Proton Therapy and variations in RBE - A clinical perspective -

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Learning objectives

- To outline the limitations when deducing RBE values from clinical data
- To present clinical evidence for RBE variations
- To outline a potential way forward
What do we know about proton RBE from laboratory data?

RBE = 1.1 is a conservative estimate

Dose = 2Gy
\((\alpha/\beta)_x = 2Gy\) (solid)
\((\alpha/\beta)_x = 10Gy\) (dashed)

\(\text{LET}_d = 2.5\text{keV/\mu m}\)
\((\alpha/\beta)_x = 2Gy\) (solid)
\((\alpha/\beta)_x = 10Gy\) (dashed)

Dose = 2Gy
\(\text{LET}_d = 2\text{keV/\mu m}\) (solid)
\(\text{LET}_d = 10\text{keV/\mu m}\) (dashed)

McNamara, Schuemann, Paganetti: A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published in vitro cell survival data. Phys Med Biol 2016 60: 8
Obstacles when identifying RBE effects in vivo

TCP: Tumor control is typically quite high
NTCP: Severe normal tissue toxicities are relatively rare

Where are we on the NTCP and/or TCP curve?

Tumor control
Normal tissue damage

TCP (prostate)
NTCP (rectal toxicity)

Martinsdottir et al. 2018
Obstacles when identifying RBE effects in vivo

Patient specific RBE (radiosensitivity)

“Repair kinetics in HR-deficient cells were significantly delayed after proton irradiation, with elevated amounts of residual $\gamma$H2AX foci”


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


Plan specific RBE (systemic effects)

Difference in dose distribution

Difference in delivery time distribution

Dose bath impacts dose to circulating lymphocytes
Is there evidence for RBE variations in patients?

Radiographic (MR) changes (necrosis)

All 119 patients had similar LET distributions
Only 4 with symptomatic treatment change
Only 1 symptomatic change correlated with LET

LET is not the sole contributing factor to toxicities!

LET/RBE variations might be smaller than variations in patient radiosensitivity

Is there evidence for RBE variations in patients?

Radiographic (MR) changes (necrosis)

50 adult patients with necrosis

Voxels within one patient are correlated

CNS

No correlation between necrotic areas and elevated LET/RBE

Variation in patients specific radiosensitivity are likely larger than variations in LET/RBE

H&N
Rib fractures in proton therapy breast patients

Rib fractures are correlated with an end-of-range LET effect with an RBE of ~1.25

Wang et al. Int J Radiat Oncol Biol Phys; under review
Clinical evidence:
Radiographic (CT) changes (fibrosis)
- Chest wall patients -

The proton RBE for non-symptomatic lung-density changes exceeds 1.1 (~3.5)

Differences in DNA damage complexity may result in different repair pathways and thus differences in inflammatory response.
Is there evidence for RBE variations in patients?

- No difference between protons and photons was seen in SBRT patients (large dose per fraction).
- Inflammation occurred earlier after proton irradiation.

Radiation Fibrosis in lung SBRT
6 months post treatment

Li et al. Radiotherapy & Oncology 2019
How should we move forward?

Based on available clinical data, implementing empirical RBE models based on clonogenic cell survival into treatment optimization is (in my opinion) dangerous as it might lead to decreasing TCP and increasing NTCP

... on the other hand
How should we move forward?

**Dose volume histograms (RBE=1.1)**

- **CTV**
- **Brainstem**
- **Plan 1**

**LET volume histograms**

- **Chiasm**
- **Plan 2**

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Plan 1 (RBE=1.1)

Plan 2 (RBE=1.1)

Plan 1 (RBE varies; a/b=2 Gy)

Plan 2 (RBE varies; a/b=2 Gy)

Plan 2 reduces the OAR dose for RBE=1.1

Plan 2 increases the OAR dose when using a variable RBE

How should we move forward?
Even though uncertainties in patient specific RBE values are significant, we can reduce the RBE in organs at risk without knowing (patient specific) RBE values because the improvement is relative for each patient.

How should we move forward?

\[
S = \exp(-\alpha d) \quad \alpha = \alpha_0 (1 + cLET)
\]

\[
RBE \cdot d = -\frac{\log(S)}{\alpha_0}
\]

\[
= (1 + cLET) d = d + cLET \cdot d
\]

Goal: avoid high LET (biological extra dose) in serial critical structures near and within the target

RBE “model” is solely used to guide the optimizer, not to alter the prescription / dose constraints

How should we move forward?

Example: Skull-base Chordoma

\[ \kappa \times \text{LET} \times \text{dose (Gy)} \]
Take-home message

- RBE models based on clonogenic cell survival can be used when analyzing clinical trends and to guide treatment planning
- Outcome analysis needs to consider RBE variations
- RBE models based on clonogenic cell survival should not be used for treatment plan optimization

- Photon NTCP models may not be fully applicable in proton therapy
- Systemic effects may overshadow “voxelized” RBE concept

- Biologically motivated treatment planning is feasible for proton therapy using LET