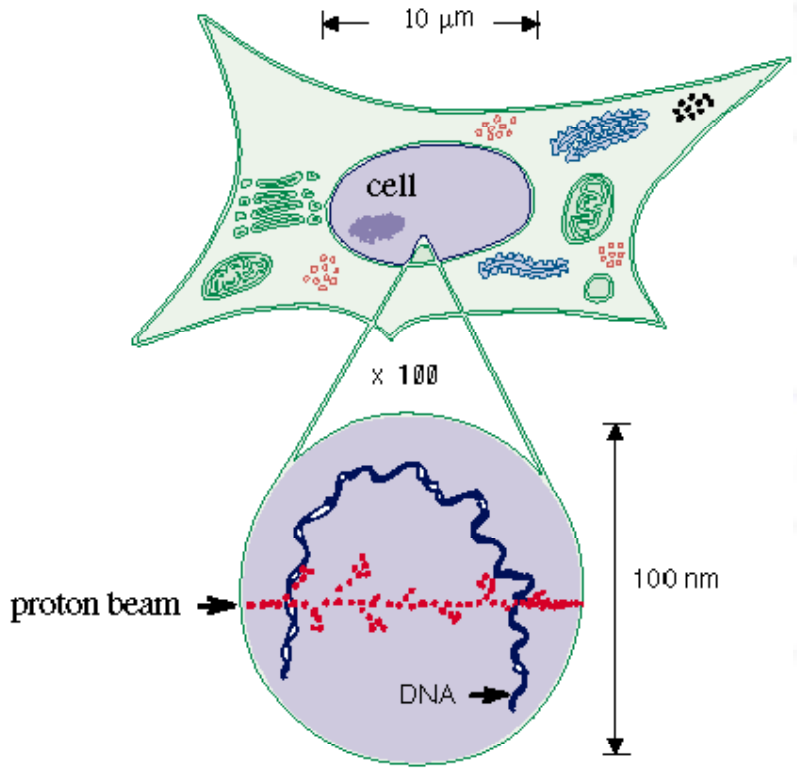
Biological Uncertainties in Proton (Ion) Therapy



Harald Paganetti PhD

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

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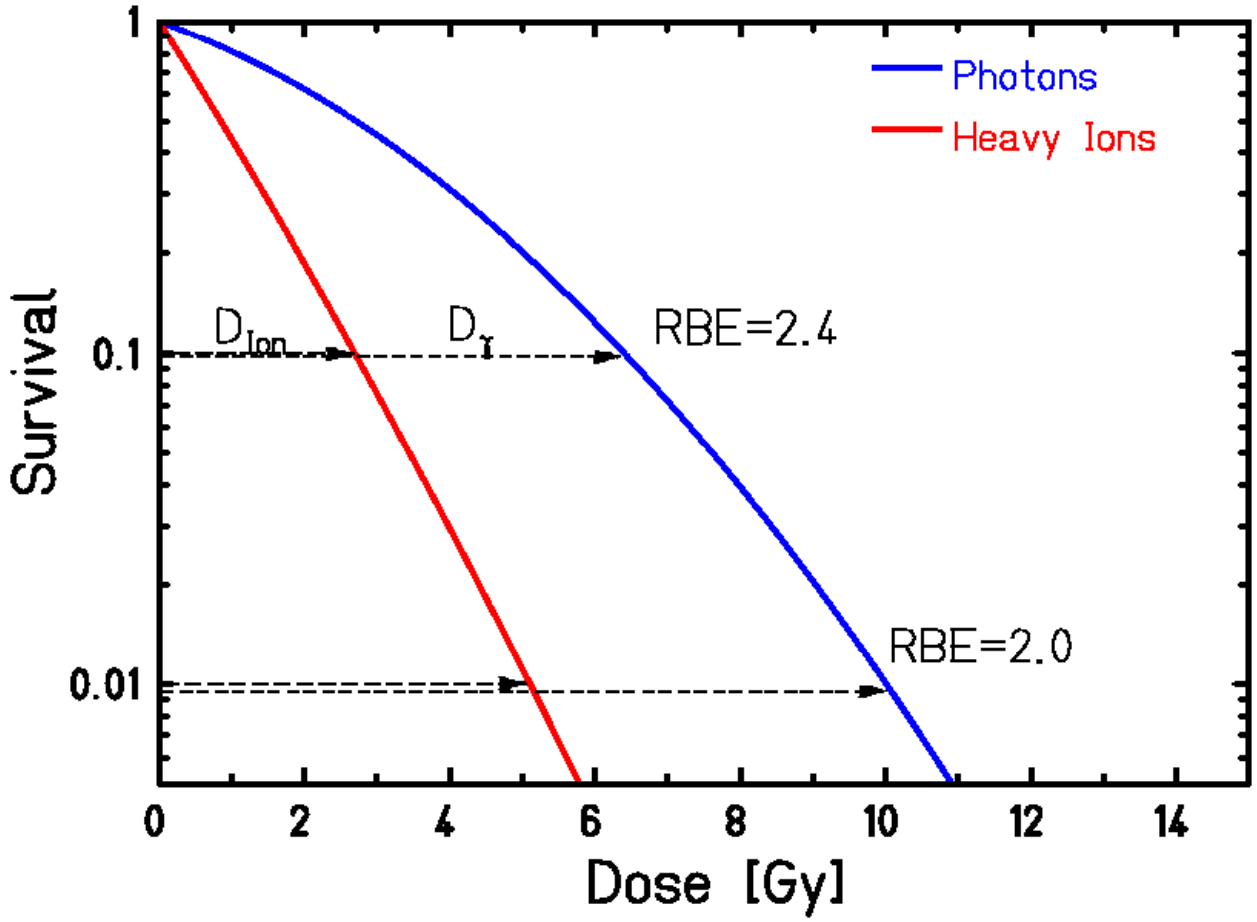
Definition of RBE



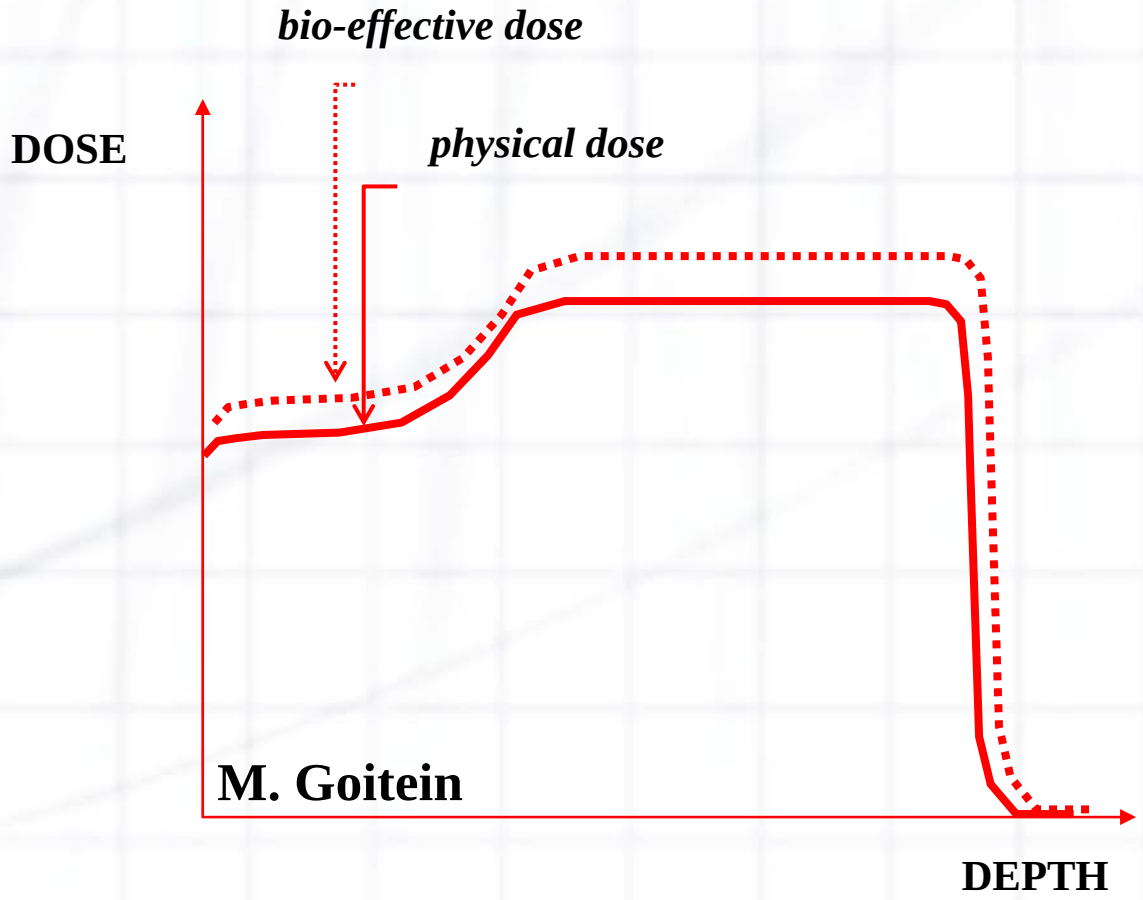
M. Krämer, W. K. Weyrather, M. Scholz: Techn. Cancer Res. Treatm. 2, 427-436, 2003

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

Clinical RBE

Proton therapy: RBE = 1.1

Protons



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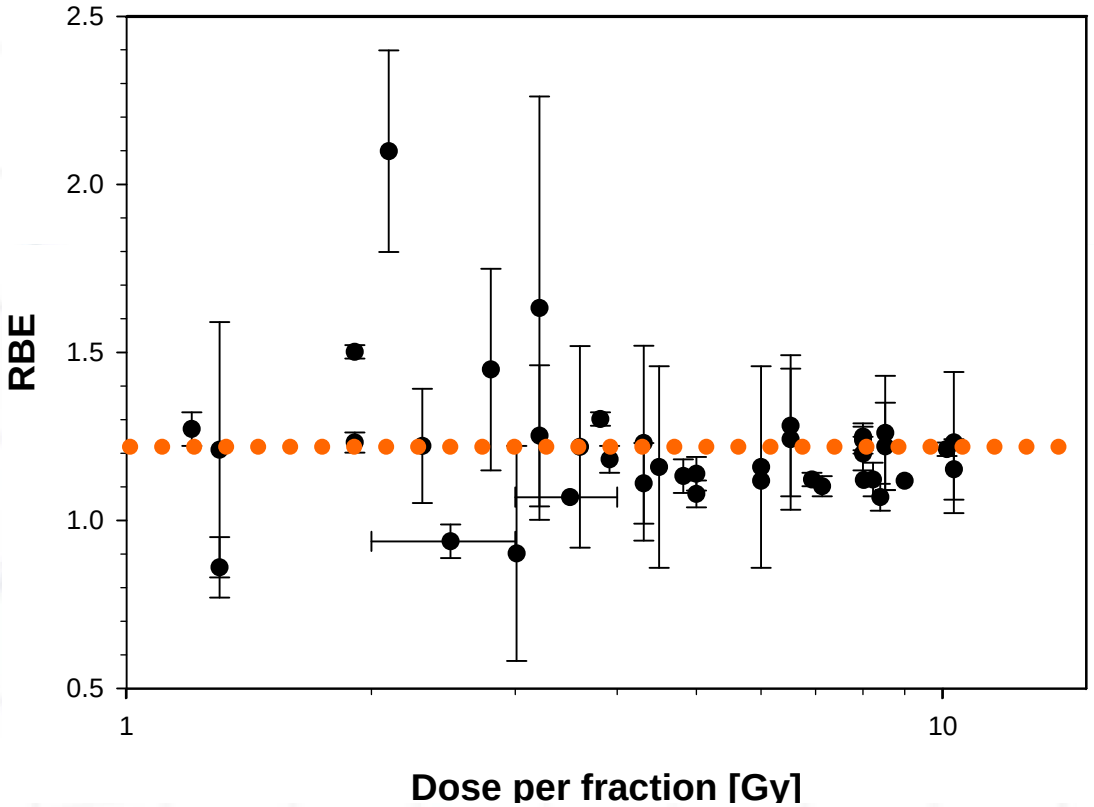
Clinical RBE

