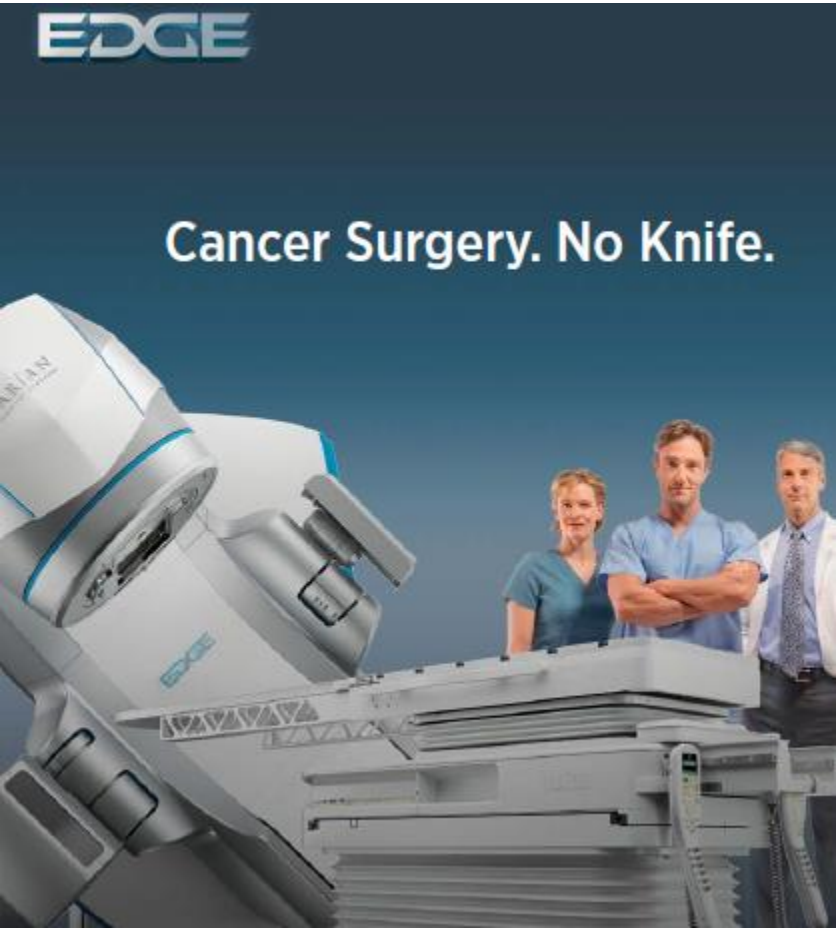
Hypofractionation in particle therapy

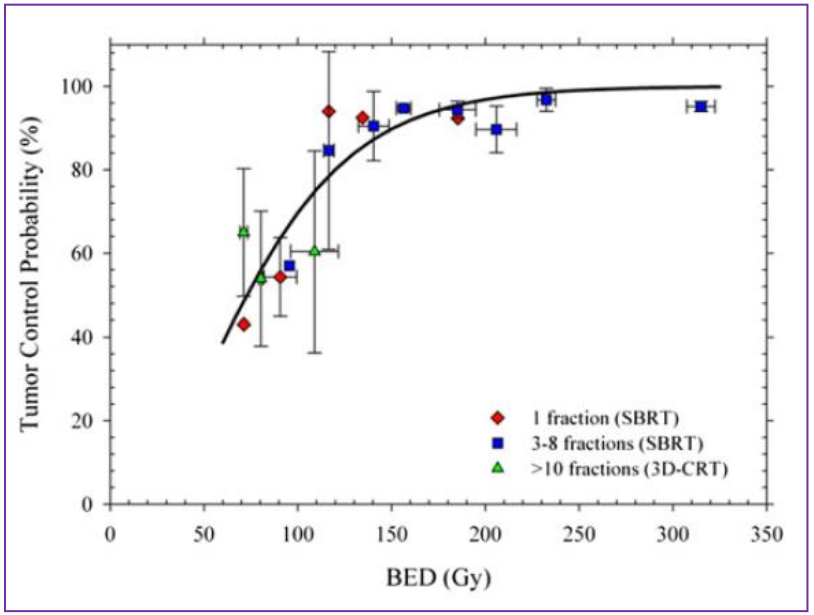
Marco Durante

Radiosurgery (SBRT): the new frontier in stereotactic image-guided radiotherapy



- Stage I (T1N0M0) NSCLC
- Oligometastases
  - Hepatocellular carcinoma
  - Advanced (T2-T4; >3 cm) NSCLC
  - Localized tumors in kidney, prostate, pancreas, adrenal gland, pravertebal tumors etc.

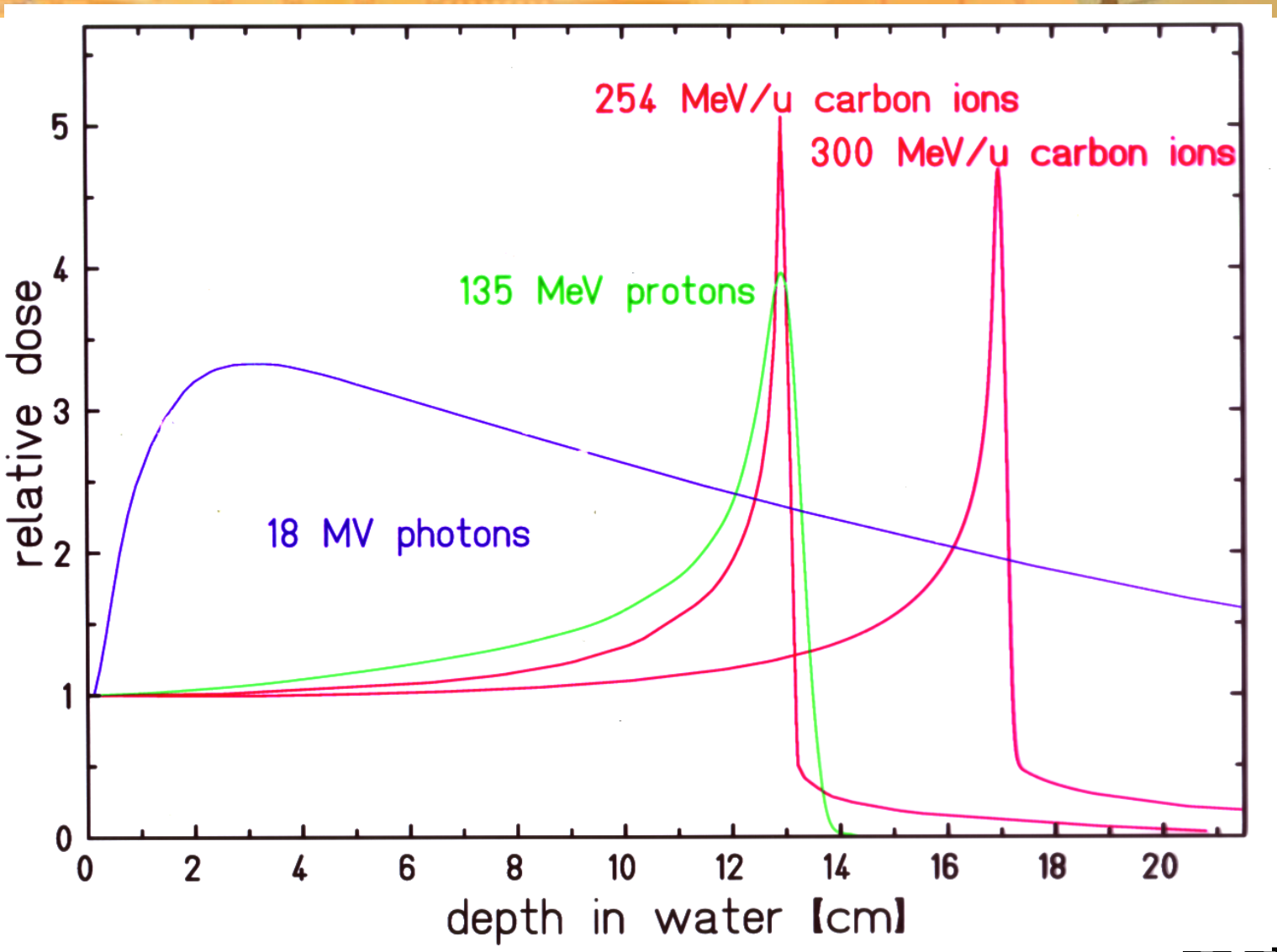
$$BED_{\alpha/\beta} = nd\,[1 + d/(\alpha/\beta)]$$ (LQ model)



