Radiobiology in heavy ion therapy

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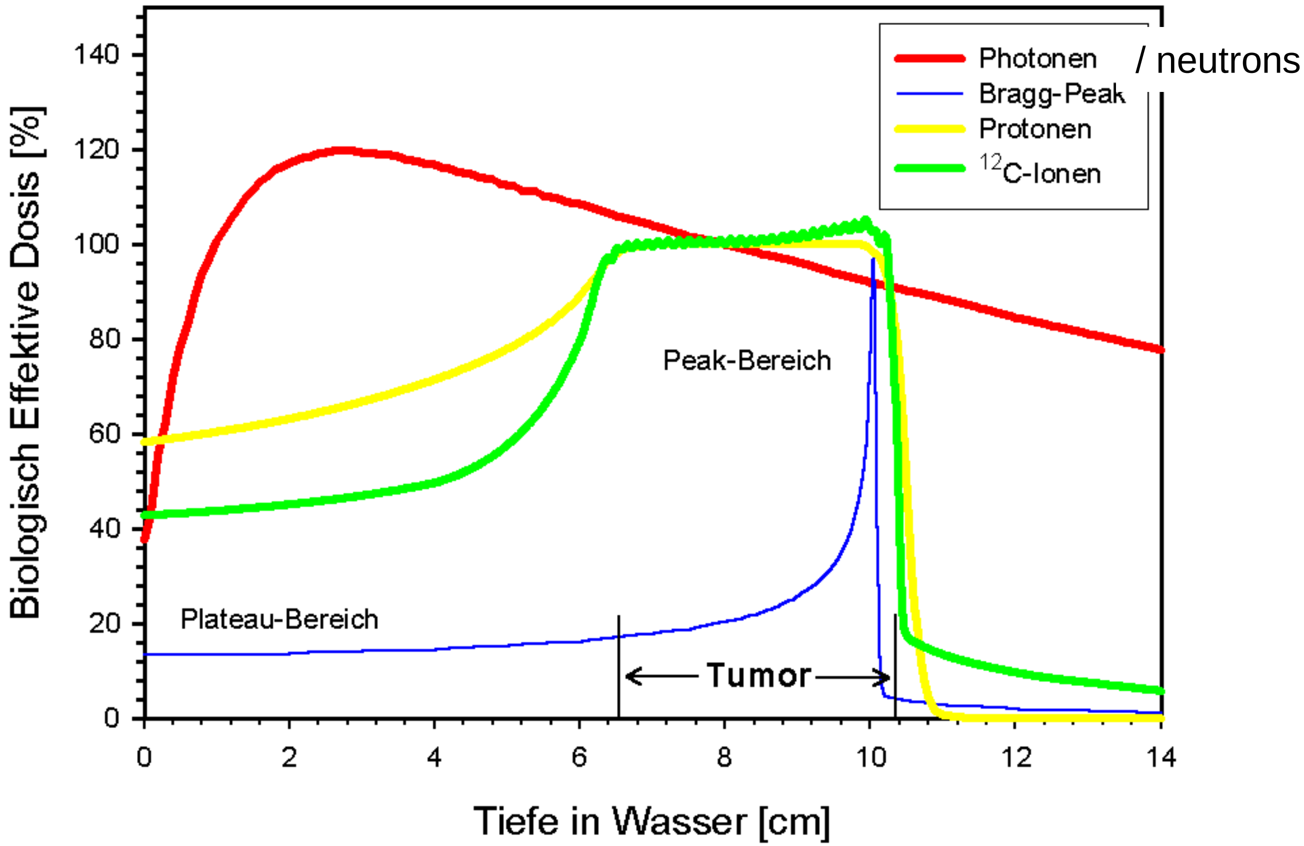
dkfz.

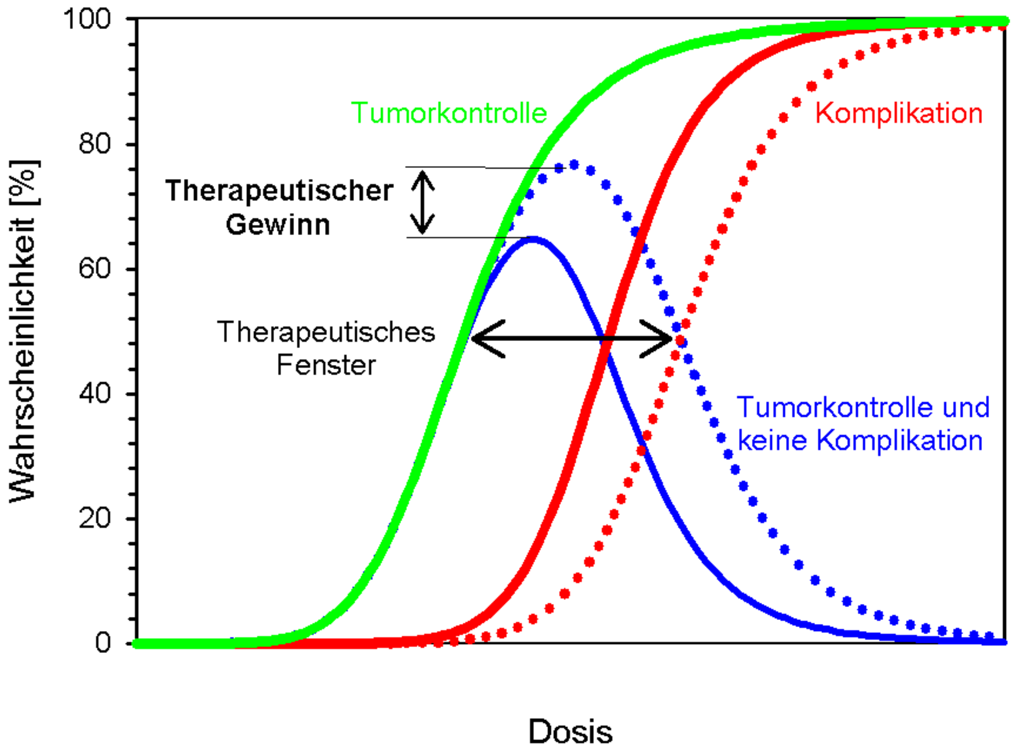
Depth dose distributions of Hadron beams



- Neutrons are very similar to photons in terms of depth dose
- Ions show reduced entrance dose
- No / little dose behind the tumor

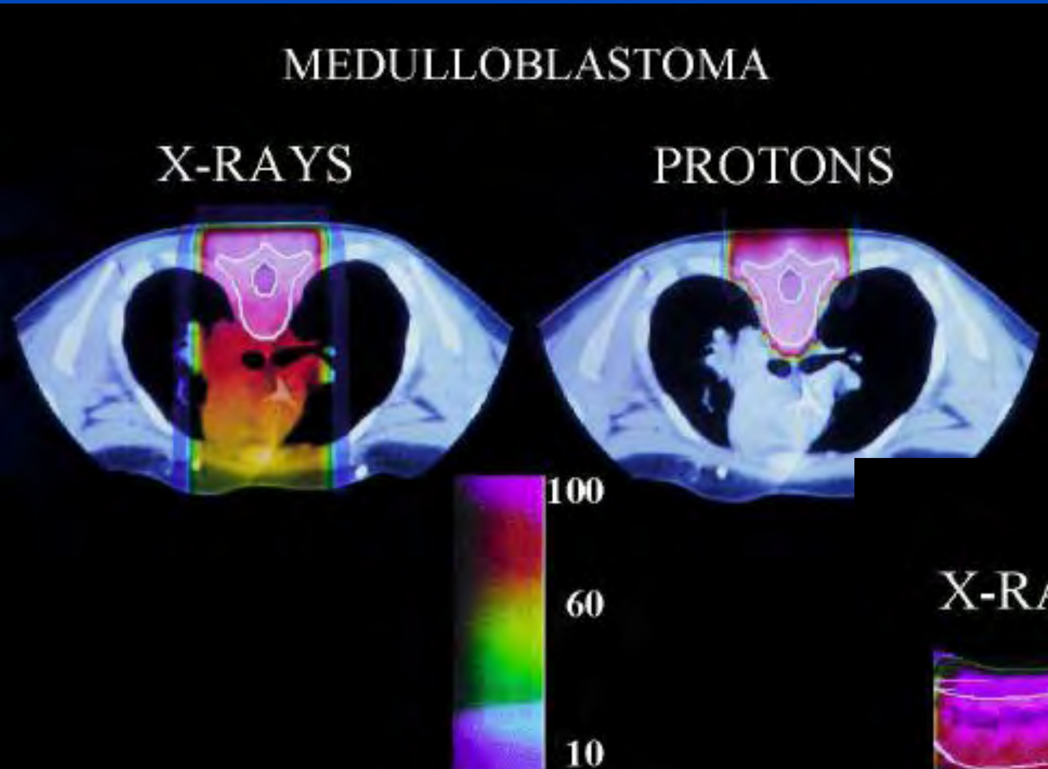
The Rationale for Conformal Radiation Therapy

