AAPM 2014 innovation
56th Annual Meeting & Exhibition • July 20–24, 2014 • Austin, TX

Therapy Symposium
The Relative Biological Effectiveness of Proton Beams Relative to Photon Beams

Laboratory and Clinical Evidence for and Against a Spatially Invariant RBE
H Paganetti, Massachusetts General Hospital, Boston
Models and Mechanisms Connecting Physics and Biology at Multiple Scales in the Biological Hierarchy
R Stewart, University of Washington, Seattle
Development and delivery of biologically optimized treatment plans in proton radiotherapy
A Carabe-Fernandez, University of Pennsylvania, Philadelphia

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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

Massachusetts General Hospital Radiation Oncology | Harvard Medical School

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

Massachusetts General Hospital Radiation Oncology | Harvard Medical School

Introduction

$$RBE(Dose, EndpointX, proton\ beam\ properties) = \frac{Dose_{reference}(EndpointX)}{Dose_{protons}(EndpointX)}$$

- 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 ^{60}Co.*

Paganetti et al.: *Int.J.Radiat.Oncol.Biol.Phys.* 2002; 53, 407

Laboratory and Clinical Evidence for and Against a Spatially Invariant RBE

Massachusetts General Hospital Radiation Oncology
Harvard Medical School
Harald Paganetti PhD
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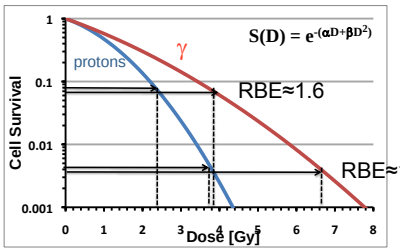
Director of Physics Research, Massachusetts General Hospital, Department of Radiation Oncology

RBE from experimental data

Clinical evidence for RBE variations

Biological treatment planning

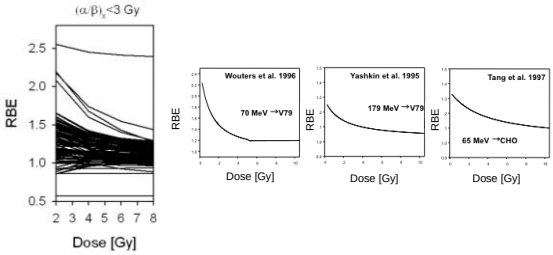
RBE from experimental data – Dose dependency



$$RBE\left[L,d_H,(\alpha/\beta)_L\right]=\frac{\sqrt{\left((\alpha/\beta)_L\right)^2+4(\alpha/\beta)_L\,RBE_{max}\,d_H+4RBE_{min}^2\,d_H^2}-(\alpha/\beta)_L}{2d_H}$$

RBE from experimental data – Dose dependency

RBE (typically) increases with decreasing dose, particularly for low α/β



RBE from experimental data – Dose dependency

- 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 from experimental data – Endpoint dependency

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 …

RBE from experimental data – Endpoint dependency

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

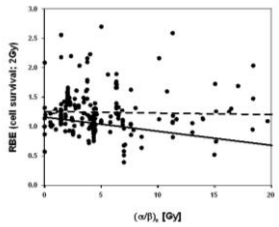
RBE from experimental data – Endpoint dependency

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

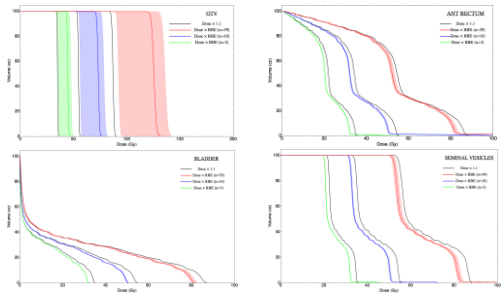


low $(\alpha/\beta)_x$ ($\leq$ 5 Gy) late responding healthy tissue

high $(\alpha/\beta)_x$ (> 5 Gy) early responding tumor tissue

RBE from experimental data – Endpoint dependency

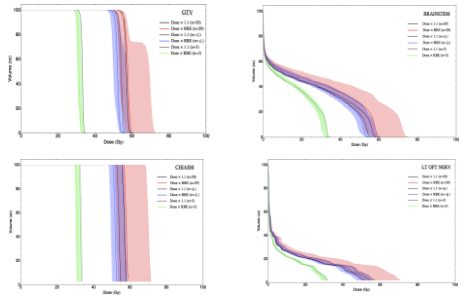
Uncertainties due to α/β ratio uncertainties in prostate