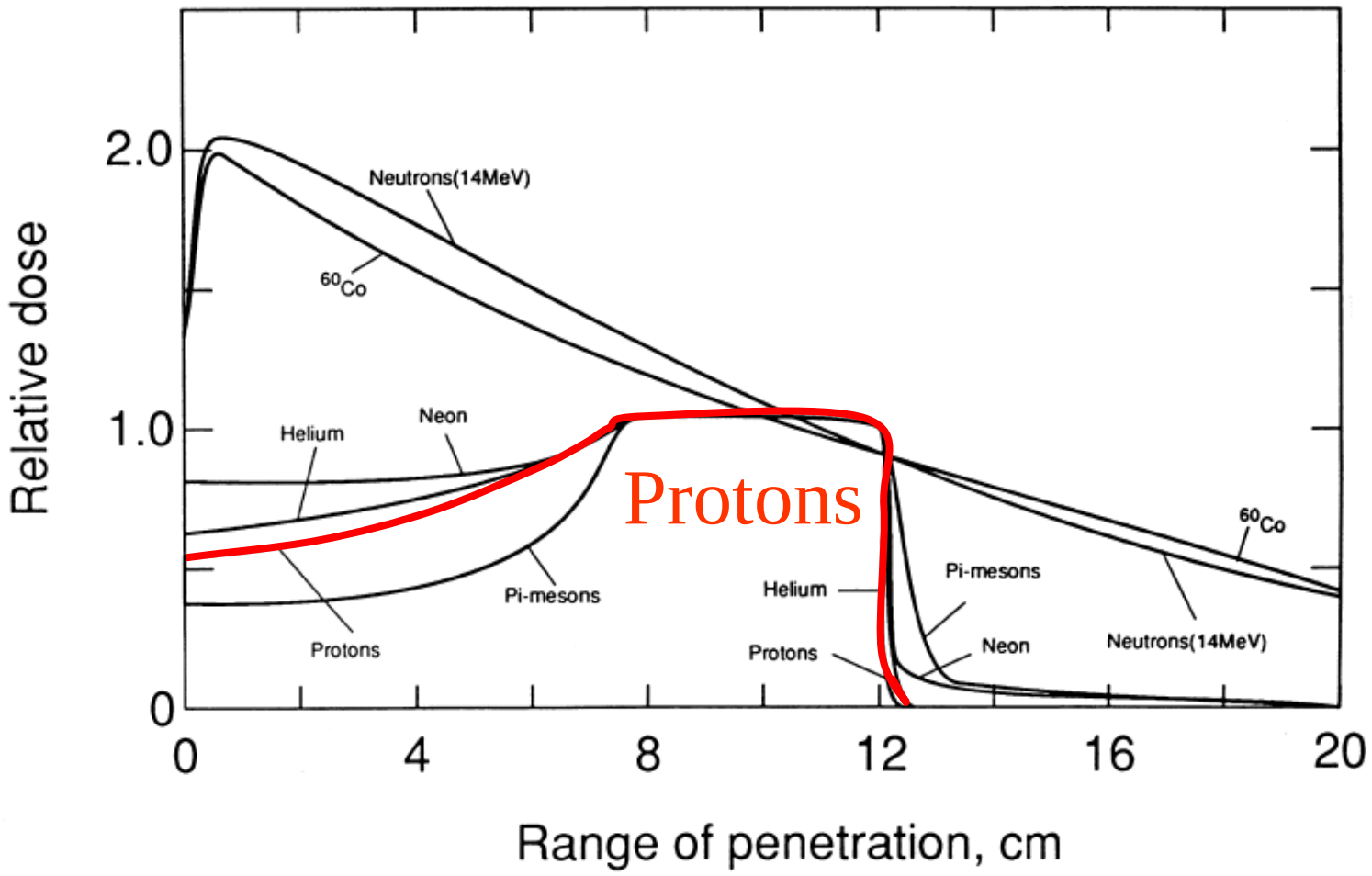
Brown *et al., Int. J. Radiat. Oncol. Biol. Phys*. 2013

SBRT only possible thanks to IGRT and to the low *mean* dose to parallel organs

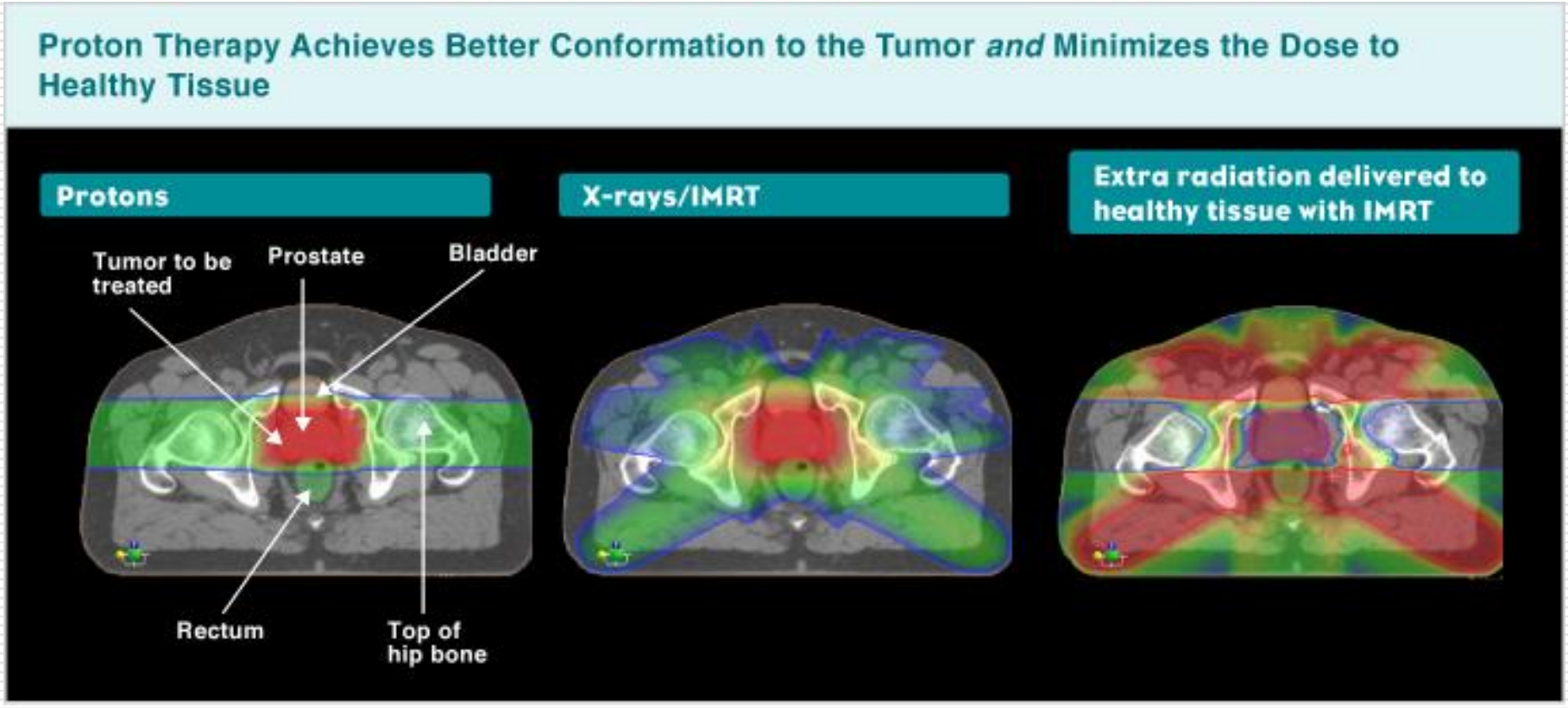
Depth dose distribution of various radiation qualities