RBE from experimental data

Protons

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



1.21 ± 0.20

Endpoint: Cell Survival

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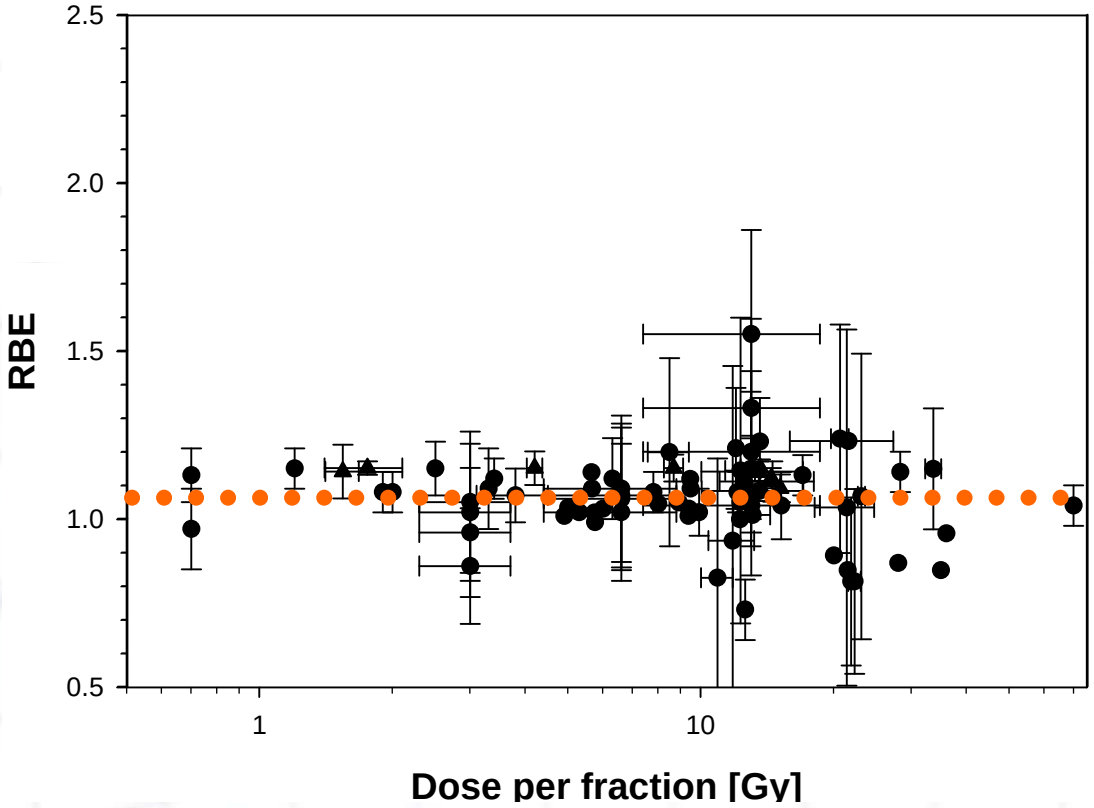
Paganetti et al.: *Int. J. Radiat. Oncol. Biol. Phys.* 2002; 53, 407

Clinical RBE

RBE from experimental data

Protons

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



1.07 ± 0.12

Mice data: Lung tolerance, Crypt regeneration, Acute skin reactions, Fibrosarcoma NFSa

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

Clinical RBE

RBE from clinical data

Example: Debus et al. IJROBP 1997; 39: 967-975

Protons

- Evaluation of brain stem morbidity following 348 proton patients with skull-base sarcomas
- tumors approached very closely, abutted, or displaced the brain stem
- total dose to the brain stem from the end of range of a field was limited to <10 Gy_{RBE}
- if the dose increment is 10%, the increase in dose in that volume would have been 1.0 Gy_{RBE}

Clinical RBE

RBE from clinical data

Outcome: brain stem toxicity free survival at 10 years = ~88%

→ RBE value of 1.10 for brain stem damage in patients free of known risk factors appears to be reasonable

This does not prove that the RBE of 1.1 is correct !

Protons

Problems in estimating RBE values based on clinical data:

- heterogeneity of dose
  photons generally deliver a more uniform dose to critical structures
- proton and photon treatment volumes are different and the probability of radiation damage for a specified dose is sensitive to the volume of normal tissues irradiated

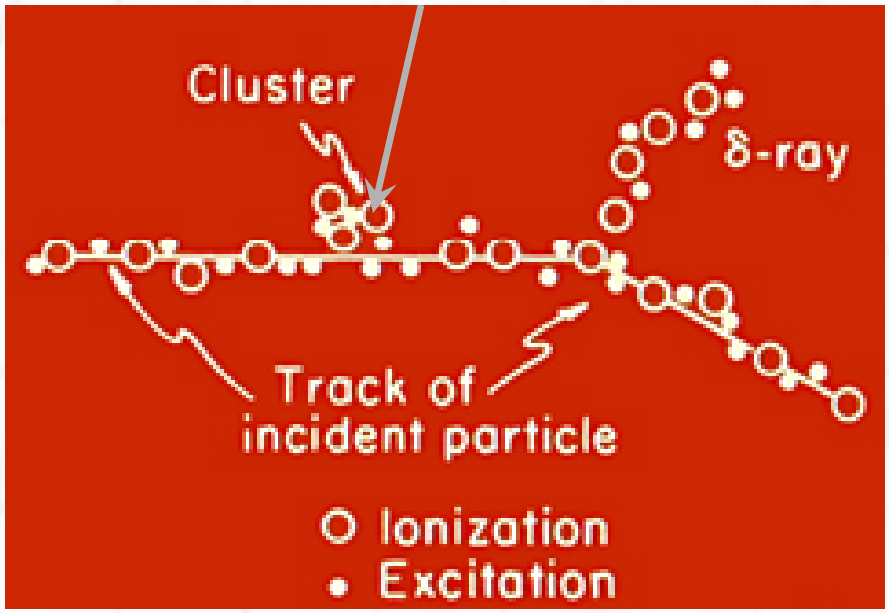
Protons

Experimental data in vivo are supporting the use of an RBE of 1.1in proton therapy

Our clinical experience does not indicate that the RBE of 1.1 for proton therapy is incorrect

Damage as a function of LET

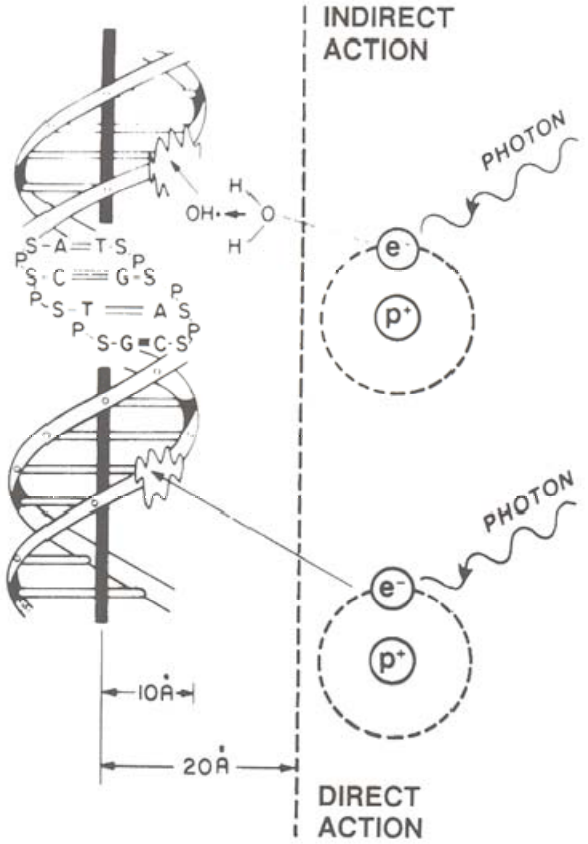
Lesion complexity



Lesions can be repairable or non-repairable
High-LET radiation produces more non-repairable lesions

Curtis: Radiat Res 1986; 106 252-270
Paganetti H: Medical Physics 2005: 32, 2548-2556

Oxygen Enhancement Ratio



Hypoxic cells are more radio-resistant than well oxygenated cells for low-LET radiation

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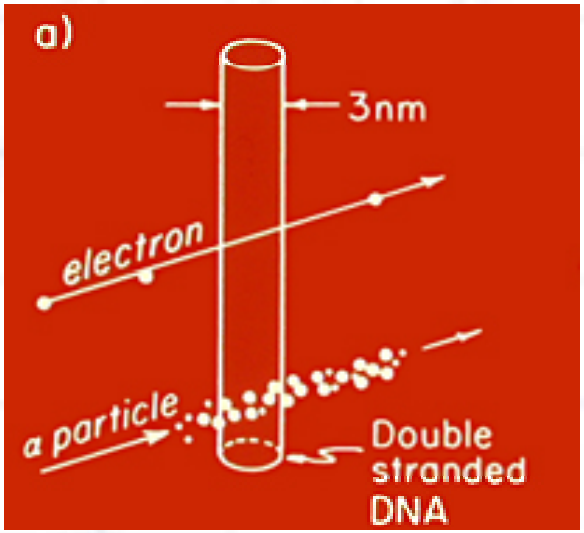
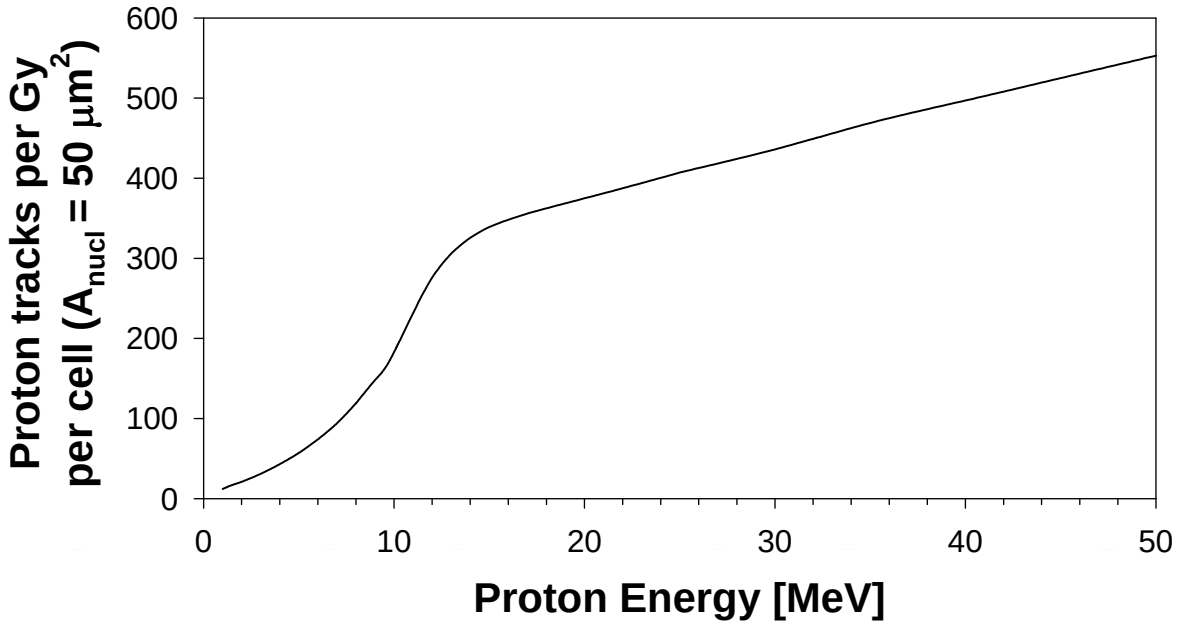
Damage as a function of LET & fluence





Paganetti H:
Med Phys 2005: 32, 2548-2556

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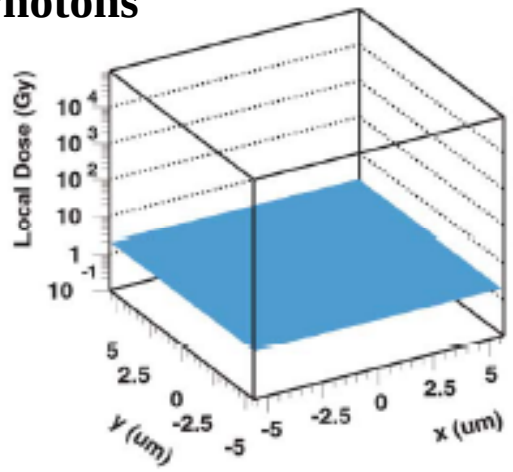
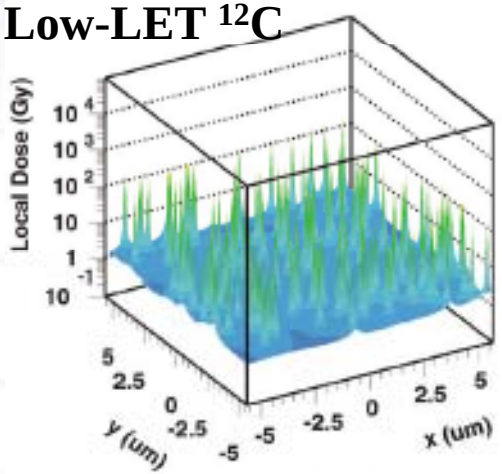
Dose = Fluence [1/cm^2] × LET [keV/cm] / ρ [g/cm^3]

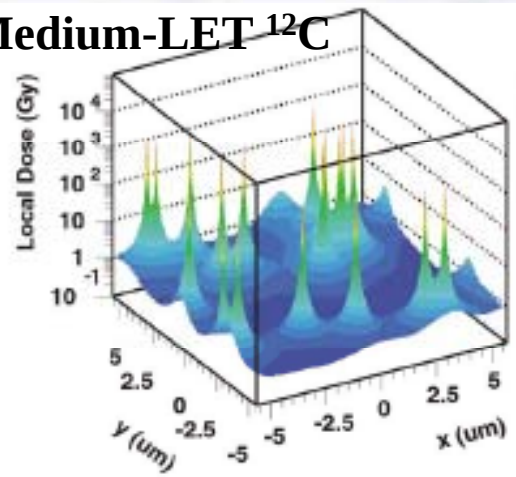
Photons



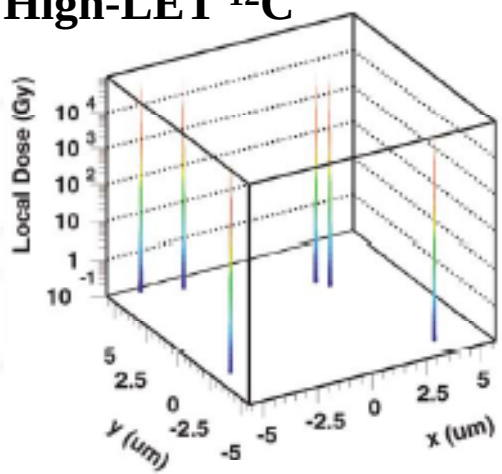
Low-LET ^{12}C



Medium-LET ^{12}C



High-LET ^{12}C



M. Krämer et al.:
Techn. Cancer Res. Treatm. 2, 427-436, 2003

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

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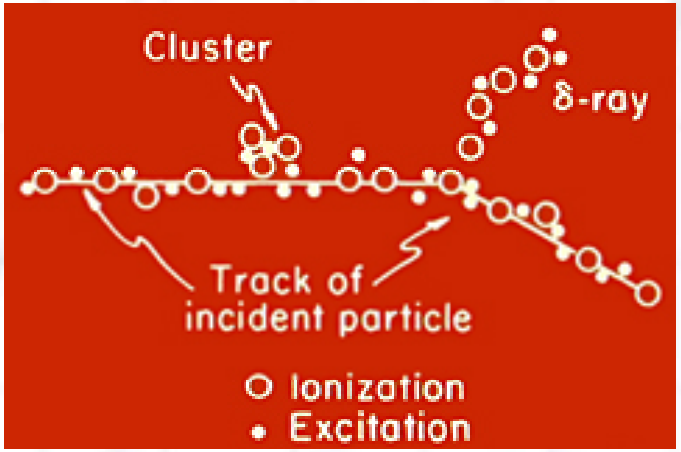
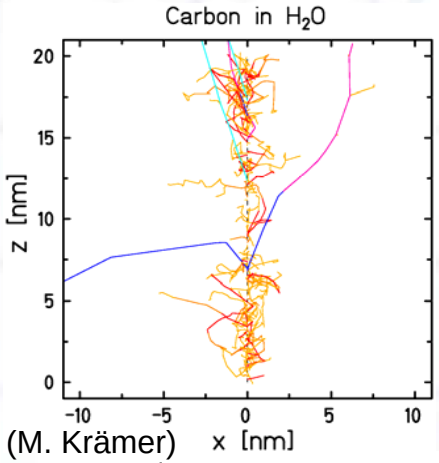




