Biological considerations in proton therapy

MASSACHUSETTS GENERAL HOSPITAL
RADIATION ONCOLOGY

HARVARD MEDICAL SCHOOL

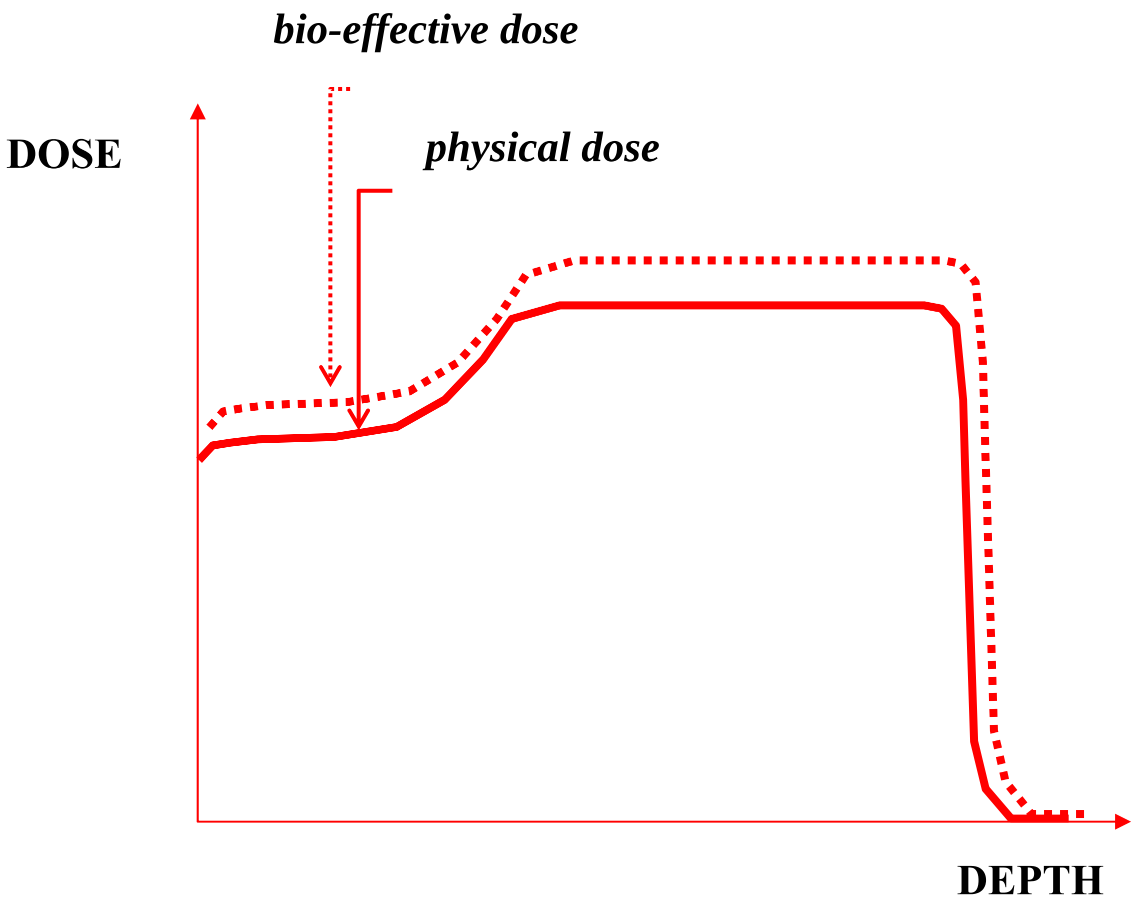
Harald Paganetti PhD
Professor of Radiation Oncology, Harvard Medical School
Director of Physics Research, Massachusetts General Hospital, Department of Radiation Oncology

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

1. Generic and variable RBE

Clinical RBE

Proton therapy: RBE = 1.1

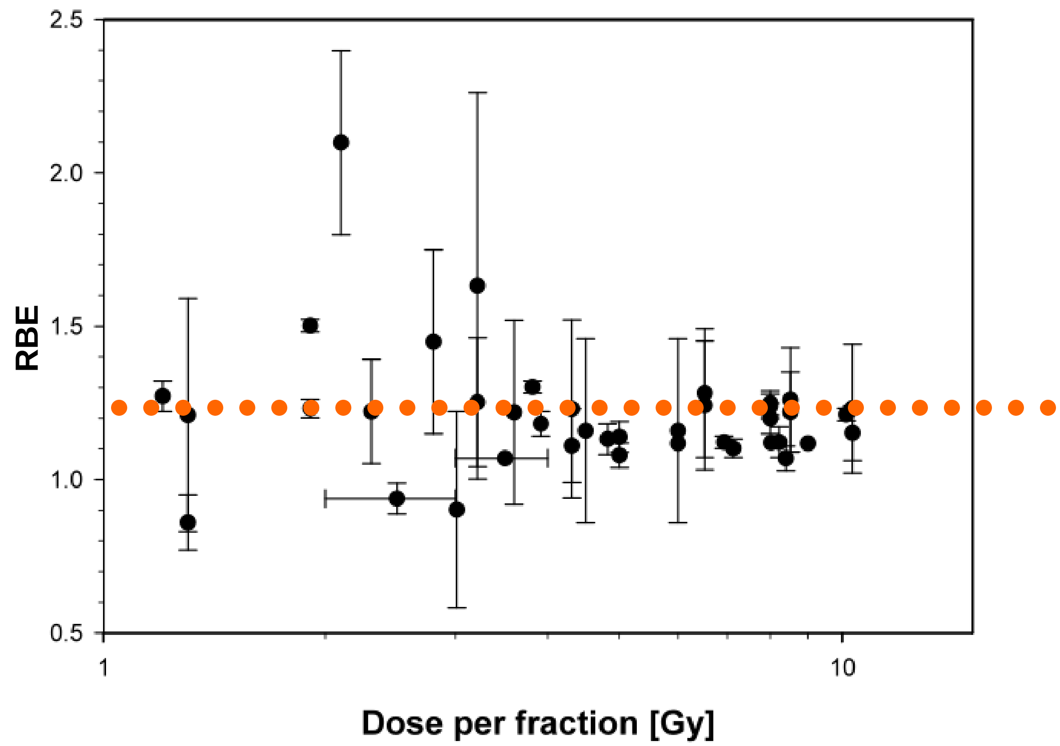


Dose in proton therapy is prescribed as Gy(RBE)

