Biological considerations in proton therapy

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1. Generic and variable RBE
2. Proton therapy outcome
3. Neutron worries
1. Generic and variable RBE
Proton therapy: RBE = 1.1

Dose in proton therapy is prescribed as Gy(RBE)
Clinical RBE

RBE from experimental data

RBE values *in vitro* (center of SOBP; relative to $^{60}$Co)

1.21 ± 0.20

Endpoint: Cell Survival

Clinical RBE

RBE from experimental data

RBE values *in vivo* (center of SOBP; relative to $^{60}$Co)

![Graph showing RBE values](image)

\[ \text{RBE} = 1.07 \pm 0.12 \]

Mice data: Lung tolerance, Crypt regeneration, Acute skin reactions, Fibrosarcoma NFSa
Experimental data in vivo are supporting the use of a clinical RBE of 1.1 in proton therapy.

Our clinical experience (with current margins and passive scattering) does not indicate that the RBE of 1.1 for proton therapy is incorrect.
RBE as a function of dose

\[ S(D) = e^{-(\alpha D + \beta D^2)} \]
RBE as a function of dose

**in vitro**

![Graph showing RBE as a function of dose in vitro](image1)

**in vivo**

![Graph showing RBE as a function of dose in vivo](image2)

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**Wouters et al. 1996**

70 MeV → V79

![Graph showing RBE for 70 MeV radiation](image3)

**Yashkin et al. 1995**

179 MeV → V79

![Graph showing RBE for 179 MeV radiation](image4)

**Tang et al. 1997**

65 MeV → CHO

![Graph showing RBE for 65 MeV radiation](image5)
RBE as a function of dose

- RBE increases with decreasing dose; the effect seems to be small for protons
- There are only a few data points regarding dose dependency of RBE in vivo
- Indicates higher RBE for OAR
RBE as a function of tissue/endpoint

RBE values *in vitro* (center of SOBP; relative to $^{60}$Co)

- V79 cells only

RBE as a function of tissue/endpoint

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

V79 \((\alpha/\beta \sim 3\text{Gy})\)
RBE as a function of tissue/endpoint

Belli et al. 2000
Bettega et al. 1979

Proton Energy [MeV]

RBE in vitro

human cells
RBE as a function of tissue/endpoint

- We cannot measure RBE for all endpoints
- Do cells with higher repair capacity show higher RBE?

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

Paganetti, Gerweck, Goitein

Gerweck and Kozin
Radiother. Oncol. 1999
RBE as a function of tissue/endpoint

Uncertainties due to $\alpha/\beta$ 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
We have to be careful when using V79 cell data to estimate RBE effects in clinical scenarios.

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

- RBE might be higher for non-lethal injuries.
RBE as a function of energy/LET

![Graph showing RBE in vitro as a function of proton energy (MeV).](image-url)
RBE as a function of energy/LET

Implication of RBE(LET) for RBE(depth)

\[
\text{Dose} = \text{Fluence} \left[ \text{1/cm}^2 \right] \times \text{LET} \left[ \text{keV/cm} \right] / \rho \left[ \text{g/cm}^3 \right]
\]
RBE as a function of energy/LET

Fit of all available RBE values:
- RBE increased by 5% at 4 mm from the distal edge
- RBE increased by 10% at 2 mm from the distal edge
An increasing RBE with depth cause an extended biologically effective range (1-2 mm)
RBE as a function of energy/LET

Range Shift

@ 2Gy

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
Grassberger et al.: 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

RBE as a function of energy/LET

- Increased effectiveness as a function of depth

- Extended beam range (i.e. range uncertainty; to be considered when pointing a field towards a critical structure)

- RBE might be higher close to the ‘target’ edge (mainly in OAR)

- RBE might be higher in beam scanning

- LET is well understood and could potentially be used in biological treatment optimization
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.

Clinical significance of RBE variations still needs to be shown.
2. Proton therapy outcome
Proton Therapy Outcome

- NTCP considerations in treatment planning are based on photon dose distributions (mostly mean dose).
- Organ doses in proton therapy are more heterogeneous. There are no proton specific normal tissue constraints.

Both lung and heart irradiation cause cardiac and pulmonary toxicity via different mechanisms showing evidence for a multi-organ complication.

Ghobadi et al. Physiological Interaction of Heart and Lung in Thoracic Irradiation
Int J Radiat Oncol Biol Phys 2012
Outcome - Conclusions

• If the total reduced dose to critical structures would be all that mattered, there would be no need for clinical trials.
• Assessing clinical impact is difficult because proton dose distributions in critical structures are typically more heterogeneous compared to photon therapy but most dose constraints are defined based on mean dose.
• When interpreting side effects we might have to investigate physiological interactions of different organs.
3. Neutron worries
Neutron dose controversies

Zacharatou Jarlskog & Paganetti;

Neutron dose dependencies

The neutron dose generated in the treatment head decreases with increasing aperture opening.

The neutron dose generated in the patient increases with increasing treatment volume.

passive scattering

passive scattering beam scanning
Doses averaged over 6 fields assuming a 8-year old female patient

Neutron “RBE”

Neutron radiation weighting factor
\[ H = D \times w_R[\text{particle, energy}] \]

Neutron radiation quality factor
\[ H = D \times Q[\text{LET}_\infty] \]

*Annals of the ICRP: ICRP 92*
Neutron “RBE”

Proton Therapy Physics (Paganetti Edt.); Taylor&Francis CRC Press 2011
Second malignancies: protons versus photons

MGH-Harvard Cyclotron Laboratory
◆ Matched 503 HCL proton patients with 1591 SEER patients
◆ Median f/u: 7.7 years (protons) and 6.1 years (photon)
◆ Median age 56 (protons) and 59 (photons)
◆ Second malignancy rates
  ◆ 6.4% of proton patients (32 patients)
  ◆ 12.8% of photon patients (203 patients)
◆ Photons are associated with a higher second malignancy risk

Second malignancies: protons versus photons

The in-field risk is expected to be much lower in proton therapy compared to IMRT (due to a lower integral dose). Most second cancers occur in the primary radiation field.
Neutrons - Conclusions

The out-of-field cancer risk from neutrons is typically comparable with the out-of-field risk in IMRT.

Passive scattering proton therapy with large fields blocked by an aperture with a small opening or with a degrader in the room are of potential concern (in particular for pediatric patients).

The in-field risk is expected to be much lower in proton therapy compared with IMRT (due to a reduced integral dose)!