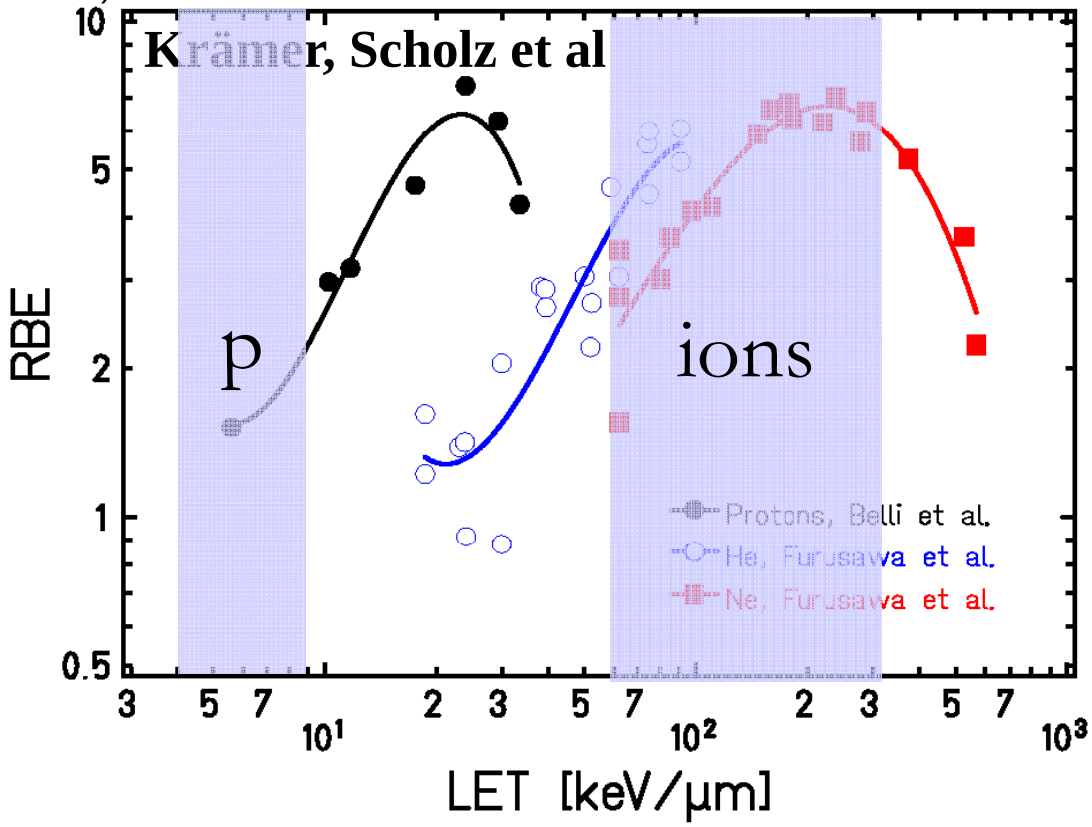
(M. Krämer)

Protons vs Carbon ions

protons create lower energy δ-rays (smaller track halo) compared to heavy ions at a given LET

⇒ higher local dose

⇒ proton RBE > ion RBE at a given LET



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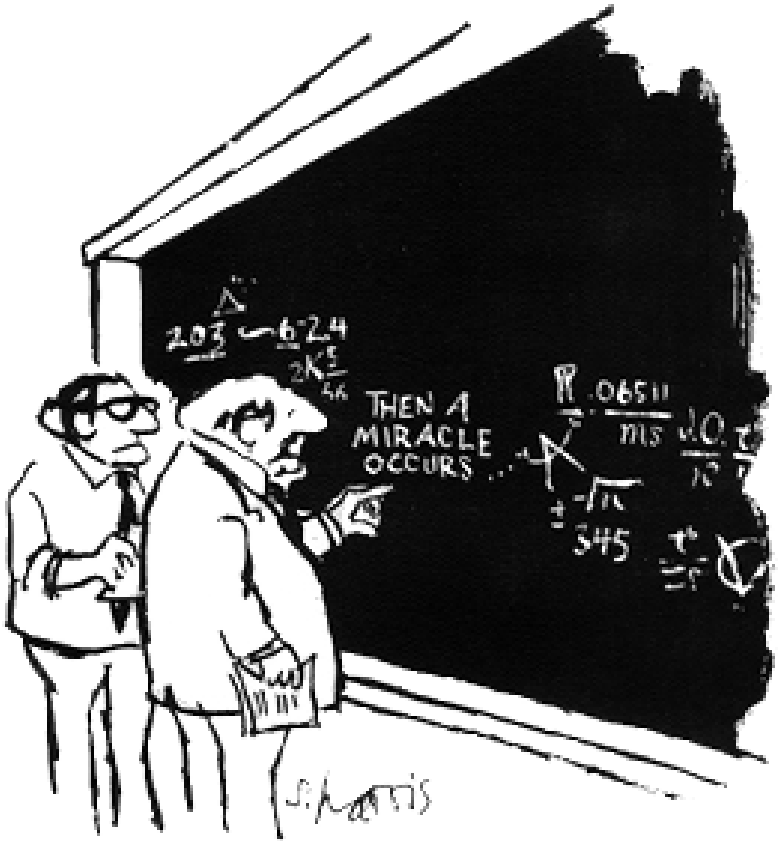
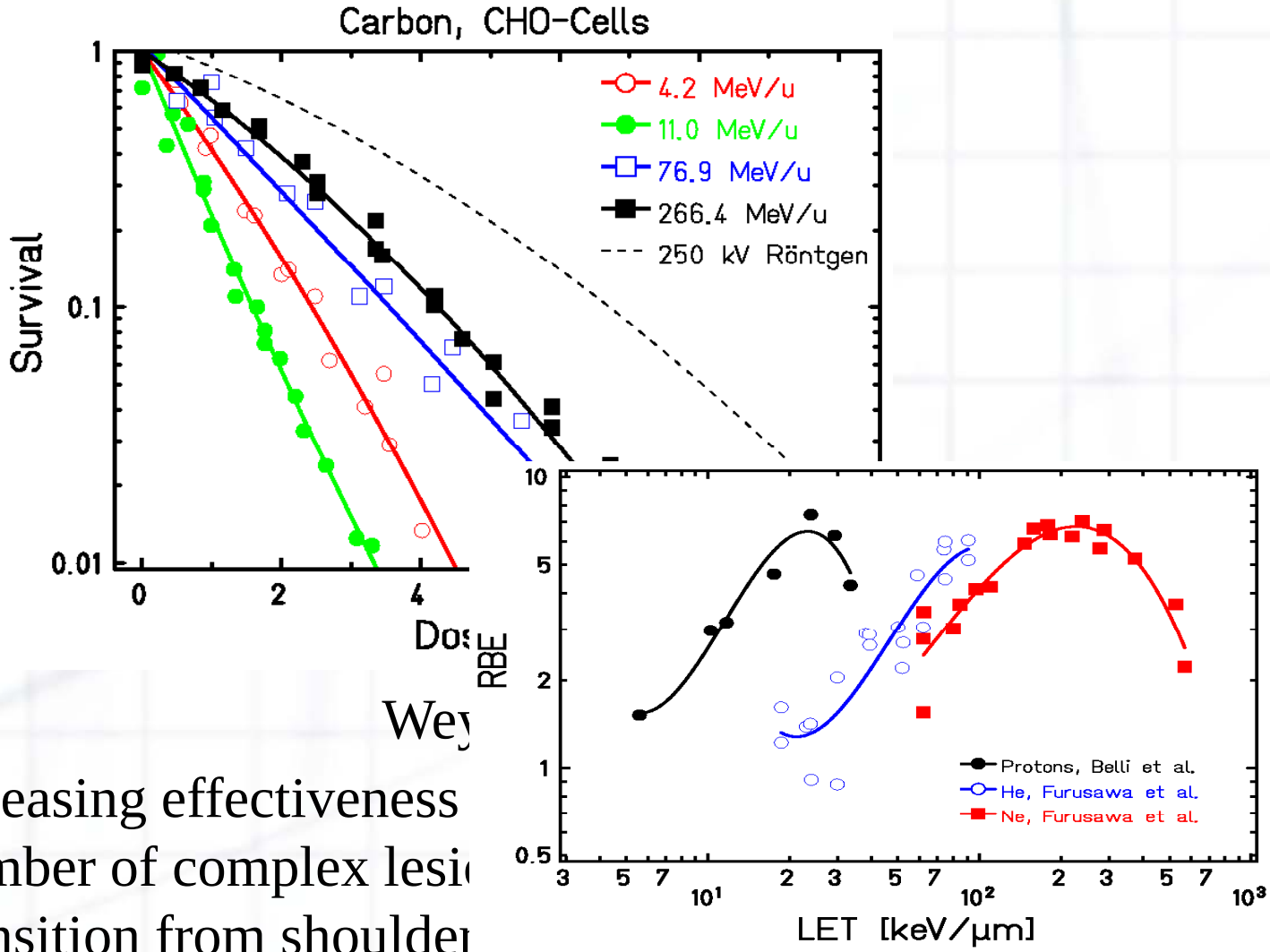
RBE depends on

- energy/LET
- dose
- tissue



"I think you should be more explicit here in step two."

RBE as a function of particle energy / LET



- Increasing effectiveness
- Number of complex lesi
- Transition from shoulde
- Saturation effects at very low energies

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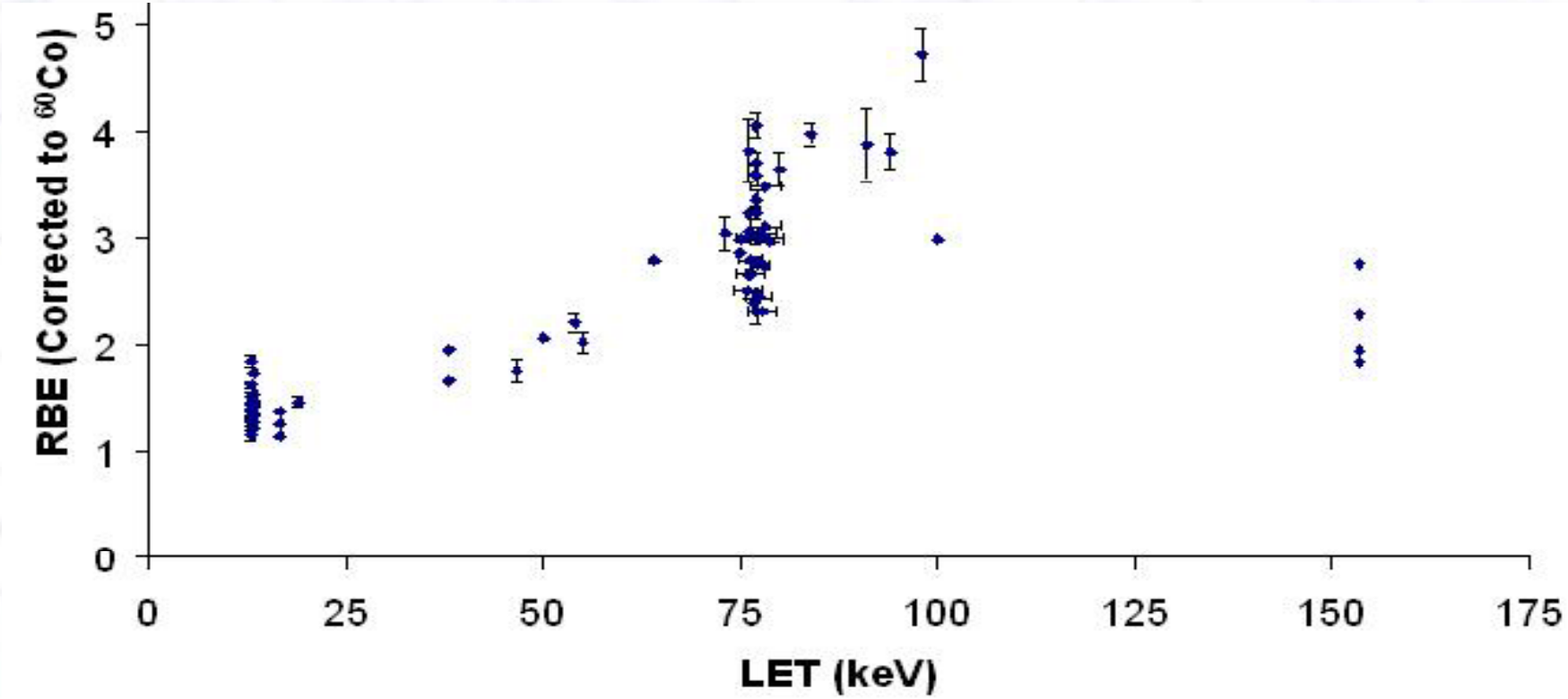
RBE as a function of particle energy / LET