Clinical RBE

RBE from experimental data

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



1.21 ± 0.20

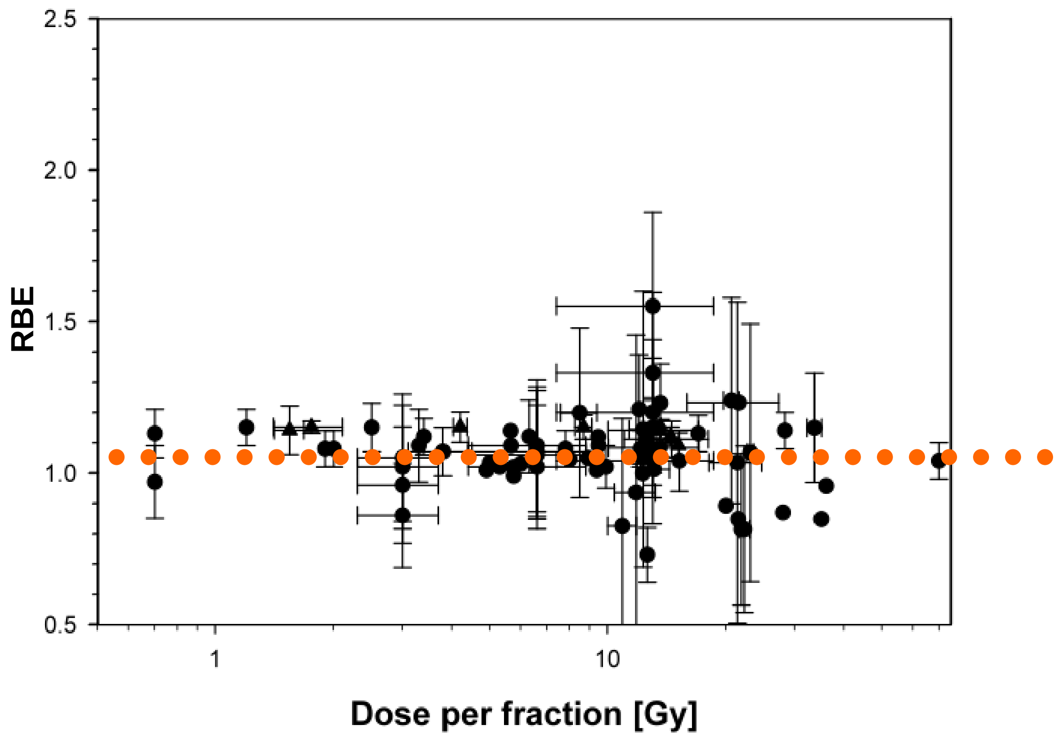
Endpoint: Cell Survival

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

Clinical RBE

RBE from experimental data

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

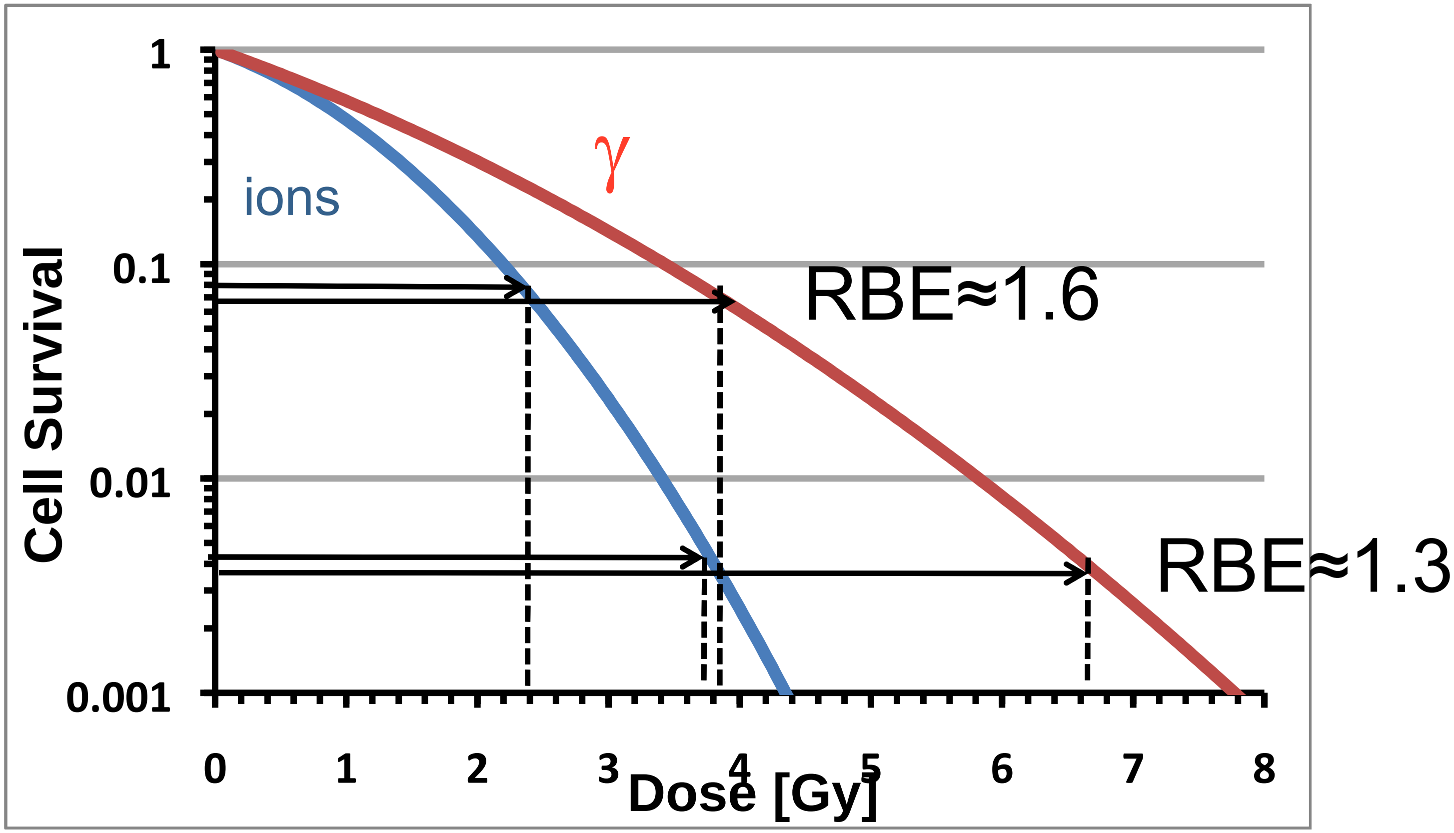
Paganetti et al.: *Int.J.Radiat.Oncol.Biol.Phys.* 2002; 53, 407

