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

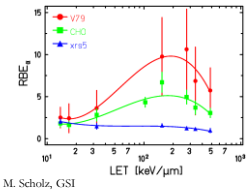
- The RBE is defined as the ratio of doses to reach the same level of effect when comparing two modalities
- RBE for TCP could potentially deduced from tumor control data
- RBE for NTCP is difficult to assess based on clinical data because photons generally deliver a more uniform dose to critical structures 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

RBE for cell survival – Endpoint dependency

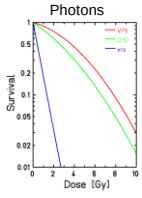
$$S(D) = e^{-(\alpha D + \beta D^2)}$$

Cells with higher repair capacity (low α/β) show higher RBE

Carbon ions



Photons



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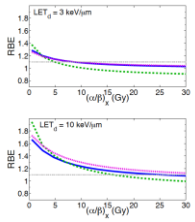
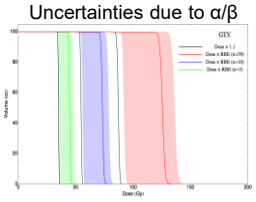
RBE for cell survival – Endpoint dependency



McNamara, Schuemann, Paganetti:
Phys Med Biol 2015 60; 8399-8416

Uncertainties due to α/β



Carabe, España, Grassberger, Paganetti:
Phys Med Biol 2013 58: 2103-2117

RBE for cell survival – Endpoint dependency

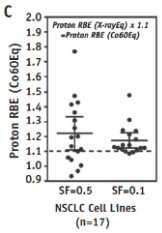
Inter-patient variability on cell survival RBE can be substantial

"Links Fanconi Anemia/BRCA pathway defects to elevated proton RBE"

Liu, Ghosh, Magpayo, Testa, Tang, Biggs, Paganetti, Efstathiou, Lu, Held, Willers:
Int J Radiat Oncol Biol Phys 2015 91: 1081-1089

"Repair kinetics in HR-deficient cells were significantly delayed after proton irradiation, with elevated amounts of residual gH2AX foci"

Grosse, Fontana, Hug, Lomax, Coray, Paganetti, Sartori, Pruschy:
Int J Radiat Oncol Biol Phys 2014 88: 175-181



RBE for cell survival – Endpoint dependency

RBE relevant for NTCP:

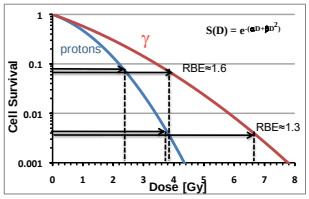
Effect of interest (organ level):

- early effects such as erythema
- late effects such as lung fibrosis, lung function, spinal cord injury, or necrosis

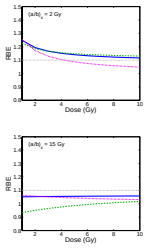
Typically measured other than cell survival (cellular level):

- Double-strand break induction
- Foci formation
- Chromosome aberrations
- Micronuclei formation
- Cell cycle disruption …

RBE for cell survival – Dose dependency



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

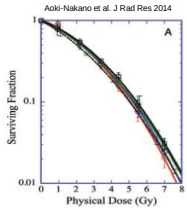


McNamara, Schuemann, Paganetti: Phys Med Biol 2015 60; 8399-8416

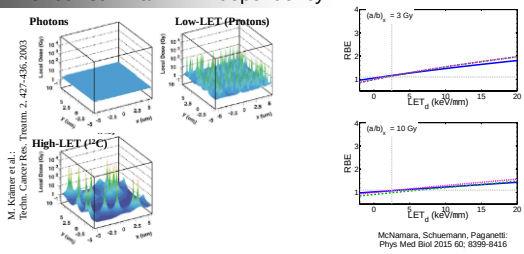
RBE for cell survival – Dose dependency

- **Most experiments in vitro look at cell survival**
- **Precise measurements of cell survival below 2 Gy are sparse**
- **Prescription doses are typically 2Gy/fraction**
- **There are only a few data points regarding dose dependency of RBE in vivo below 4 Gy for protons**