A Carabe, S España, C Grassberger, H Paganetti: Clinical consequences of Relative Biological Effectiveness variations in proton radiotherapy of the prostate, brain and liver. Physics in Medicine and Biology 2013 58: 2103-2117

RBE from experimental data – Endpoint dependency

Uncertainties due to α/β ratio uncertainties in brain

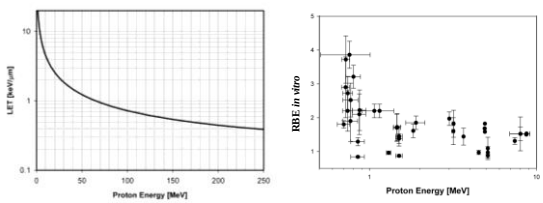


A Carabe, S España, C Grassberger, H Paganetti: Clinical consequences of Relative Biological Effectiveness variations in proton radiotherapy of the prostate, brain and liver. Physics in Medicine and Biology 2013 58: 2103-2117

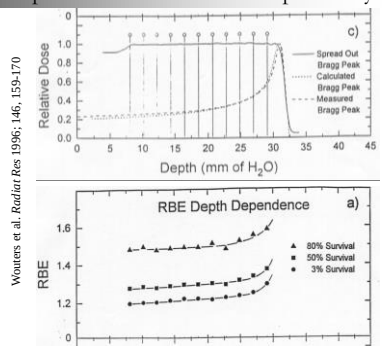
RBE from experimental data – Endpoint dependency

- 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



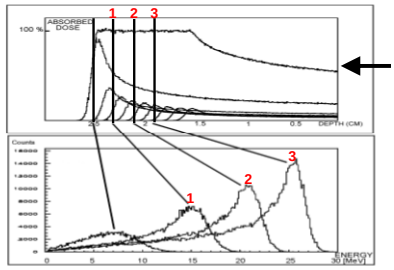
RBE from experimental data – LET dependency



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

RBE from experimental data – LET dependency

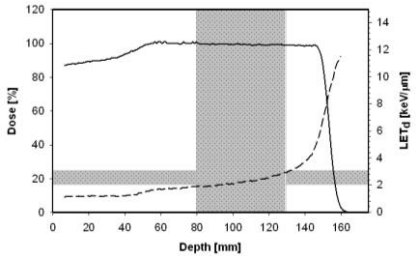
Implication of RBE(LET) for RBE(depth)



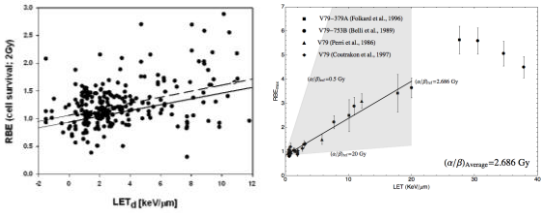
Paganetti: *Phys. Med. Biol.* 1998; 43, 2147-2157

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

RBE from experimental data – LET dependency

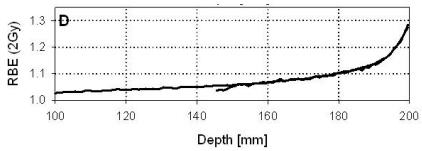


RBE from experimental data – LET dependency



Carabe-Fernandez; Dale; Hopewell; Jones; Paganetti: Fractionation effects in particle radiotherapy: implications for hypo-fractionation regimes. Physics in Medicine and Biology: 2010 55:5685-5700

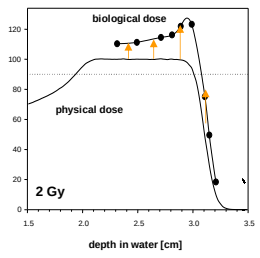
RBE from experimental data – LET dependency



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)

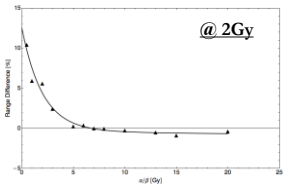
RBE from experimental data – LET dependency



Paganetti, Goitein: *Med. Phys.* 2000; 27, 1119-1126

RBE from experimental data – LET dependency

Range Shift



Carabe A; Moteabbed M; Depauw N; Schuemann J and Paganetti H: Range uncertainty in proton therapy due to variable biological effectiveness. Physics in Medicine and Biology 2012 57: 1159–1172