Clinical RBE

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

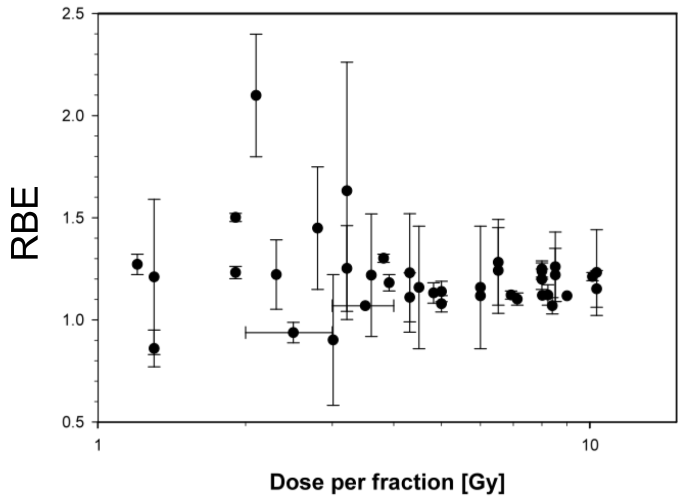
RBE as a function of dose

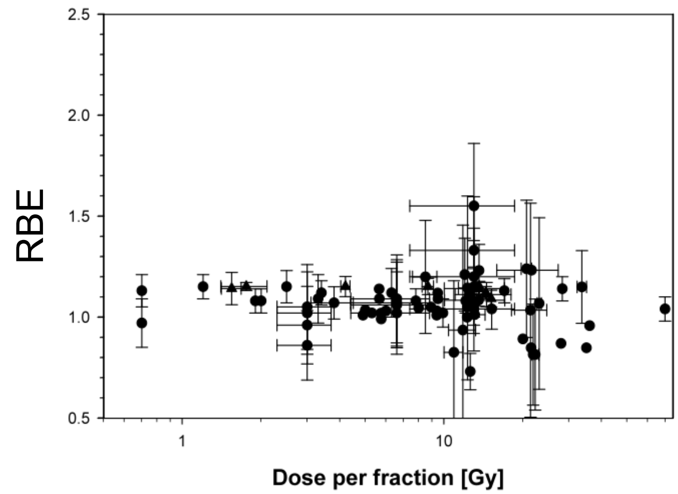


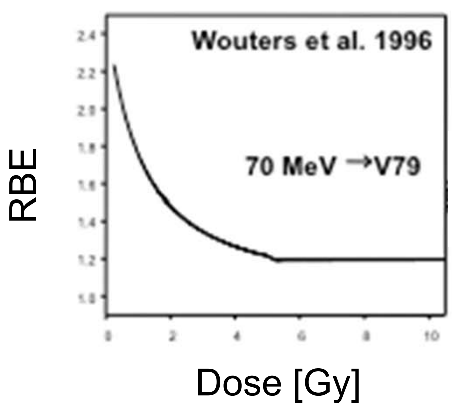
$$S(D) = e^{-(\alpha D+\beta D^2)}$$

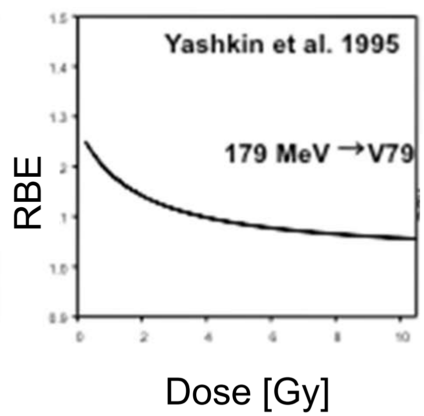
RBE as a function of dose

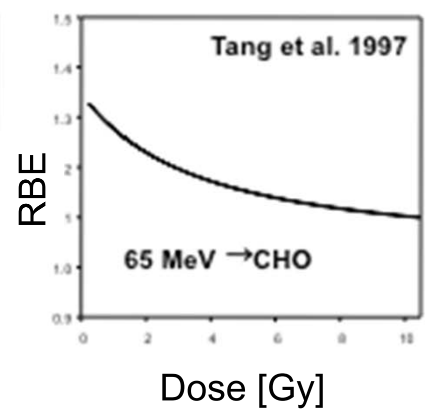
in vitro **in vivo**











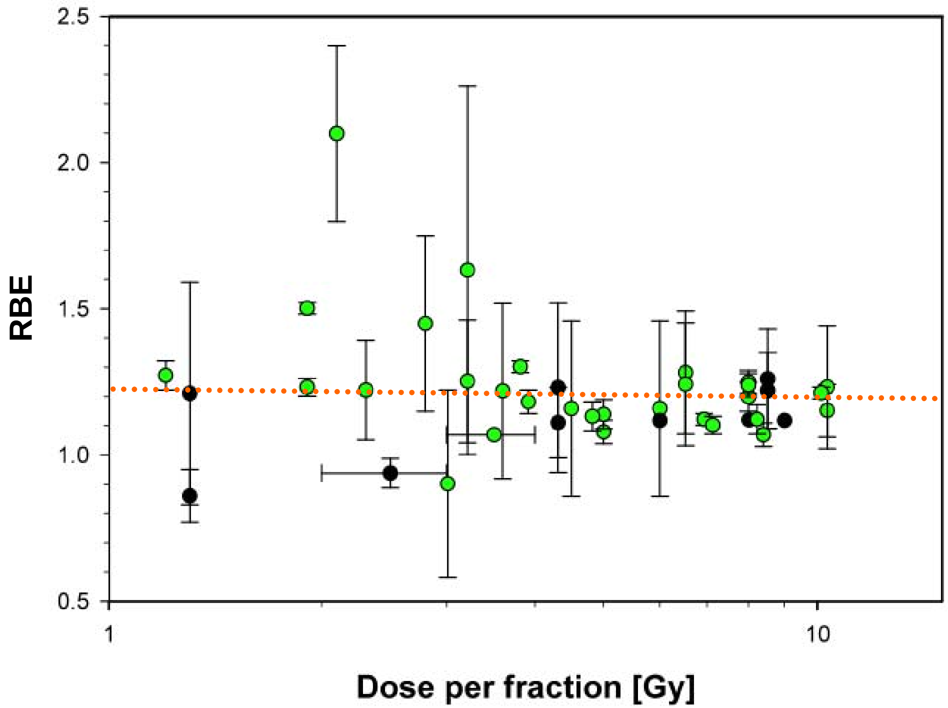
RBE as a function of dose

- **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

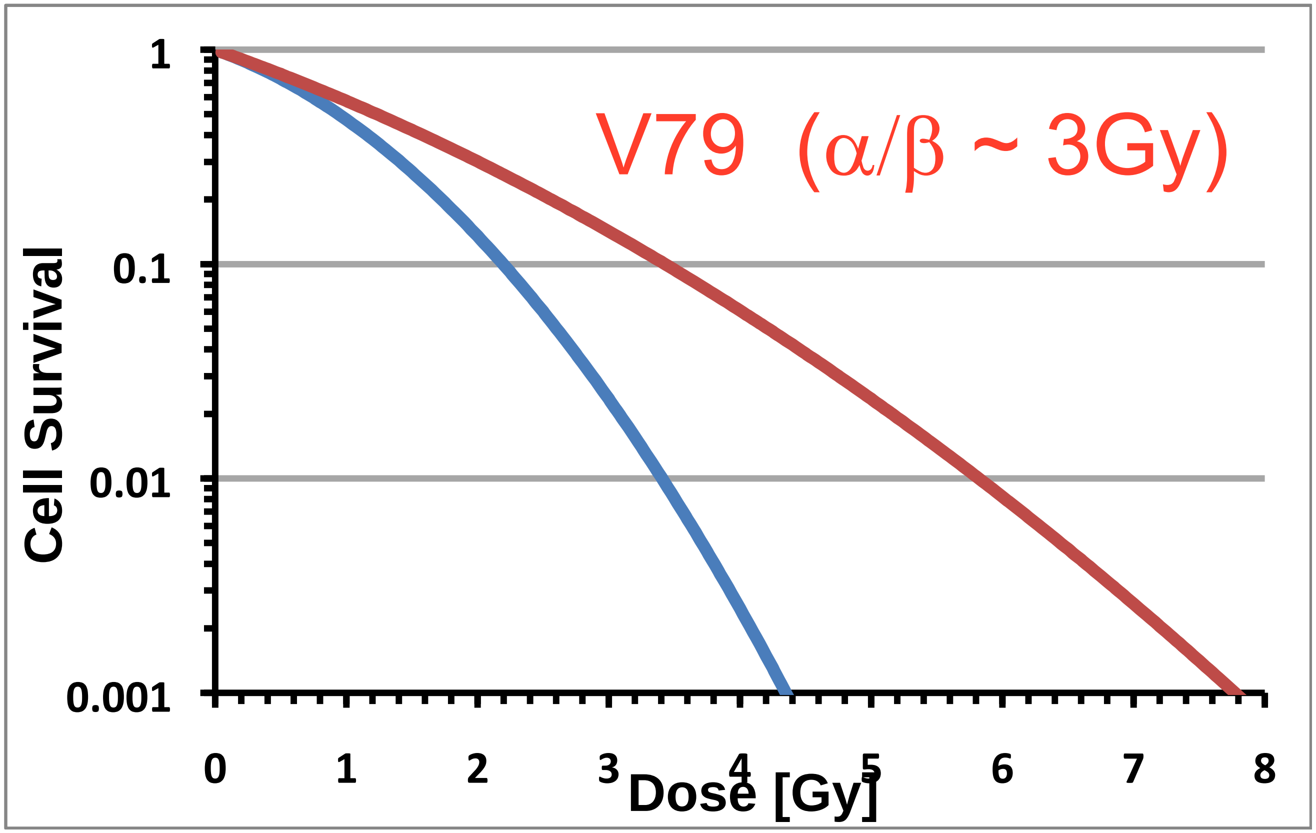
RBE values *in vitro* (center of SOBP; relative to ^{60}Co)

● **V79 cells only**



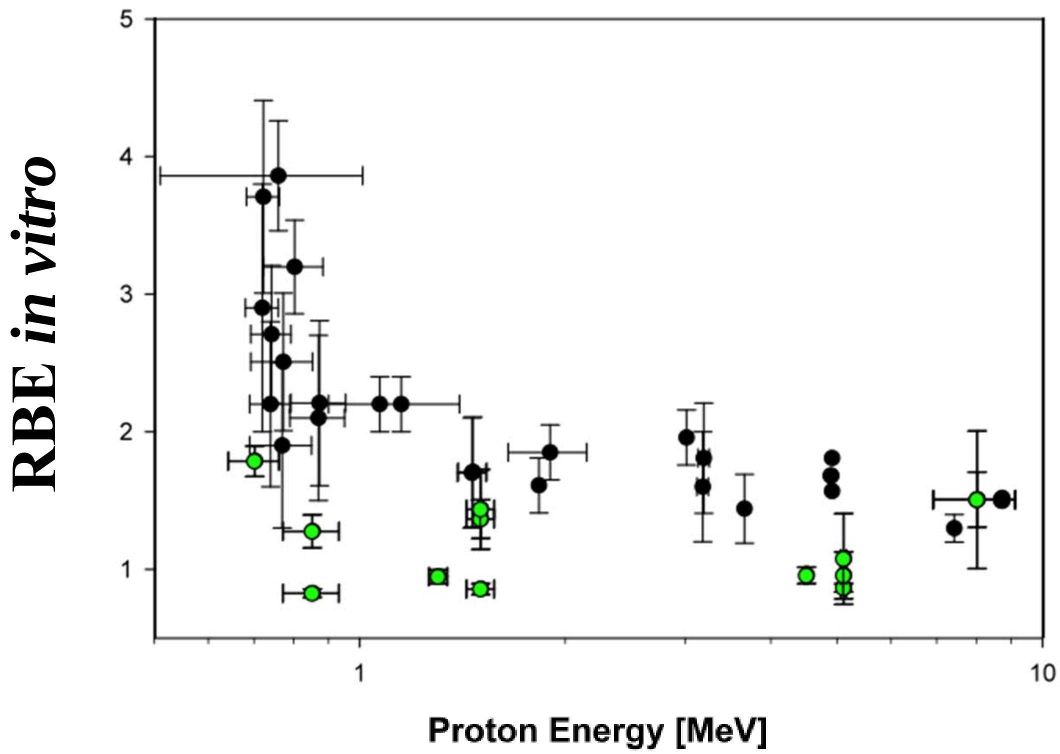
Paganetti et al.: *Int. J. Radiat. Oncol. Biol. Phys.* 2002; 53, 407-421

RBE as a function of tissue/endpoint



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

RBE as a function of tissue/endpoint



human cells

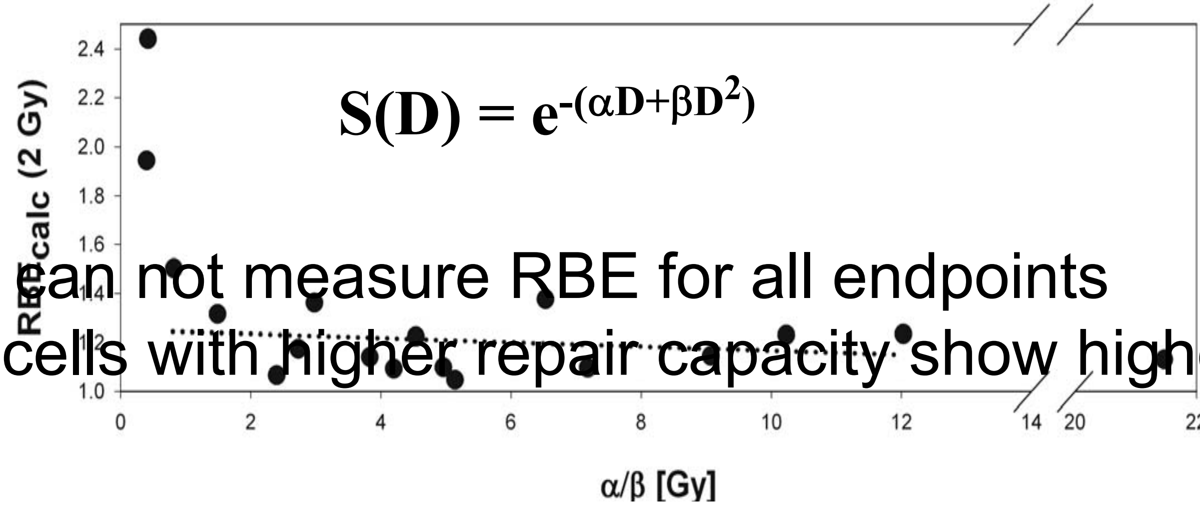
Belli et al. 2000
Bettega et al. 1979

RBE as a function of tissue/endpoint

low $(\alpha/\beta)_x$ (≤ 5 Gy)
late responding
healthy tissue

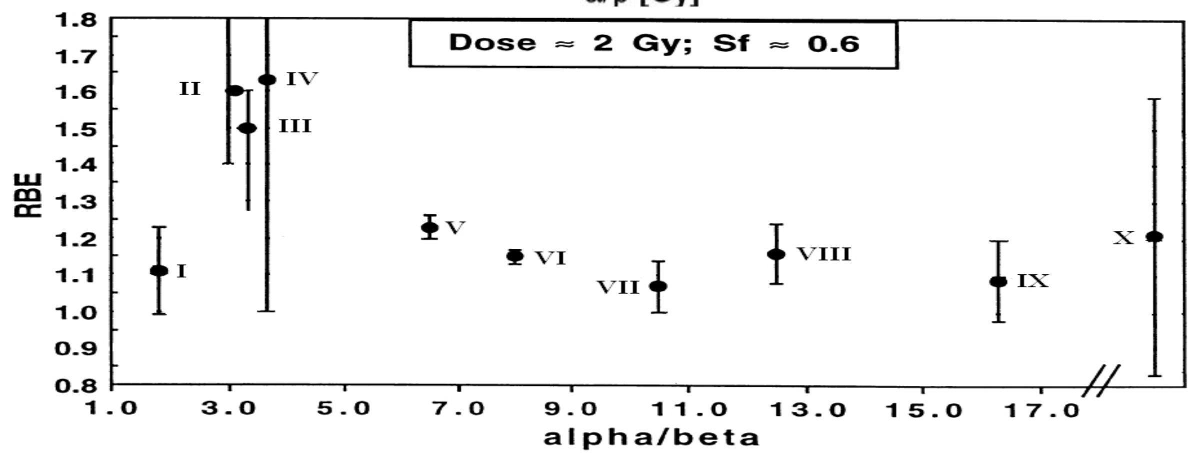
high $(\alpha/\beta)_x$ (> 5 Gy)
early responding
tumor tissue

