$$S(D) = e^{-(\alpha D + \beta D^2)}$$

Cells with higher repair capacity (low $\alpha/\beta$) show a higher RBE

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Uncertainties due to $\alpha/\beta$ uncertainties (e.g. prostate)

What are the relevant experimental data to define an RBE for a clinical endpoint?

- Tumor control probability: Cell survival
- Normal tissue complication probability: ???
RBE for normal tissue complication probability (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 (cellular level):
- Double-strand break induction
- Foci formation
- Chromosome aberrations
- Micronuclei formation
- Cell cycle disruption …
The RBE is expected to increase with increasing LET

Radiation is more effective when energy depositions are more concentrated in space

Healthy tissue

1.1 is a conservative estimate!

(values averaged over all cell lines and SOBPs)
The RBE as a function of dose, LET and $\alpha/\beta$

- D = 2 Gy

- The majority of the experimental data are on cell survival in vitro
- Experimental data have large error bars (if reported)
- This leads to large uncertainties in the model prediction
Why do we need the RBE concept in clinical proton therapy?

What can we expect in terms of RBE variations in patients?

Is there clinical evidence that it matters?
Evidence 1 (?):

Lung density changes following chest RT

Tracy Underwood
Evidence 2 (?): Radiographic (MRI) tissue changes (e.g. necrosis)
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
Why do we need the RBE concept in clinical proton therapy?

What can we expect in terms of RBE variations in patients?

Is there clinical evidence that it matters?

Are we considering potential RBE effects in the clinic?
The current clinical practice is the use of an $RBE = 1.1$

Variable $RBE$ values are considered in a non-quantified way similar to range uncertainties.
Example 1: RBE concerns for the brainstem for ependymoma

Planning technique maximizing target conformality

Dose x 1.1  LET  Dose x RBE

Example 1: RBE concerns for the brainstem for ependymoma
Planning technique minimizing maximum LET in the brainstem

Dose x 1.1

LET

Dose x RBE

RBE-weighted Dose volume histograms

Example 2: RBE concerns for the rectum in prostate cancer
Example 2: RBE concerns for the rectum in prostate cancer

DVH data for eight patients showing rectum dose assuming RBE=1.1 (left) and variable RBE with the Wedenborg model, $\alpha/\beta=3$ Gy (right).

Max Gy(RBE) dose to 1cc of the rectal wall. Box and whisker plots for eight patients assuming either RBE=1.1 or variable RBE (three models plus a range of $\alpha/\beta$ ratios) for SB proton plans (left) and AO proton plans (right).
What can we expect in terms of RBE variations in patients?

Is there clinical evidence that it matters?

Are we considering potential RBE effects in the clinic?

Should we do more?
“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”
Why do we need the RBE concept in clinical proton therapy?

What can we expect in terms of RBE variations in patients?

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Should we do more?

Can we do more?
Can we do something without knowing RBE values?

**PLAN 1**

**Dose**

**LET**

**PLAN 2**
LET based optimization: consider simple RBE model

\[ S = \exp(d) = a_0 (1 + c \text{LET}) \]

\[ \text{RBE} \times d = \frac{\log(S)}{a_0} \]

\[ = (1 + c \text{LET}) d = d + c \text{LET} \times d \]

Goal: avoid high LET in serial critical structures near and within the target

LET optimization - Example 1: atypical meningioma

CTV overlaps with
- optic nerve
- chiasm
- brainstem

LET optimization - Example 1: atypical meningioma

Method

1. Physical dose objectives
   • homogeneous prescription of 50 Gy (physical dose)
   • optics, brainstem, pituitary below 50 Gy
   • brainstem gEUD
   • brain mean dose

2. Re-optimization (prioritized optimization)
   • allow 3% increase in brainstem gEUD and mean brain dose
   • other objective remain the same
LET optimization - Example 1: atypical meningioma

LET optimization - Example 2: base-of-skull chordoma

Take-Home Messages

- 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 $\alpha/\beta$.
- The relevance of endpoints other than cell survival for defining clinical RBES is unclear.
- There is no evidence (yet) for a correlation between LET and toxicity or recurrence.
- For a given dose and organ, the RBE dependency on LET is monotone (reasonably linear).
- RBE/LET optimization may improve treatment outcome.
- Inter-patient variability (biomarkers?) is not well understood.
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