Charged particle physics reduces the dose to the normal tissue and thus makes hypofractionation easier



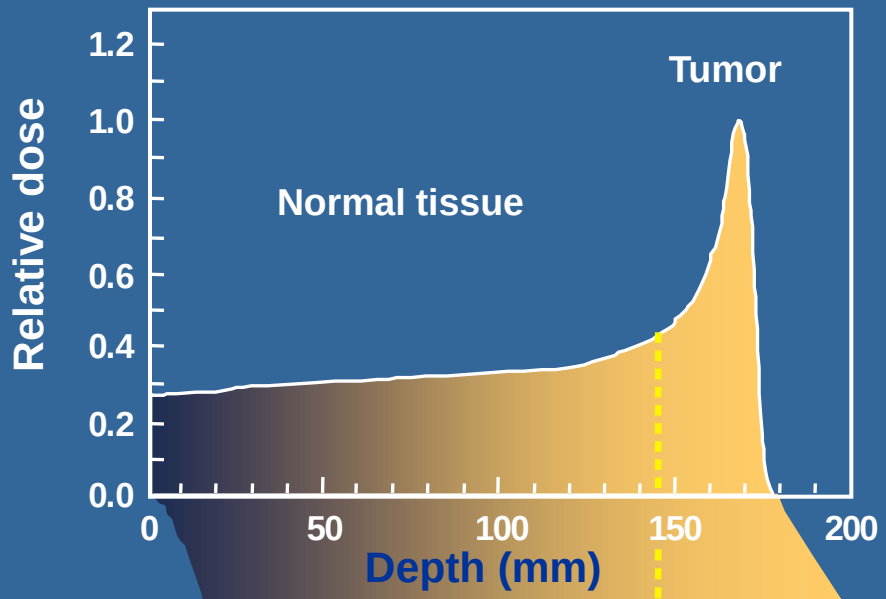
Treatment plans with protons: prostate



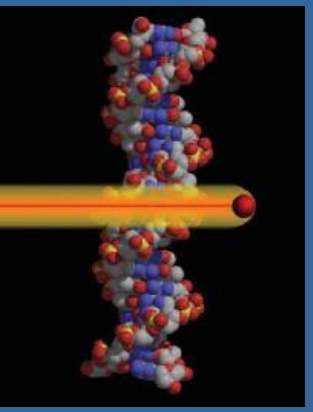
Courtesy of Reinhold Schulte, LLUMC

Durante & Loeffler,

Nature Rev Clin Oncol 2010



Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low
Angiogenesis	Increased	Decreased
Cell migration	Increased	Decreased

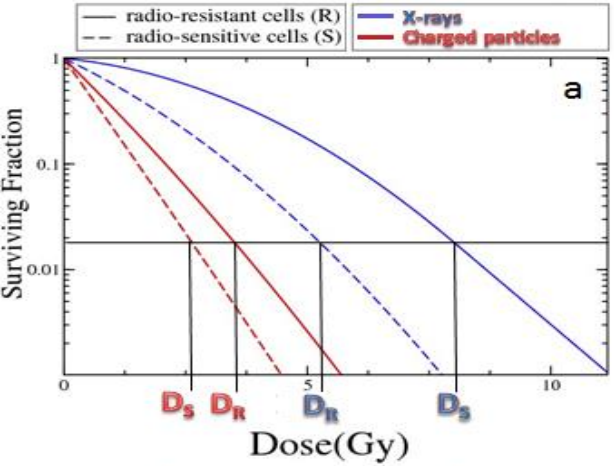


Potential advantages

- High tumor dose, normal tissue sparing
- Effective for radioresistant tumors
- Effective against hypoxic tumor cells
- Increased lethality in the target because cells in radioresistant (S) phase are sensitized
- Fractionation spares normal tissue more than tumor
- Reduced angiogenesis and metastatization

The radiobiological adavantages of particle therapy

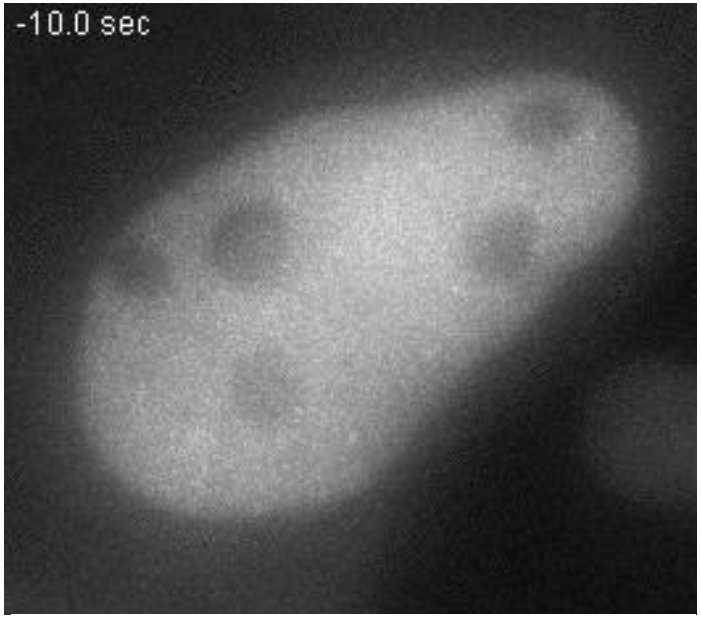
Jakob et al.,
PNAS 2009

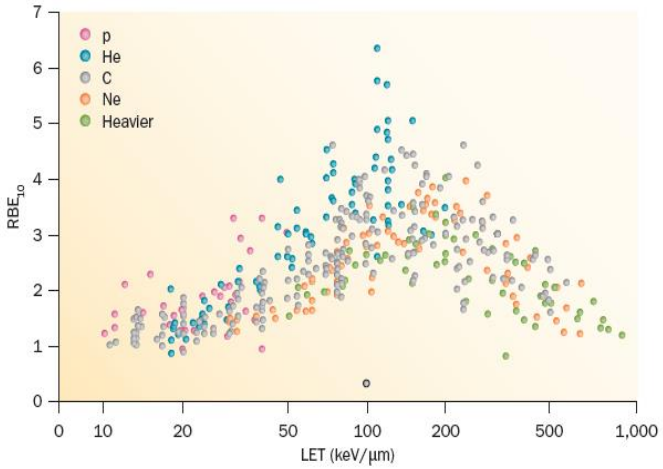


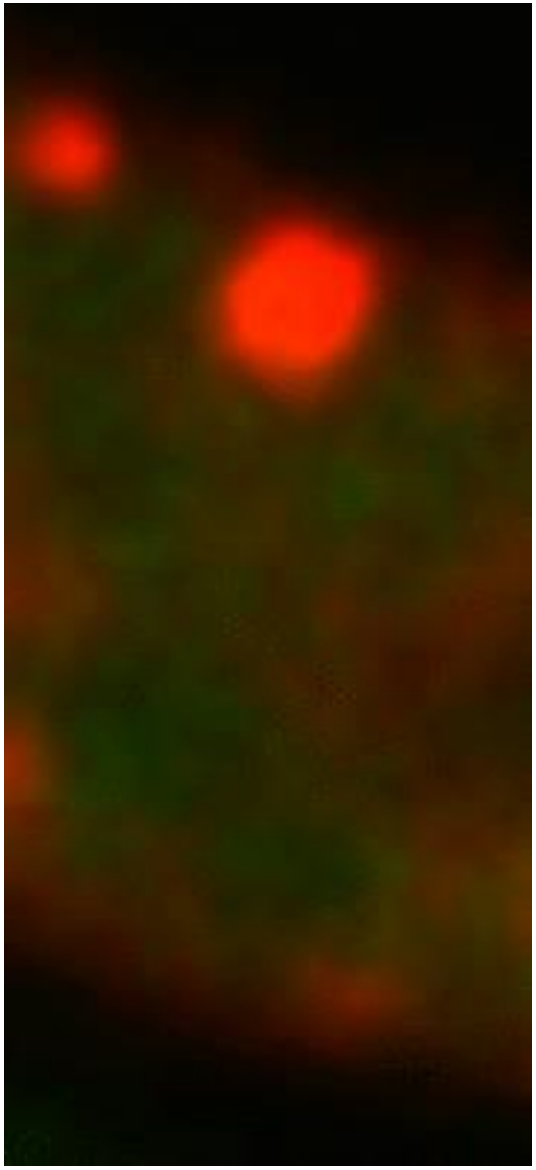
$$RBE_R = \frac{D_{R(photons)}}{D_{R(ions)}} > RBE_S = \frac{D_{S(photons)}}{D_{S(ions)}}$$