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



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

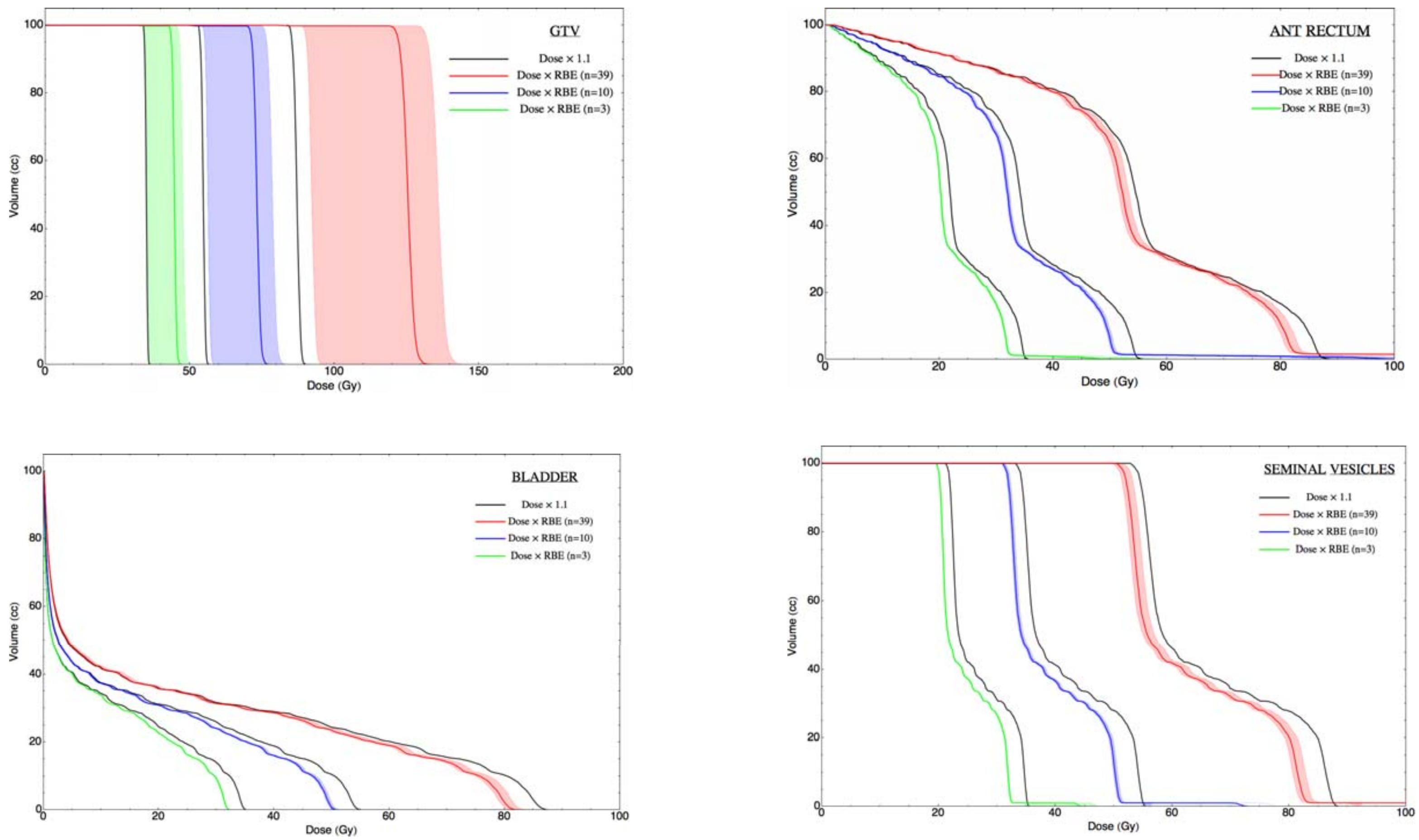
Paganetti,Gerweck,Goitein *Int. J. Radiat. Biol.* 2000: 76, 985-998



Gerweck and Kozin *Radiother. Oncol.* 1999

RBE as a function of tissue/endpoint

Uncertainties due to α/β ratio uncertainties in prostate

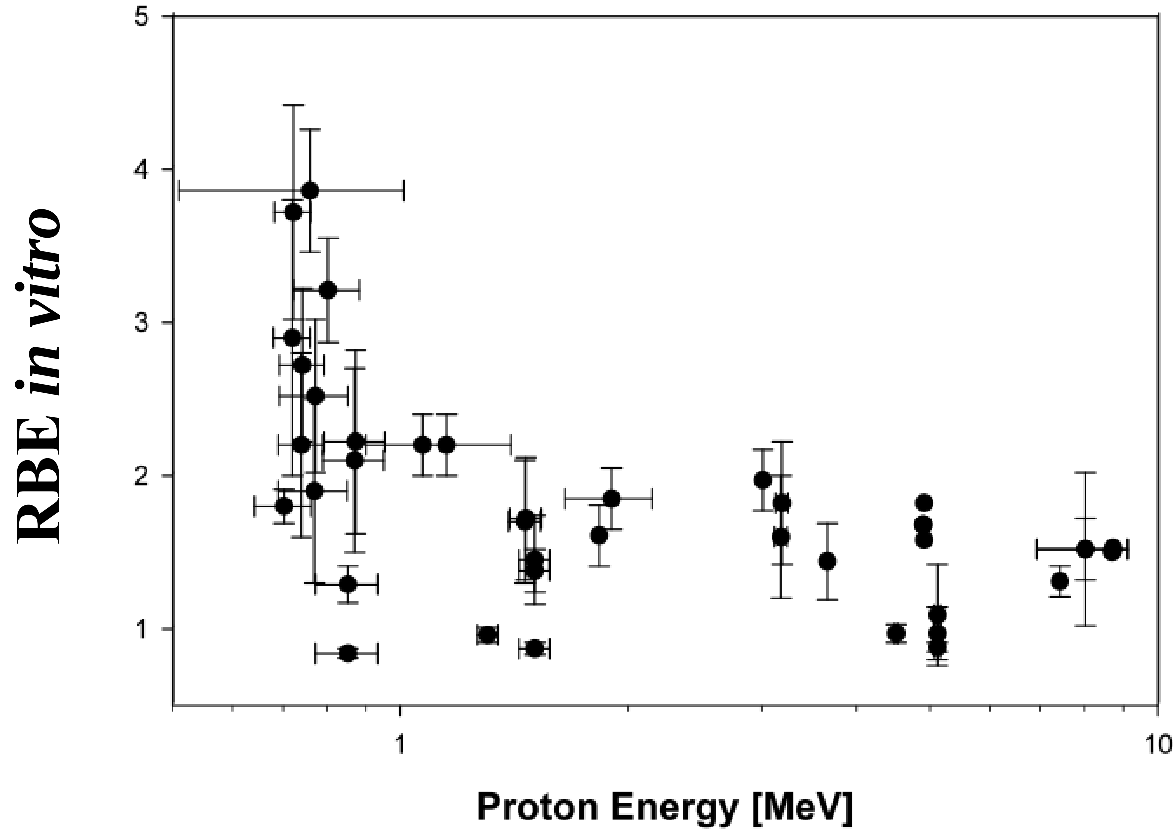


A Carabe, S España, C Grassberger, H Paganetti: Clinical consequences of Relative Biological Effectiveness variations in proton radiotherapy of the prostate, brain and liver; Physics in Medicine and Biology 2013

RBE as a function of tissue/endpoint

- **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 α/β ratio (mainly organs at risk); could impact prostate treatments and trials (IMRT versus protons)**
- **RBE might be higher for non-lethal injuries**

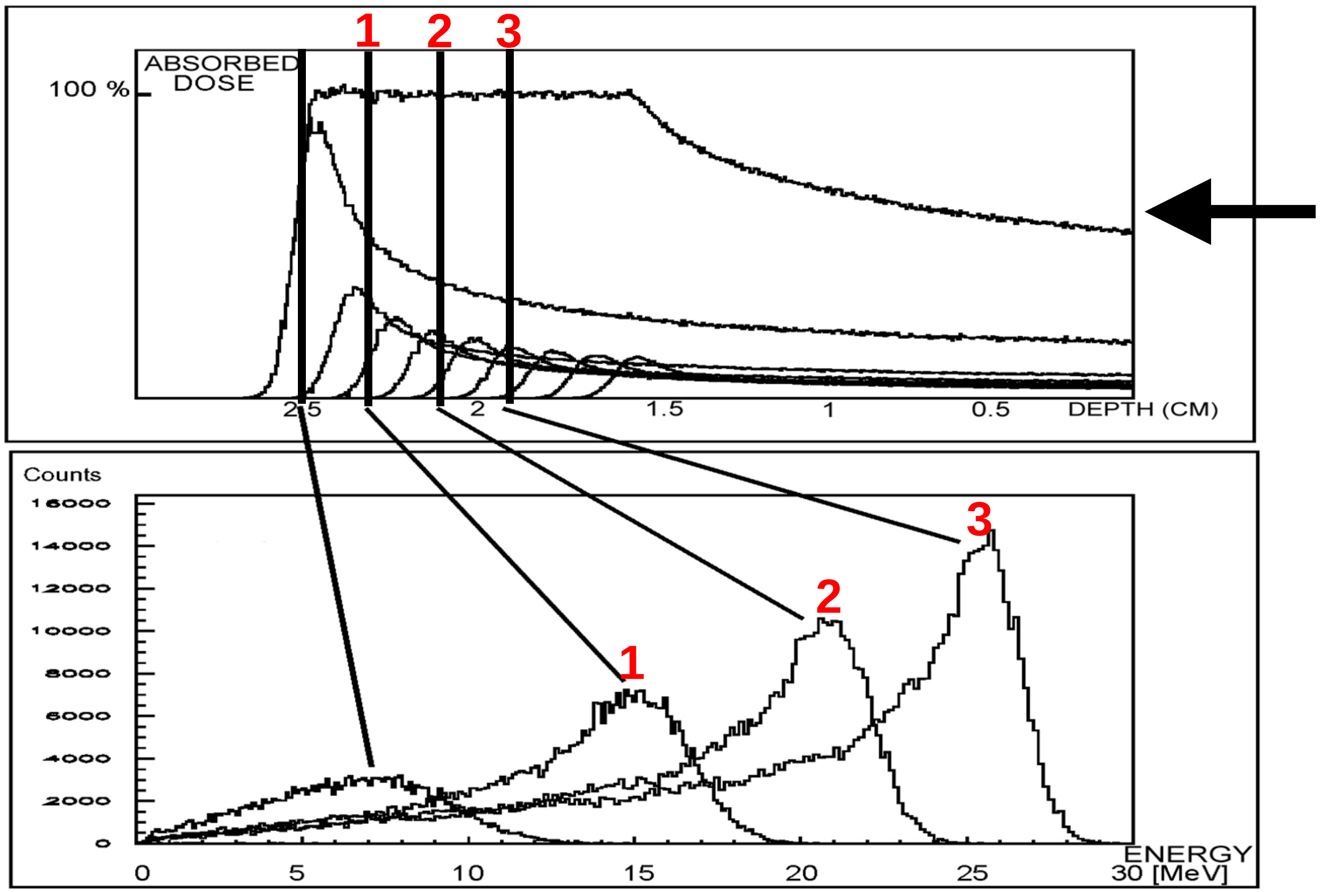
RBE as a function of energy/LET



RBE as a function of energy/LET

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

Implication of RBE(LET) for RBE(depth)



$$\text{Dose} = \text{Fluence}\ _{[1/cm^2]} \times \text{LET}\ _{[keV/cm]} \,/\, \rho\ _{[g/cm^3]}$$