RBE from experimental data – LET dependency

- 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)

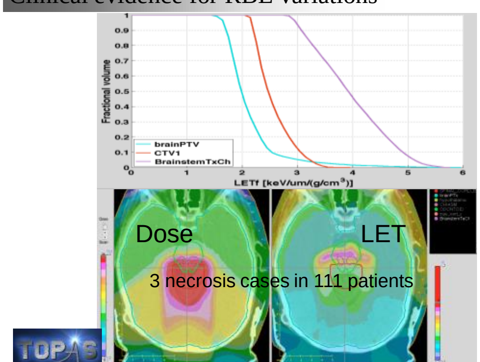
RBE from experimental data | Clinical evidence for RBE variations | Biological treatment planning

RBE increase with
- decreasing dose
- increasing LET
- decreasing α/β

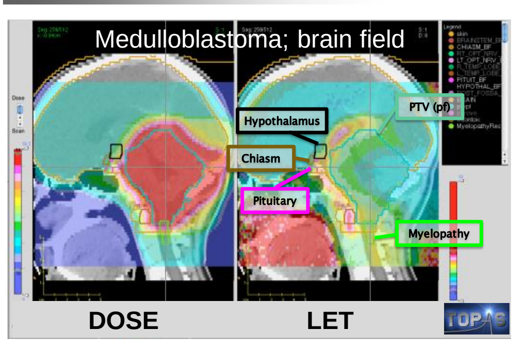
Clinical evidence for RBE variations

- 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

Clinical evidence for RBE variations

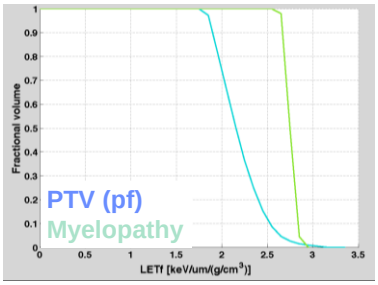


Clinical evidence for RBE variations



Sethi; Giantsoudi; Raiford; Rappalino; Caruso; Yock; Tarbell; Paganetti; MacDonald: Patterns of failure following proton therapy in medulloblastoma; LET distributions and RBE associations for relapses. International Journal of Radiation Oncology, Biology, Physics 2014 88: 655-663

Clinical evidence for RBE variations



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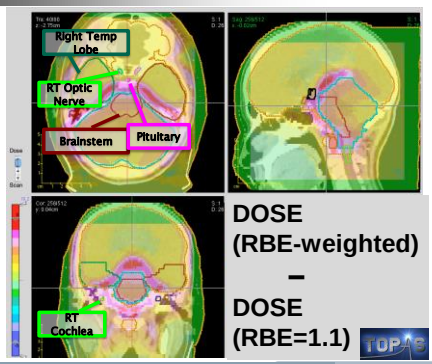
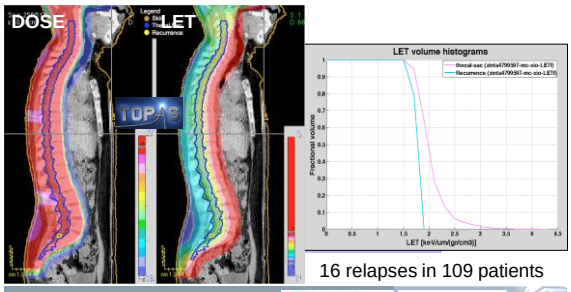


Sethi; Giantsoudi; Raiford; Rappaport; Caruso; Yock; Tarbell; Paganetti: Medulloblastoma; LET distributions and RBE associations for relapses. International Journal of Radiation Oncology, Biology, Physics 2014 88: 655-663

Clinical evidence for RBE variations

The clinical significance of RBE variations depends α/β

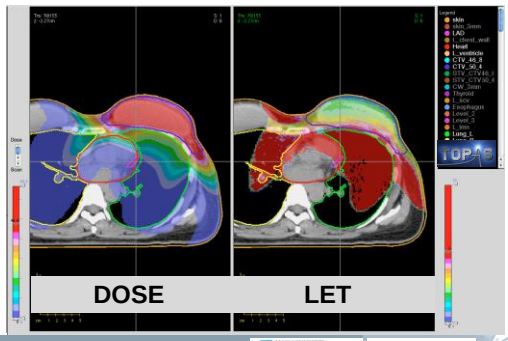


16 relapses in 109 patients

Sethi; Giantsoudi; Raiford; Rappaport; Caruso; Yock; Tarbell; Paganetti: Medulloblastoma; LET distributions and RBE associations for relapses. International Journal of Radiation Oncology, Biology, Physics 2014 88: 655-663

