Therapy Symposium

The Relative Biological Effectiveness of Proton Beams Relative to Photon Beams

Laboratory and Clinical Evidence for and Against a Spatially Invariant RBE

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Models and Mechanisms Connecting Physics and Biology at Multiple Scales in the Biological Hierarchy

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Development and delivery of biologically optimized treatment plans in proton radiotherapy

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Learning Objectives:

1. To review laboratory and clinical evidence for and against the continued use of a constant RBE of 1.1
2. To understand major mechanisms connecting proton LET to RBE at the molecular, cellular and tissue levels.
3. To quantify the potential opportunities and potential pitfalls of neglecting spatial variations in proton RBE in treatment plans

Introduction

Why RBE?

- When using different modalities one has to consider the difference in biological effectiveness because prescriptions are based on dose, not outcome
- The dose in proton therapy is prescribed as Gy[RBE]; RBE is related to TCP and NTCP as a dose modifying factor.
- The RBE is defined as the ratio of doses to reach the same level of effect when comparing two modalities, e.g. a reference radiation and proton radiation
Introduction

\[ \text{RBE}(\text{Dose}, \text{EndpointX, proton beam properties}) = \frac{\text{Dose}_{\text{eff,ref,}}(\text{endpointX})}{\text{Dose}_{\text{proton}}(\text{endpointX})} \]

- The RBE varies with dose, biological endpoint, energy deposition characteristics

**Clinical RBE**

- The current clinical practice is the use of an RBE = 1.1

- This value is based on measured RBE values in vivo in the center of an SOBP relative to 60Co.


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**Laboratory and Clinical Evidence for and Against a Spatially Invariant RBE**

- RBE from experimental data
- Clinical evidence for RBE variations
- Biological treatment planning

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RBE from experimental data – Dose dependency

\[ S(D) = e^{-aD + bD^2} \]

\[ \text{RBE} = 1.6 \]

\[ \text{RBE} = 1.3 \]

\[ \text{RBE} \approx 1.3 \]

\[ \text{RBE} \approx 1.6 \]

RBE (typically) increases with decreasing dose, particularly for low \( \alpha/\beta \)

- RBE increases with decreasing dose
- There are only a few data points regarding dose dependency of RBE in vivo below 4 Gy
- Indicates higher RBE for OAR
RBE from experimental data – Endpoint dependency

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

- Tumor control probability: Cell survival
- Normal tissue complication probability: ???

RBE relevant for normal tissue complication probability:

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 …

Known facts from cell experiments with respect to radiation damage (protons versus photons)

- Differences in residual DSB lesions
- Differences in lesion complexity (clustered damage)
- Differences in foci numbers and size
- Differences in inducing radical oxygen species
- Differences in gene expression profiles
- Differences in apoptosis signaling pathways
RBE from experimental data – Endpoint dependency

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

- Tumor control probability: Cell survival
- Normal tissue complication probability: ???

RBE from experimental data – Endpoint dependency

Proton RBE for clonogenic cell survival

low (α/β)I (≤ 5 Gy)
late responding healthy tissue

high (α/β)I (> 5 Gy)
early responding tumor tissue

RBE from experimental data – Endpoint dependency

Uncertainties due to α/β ratio uncertainties in prostate

RBE from experimental data – Endpoint dependency

Uncertainties due to α/β ratio uncertainties in brain

- RBE seems to be higher for tissues with a low α/β ratio (mainly organs at risk); could impact prostate treatments and trials (IMRT versus protons)

- RBE values for endpoints other than cell survival are less well known. The RBE for normal tissue response is unclear

- Inter-patient variability could be substantial

RBE from experimental data – LET dependency
RBE from experimental data – LET dependency

Dose = Fluence [1/cm²] × LET [keV/μm] / ρ [g/cm³]

Implication of RBE(LET) for RBE(depth)


Wouters et al. Radiat Res 1996; 146, 159-170

RBE from experimental data – LET dependency
RBE from experimental data – LET dependency

Average RBE across a typical SOBP: 1.1

Increase with depth
Entrance region: ~1.0
SOBP center: ~1.05
Distal edge: ~1.25
Distal fall-off: ~1.5
(values averaged over all cell lines)
RBE from experimental data – LET dependency

Range Shift

- Increased effectiveness as a function of depth
- RBE might be higher close to the ‘target’ edge (mainly in OAR)
- Average across a typical SOBP: 1.1
- Increase with depth from ~1.0 in the entrance region, to ~1.05 in the center, ~1.25 at the distal edge and ~1.5 in the distal fall-off (values averaged over all published cell experiments)

RBE increase with
- decreasing dose
- increasing LET
- decreasing α/β
Clinical evidence for RBE variations

- RBE for TCP could potentially be deducible 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.

Clinical evidence for RBE variations

- Clinical evidence for elevated tissue response at the end of range: 3 necrosis cases in 111 patients.

Clinical evidence for RBE variations


Clinical evidence for RBE variations

- Medulloblastoma; brain field. DOSE and LET.
Clinical evidence for RBE variations

The clinical significance of RBE variations depends $\alpha/\beta$

DOSE (RBE-weighted) – DOSE (RBE=1.1)

16 relapses in 109 patients
Clinical evidence for RBE variations

Chest wall irradiation

RBE from experimental data
Clinical evidence for RBE variations
Biological treatment planning

RBE increase with:
- decreasing dose
- increasing LET
- decreasing $\alpha/\beta$

No clear evidence (yet)
Biological treatment planning

**Multi-Criteria Optimization (MCO)**

1. Define a set of (competing) objectives for planning
   - E.g., maximize target dose / homogeneity, minimize OAR max (min, EUD) dose
2. Identify "anchor" plans which best satisfy each of specific goal:
   - All plans are Pareto-optimal: if a plan improves by one measure, it gets worse by other(s)
3. Navigate the multi-dimensional Pareto-space to find the most suitable solution

**LET-guided MCO**
Biological treatment planning

LET-guided MCO

Variable RBE values are currently not considered in proton therapy
The main reason is the lack of experimental data to define accurate input parameters for RBE models

DOSE: RBE increases with decreasing dose
TISSUE: RBE increases with decreasing $\alpha/\beta$
LET: RBE increases as a function of depth
Conclusion

Our clinical experience does not indicate that the RBE of 1.1 for proton therapy is incorrect

* with current margins (which might decrease)
* based on current data (which will increase)
* for SOBP delivery (which will change in IMPT)
* for the ‘average’ patient (biomarkers?)
* missing an opportunity to exploit a variable RBE

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