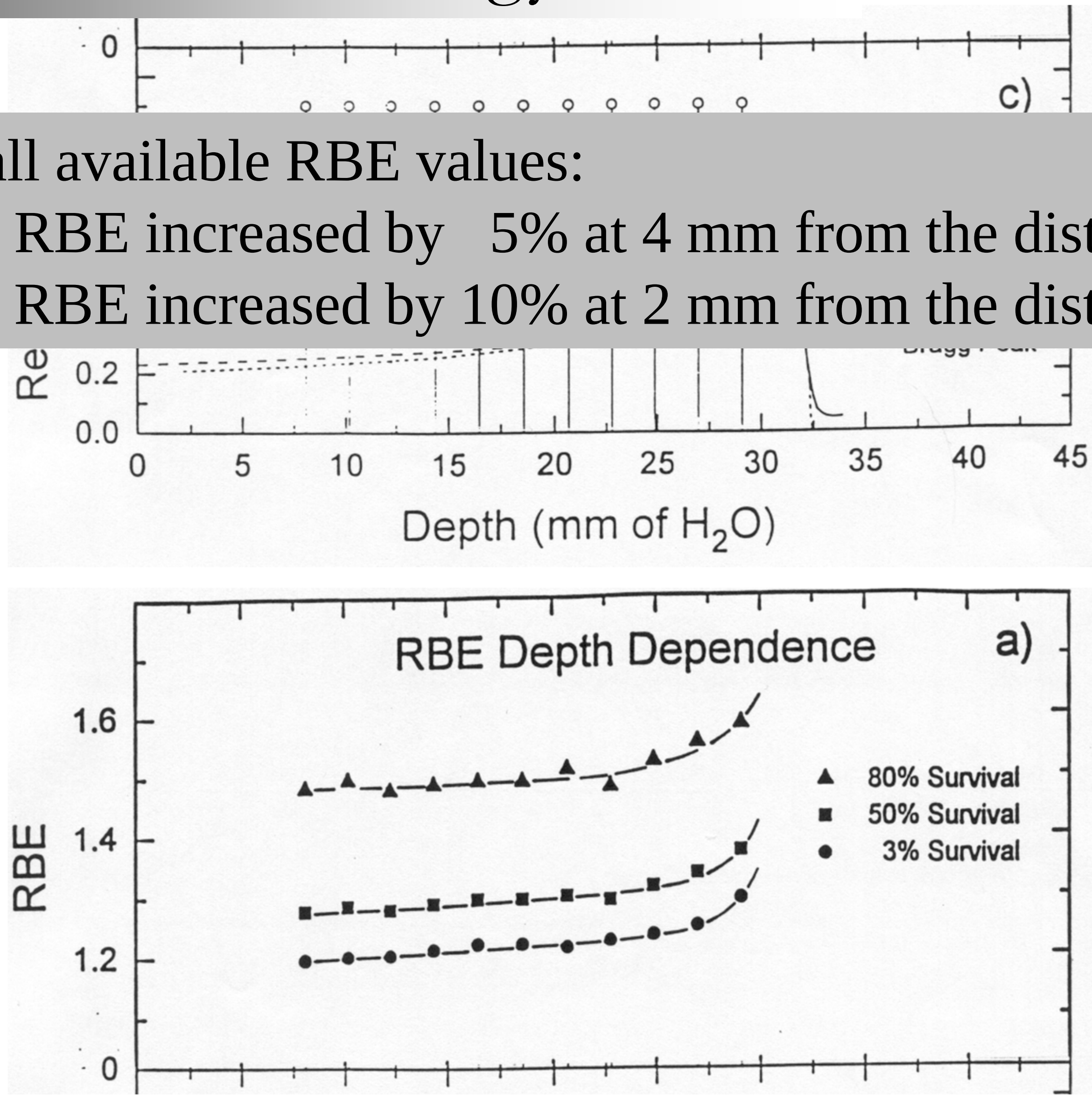
RBE as a function of energy/LET

Fit of all available RBE values:

RBE increased by 5% at 4 mm from the distal edge

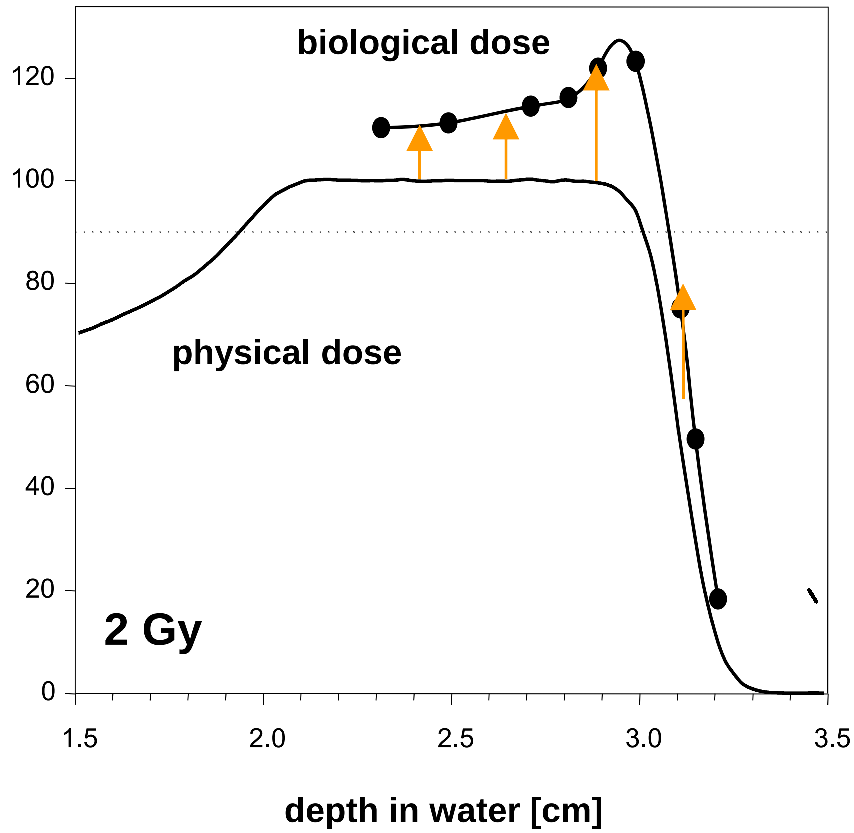
RBE increased by 10% at 2 mm from the distal edge

Wouters et al. *Radiat Res* 1996; 14



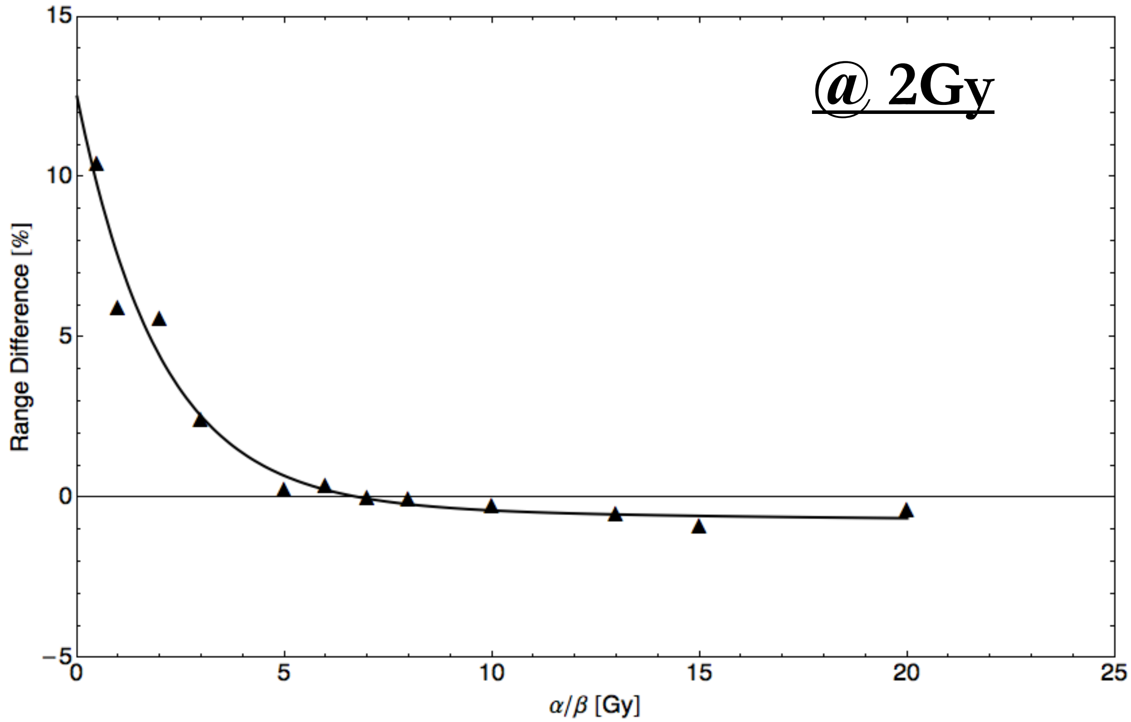
RBE as a function of energy/LET

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



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

Range Shift



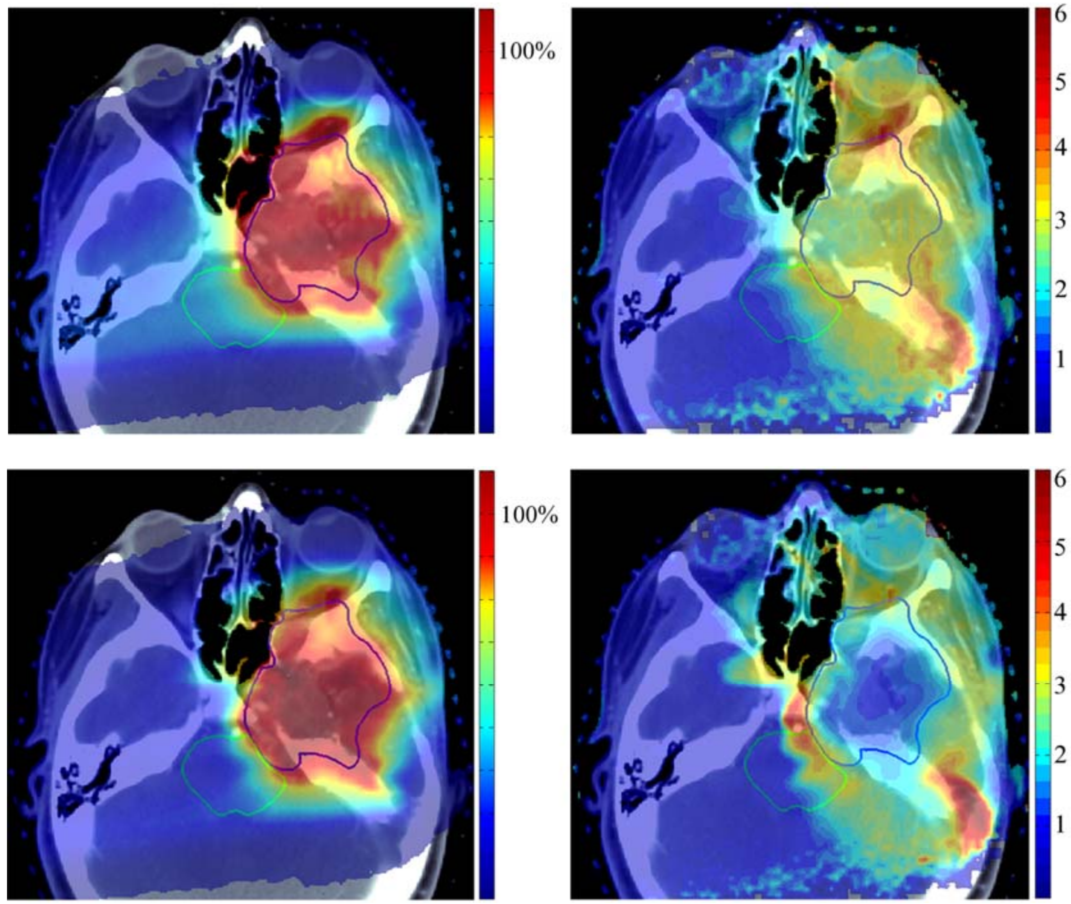
Carabe A; Moteabbed M; Depauw N; Schuemann J and Paganetti H: Range uncertainty in proton therapy due to variable biological effectiveness. Physics in Medicine and Biology 2012 57: 1159–1172