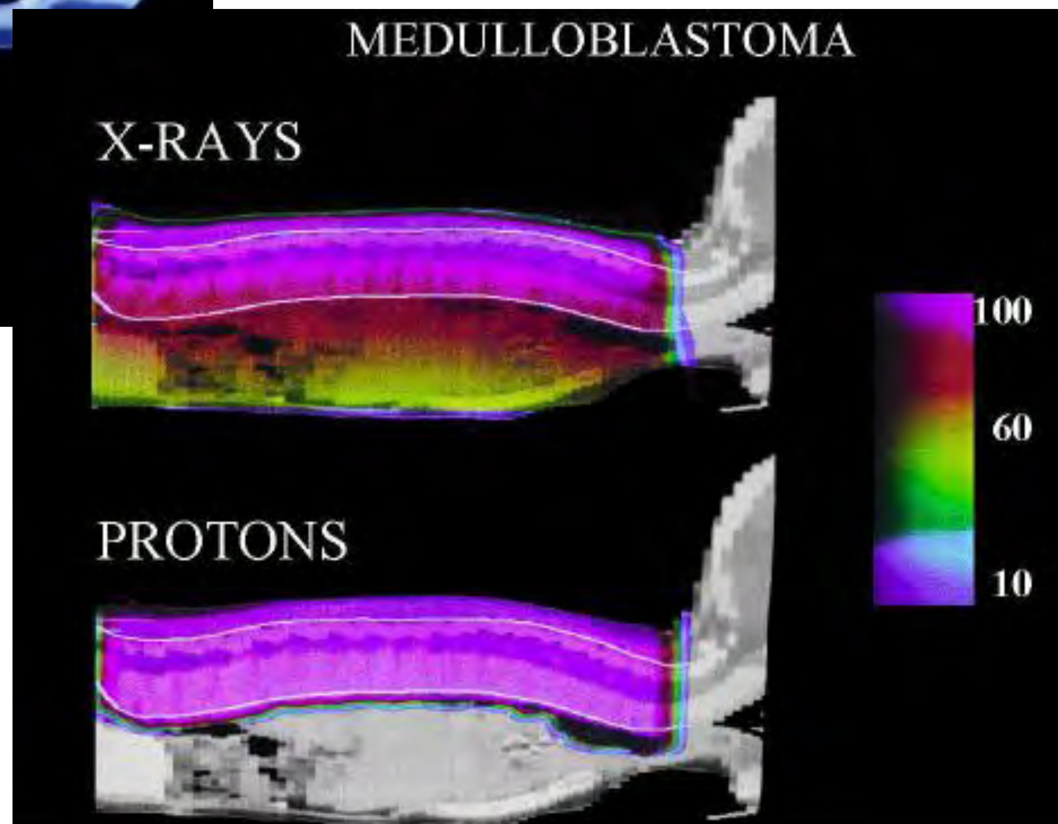
- Dose (and tumor control) are limited due to tolerance of OAR
- Volume effect: increase of tolerance if smaller volume irradiated



Better conformation of dose enables application of higher doses & higher tumor control without increasing normal tissue complication rate

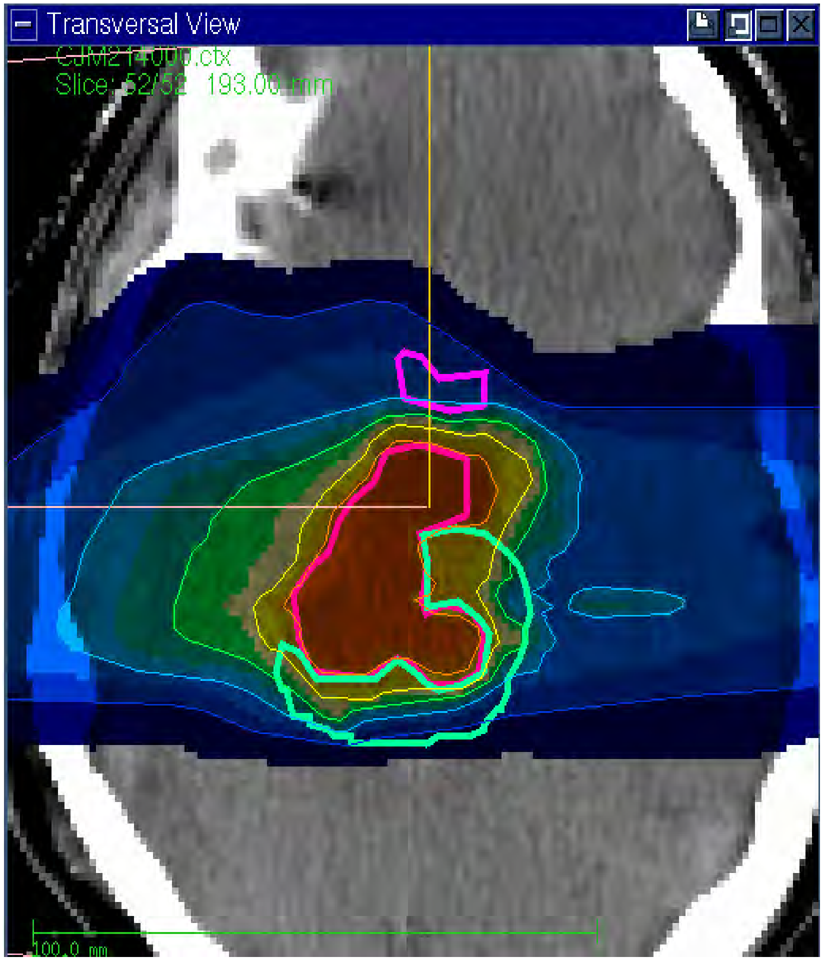
Bragg peak for Medulloblastoma treatments: γ vs. p

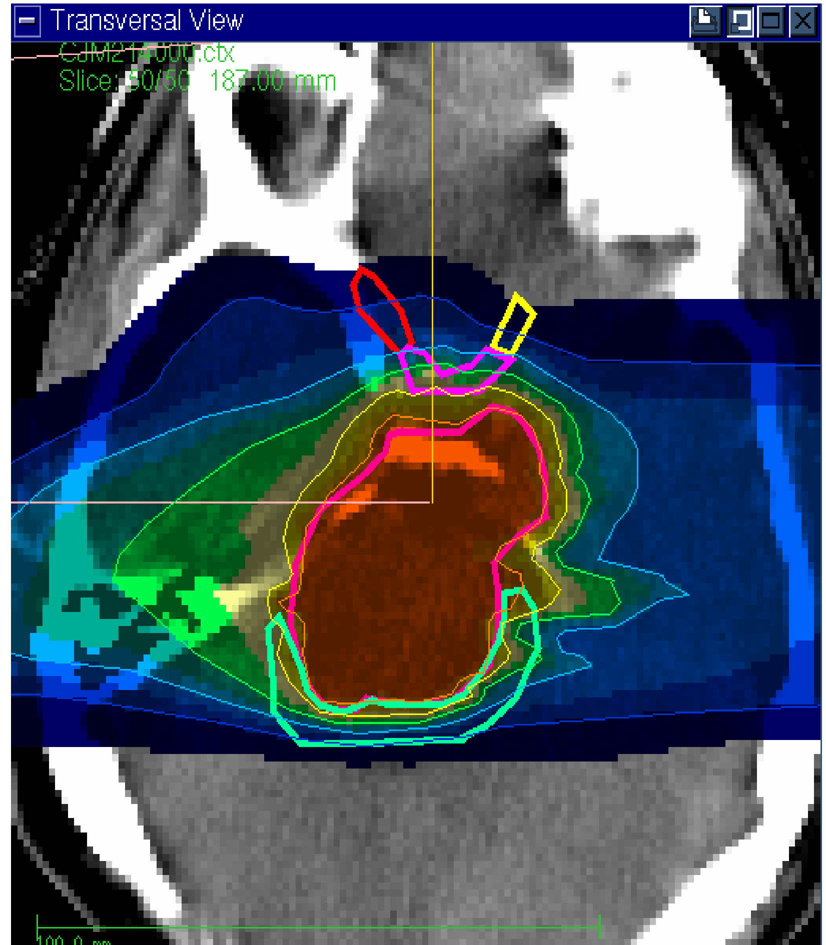




Dose sparing of Mediastinum, intestine and bone marrow

The dose conformation potential: Carbon ion RT of skull base chordomas





Excellent sparing of normal tissue and highly effective RT

Radiobiology of high and low LET radiation

Ionisation tracks

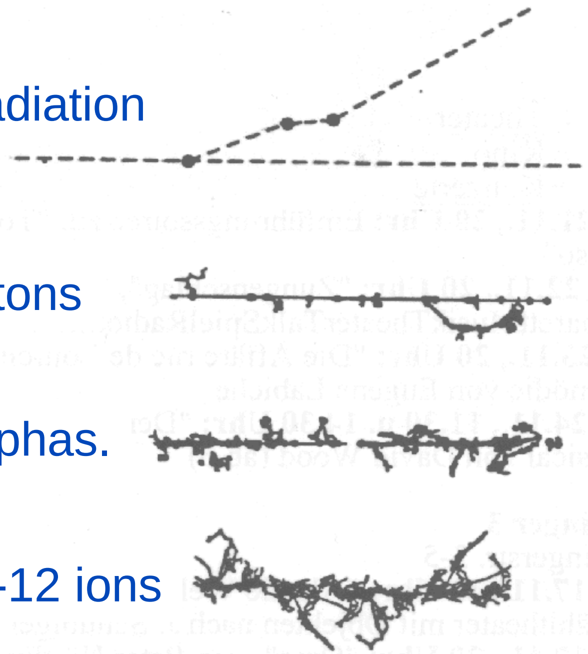
LET

Gamma radiation

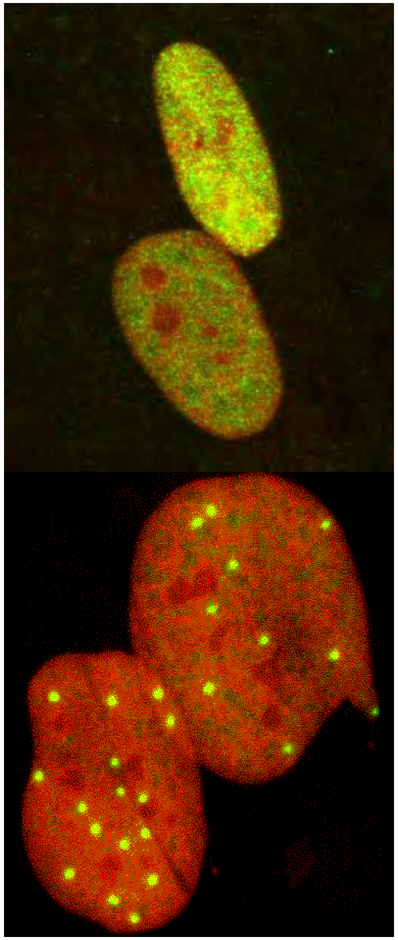
1MeV Protons

1MeV/u alphas.