Aoki-Nakano et al. J Rad Res 2014



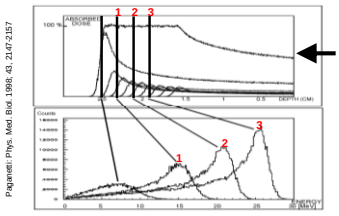
RBE for cell survival – LET dependency



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

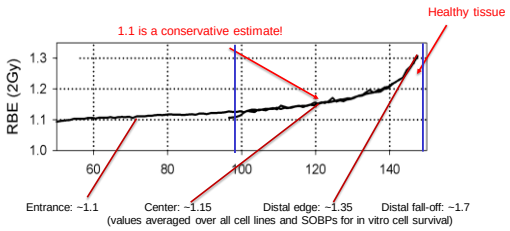
RBE for cell survival – LET dependency

Implication of RBE(LET) for RBE(depth)



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

RBE for cell survival – LET dependency



Paganetti H: Phys Med Biol 2014 59: R419-R472

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

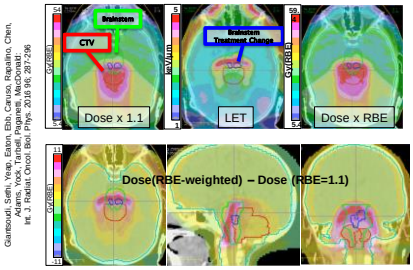
RBE depends on α/β

- RBE seems to be higher for tissues with a low α/β 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

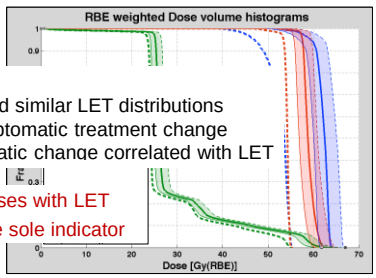
Clinical evidence ?



Giantsoudi, Seth, Yeap, Eaton, Ebb, Caruso, Papaiano, Chen, Adams, Yock, Paganetti, Int. J. Radiat Oncol Biol. Phys. 2016 96; 287-296

Clinical evidence ?

Correlation of toxicity and LET



Giantsoudi, Seth, Yeap, Eaton, Ebb, Caruso, Papaiano, Chen, Adams, Yock, Paganetti, Int. J. Radiat Oncol Biol. Phys. 2016 96; 287-296

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

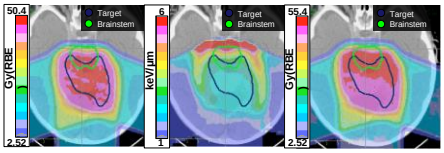
Clinical evidence ?

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 conformality

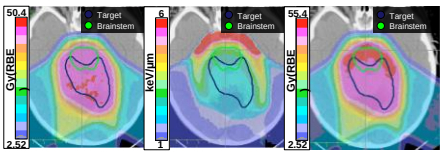


Dose x 1.1 LET Dose x RBE

Giantsoudi, Adams, Kim, MacDonald, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2016 under review

RBE considerations in treatment planning

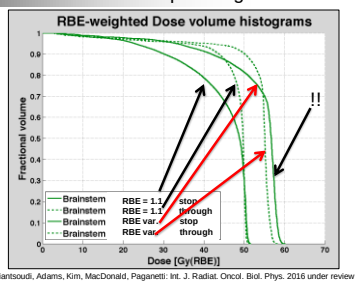
Planning technique minimizing maximum LET in the brainstem



Dose x 1.1 LET Dose x RBE

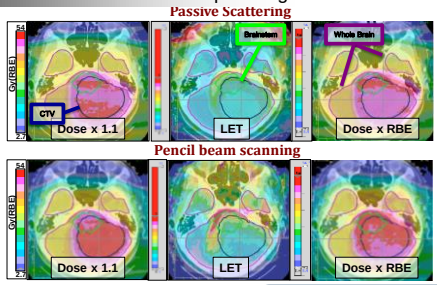
Giantsoudi, Adams, Kim, MacDonald, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2016 under review