Carbon ion RBE at 2Gy for various endpoints

Carbon Ions



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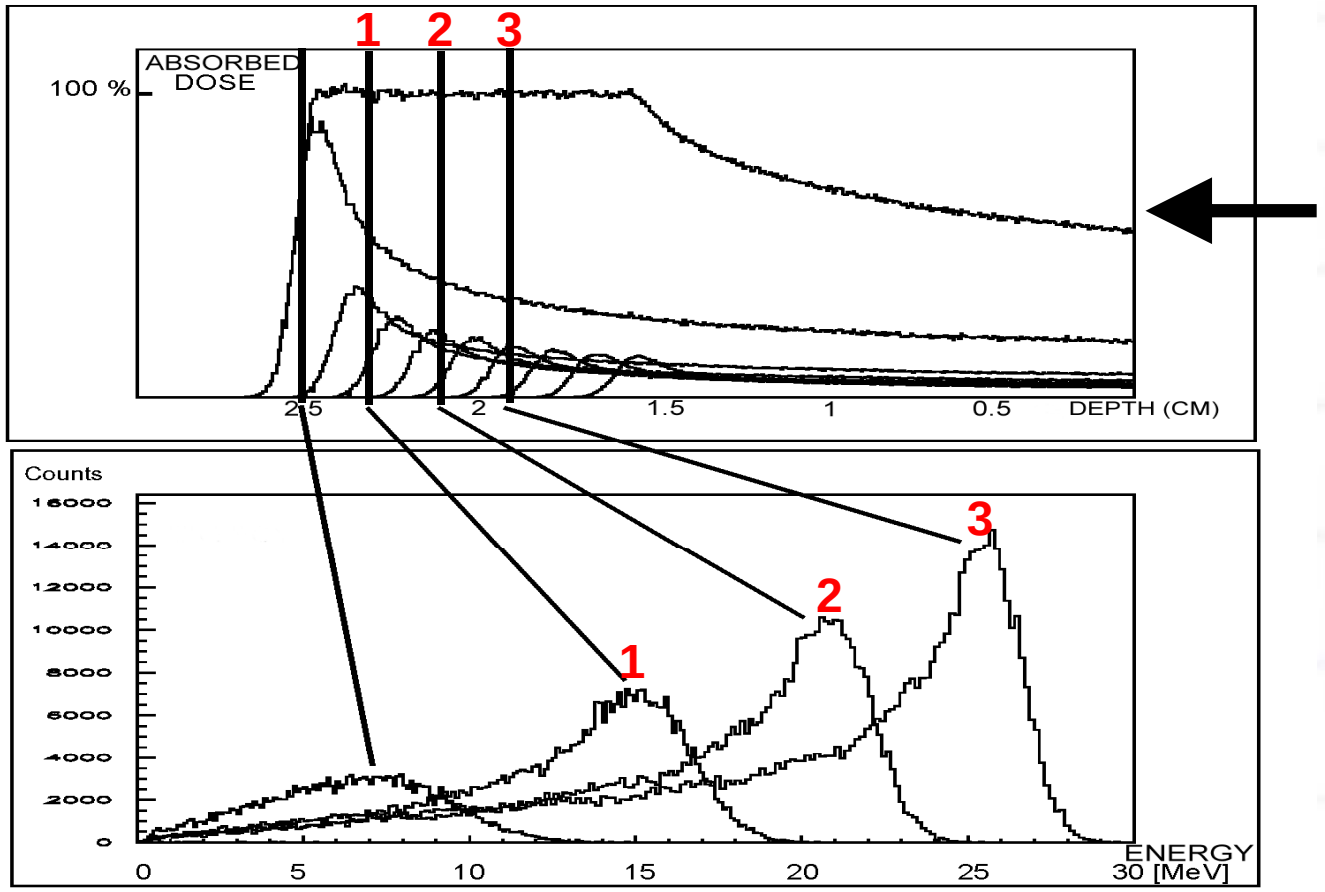
RBE as a function of particle energy / LET

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

Implication of RBE(LET) for RBE(depth)



Dose = Fluence [1/cm^2] × LET [keV/cm] / ρ [g/cm^3]

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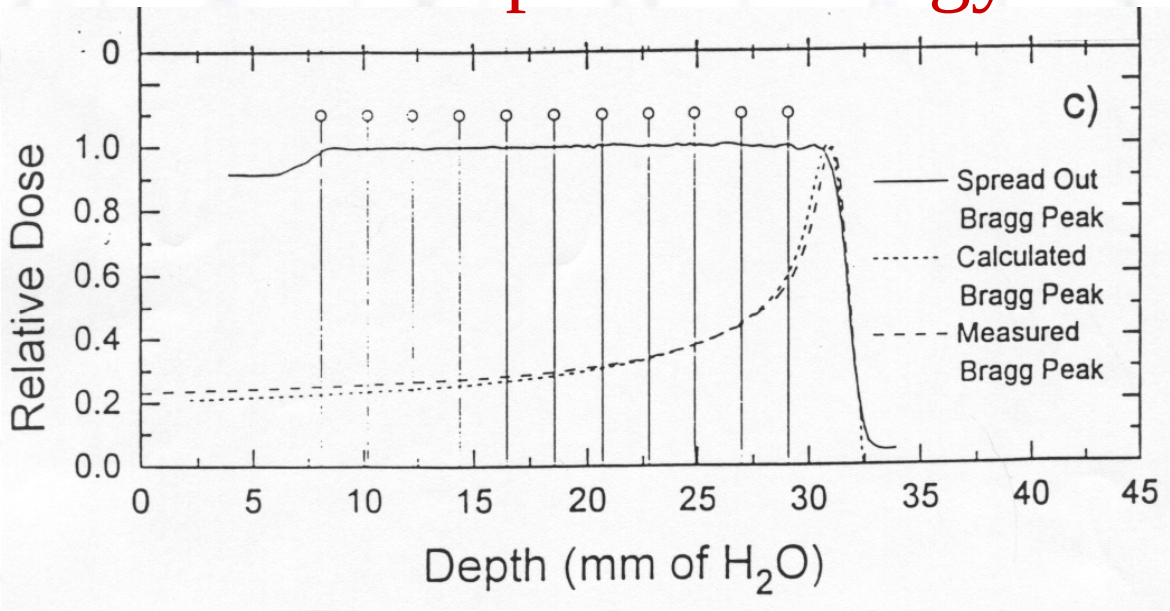
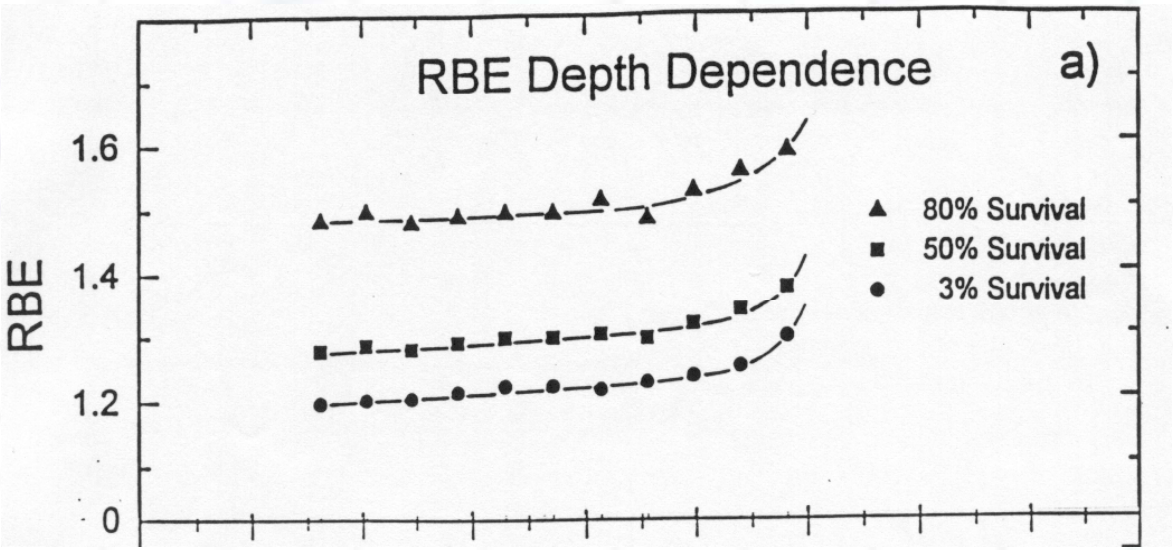
RBE as a function of particle energy / LET

Protons

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





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RBE as a function of particle energy / LET

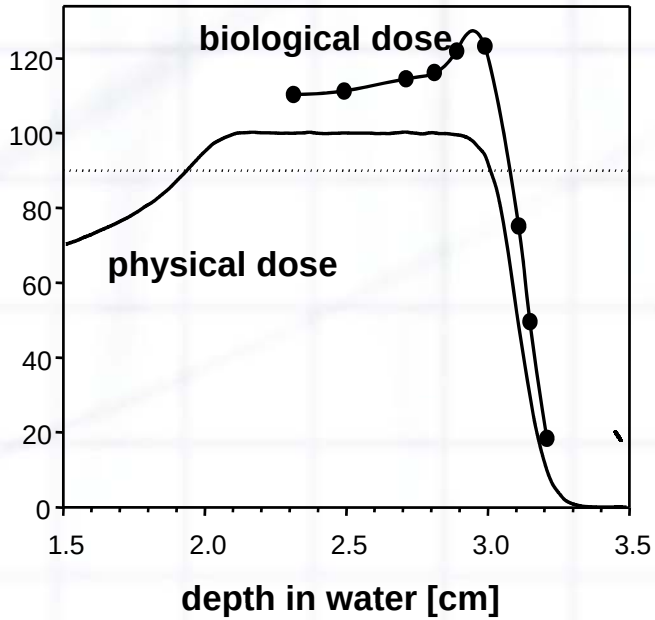
RBE (depth)

Protons

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



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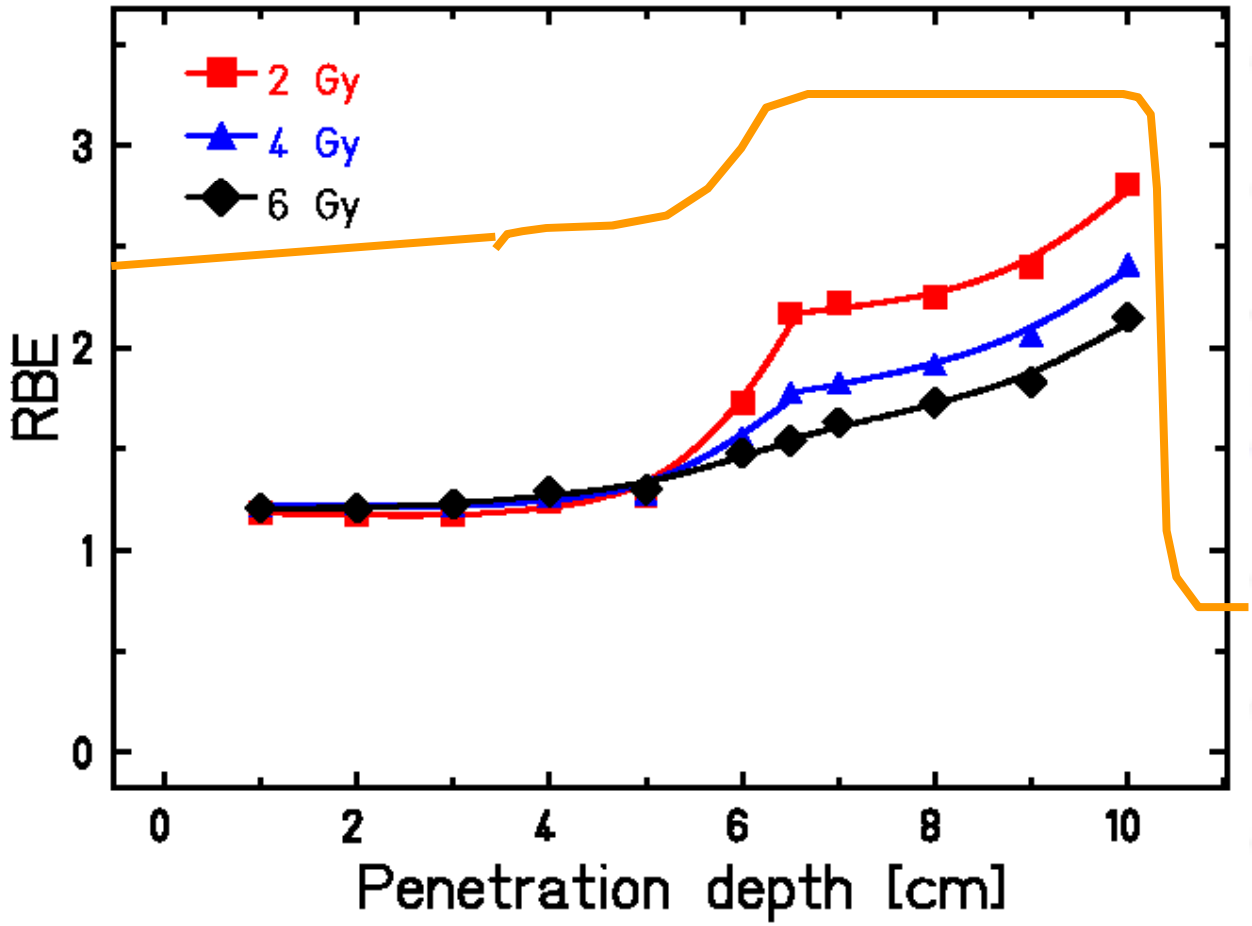
RBE as a function of particle energy / LET