1MeV/u C-12 ions



Damage in nucleus



Low LET

Homogeneous deposition of dose

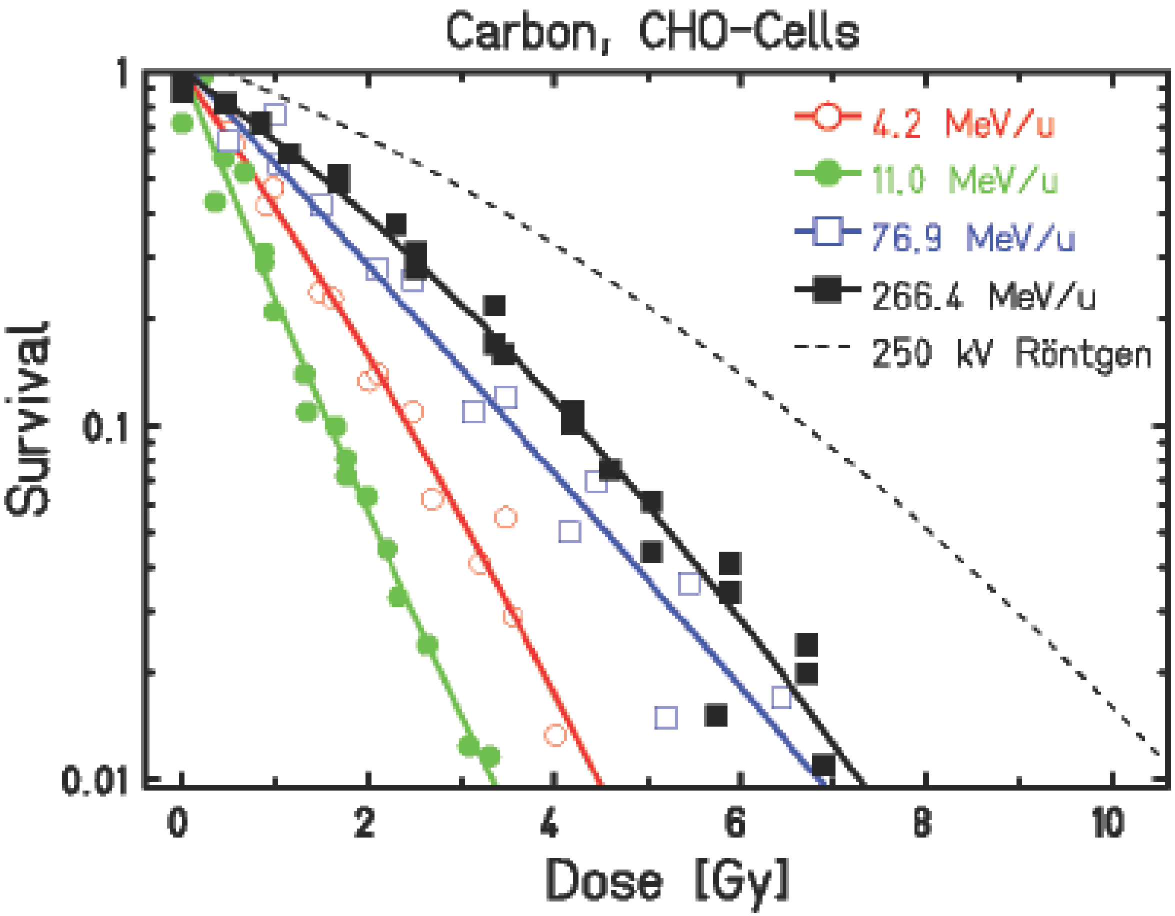
High LET

Local deposition of high doses

M. Scholz et al. Rad. Res. 2001 Immunoflourescence image of the repair protein p21;

Increase of **direct radiation damage & RBE** for high-LET

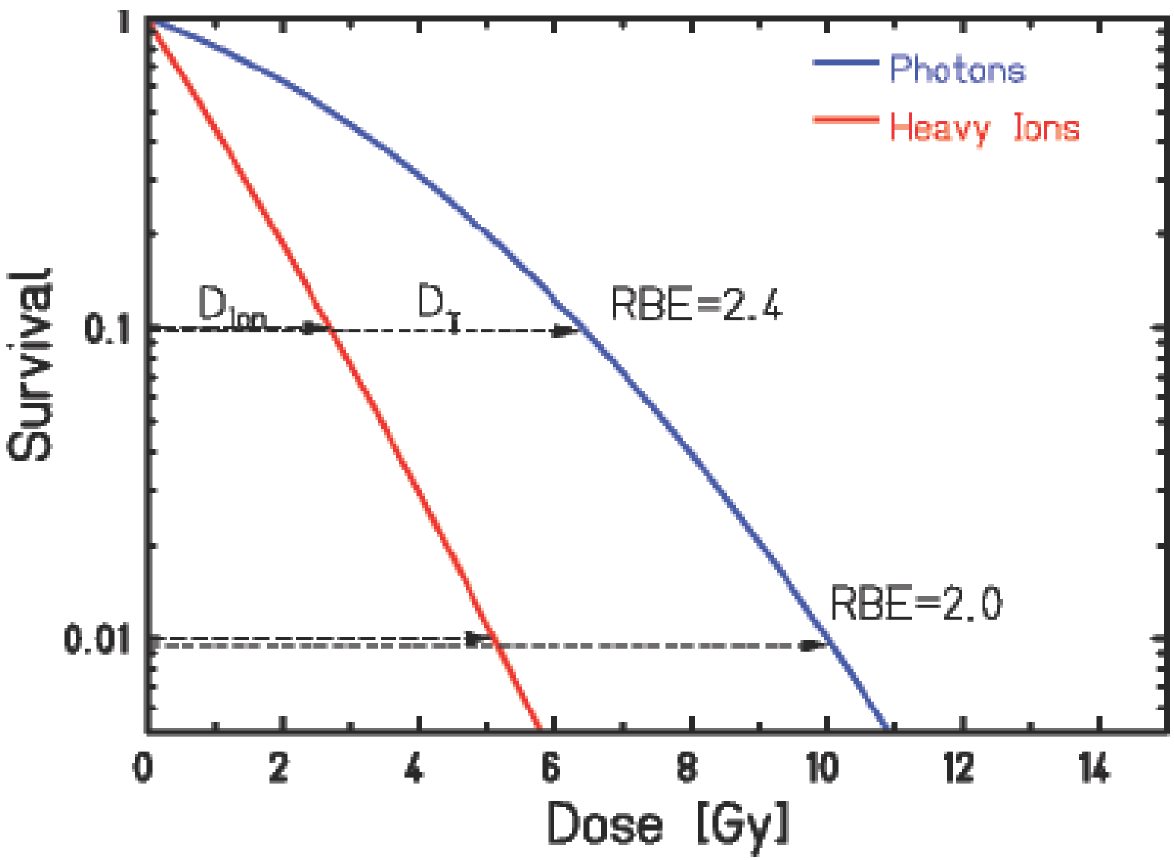
Cell survival curves for high LET radiation



Weyrather et al., IJRB 1999

Increasing effectiveness with decreasing energy
Transition from shouldered to straight survival curves
Saturation effects at very low energies (<10 MeV/u)