RBE as a function of energy/LET

Dose $\quad$ LET_d

IMPT Plan 1

IMPT Plan 2



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
Giantsoudi et al.: Linear energy transfer (LET)-Guided Optimization in intensity modulated proton therapy (IMPT): feasibility study and clinical potential. Int. J. Radiat. Oncol. Biol. Phys. 2013; in press

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 used in biological treatment optimization**

RBE - Conclusions

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 α/β
LET:	RBE increases as a function of depth

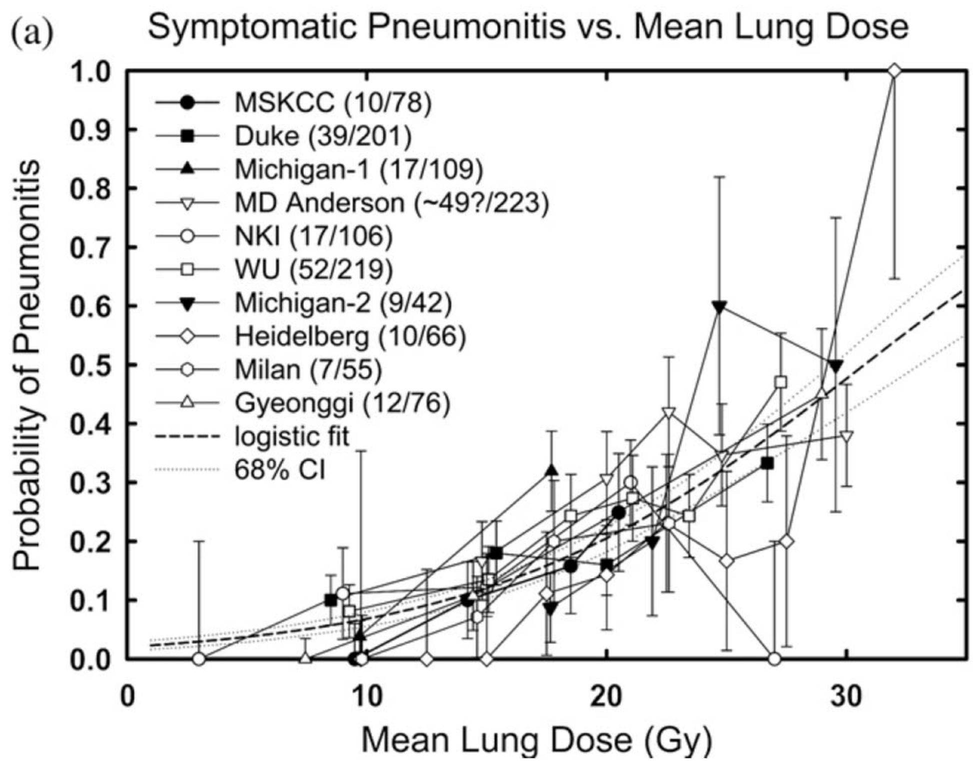
Clinical significance of RBE variations still needs to be shown

2. Proton therapy outcome

Proton Therapy Outcome

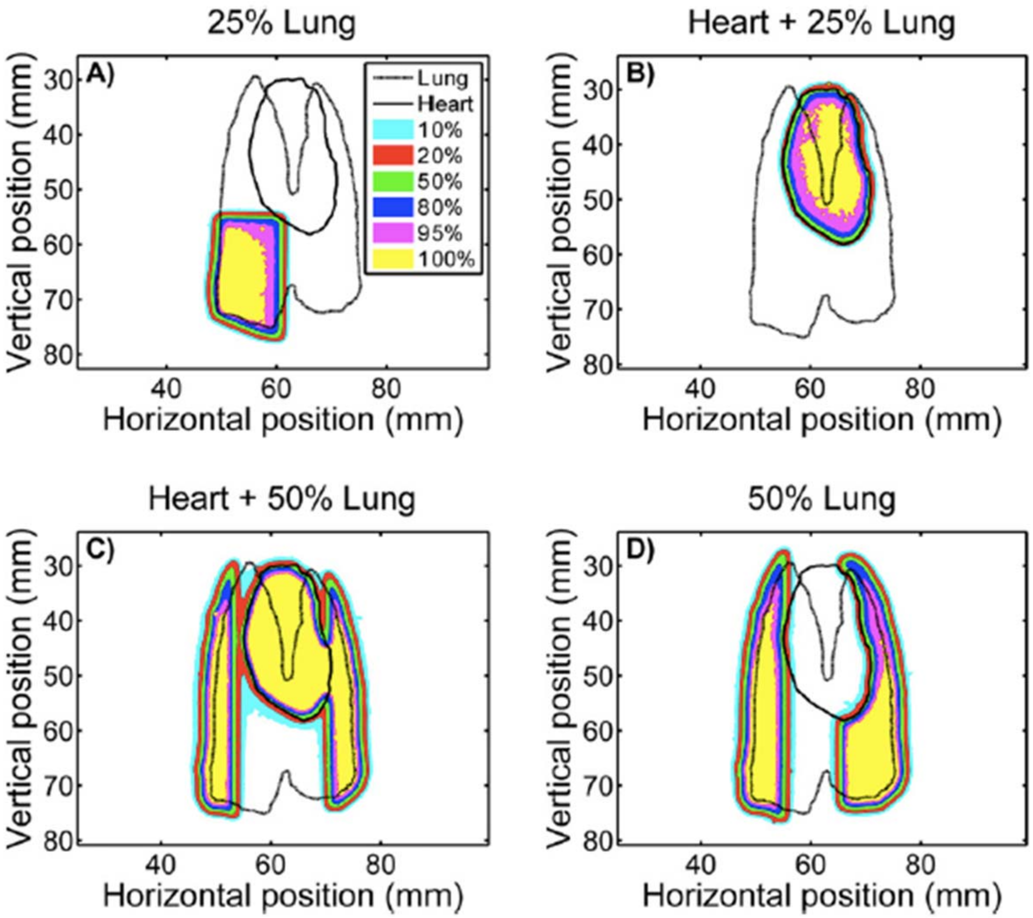
- NTCP considerations in treatment planning are based on photon dose distributions (mostly mean dose)
- Organ doses in proton therapy are more heterogeneous. There are no proton specific normal tissue constraints

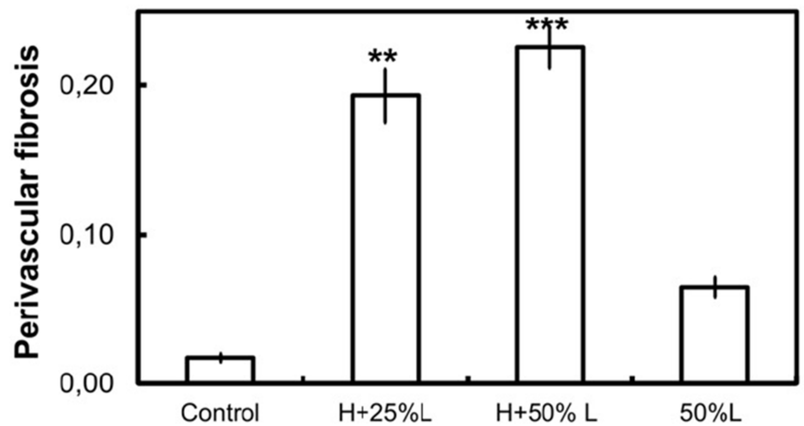
(a)



QUANTEC: Marks et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010

The “dose bath” effect





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

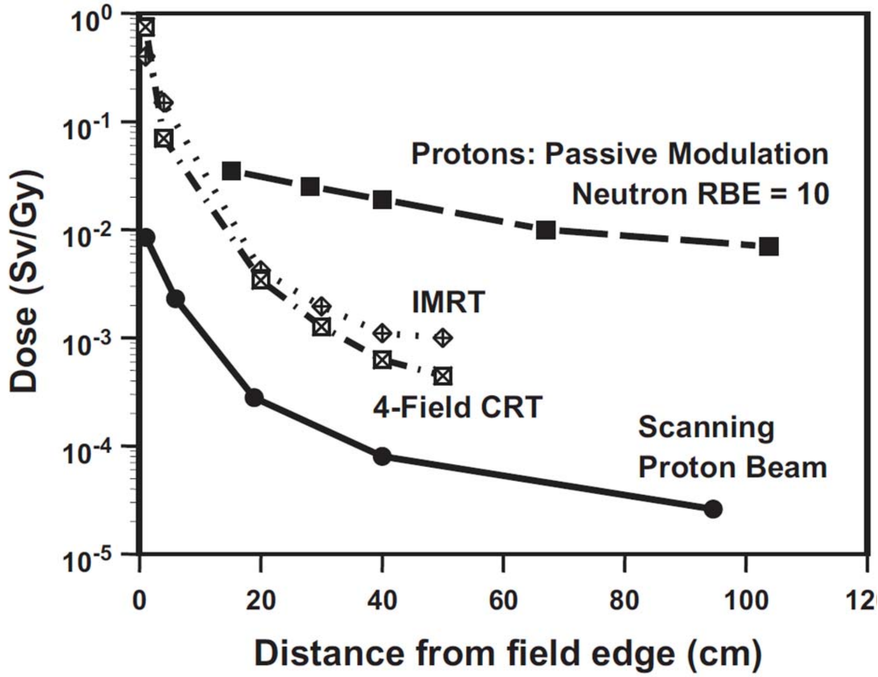
Ghobadi et al. Physiological Interaction of Heart and Lung in Thoracic Irradiation
Int J Radiat Oncol Biol Phys 2012