Overcoming resistance of cancer stem cells

www.thelancet.com/oncology **Vol 13 May 2**







PIDE database – http://www.gsi.de/bio-pide
Friedrich *et al., J. Radiat. Res*. 2013

CLINICAL INDICATIONS

Established clinical indications

- Skull base tumors
- Spine tumors
- Eye tumors (p)

Solid literature results

- Pediatric tumors (p)
- Head and Neck tumors
- Prostate tumors

Courtesy of Marco Krengli, Novara

- Adult
  - Base of Skull & Spinal Chordoma
  - Base of Skull Chondrosarcoma
  - Spinal & Paraspinal Bone/Soft Tissue Sarcomas (Non Ewing's)
- Paediatric
  - Base of Skull & Spinal Chordoma
  - Base of Skull Chondrosarcoma
  - Spinal & Paraspinal 'adult type' Bone and Soft Tissue Sarcomas
  - Rhabdomyosarcoma
  - Orbit
  - Parameningeal & Head & Neck
  - Pelvis
  - Ependymoma
  - Ewing's Sarcoma
  - Retinoblastoma
  - Pelvic Sarcoma
  - Optic Pathway and other selected Low Grade Glioma
  - Craniopharyngioma
  - Pineal Parenchymal Tumours (not Pineoblastoma)
  - Esthesioneuroblastoma

UK overseas clinical indications for protontherapy, courtesy of Simon Jolly, UCL

UK list of typical indications <2% patients

ITALIAN NETWORK FOR HADRONTHERAPY

EXISTING CENTRES

FINANCED CENTRES

INTEREST FOR PROTONS

Working Group of AIRO, 2003, 2008, 2009

(120'000 new cases/year with conventional RT):

protontherapy - elective:	1'885	pts/year
protontherapy – clinical trials:	14'490	pts/year
therapy with ^{12}C-ions – cl. trials	6'860	pts/year

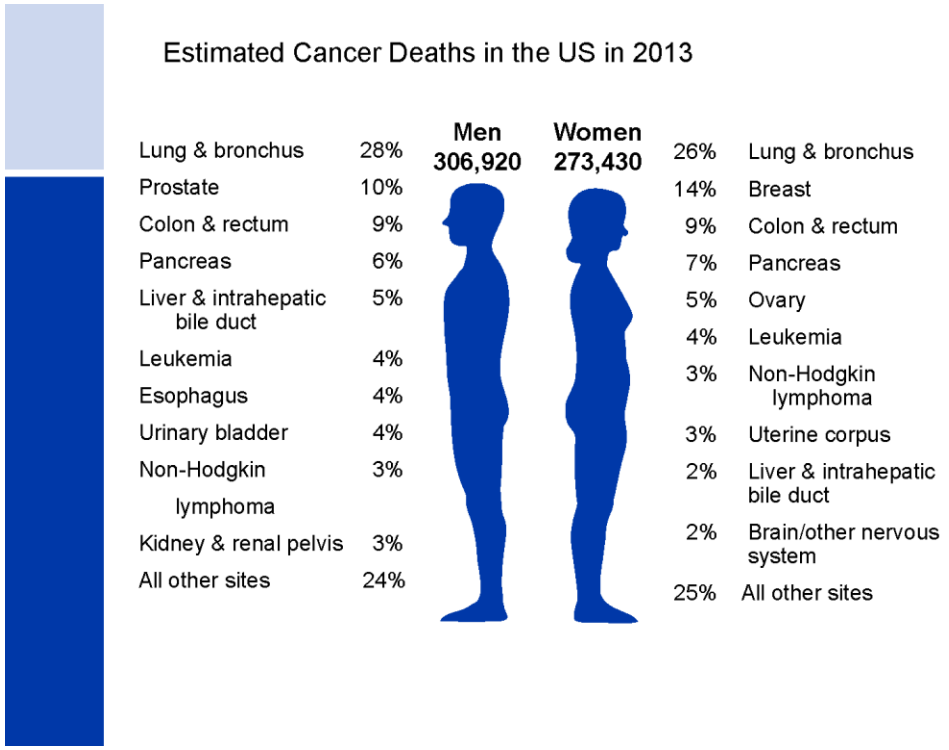
Conclusions of AIRO:

1 centre for ions

4-5 centres for protons

New cancers where particles may potentially lead to a breakthrough

- Lung
- Pancreas
- Local recurrence of rectal cancer
- Breast
- Hepatocellular carcinoma
- Glioblastoma



Siegel *et al., CA Cancer J Clin* 2013

Lung cancer: 2nd in incidence and 1st in mortality for both sexes in US

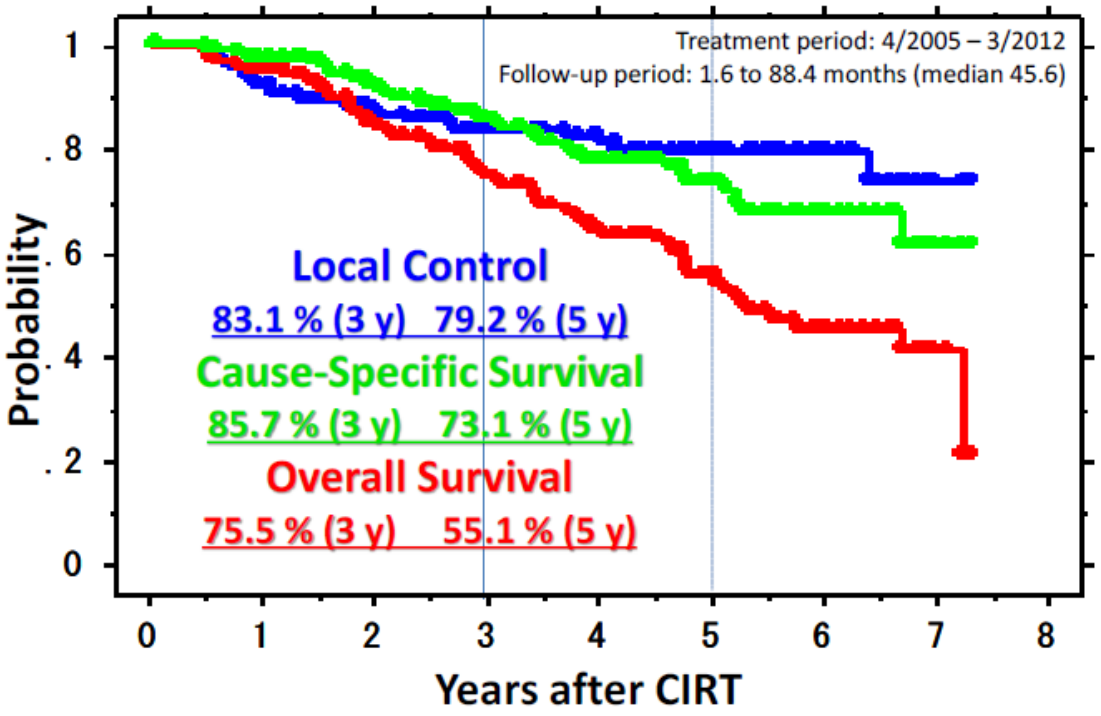
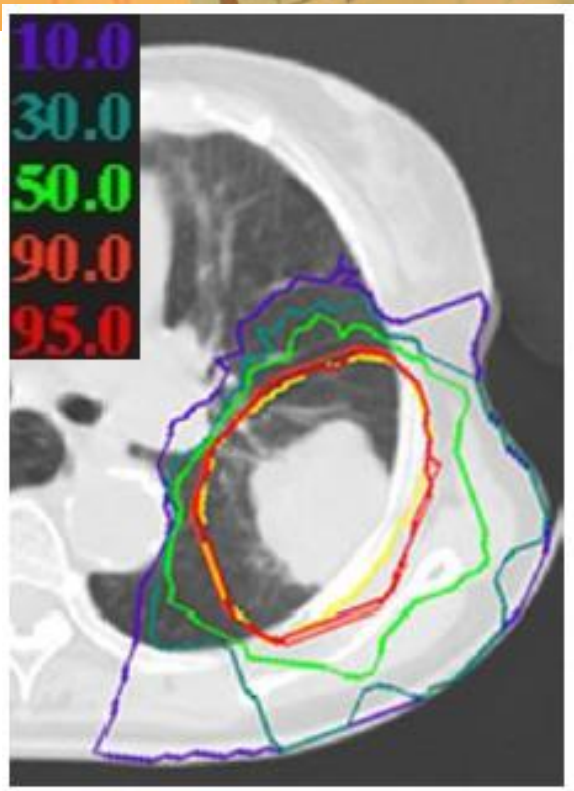