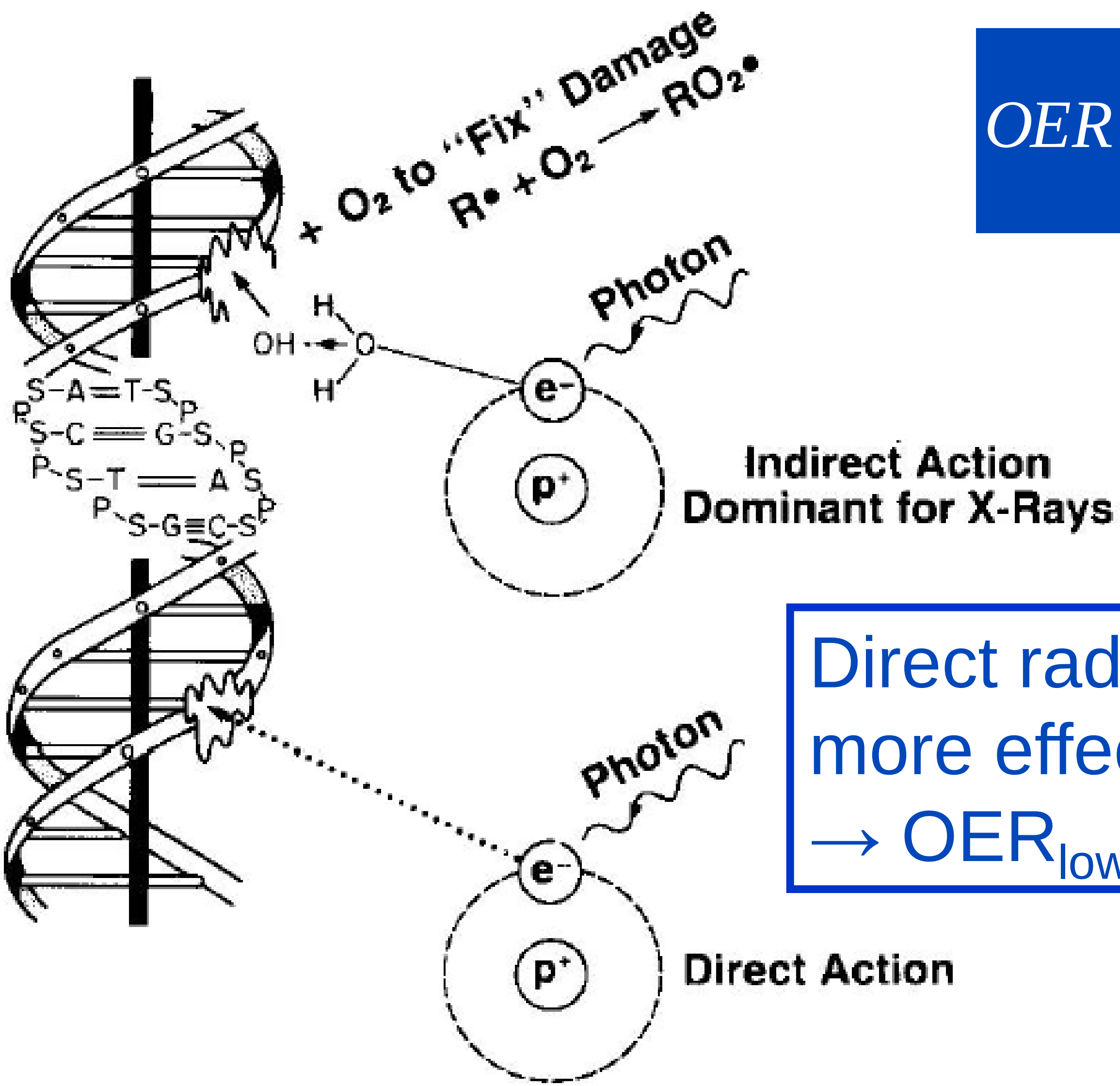
Definition of RBE



$$RBE = \frac{D_\gamma}{D_{Ion}}\Bigg|_{Isoeffect}$$

Due to the shouldered photon response curve, RBE is dose dependent!

Oxygen Effect



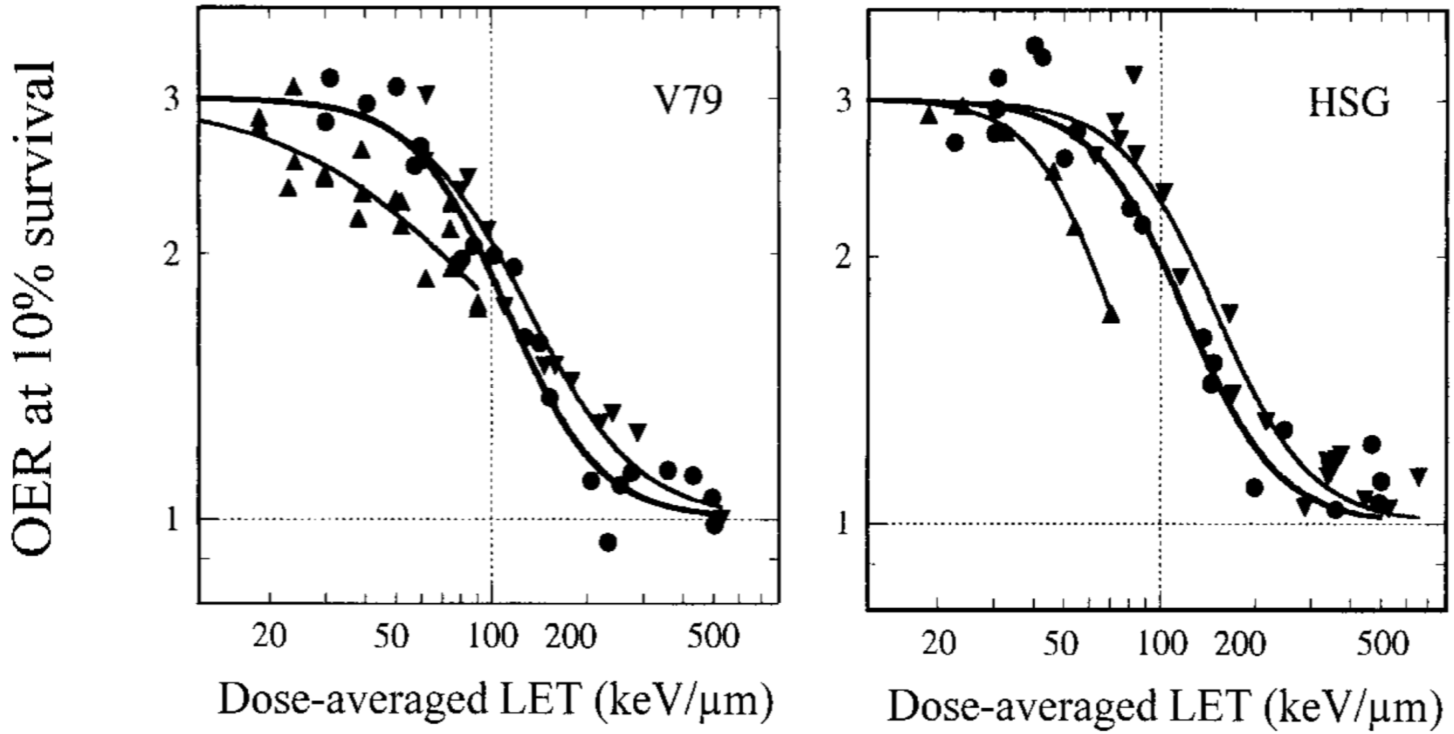
$$OER = \left. \frac{D_{hypoxic}}{D_{oxygenated}} \right|_{Isoeffekt}$$

Direct radiation effects are more effective for high LET

$\rightarrow OER_{\text{low LET}} > OER_{\text{high LET}}$

Oxygen Effect in vitro

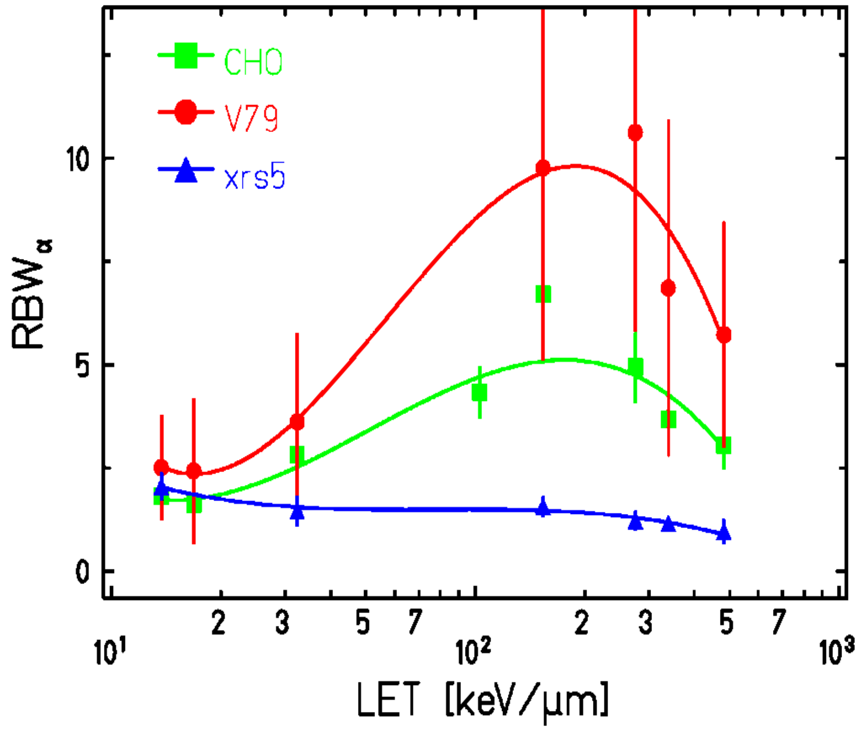
OER as function of LET at 10% survival for V79 and HSG cells exposed to helium (He: ▲), carbon (^{12}C: ●), or neon (^{20}Ne: ▼)



Furusawa et al Rad. Res.154 (2000)

There is a potential to improved outcome for hypoxic tumors.