RBE considerations in treatment planning



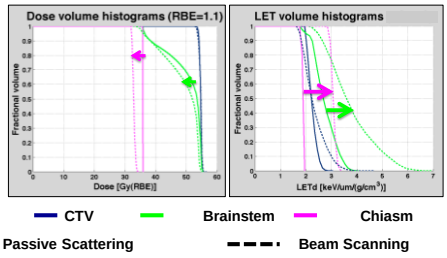
Giantsoudi, Adams, Kim, MacDonald, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2016 under review

RBE considerations in treatment planning



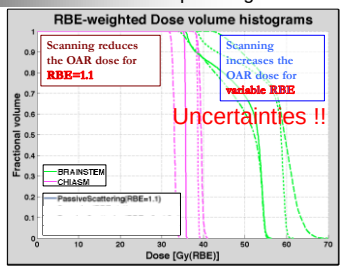
Giantsoudi, Adams, MacDonald, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2016 in preparation

RBE considerations in treatment planning



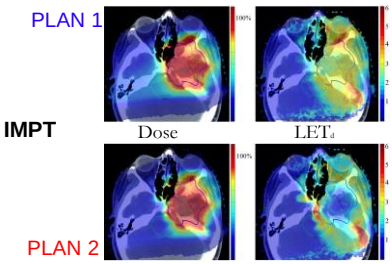
Giantsoudi, Adams, MacDonald, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2016 in preparation

RBE considerations in treatment planning



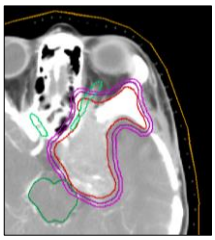
Giantsoudi, Adams, MacDonald, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2016 in preparation

Biological treatment planning using physics information



Grassberger, Tinnefeld, Lomax, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2011 80:1559-1566

Biological treatment planning using physics information



atypical meningioma

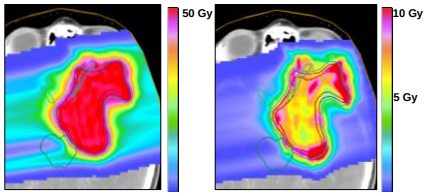
CTV overlaps with

- **optic nerve**
- **chiasm**
- **brainstem**

Unkelbach, Botas, Grassberger, Giantsoudi, Paganetti: Int. J. Radiat. Oncol. Biol. Phys. 2016 under review

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**

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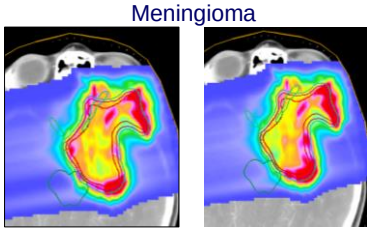
Int. J. Radiat. Oncol. Biol. Phys. 2016 under review

Biological treatment planning using physics information

Meningioma

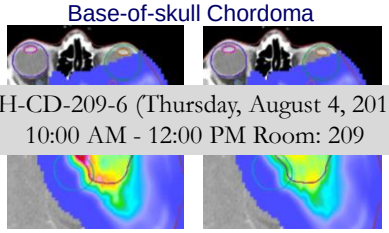


reference plan **re-optimized**

Unkelbach, Botas, Grassberger, Giantsoudi, Paganetti:
Int. J. Radiat. Oncol. Biol. Phys. 2016 under review

Biological treatment planning using physics information

Base-of-skull Chordoma



TH-CD-209-6 (Thursday, August 4, 2016)
10:00 AM - 12:00 PM Room: 209

reference plan **re-optimized**

Unkelbach, Botas, Grassberger, Giantsoudi, Paganetti:
Int. J. Radiat. Oncol. Biol. Phys. 2016 under review

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

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