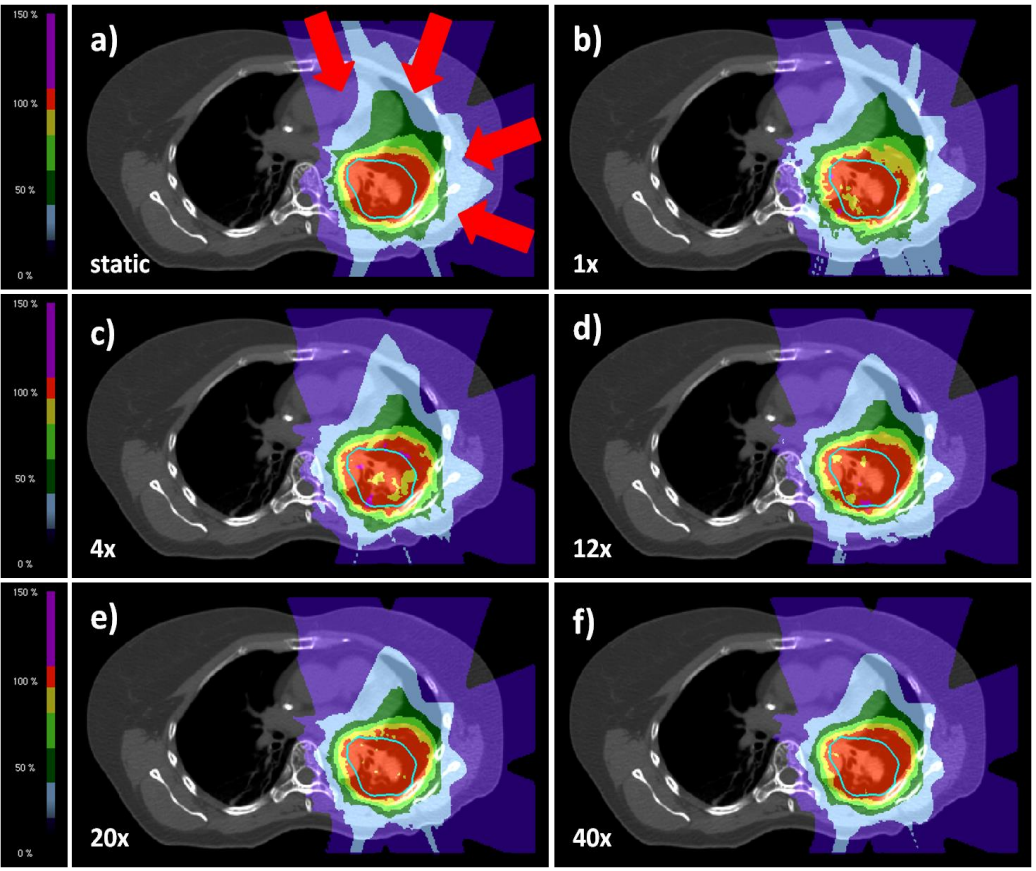
Fig.1. The survival and local control rates after CIRT using single fractionation



