Biological Plan Optimization of Carbon Ion Therapy

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Increased Relative Biological Effectiveness: RBE

Differential Effect:

Enhancement(Peak) >>
Enhancement(Plateau)

Neutrons: Enhancement everywhere!!!

Carbon 195 MeV/u

Absorbed Dose
„Effective“ Dose

Survival
RBE

Penetration depth [mm]

Weyrather et al.
**Definition:** Relative Biological Effectiveness (RBE)

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

\[ \alpha_{Ion} \geq \alpha_{Photon} \]

\[ \beta_{Ion} \leq \beta_{Photon} \]

\[ RBE = \frac{D_{Photon}}{D_{Ion}} \mid_{Isoeffect} \]

\[ RBE_\alpha = \frac{\alpha_{Ion}}{\alpha_{Photon}} \]
Challenge:
Homogenous distribution of effective dose in treatment volume
Effective dose distribution in normal tissues

\[ D_{RBE} = D_{Phys} \cdot RBE \]

RBE depends on several factors:
• Particle species / LET
• Dose
• Cell / Tissue type
• Oxygen status
• ...
LET ↔ Depth Dependence of RBE

Weyrather et al. IJRB 1999
Depth Dependence of RBE

Reduction of dose towards distal peak to account for increase of RBE
Dose Dependence of RBE

**In-vitro:**
Cell survival / CHO-cells

- RBE=3.2
- RBE=4.2
- RBE=5.8

**In-vivo:**
Tolerance of Rat Spinal Cord

- RBE decreases with Dose

Weyrather et al., IJRB 1999
Karger et al. IJROBP 2006

**RBE decreases with Dose**
Dependence of RBE on Effect Level

Endpoint: HSG cell survival in-vitro

Shape depends on effect level
Relevant for hypofractionation
Cell type dependence of RBE

RBE is correlated with repair capacity
(In terms of LQ-model: with $(\alpha/\beta)_{\text{Photon}}$-ratio)

Weyrather et al. IJRB 1999
Complex RBE dependencies: E, LET, D, cell type,…

Interpolation/extrapolation required for treatment planning in HI therapy

HIMAC
Experimental Data
+ Clinical Neutron Experience
(\textit{Fixed} RBE-scheme)

GSI / HIT
Biophysical Modelling
(Local Effect Model LEM)
(Variable RBE-scheme)
In-vitro Experiments
(Monoenergetic, high-LET)
\(\alpha_{\text{Carbon}}(x), \beta_{\text{Carbon}}(x)\)

Algorithm:
Dose Weighted Average
\[
\alpha_{\text{Mix}} = \sum_i f_i \alpha_i \quad \beta_{\text{Mix}} = \sum_i f_i \beta_i
\]

Relative Shape of Depth Dose Distribution
Absolute RBE:
Clinical Neutron Experience

Treatment Planning

PTCOG Educational Workshop
18.5.2010
GSI Approach: Basics of Modelling

Tracks

Cell nucleus

Local Dose [Gy]

Carbon ions

Cell

Local Dose [Gy] x10000

Carbon ions, local

Local Dose [Gy]

Photons

18.5.2010

PTCOG Educational Workshop
Basic Assumption:
Increased effectiveness of particle radiation can be described by a combination of the photon dose response and microscopic dose distribution

Local Effect (Photons) = Local Effect (Ions) + RBE!

LEM: Transfer of low-LET experience to high-LET
Input Parameters

• **Physics: Radial Dose Distribution:**

\[ D(r) \propto \frac{1}{r^2} \quad R_{\text{Track}} \propto E^{1.7} \]

• **Biology: **Photon** Dose Response Curve:**
  Clinical / experimental data according to LQ
  Assumption: Transition to linear shape at high doses \( D > D_t \)
  Essential parameter: Final/initial slope (\( \alpha/\beta \)-ratio)

• **Biology: Target Size (Nuclear Size):**
  Experimental Data
Treatment Planning: GSI approach

**LEM-Model**

**Feedback from Experiments**

**Evolution of LEM:**
- LEM I: 1997
- LEM II: 2007
- LEM III: 2008
- LEM IV: 2009

**LEM II:** SSB + SSB -> DSB

**LEM III:** Improved Track Structure

**LEM IV:** Effect derived from DSB distribution
- DSB + DSB -> complex DSB

Focus on **C**

Focus on **p...O**

**Biological Characteristics of Cells**
- $\alpha_{\text{Photon}}$, $\beta_{\text{Photon}}$

**Physical Characteristics of Ions**
- Track structure

**Treatment Planning**

**in-vitro-Exp. Ions**

**in-vivo-Exp. Ions**
Comparison LEM – Experimental Data

**In-vitro:**
Cell Survival

![Graph showing cell survival data for various LEMs and experimental data points.]

- **Exp. Data:** Weyrather et al., IJRB 1999
- **LEM I:** Scholz et al., Rad. Env. Biophys 1997
- **LEM II:** Elsässer et al., Rad. Res. 2007
- **LEM III:** Elsässer et al., IJROBP 2008

**In-vivo:**
Tolerance of Rat Spinal Cord

![Graph showing tolerance data for various LEMs and experimental data points.]

- **Exp. Data:** Karger et al. IJROBP 2006
- **LEM I:** Scholz et al., Rad. Env. Biophys. 1997
- **LEM II:** Elsässer and Scholz, Rad. Res. 2007
- **LEM III:** Elsässer et al., IJROBP 2008
Comparison $p$, He, C for LEM IV

Exp. Data: Belli et al., IJRB 1998

Model: Elsässer et al, accepted for publication in IJROBP
Carbon vs. proton: is there an advantage?

First radiobiology experiments at HIT facility:
- Direct comparison of protons and carbon ions
- Test of significantly improved LEM version

Experimental data: Weyrather et al.
Model: Elsässer et al, accepted for publication in IJROBP
Tissue dependence of RBE might lead to discontinuities of the RBE-weighted dose distribution!
RBE-Map

Krämer et al.
Summary

- RBE depends on position in SOBP, dose level and biological system
- Interpolation / extrapolation of experimental data and/or modelling are required to represent these dependencies in treatment planning
- LEM has been implemented in the TRiP treatment planning environment for the GSI pilot project and in the Siemens TPS
- LEM is able to predict RBE for different cell systems and for all therapeutically relevant particles from protons to carbon ions
- Differences between HIMAC and GSI/HIT approach have to be taken into account when interpreting RBE-weighted dose values