Carbon Ions



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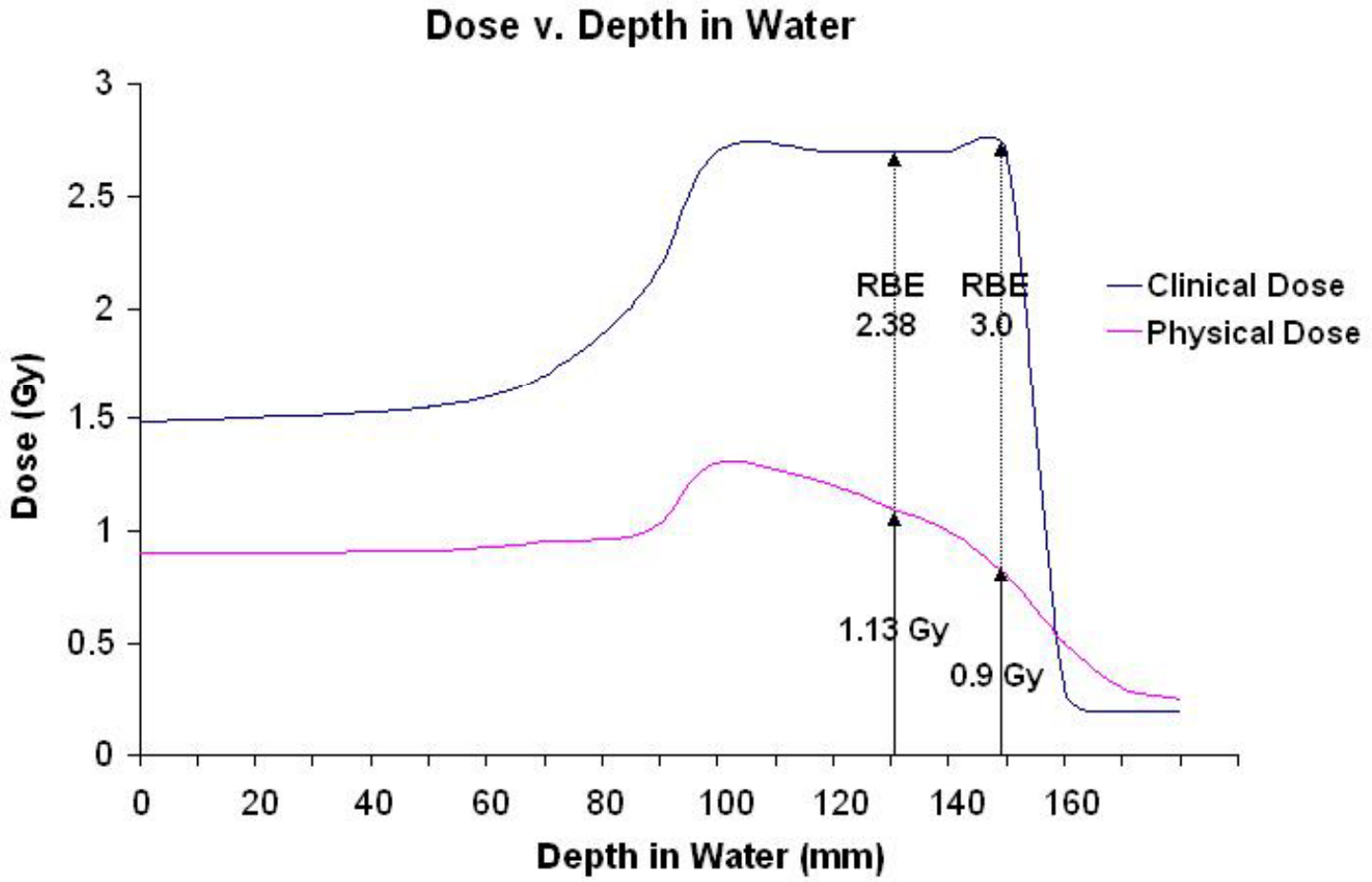
RBE as a function of particle energy / LET

Carbon Ions



*Kanai et al. Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J Radiat Oncol Biol Phys. 1999 Apr 1;44(1):201-10.

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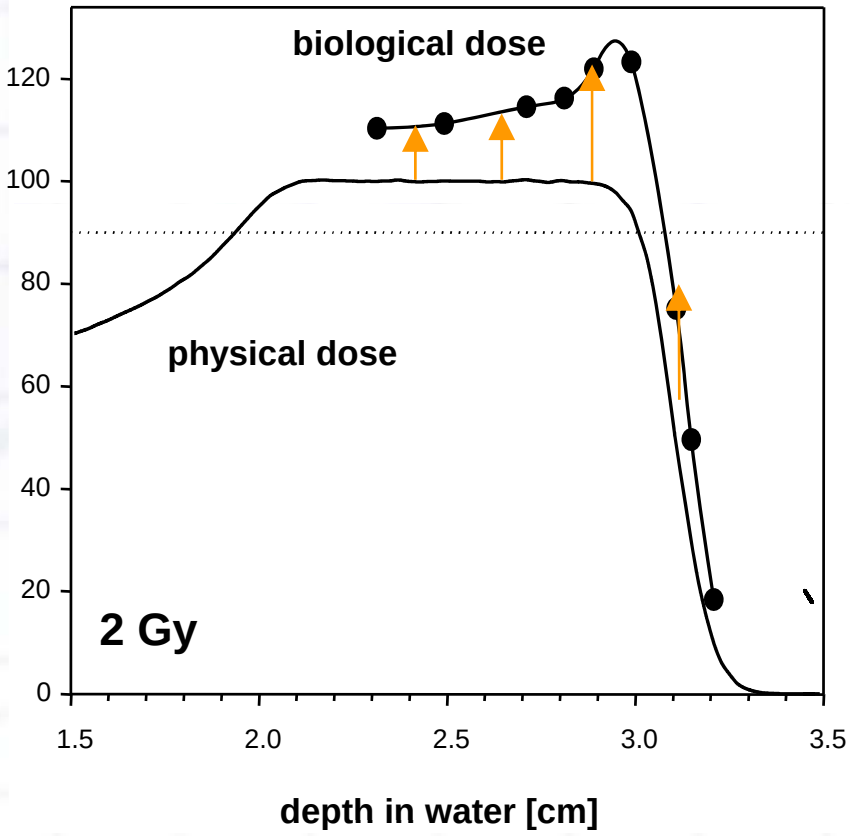
RBE as a function of particle energy / LET

An increasing RBE with depth cause an extended biologically effective range (1-2 mm)

Protons



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

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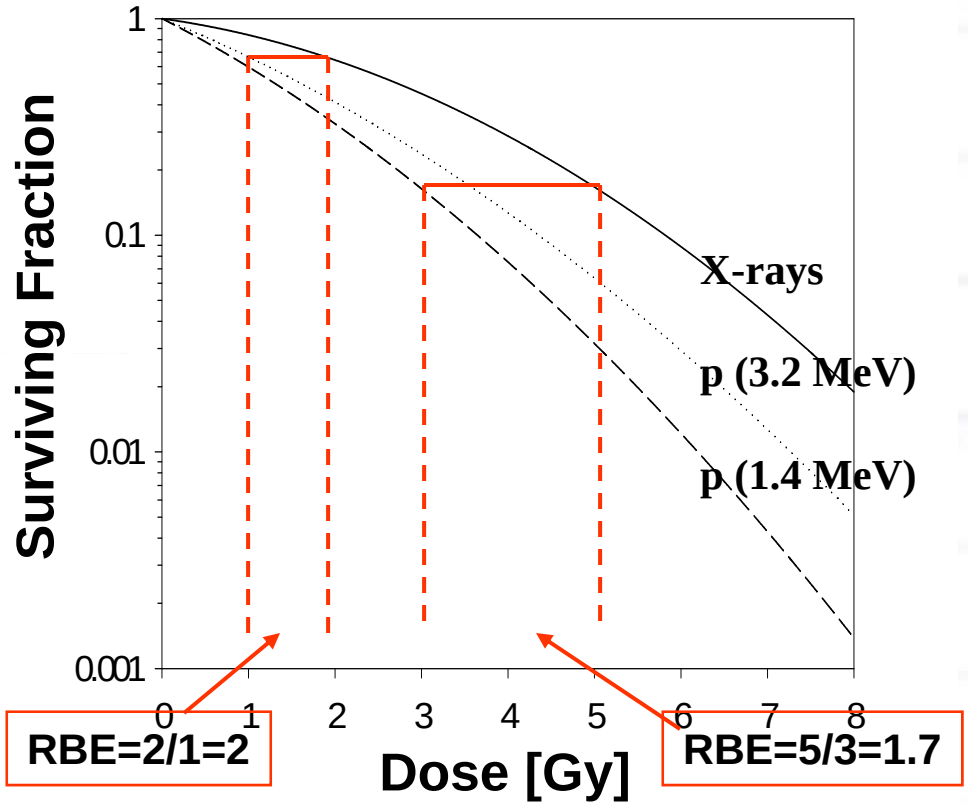
RBE as a function of particle energy / LET

Increasing effectiveness as a function of depth (affects the entire Bragg curve for Carbon beams)

Extended beam range (causes uncertainty when pointing a field towards a critical structure)

RBE as a function of dose



M. Belli et al. 1993

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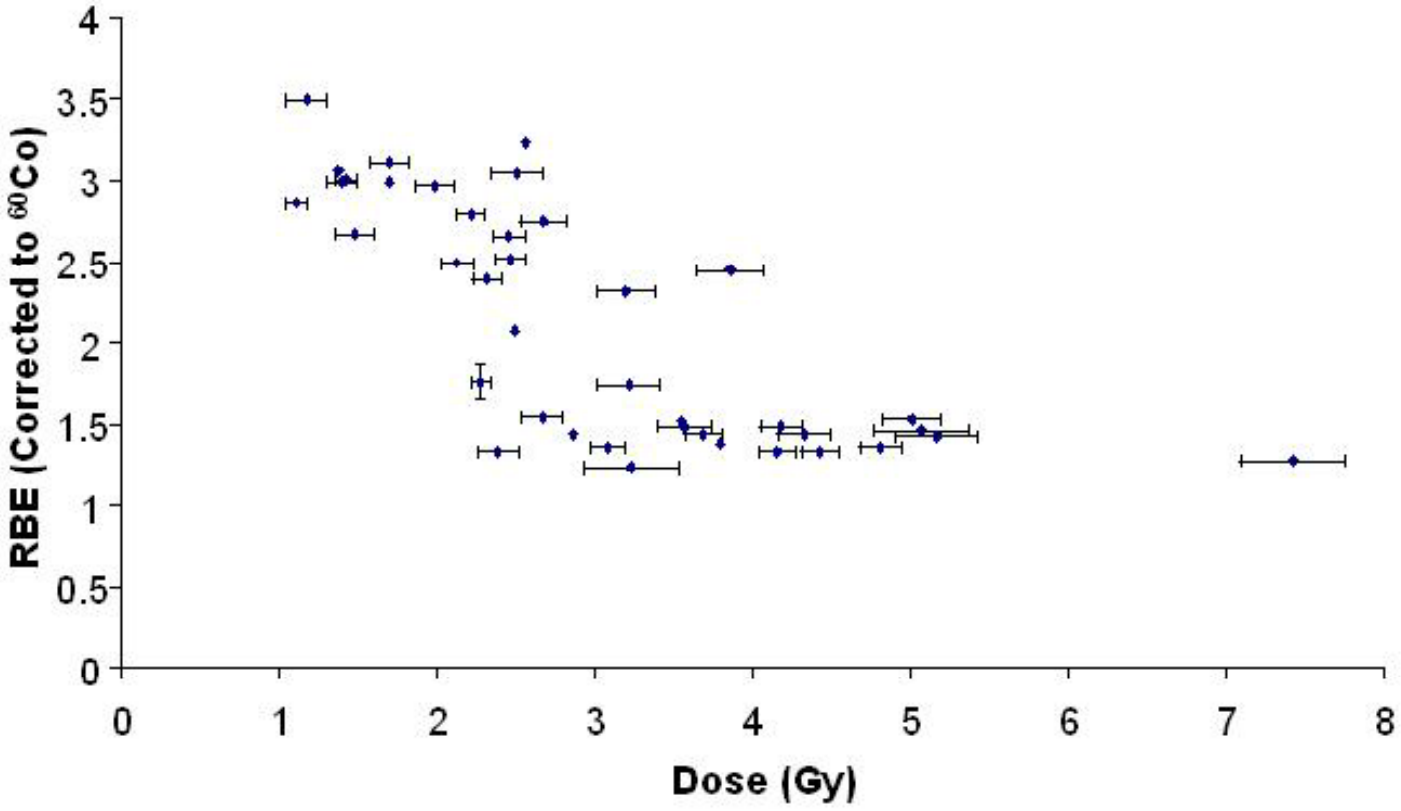
RBE as a function of dose