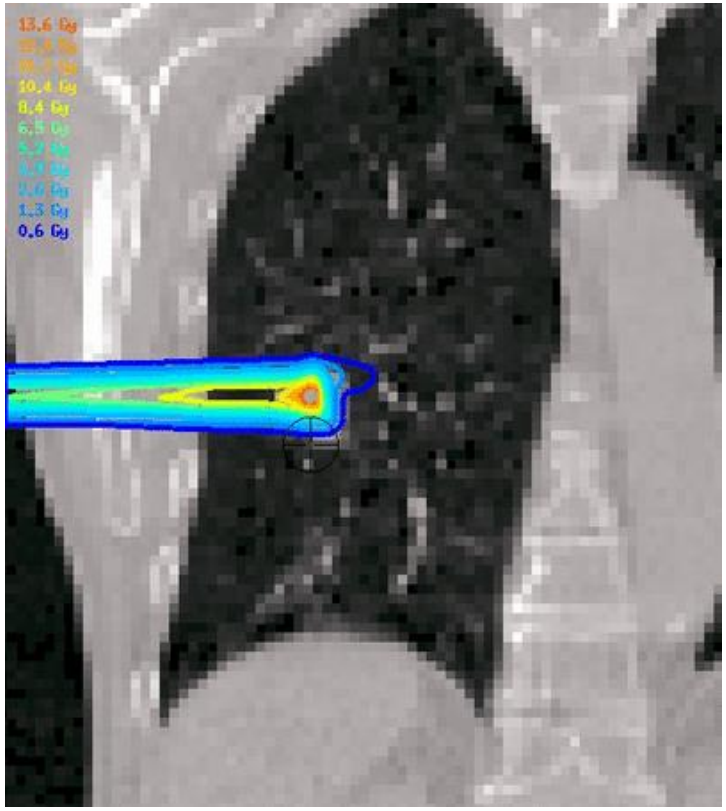
40 GyE, 1 fraction, 3 fields, gating

Tsujii *et al. Carbon Ion Radiotherapy*, Springer-Verlag, 2014

Intrafractional movements and hypofractionation in NSCLC

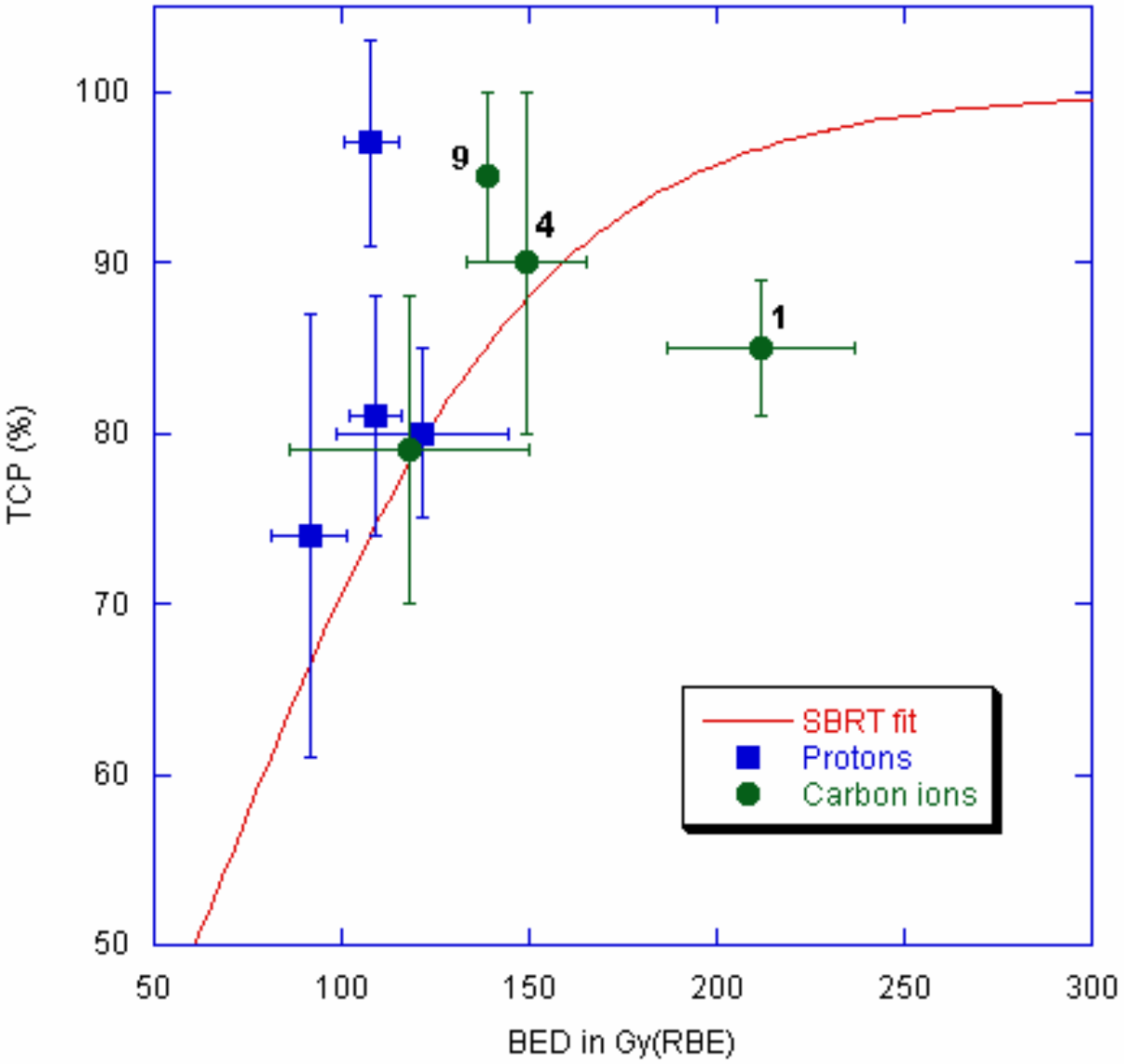


courtesy of Chritoph Bert,
University of Erlangen & GSI



Courtesy of M. Söhn, LMU

Particle therapy vs. X-rays for NSCLC

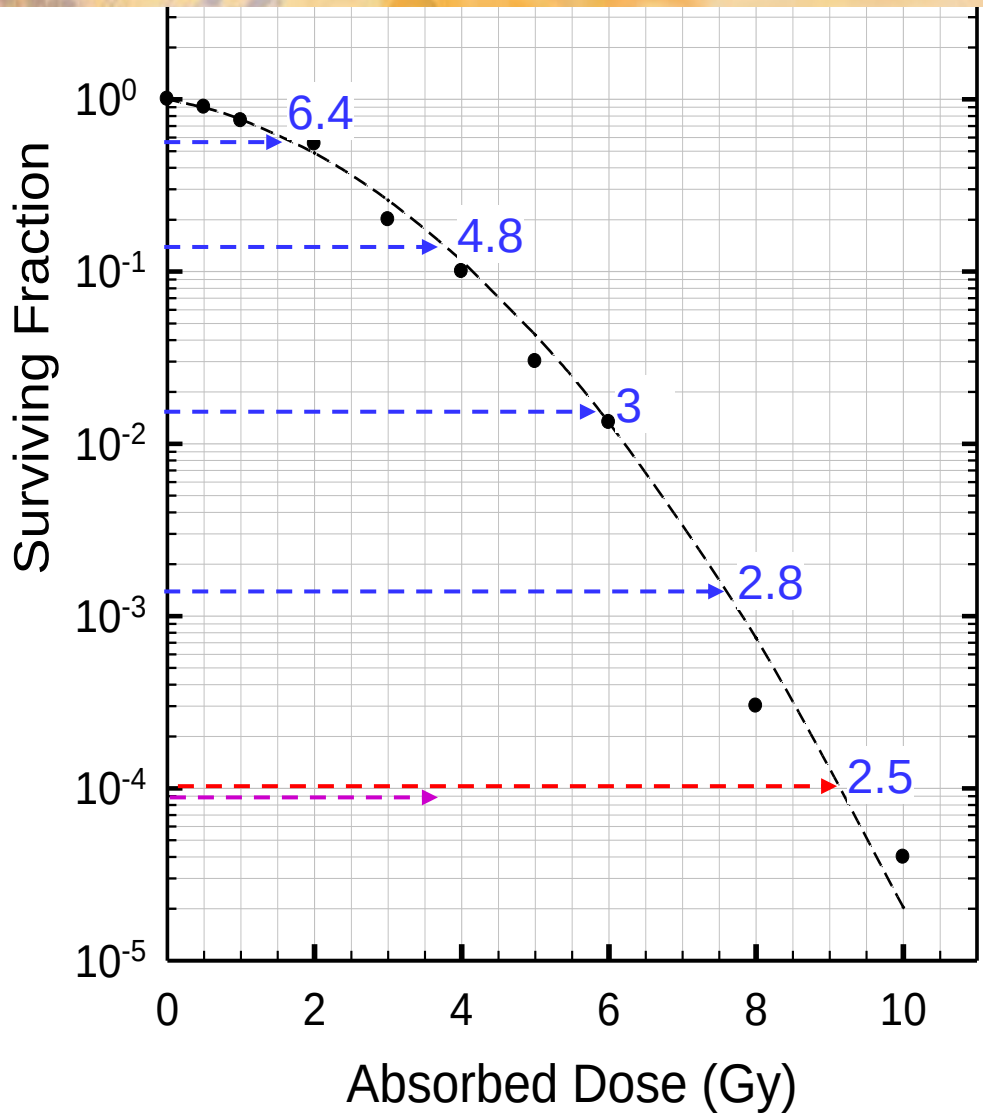


Stage I NSCLC

- **Proton data from LLUMC, HIBMC, NCCE, University of Tsukuba (10-22 fr)**
- **Carbon ion data from NIRS (hypofractionation trial)**

Durante, *Br. J. Radiol.* 2013

RBE and GyE

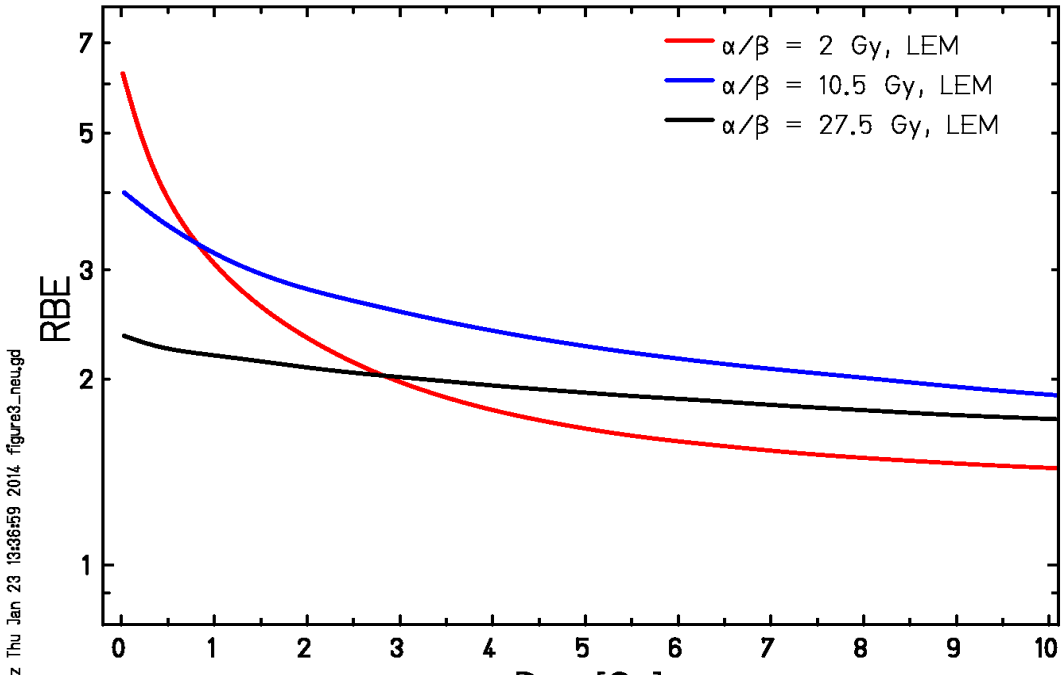


	α/β [Gy]
Early	
Skin	9-12
Jejunum	6-10
Colon	10-11
Testis	12-13
Tumor-Tissue	**~10**
Late	
Spinal Cord	1,7-4,9
Kidney	1,0-2,4
Lung	2,0-6,3
Bladder	3,1-7