Outcome - Conclusions

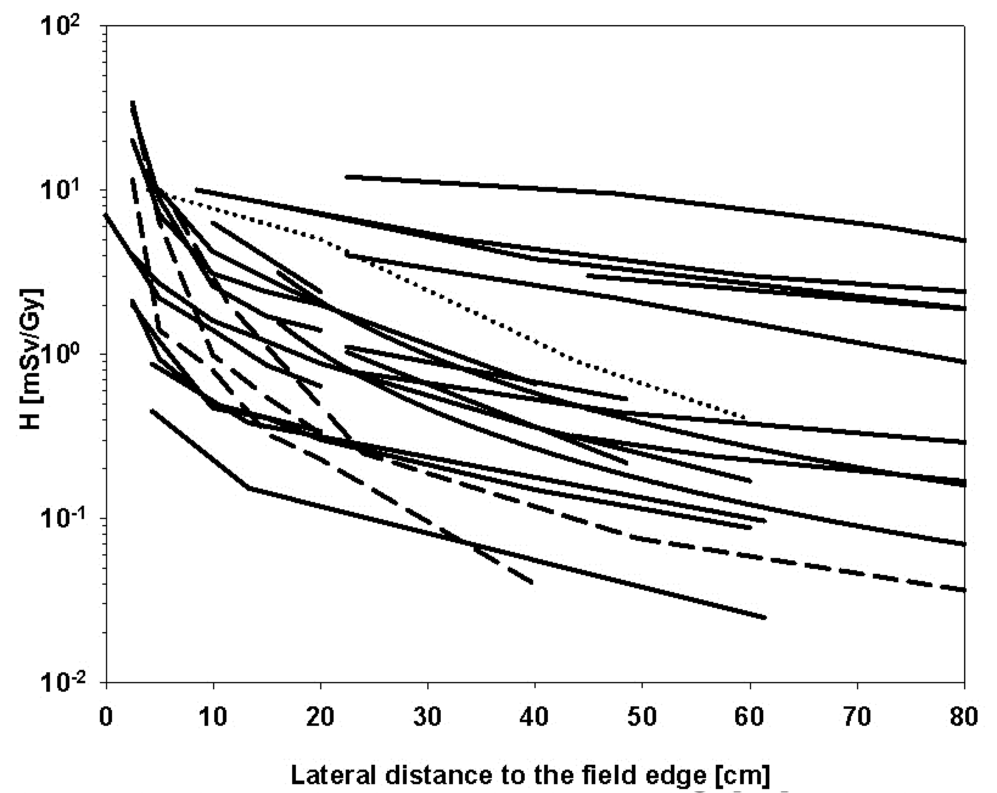
- If the total reduced dose to critical structures would be all that mattered, there would be no need for clinical trials.
- Assessing clinical impact is difficult because proton dose distributions in critical structures are typically more heterogeneous compared to photon therapy but most dose constraints 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



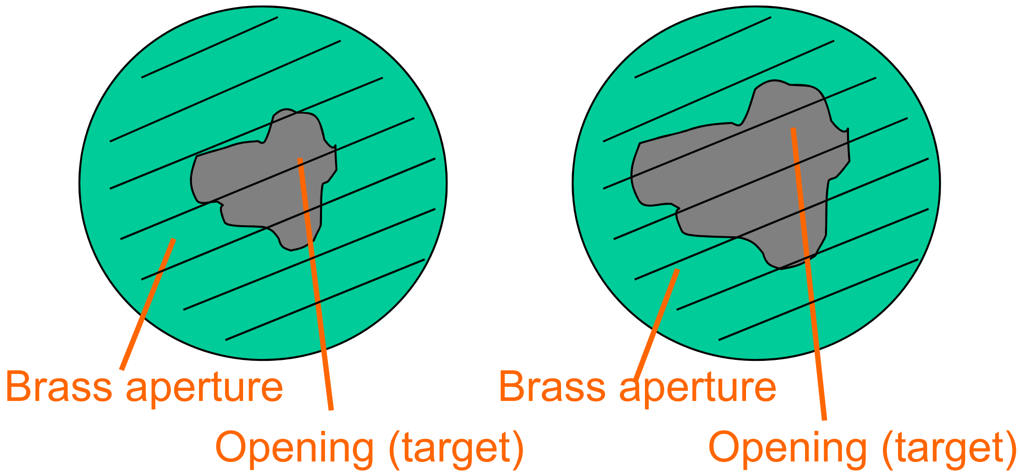
E. Hall; Int. J. Radiat. Biol. Phys. 65, 2006



Zacharatou Jarlskog & Paganetti;
Int. J. Radiat. Oncol. Biol. Phys. 2008: 69, 228-235