Carbon ion beams; RBE *in vitro*

Carbon Ions



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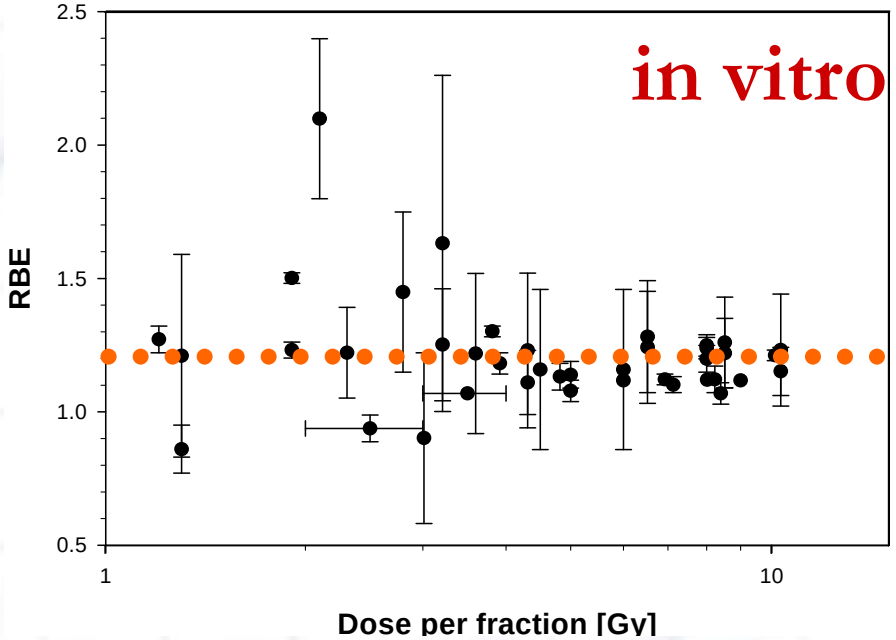
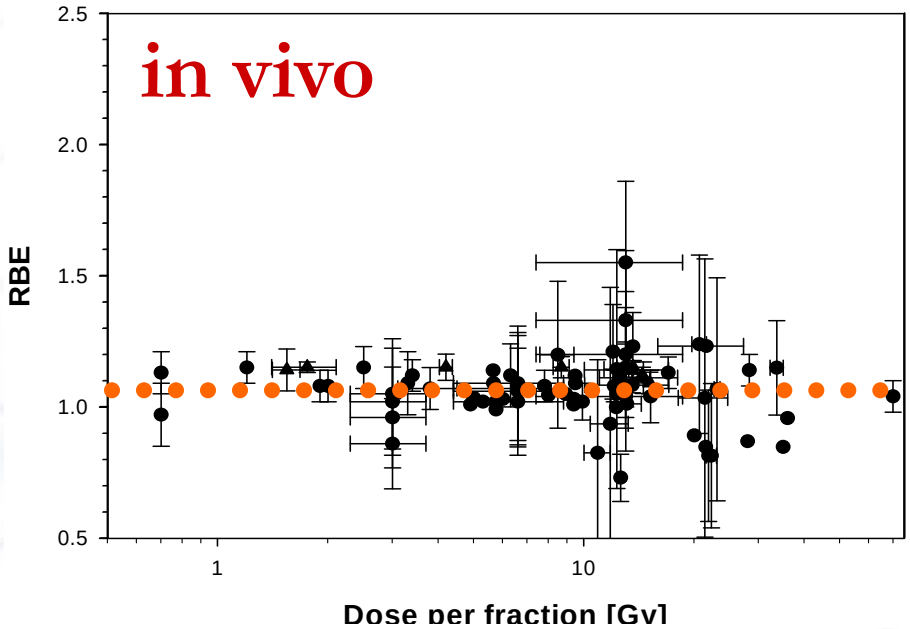
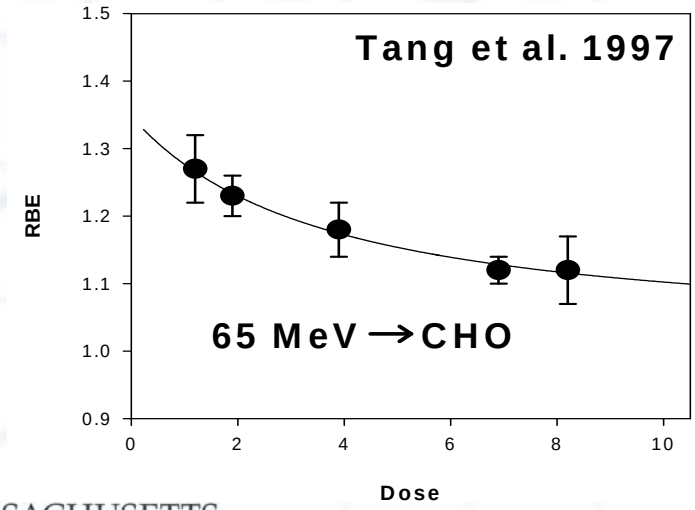
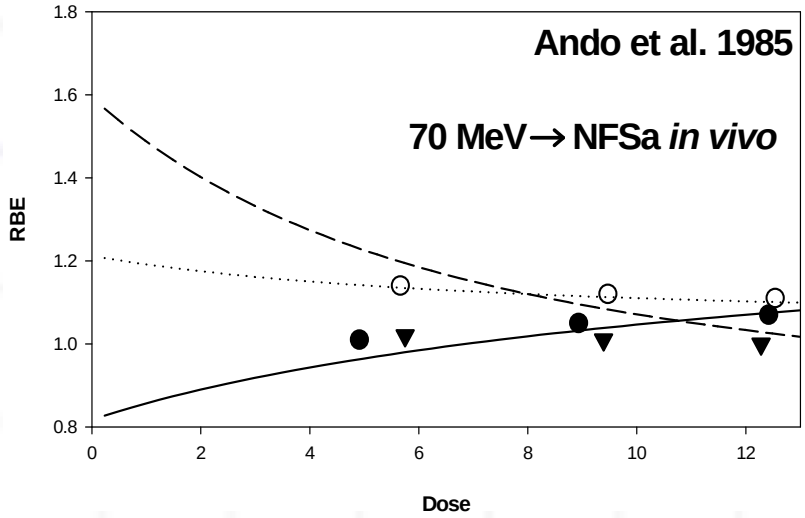
RBE as a function of dose





Protons





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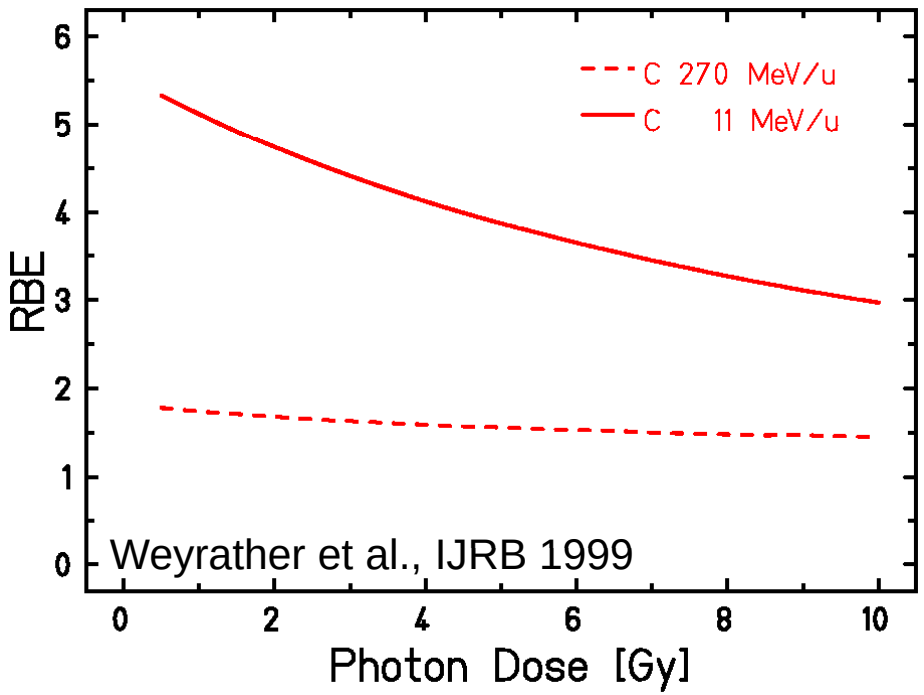
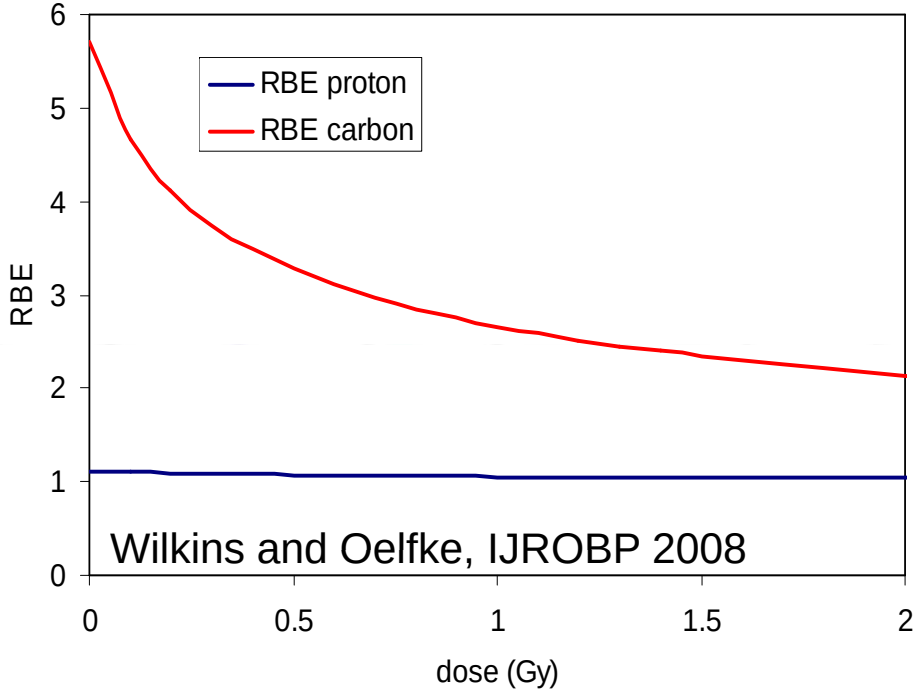
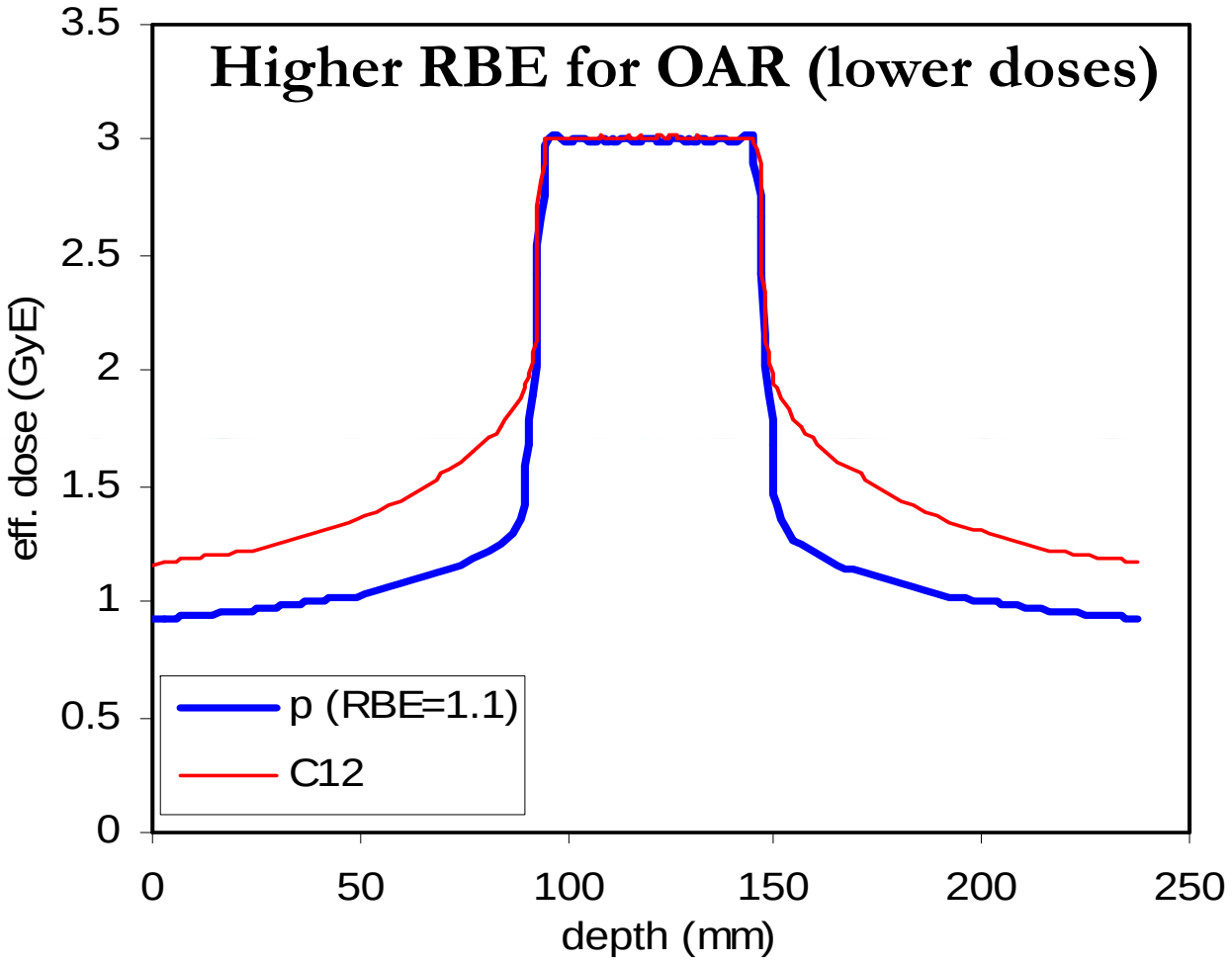
RBE as a function of dose