Dependence of RBE on LET, cell type, particle



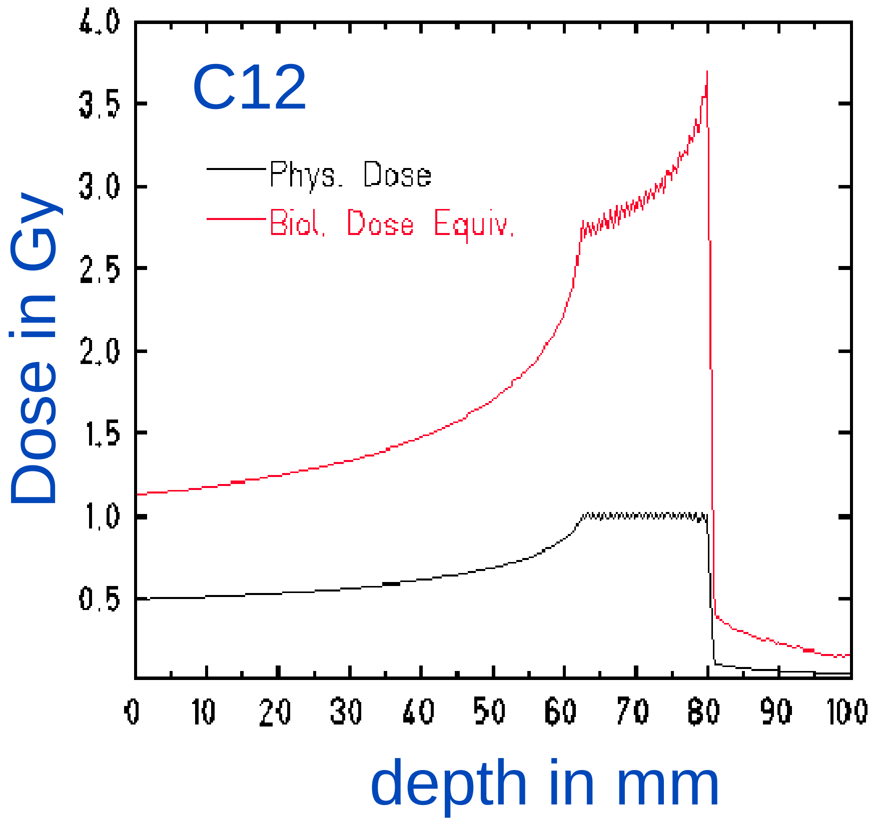
Weyrather et al., Int. J. Rad. Biol. (1999)

- Ions are probably not suited for radiosensitive tumors.
- Ions show an increased RBE in radio-resistant tumors.
- There is a potential to improved outcome for hypoxic tumors.
- There is a benefit of Carbon as compared to protons

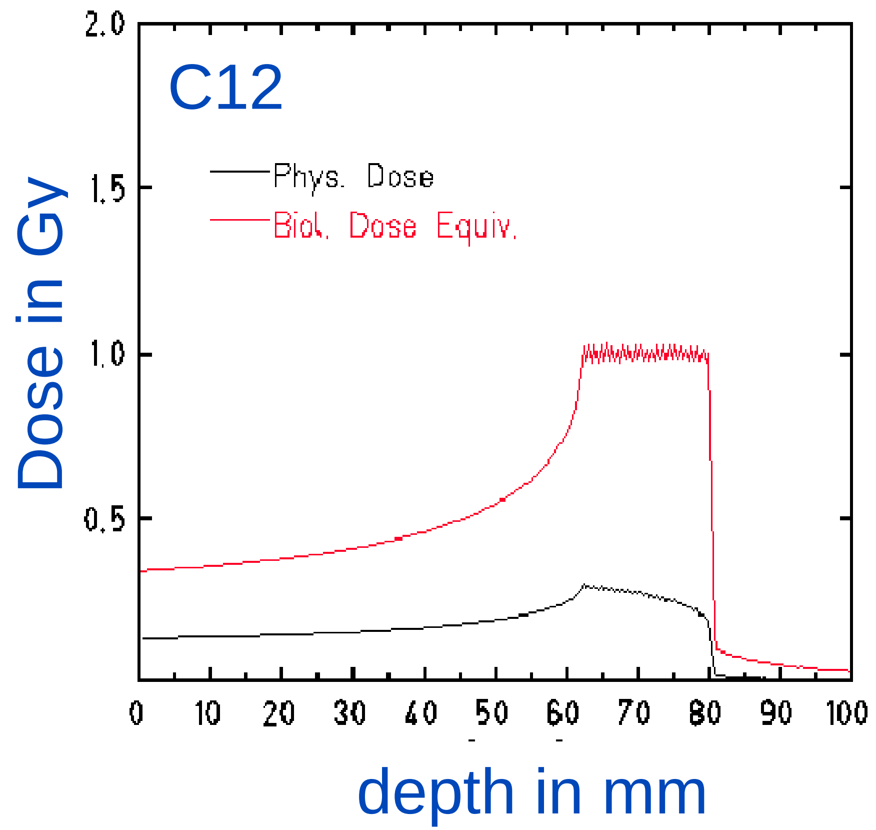
The clinical relevance of this is not yet completely clear.

Optimization of Biological effective dose

Physical dose optimization



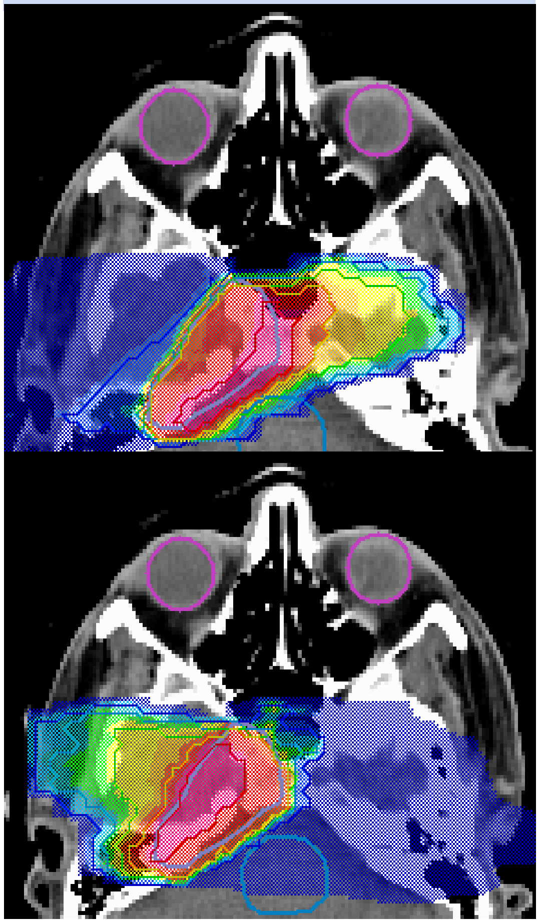
Biological dose optimization



- **The depth modulation varies f.e. point in the field**
- Account for nuclear fragmentation in every point in 3D
- Detailled biological modelling necessary

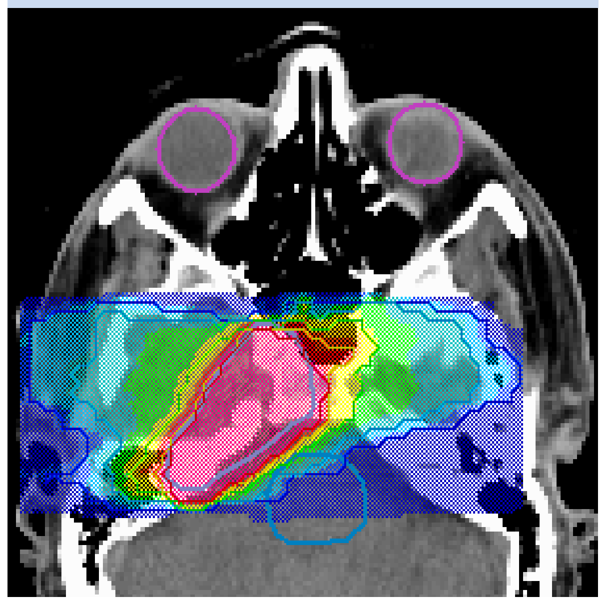
Biological treatment planning for carbon ions

Physical dose
of single fields

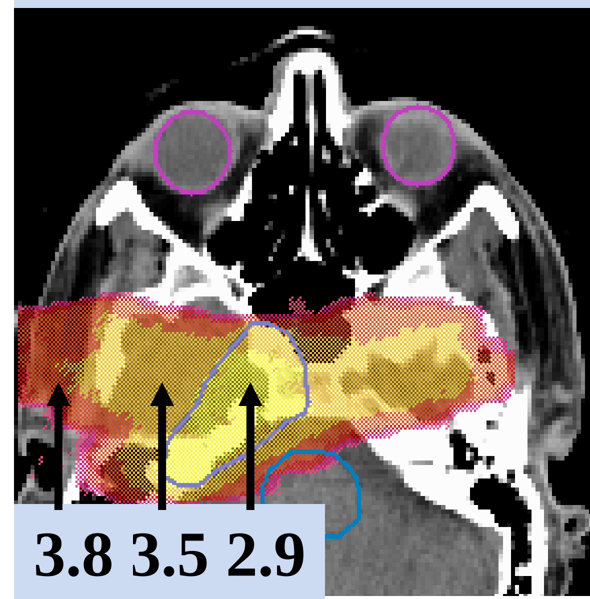


Local effect model of Scholz and Kraft:
Calculation of RBE as a 3D distribution
Input: X-ray survival curves &
fragmentation spectra