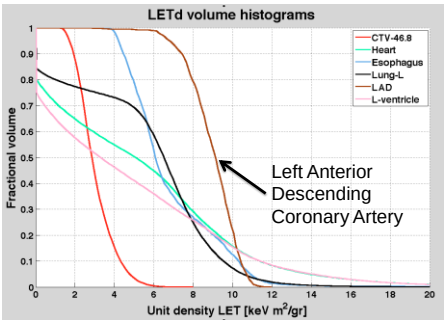
Clinical evidence for RBE variations

Chest wall irradiation



Clinical evidence for RBE variations

Chest wall irradiation

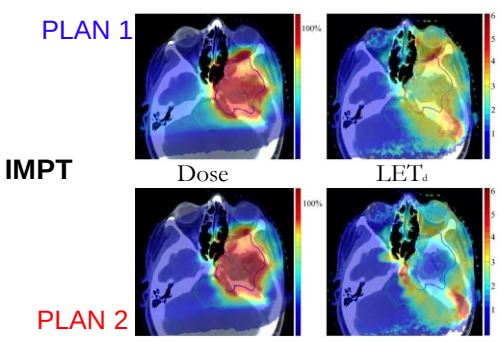


RBE from experimental data | Clinical evidence for RBE variations | Biological treatment planning

RBE increase with
- decreasing dose
- increasing LET
- decreasing α/β

No clear evidence (yet)

Biological treatment planning

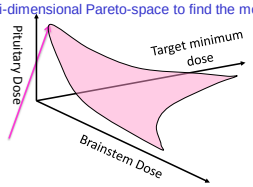


Grassberger; Trofimov; Lomax; Paganetti: Variations in linear energy transfer within clinical proton therapy fields and the potential for biological treatment planning. Int J Radiat Oncol Biol Phys 2011 80: 1559-1566

Biological treatment planning

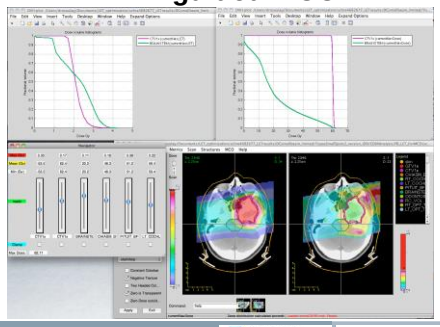
Multi-Criteria Optimization (MCO)

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



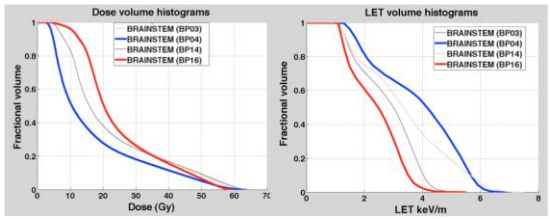
Biological treatment planning

LET-guided MCO



Biological treatment planning

LET-guided MCO



Giantsoudi; Grassberger; Craft; Niemierko; Trofimov; Paganetti: Linear energy transfer (LET)-Guided Optimization in intensity modulated proton therapy (IMPT): feasibility study and clinical potential. International Journal of Radiation Oncology, Biology, Physics 2013 87: 216-222

RBE from experimental data	Clinical evidence for RBE variations	Biological treatment planning
RBE increase with ▪ decreasing dose ▪ increasing LET ▪ decreasing α/β	No clear evidence (yet)	Might help to exploit RBE variations

Summary

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 α/β**
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

MGH Radiation Oncology Physics Research Team

MGH Radiation Oncology Monte Carlo Team

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- Federal Share on C06 CA059267
  "Accurate Monte Carlo Dose Calculation for Proton Therapy Patients"
- MGH ECOR
  "Biologically Optimized Treatment Planning for Proton Beam Therapy"
- MGH ECOR
  "GPU based dose calculation for proton therapy"