- RBE decreases with increasing dose
- The lower the LET, the smaller the effect

RBE as a function of dose



Wilkins and Oelfke:
Int. J. Radiat. Oncol. Biol. Phys. 2008

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RBE as a function of dose

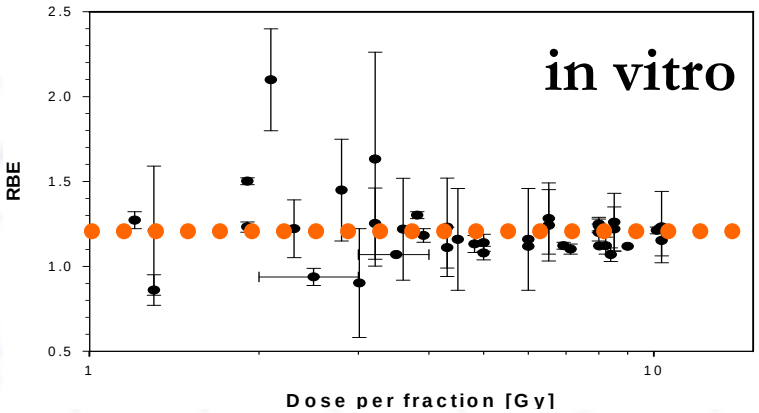
RBE increases with decreasing dose

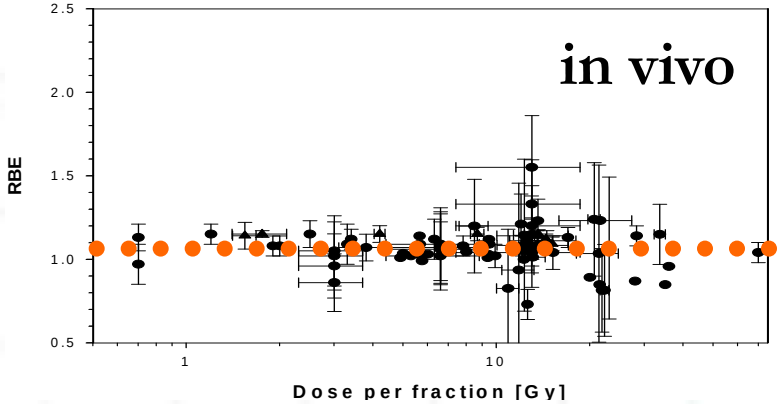
Indicates higher RBE for OAR

RBE as a function of tissue

Potential *in vivo / in vitro* difference due to

- different endpoints looked at
- re-population effects
- repair differences
- intracellular contact
- mono-layer culture vs. spherical cells





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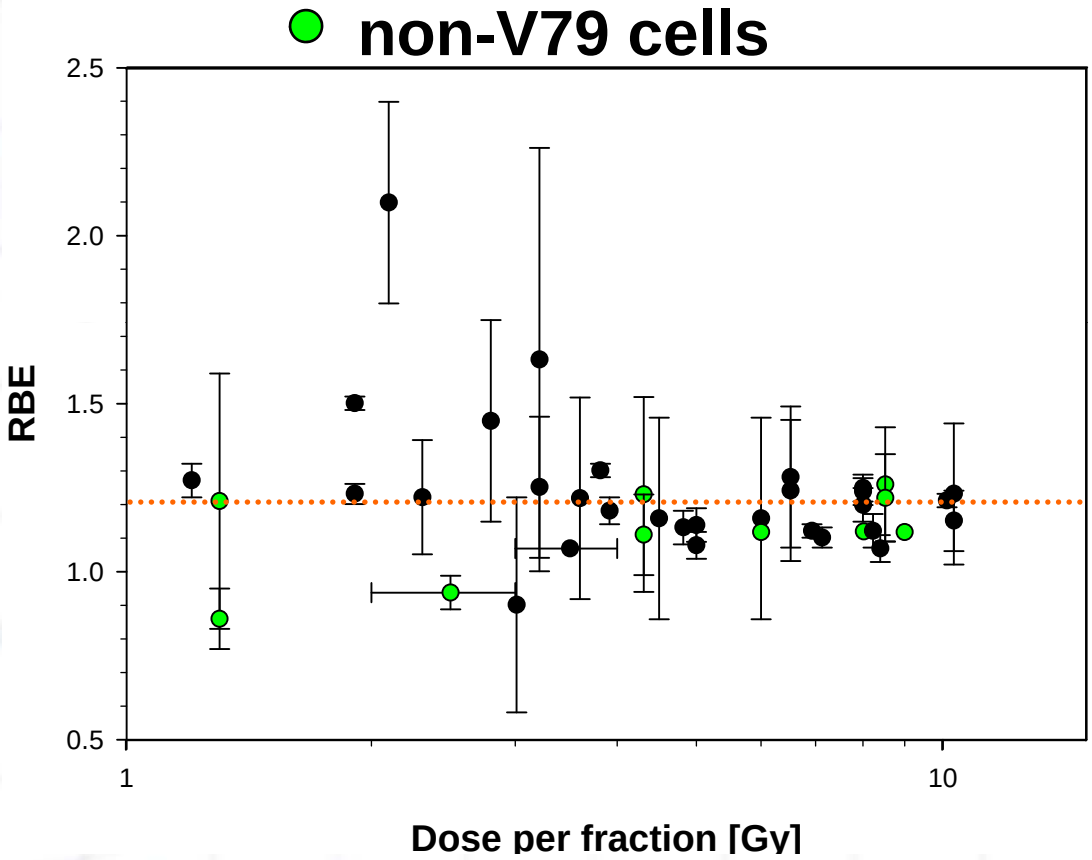
RBE as a function of tissue

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

Protons



Paganetti et al.: *Int. J. Radiat. Oncol. Biol. Phys.* 2002; 53, 407-421

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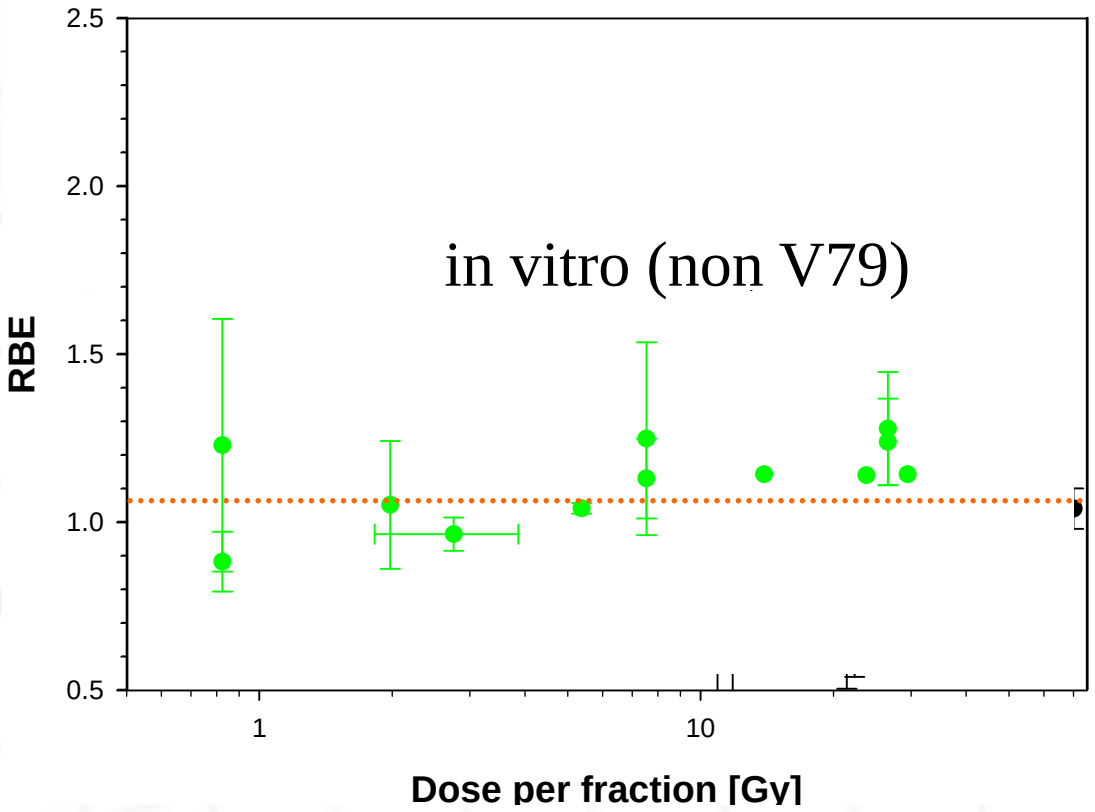
RBE as a function of tissue

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

Protons



Mice data: Lung tolerance,Crypt regeneration,Acute skin reactions,Fibrosarcoma NFSa

Paganetti et al.: *Int. J. Radiat. Oncol. Biol. Phys.* 2002; 53, 407-421

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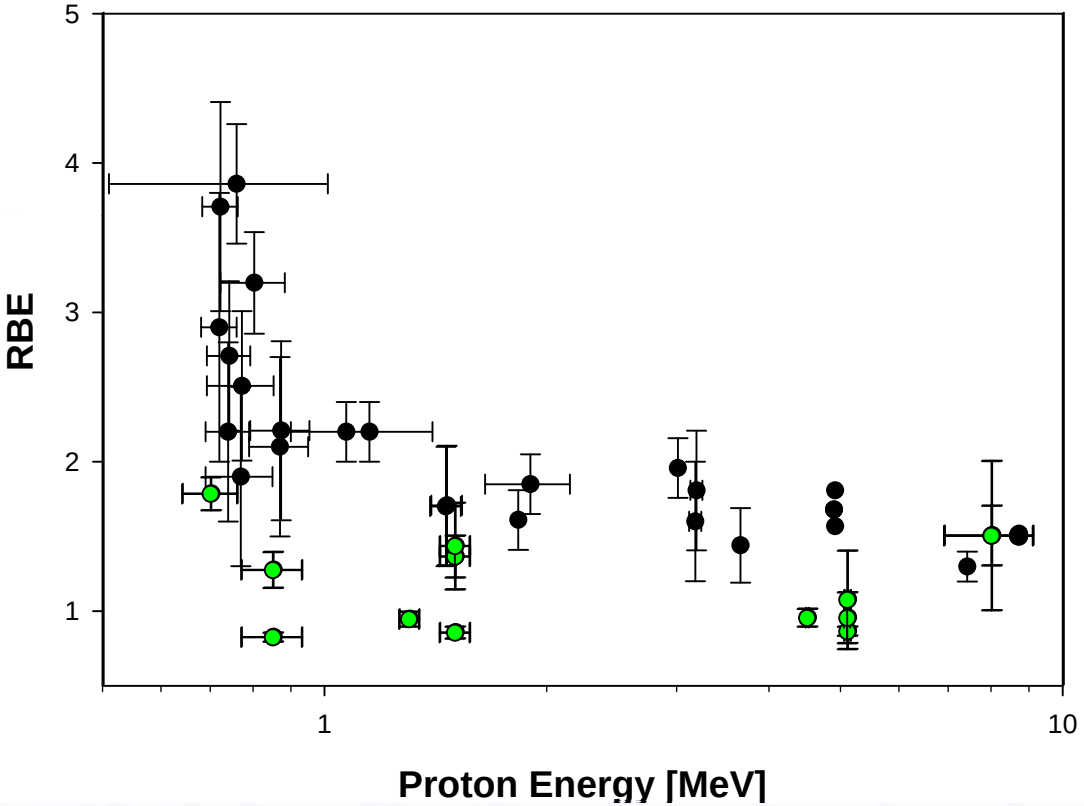
RBE as a function of tissue