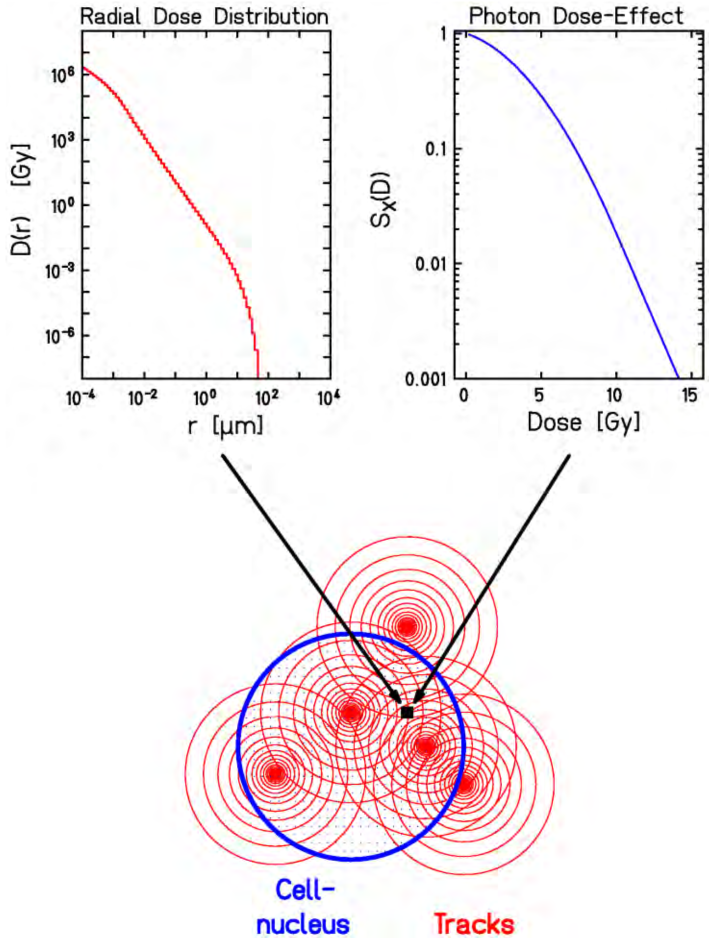
Biological effective dose



RBE-distribution



Principles of the Local Effect Model



$$\overline{N}_{lethal} = \int \frac{-\ln S_X(d(x,y,z))}{V_{Nucleus}} dV_{Nucleus}$$

Input parameters:

- Particle spectrum
- Radial Dose distribution:

$$D(r) \propto \frac{1}{r^2} \quad r_{max} \propto E^c$$

- Photon dose response

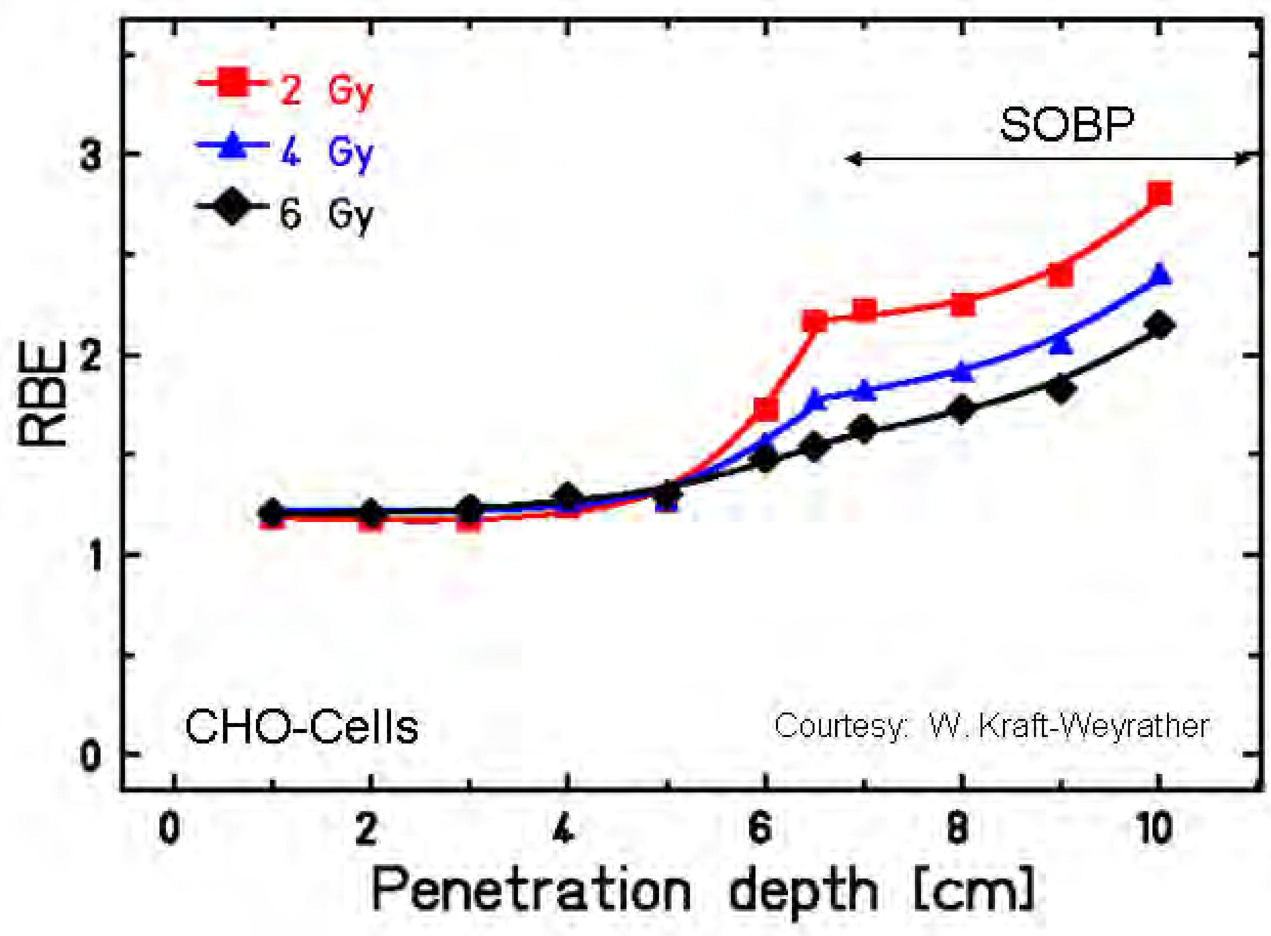
$$S(D) = e^{-(\alpha D + \beta D^2)}$$

- Target size: cell nucleus

Scholz and Kraft, Adv. Space Res. 1996
Scholz et al., Rad. Env. Biophys. 1997

Can also be used for detectors, like TLD, film etc

RBE dependence in a SOBP



→ RBE decreases with increasing dose (decreasing survival)

Radiobiology with heavy ions: C. Tobias

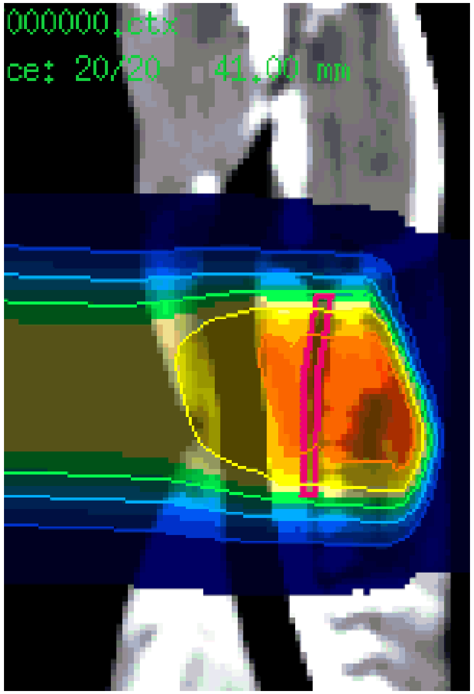
During the 1969 Apollo-11 mission to Moon, Edwin Aldrin experiences peculiar flashes and streaks of light

CORNELIUS TOBIAS DONNED A BLACK HOOD TO KEEP OUT THE LIGHT BEFORE EXPOSING HIS EYES TO A BEAM OF FAST NEUTRONS IN A 1970 EXPERIMENT AT THE 184 INCH CYCLOTRON.

HELPING TO POSITION TOBY IN THE BEAMLINE ARE JOHN LYMAN (LEFT) AND RALPH THOMAS.