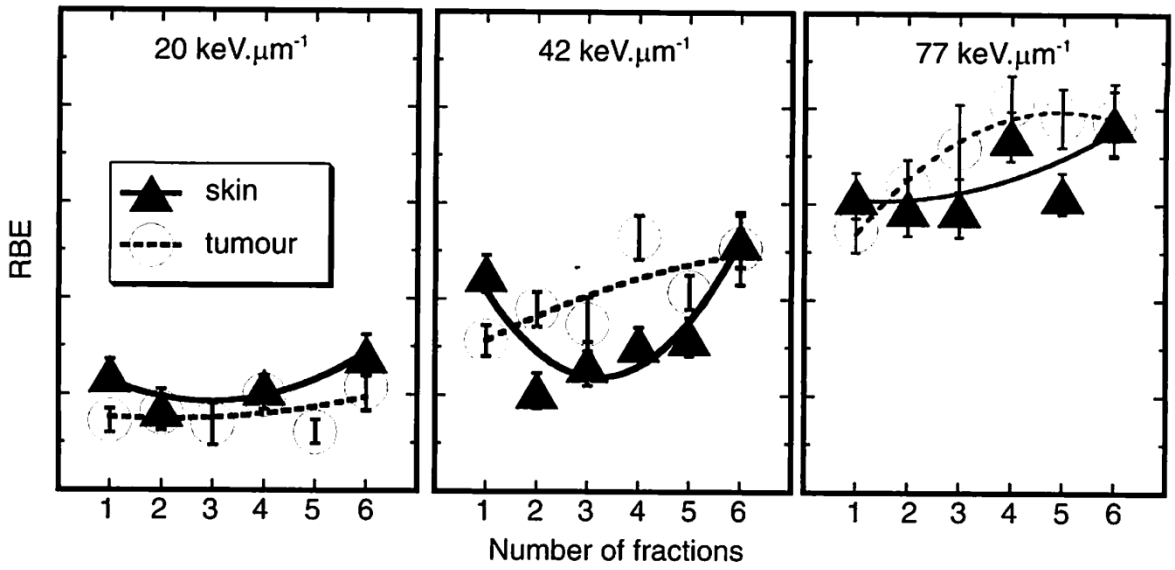
GyE=GyxRBE

Sv=GyxQ > GyE

RBE and hypofractionation: differential decrease in normal and tumor tissue

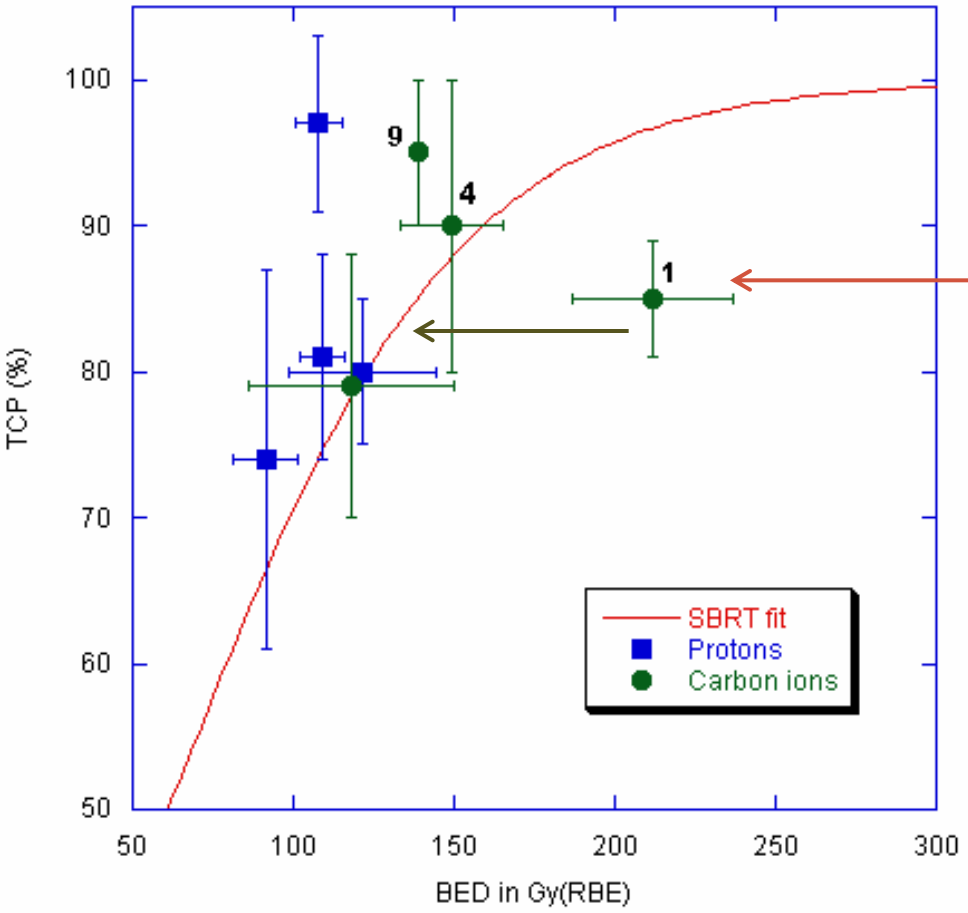


Scholz *et al., Phys. Med*. 2014



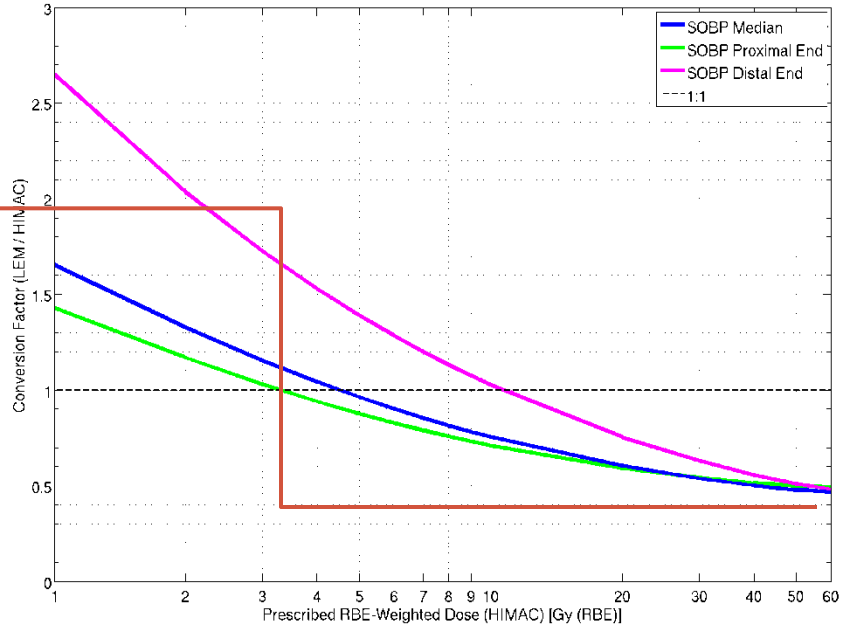
Ando *et al., Radiat. Prot. Dosim*. 2002

Ions vs. X-rays in SBRT for NSCLC



TCP vs. BED for Stage I NSCLC by X-rays or charged particles

Durante, *Br. J. Radiol*. 2013



HIMAC vs. LEM: dependence of the RBE on the dose/fraction *d*

Steinsträter *et al., Int. J. Radiat. Oncol. Biol. Phys*. 2012

Re-oxygenation in radiosurgery

- Models of oligofractionation predict failure for hypoxic tumors
- re-oxygenation between fractions is in fact essential for local control for at least some tumors (H&N, cervix, pancreas, prostate).
- if the number of fractions is severely reduced then this vital process will be rendered less effective