Protons

Proton beams of < 10 MeV; RBE *in vitro*



● **human cells**

Belli et al. 2000
Bettega et al. 1979

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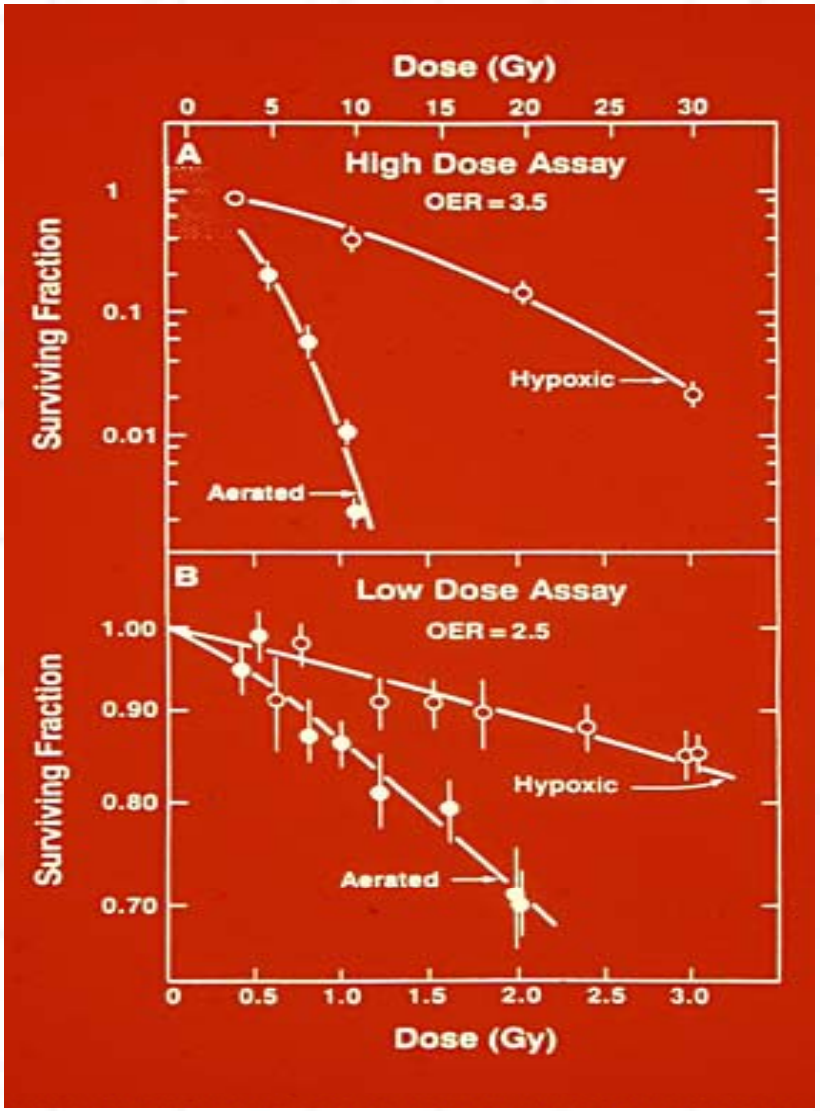
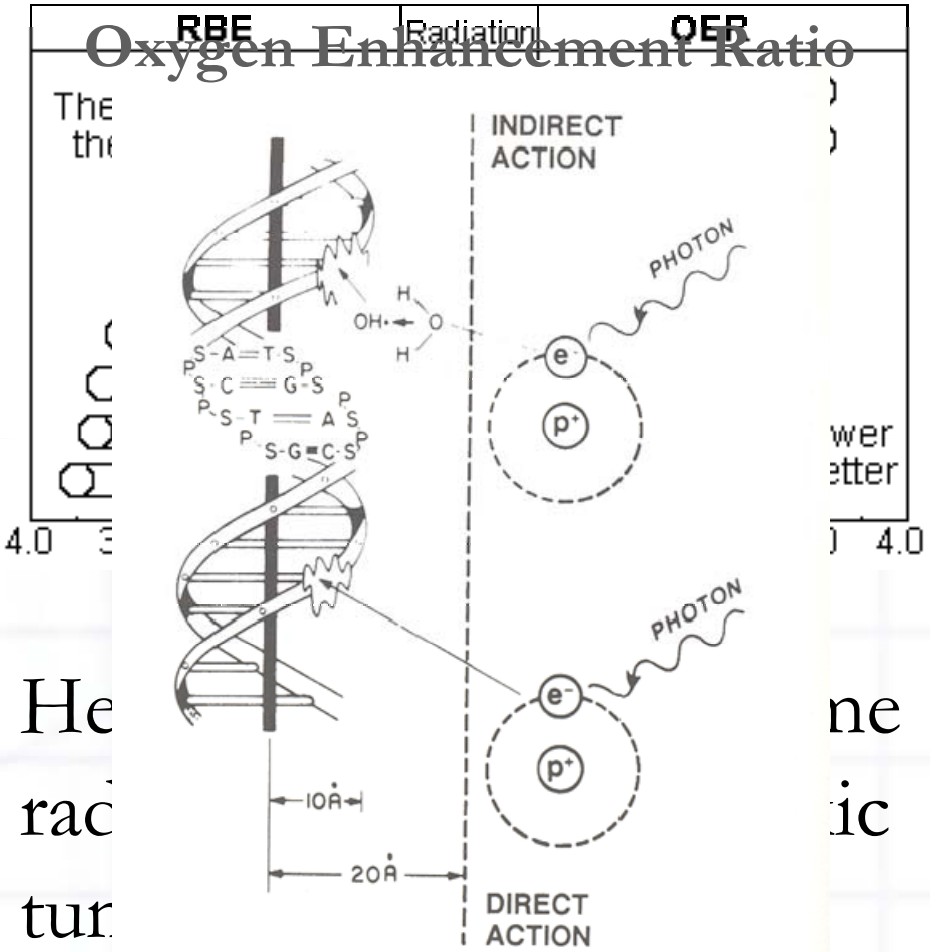
RBE as a function of tissue & LET





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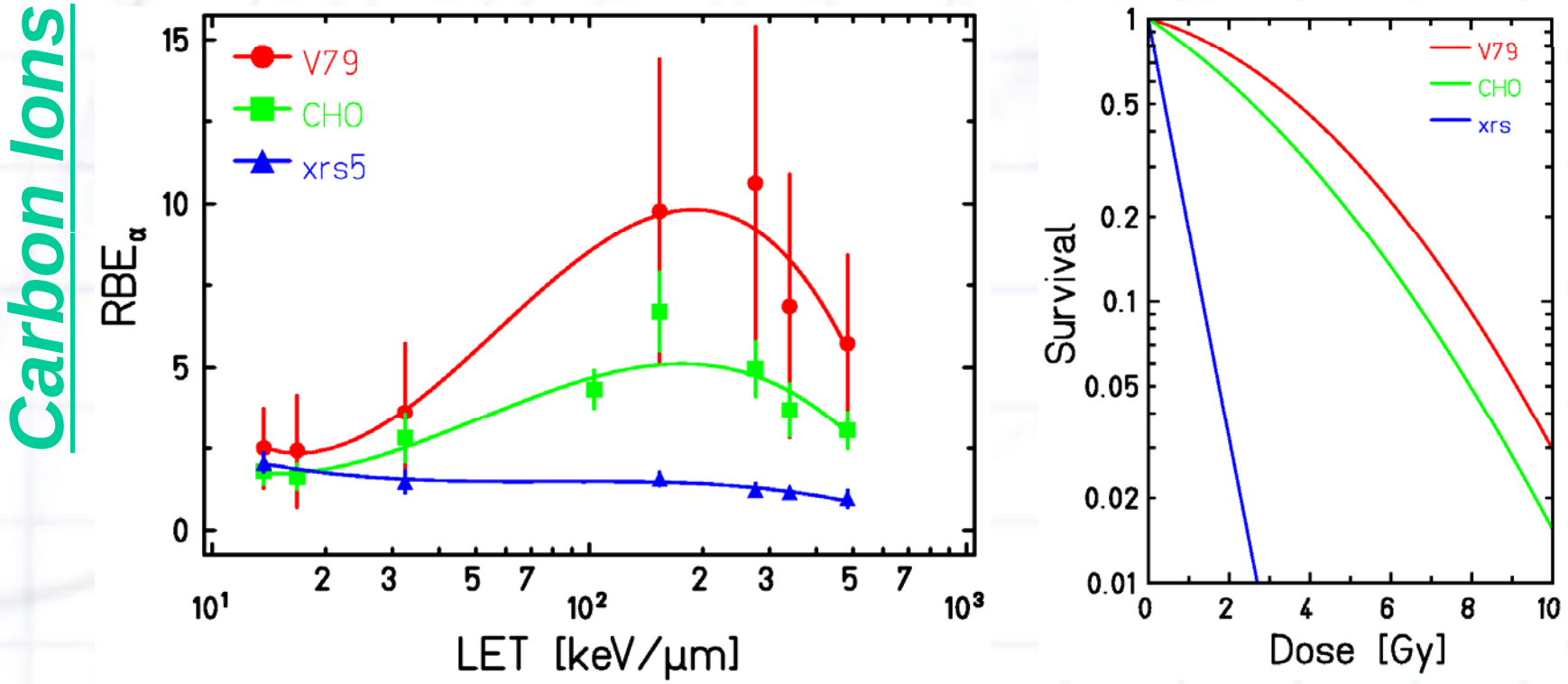
RBE as a function of repair capacity (α/β)

- Do cells with higher repair capacity show higher RBE?

Carbon ions

Photons



linear-quadratic:

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

RBE (α/β) ?

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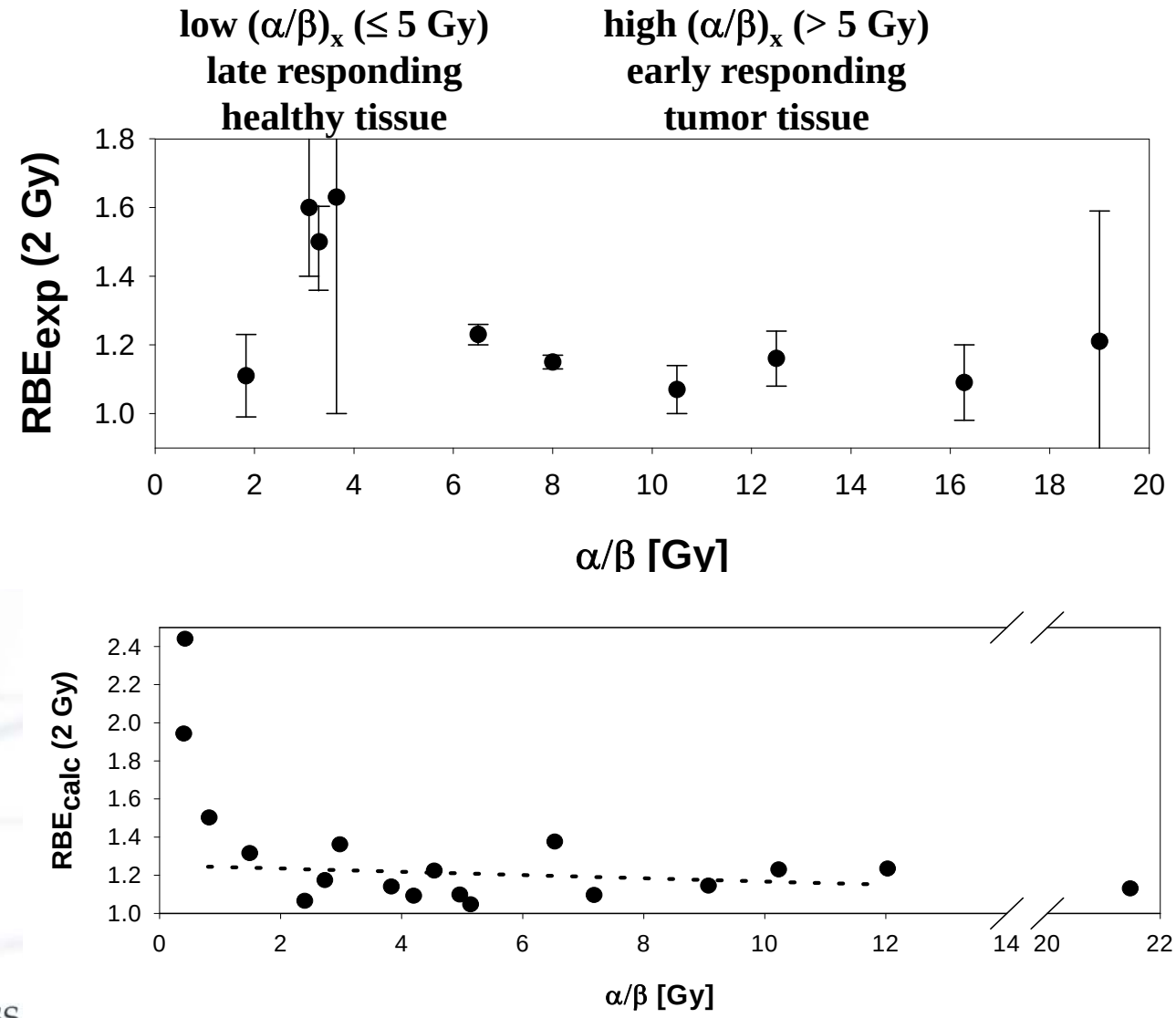
RBE as a function of repair capacity (α/β)

Protons



Gerweck, Kozin
Radiother. Oncol. 1999;
50, 135-142

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Int. J. Radiat. Biol. 2000:
76, 985-998

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RBE as a function of tissue

RBE for non-lethal injury
gene mutation, chromosomal abnormalities, carcinogenesis

Protons

dicentrics,rings in peripheral lymphocytes (Matsubara et al. 1990):

SOBP; 70 MeV proton beam

RBE increased with increasing depth (1.4 ± 0.3 (2 Gy; distal half))

RBE increased with decreasing dose (1.0±0.1 (8 Gy) to 2.3±1.2 (0.1 Gy))

induction at the HPRT locus in V79 cells (Cherubini et al. 1995):

RBE values higher for mutation compared to cell survival (up to 17%)

mutation induced by heavy ions (Cox et al. 1977):

RBE overall higher than the RBE for cell survival (human, hamster cells)

DNA damage of thyroid follicular cells (Green et al. 2001):

no significant difference compared to the cell survival RBE

micronucleus formation for Chinese hamster cells C1-1 (Sgura et al. 2000):

no significant difference compared to the cell survival RBE

RBE as a function of tissue

RBE seems to be higher for low α/β ratio (organs at risk, prostate)

RBE seems to be higher for non-lethal injuries

OER does favor heavy ions

CONCLUSIONS

Before we can implement RBE variations in proton therapy we need to understand them in vivo

We have to consider RBE variations in heavy ion radiation therapy, which does lead to considerable uncertainties

We need more in vivo experiments !

CONCLUSIONS

"high-LET radiation" versus "low-LET radiation"

High RBE is not an advantage per se

It is an advantage if it affects mainly the target due to

- high-RBE confined to the tumor
- 'targets' specific tumor cells (OER)

Hypofractionation might be advantageous for high-LET radiation (less tumor repopulation) because it causes a lack of cellular repair, i.e. reduces the advantage of fractionation

"Particles, particles, particles."