Irradiation of the rat spinal cord

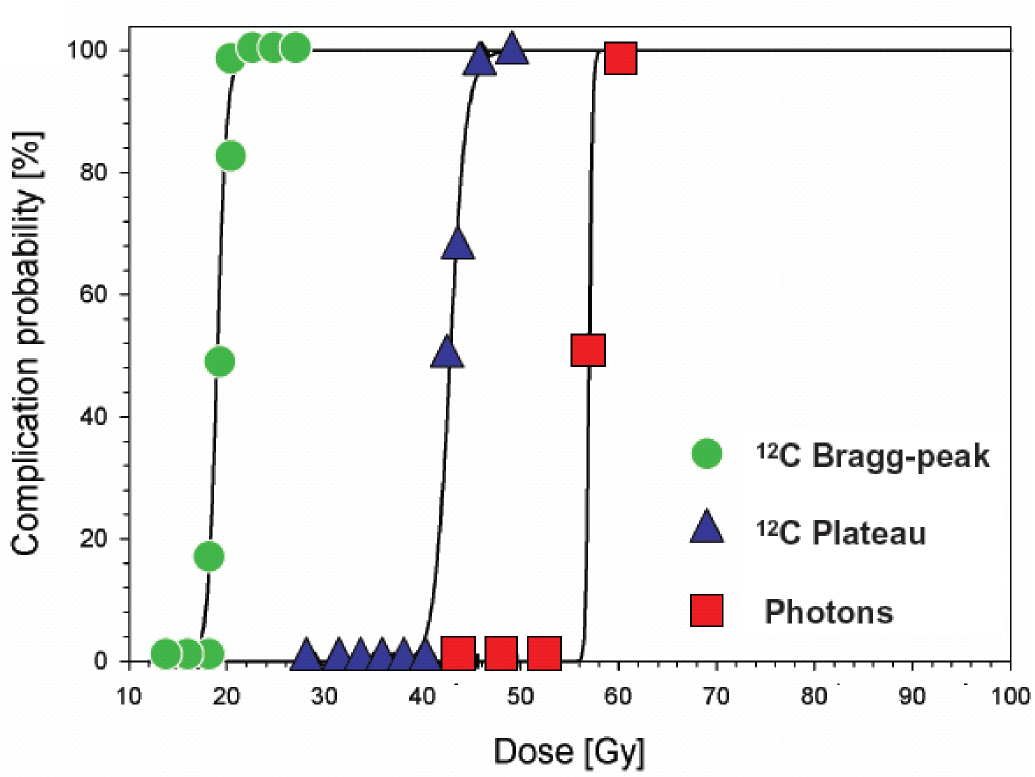
Treatment **Planning** **End Point**



Karger 2006

- Irradiations with Photons and ^{12}C-ions (peak & plateau)
- Field size: 10x15 mm^2 (Peak: 10 mm SOBP)
- 1, 2, 6, 18 fractions (>500 animals)
- Biological endpoint: Paresis °II within 10 months

Dose response after 6 fractions / 6d



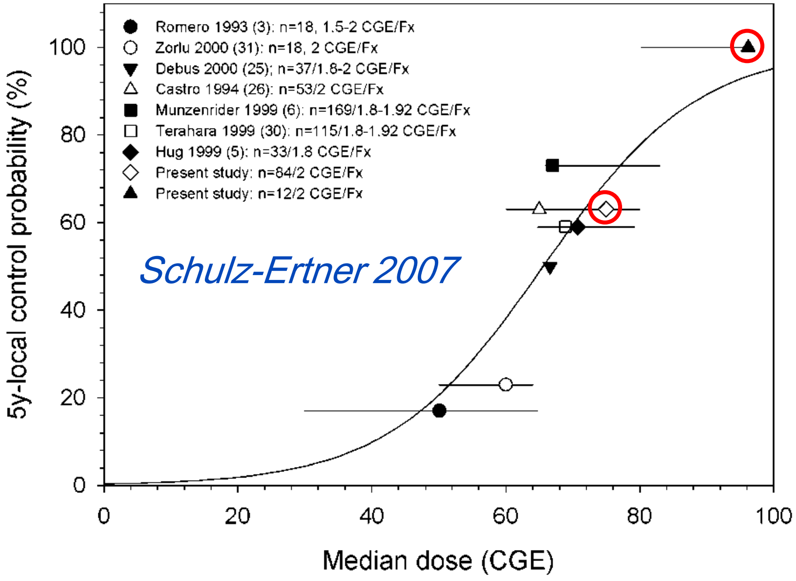
Increased Tolerance in the Plateau vs. Bragg peak

Benchmark data for radiobiological models

Experimental results vs. clinical data

Local control

- Data for ^{12}C-ions and photons/protons are described by a common dose response curve
- Assumes that chordoma-tissue behaves like CNS-tissue



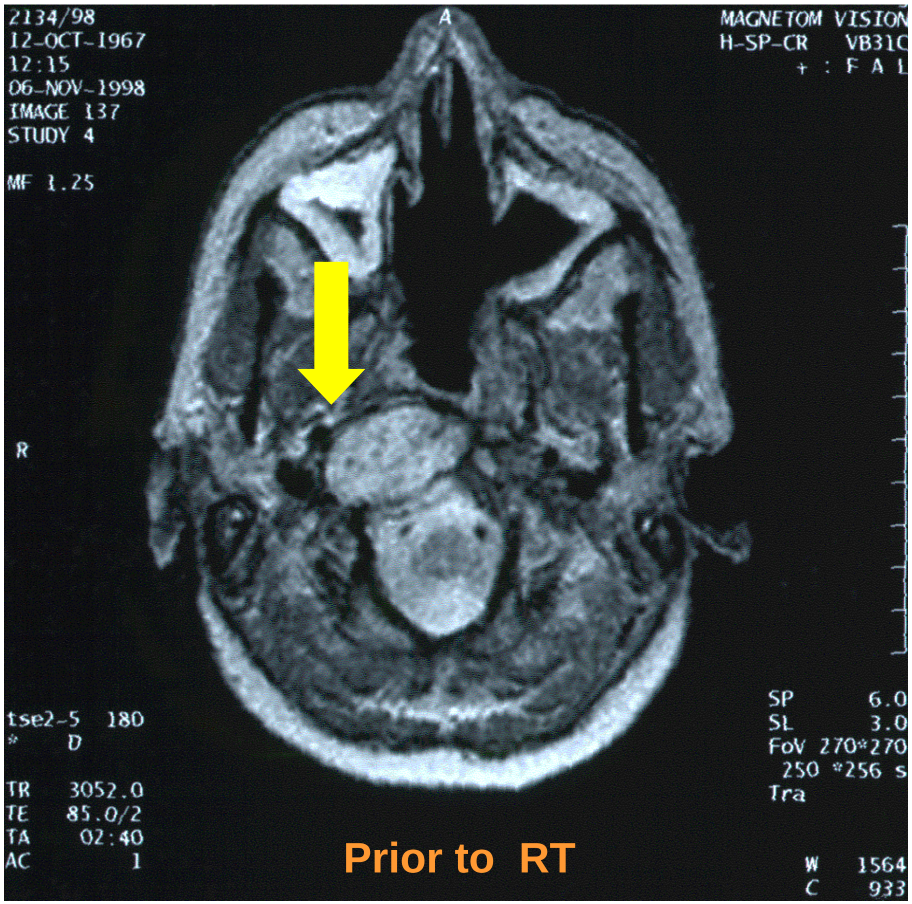
Temporal lobe injury

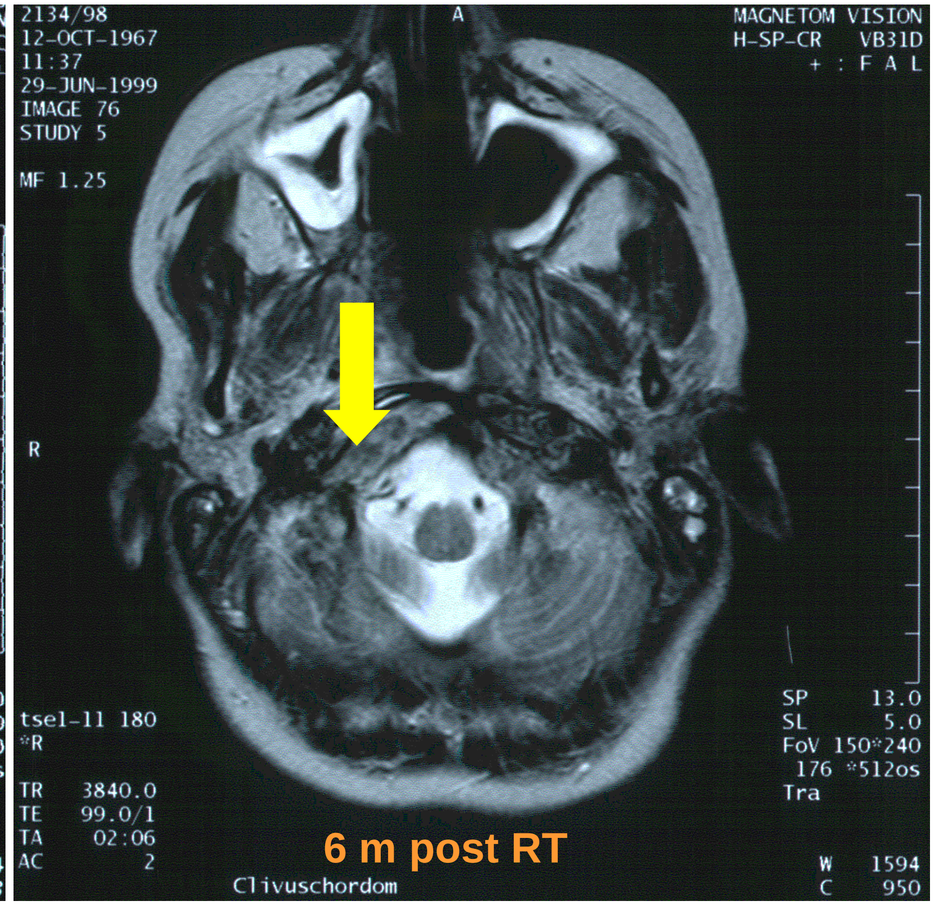
- Contrast enhancement in T1-w MRI
- Dose response curves complies with clinical experience for photons
- Conclusion is model-based (no dose response curve for photon RT)