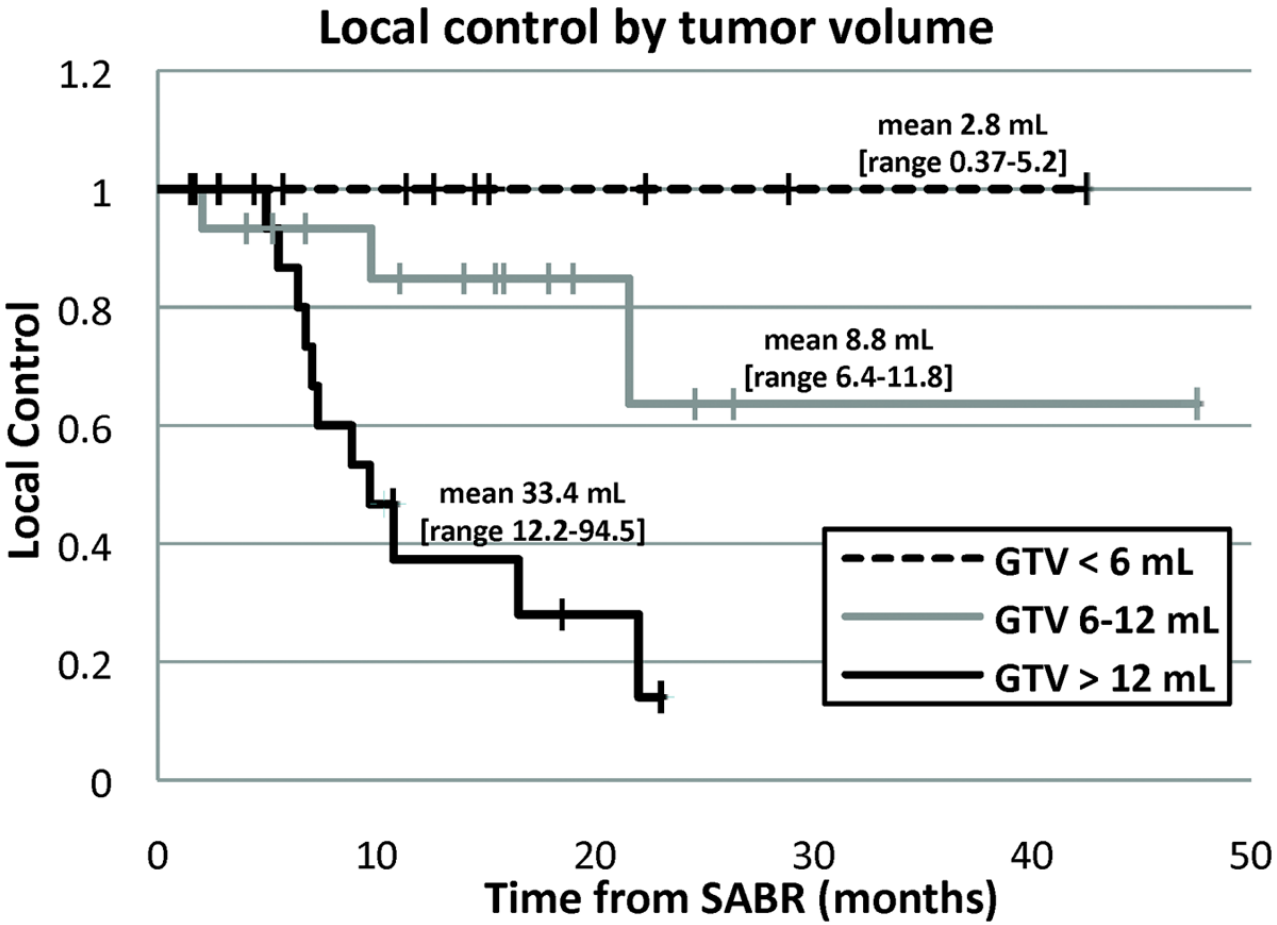
Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2010 October 1; 78(2): 323–327. doi:10.1016/j.ijrobp.2010.04.070.

Stereotactic ablative radiotherapy should be combined with a hypoxic cell radiosensitizer

heavy ions

J. Martin Brown, D.Phil., Maximilian Diehn, M.D., Ph.D., and Billy W. Loo Jr., M.D., Ph.D.
Department of Radiation Oncology

Stanford clinical trial on NSCLC – failures in large tumors attributed to hypoxia

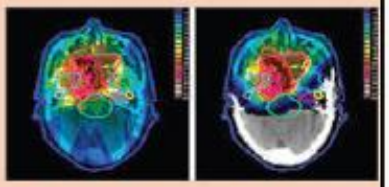


Brown *et al., Int. J. Radiat. Oncol. Biol. Phys. 2010*

Particle-induced vascular effects

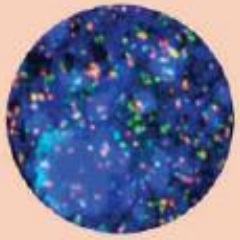
Old Paradigm:
High energy protons and photons are both low LET radiations that have nearly indistinguishable biological effects but different physical characteristics.

➢Protons have dose distribution properties that can be utilized for superior tumor targeting in the clinic.

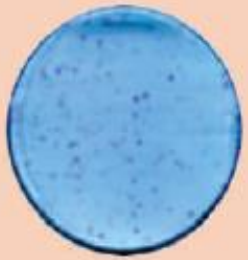


Photon Proton

➢The DNA damage induced by low LET protons and photons should be essentially equivalent, given their similar track structures at the nm scale.



➢The RBE of protons obtained from standard endpoints of cell killing is close to unity (1.1–1.2) and can be applied to more complex endpoints.

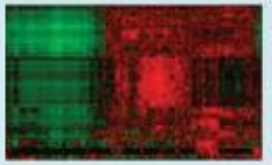


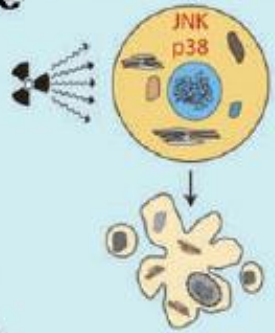
Girdhani *et al., Radiat. Res*. 2013

New Paradigm:
High energy protons and photons have distinct physical and biological properties.

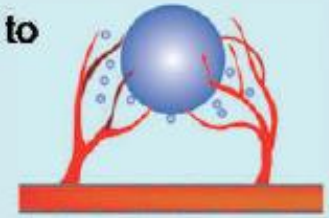
➢Limited applicability of RBE obtained through traditional endpoints that focus on cell death.

➢Protons show unique molecular and cellular responses compared to photon radiation, e.g. induction of more complex DNA damage, differential gene expression, and epigenetic modulation and induction of distinct signaling pathways.





➢Data suggest protons induce complex systems-wide responses that are divergent to those of photons, including inhibition of angiogenesis, invasion and modulation of inflammation.



„old“ or „new“ radiobiology?

1. Can the LQ models explain SBRT (Strigari *et al., Med. Phys.* 2012)?
2. What would be the prediction for particle therapy (RBE~1)?
3. If the hypoxic fraction is the main problem for SBRT, can we overcome it by heavy ions?
4. Is the heterogenous dose distribution in SBRT a sort of dose-painting (Ruggieri *et al., Acta Oncol.* 2010)?

1. Is vascular damage really important? Can we use xenografts (is vascularization the same)?
2. Comparison of clamped and very high-dose irradiated tumors?
3. In vitro data suggest that charged particles have anti-angiogenic effects and high RBE for endothelial cells, but animal data are lacking
4. A rat model was used for the lung (Tinnel *et al., Technol. Cancer Res.,* 2007)

Biophysics Department

M. Durante (Director)

G. Kraft (Helmholtz Professor)

G. Taucher-Scholz (DNA damage)

S. Ritter (Stem cells)

C. Fournier (Late effects)

C. Hartel (Clinical radiobiology)

M. Scholz (Biophysical modelling)

M. Krämer (Treatment planning)

C. Graeff (Moving targets)

C. La Tessa (Dosimetry)

Thank you very much!

http://www.gsi.de/biophysik/