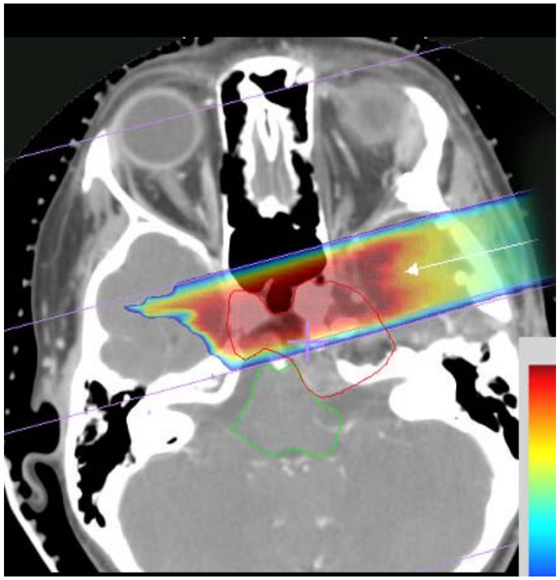
Neutron dose dependencies

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



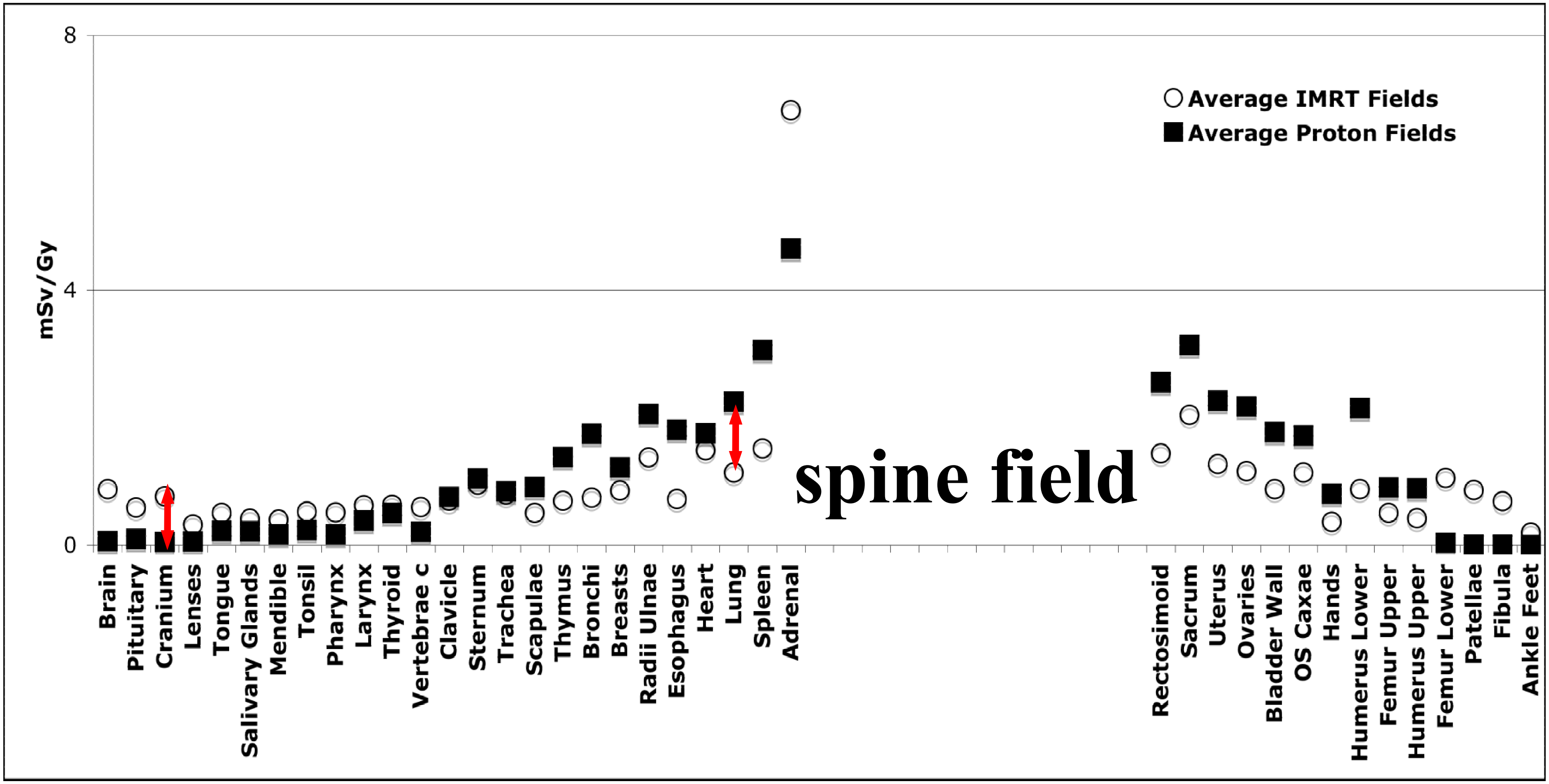
passive scattering

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



passive scattering
beam scanning

Second malignancies: protons versus photons



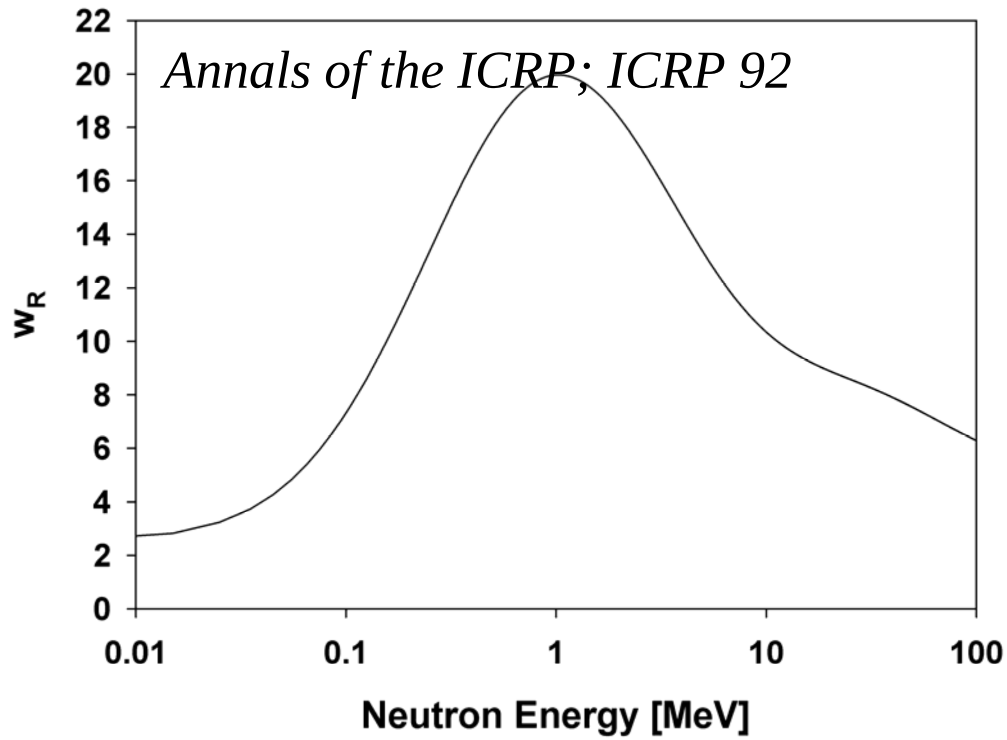
Doses averaged over 6 fields assuming a 8-year old female patient

Athar; Bednarz, Seco; Hancox & Paganetti: Phys Med Biol 55 (2010) 2879–2891

Neutron "RBE"

Neutron radiation weighting factor

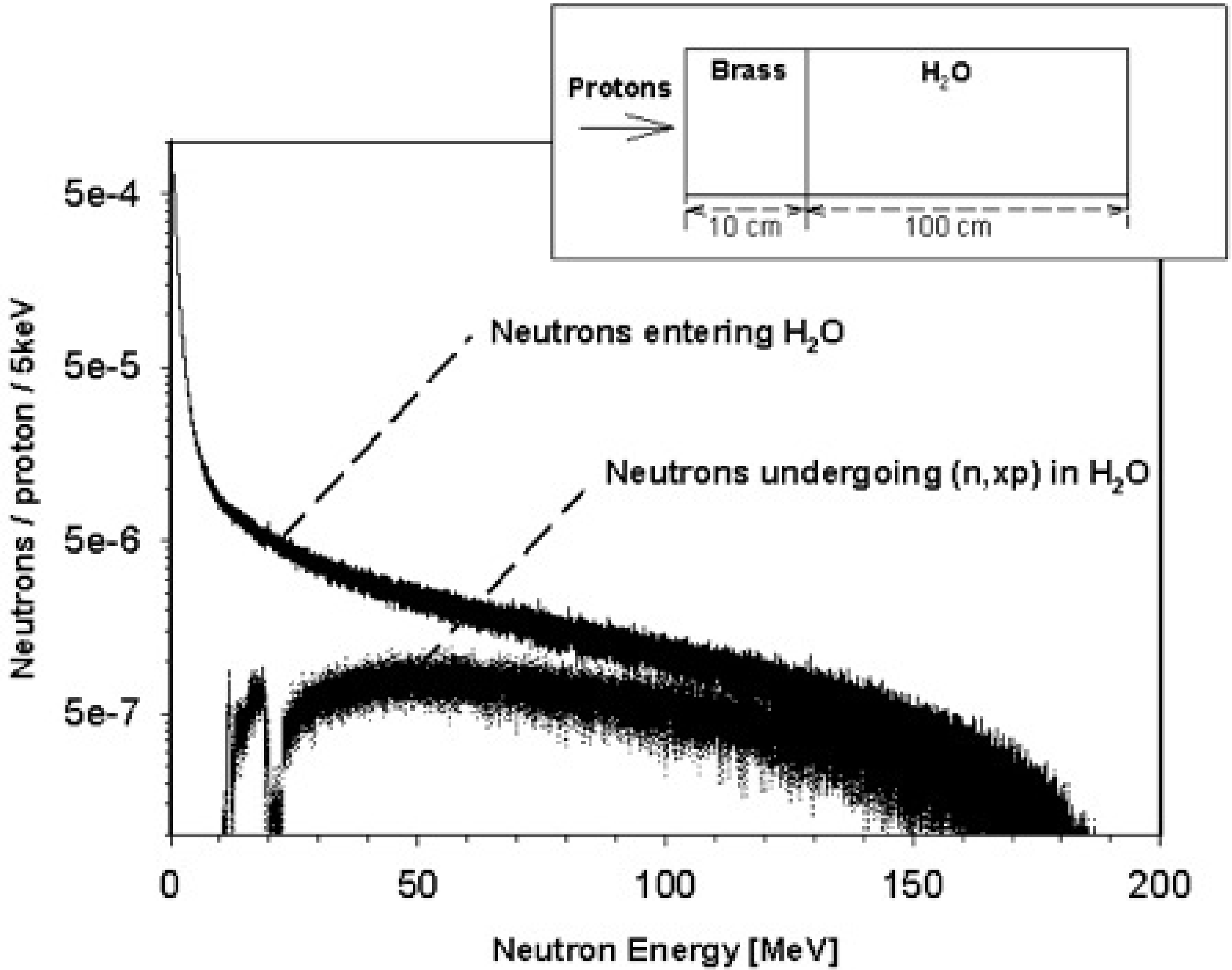
$$H = D \times w_R[\text{particle, energy}]$$



Neutron radiation quality factor

$$H = D \times Q[LET_\infty]$$

Neutron “RBE”



Proton Therapy Physics (Paganetti Edt.); Taylor&Francis CRC Press 2011

Second malignancies: protons versus photons

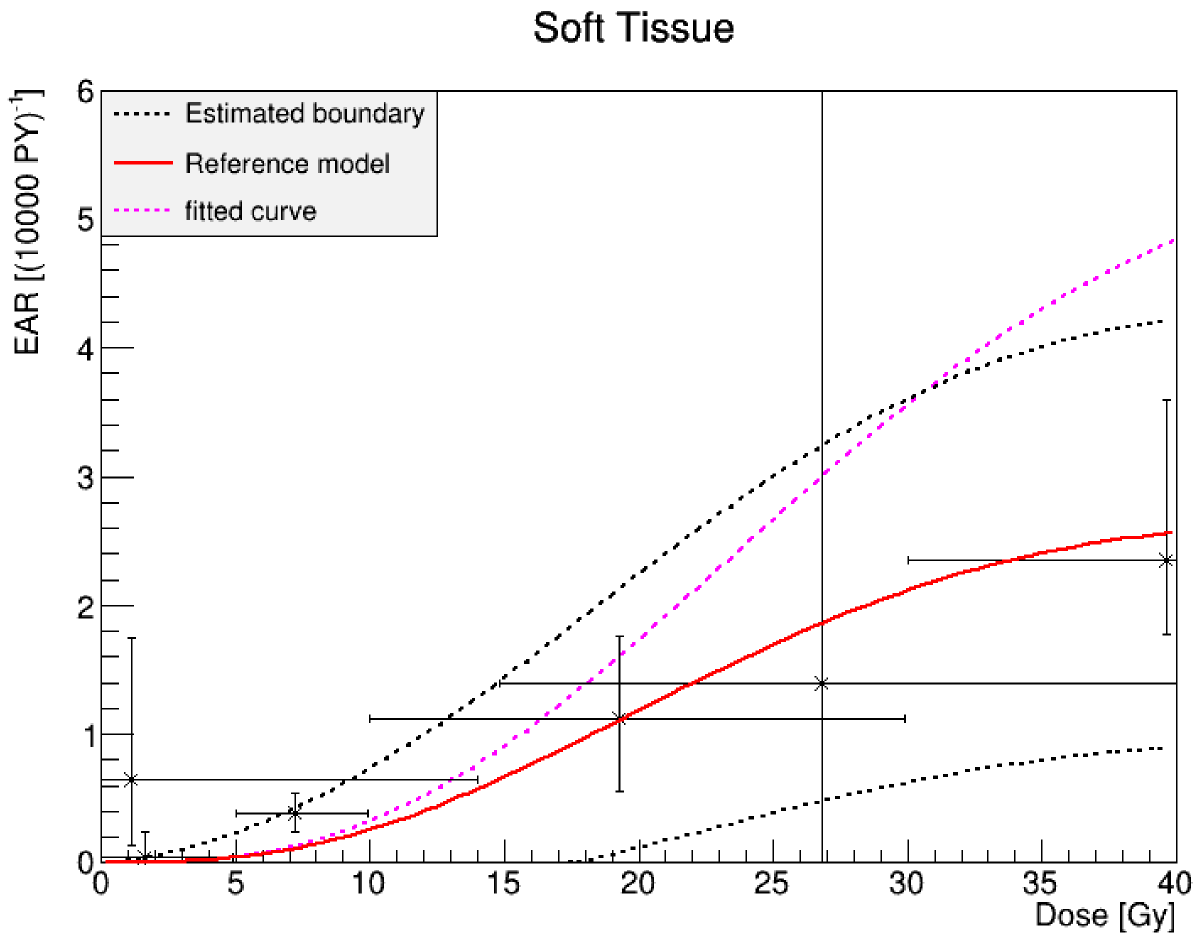
MGH-Harvard Cyclotron Laboratory

- 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

Christine S. Chung, Torunn I. Yock, Kerrie Nelson, Yang Xu,et al. Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation. Int. J. Radiat. Oncol. Biol. Phys.: in press

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) !