Clinically, there is no indication of a significantly underestimated RBE

Clinial example: Recurrent Clivuschordoma

- subtotal resection 1996
- proton therapy 79.2GyE,1996
- 11/98 20.8 Gy FSRT + 27 GyE C12 at recurrency

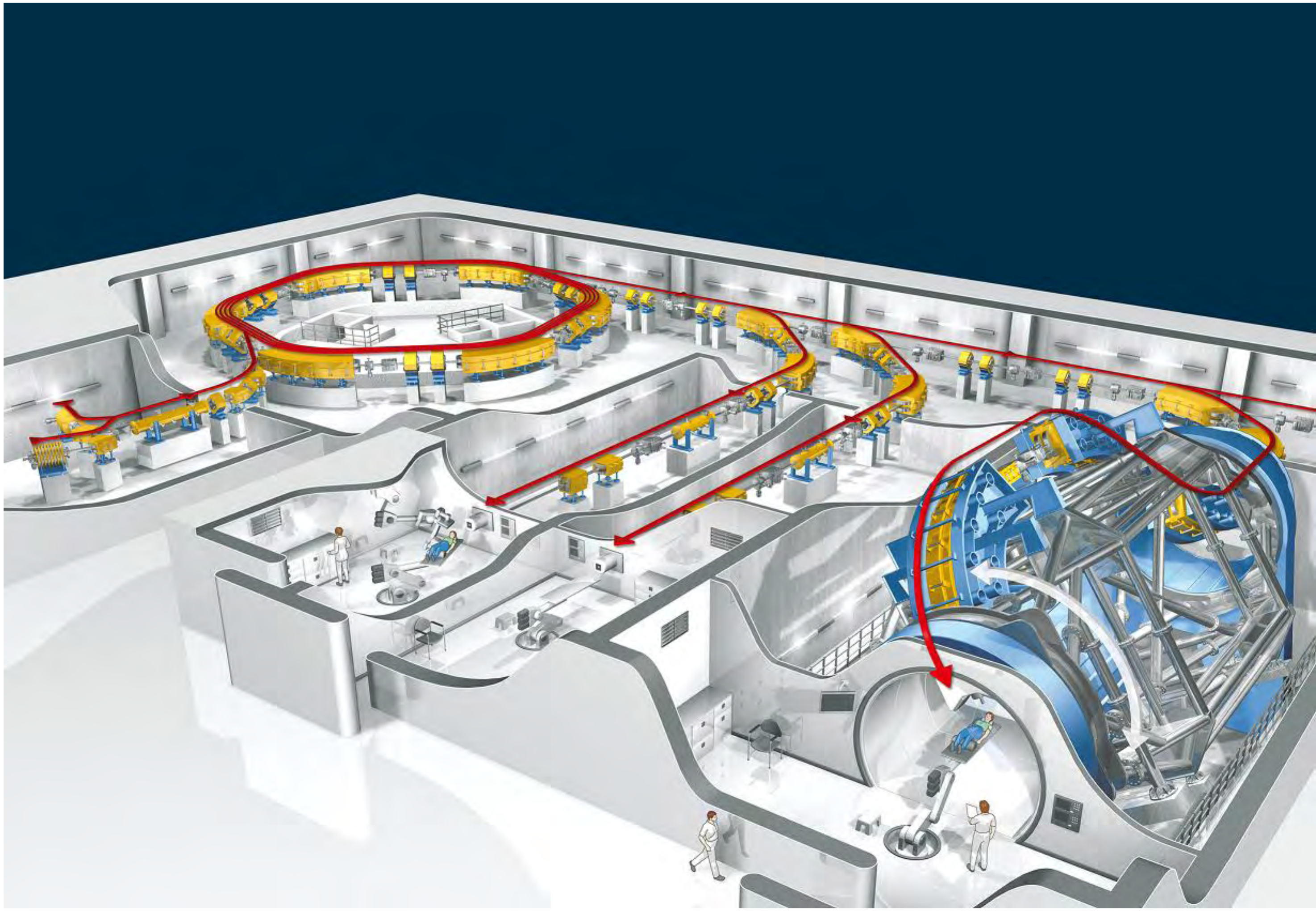




Large individual variability in radio-sensitivity is not yet understood

Heidelberg Ion Beam Therapy Center

- Compact Synchrotron
- 2 Horizontal beams
- Scanning Gantry
- QA- Room
- p,He,C,O,...
- E<430MeV/u (~30cm range)



- 1000Patients/yr

Planned Clinical Studies @ HIT

Fully Fractionated C-12 Therapy

- Chordoma & chondrosarcoma at the SB: **p vs. C12**
- Inoperable Bone and Soft tissue sarcoma: **C12**

Boost Treatments: (IMRT + C12/p-Boost)

- Spinal and Sacral Ch/CS: **C12**
- Prostate Ca. (T3, PSA 10-20ng/ml): **p vs. C12**
- Inop. early stage lung cancer, melanoma, atyp. Meningeoma: **C12**

Radiochemotherapy:

- Pancreatic Carcinoma: IMRT + C12 Boost + Cetuximab
- Glioblastoma: IMRT+C12 Boost + Temozolomide
- Adenoidcystic Carcinoma

Proton indications:

- Pediatric Tumors
- Recurrent tumors
- …

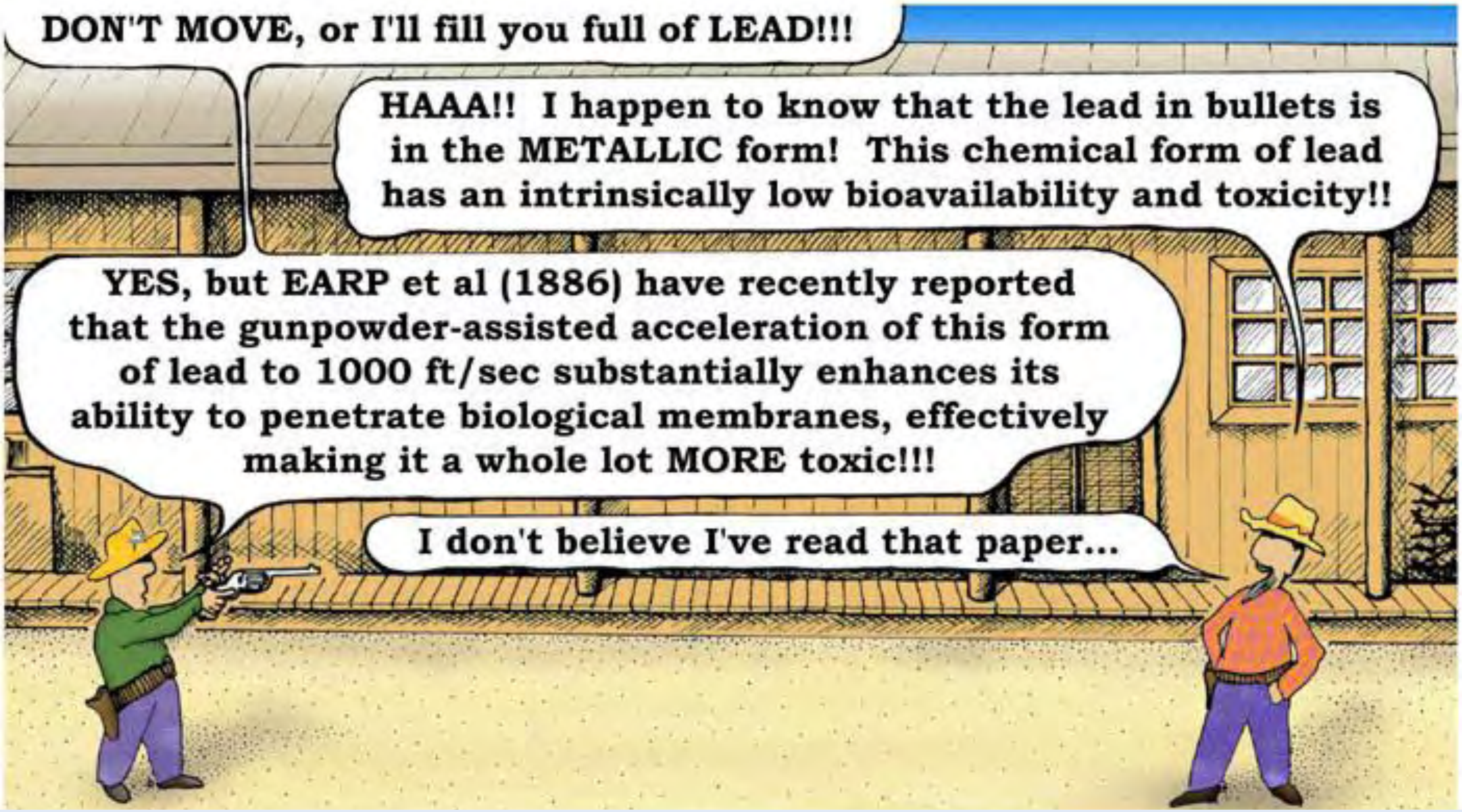
Conclusions

- Data on radiation tolerance and damage are rare
- RBE concept is widely used in radiotherapy
- RBE depends on dose, tissue, endpoint, oxygen,…
- Track structure models can be used for TP
- We are just beginning to understand the molecular mechanisms of radiation damage
- More clinical and experimental data are needed

To answer these questions, we need a number of clinical research centers

The open questions will not be answered soon

There is an ongoing discussion on the biological effectivity of heavy particles…



Thank you for your attention !