Future of ENLIGHT: research challenges

ENLIGHT

Marco Durante

Pavia, Italy, 15.9.2012

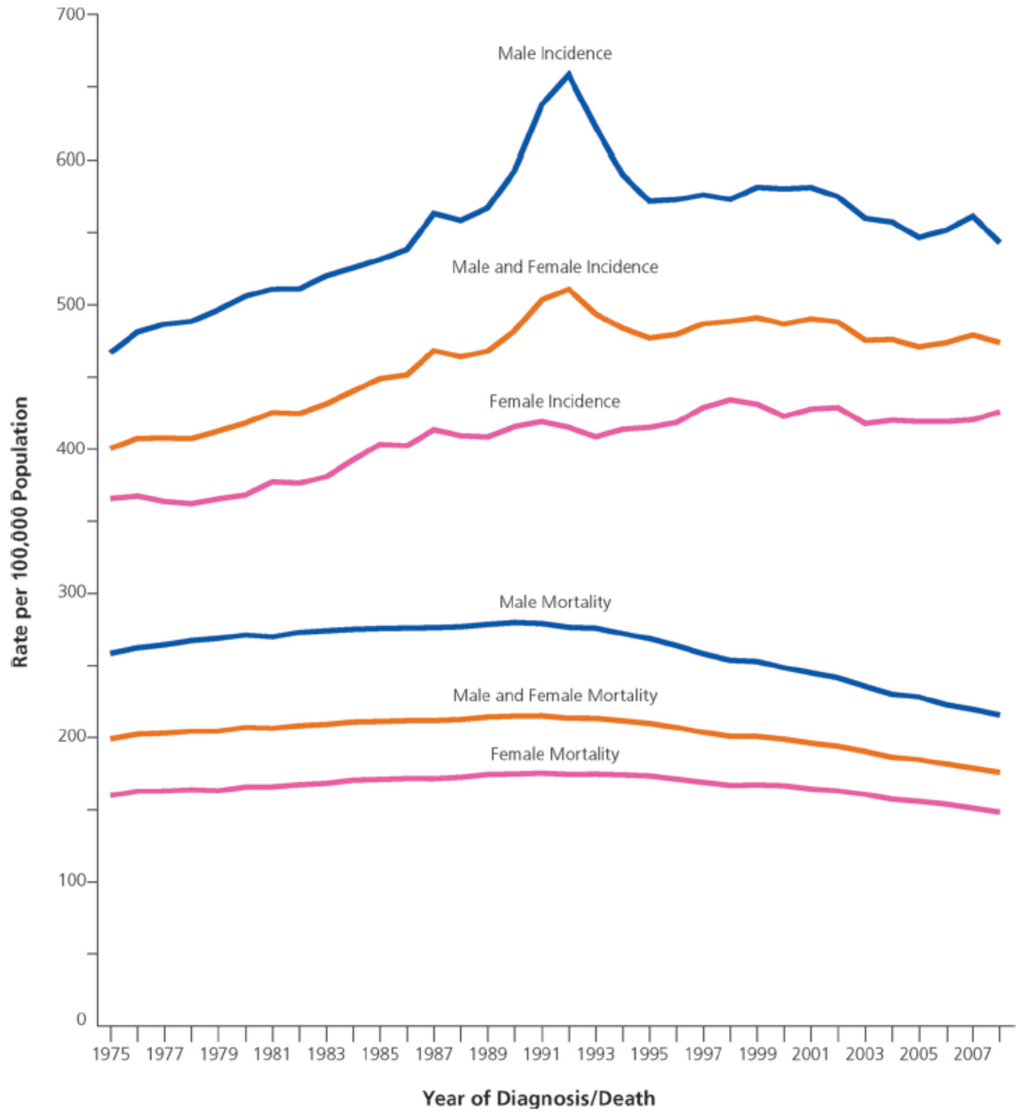
FAIR

TECHNISCHE UNIVERSITÄT DARMSTADT

FIAS Frankfurt Institute for Advanced Studies

GSI

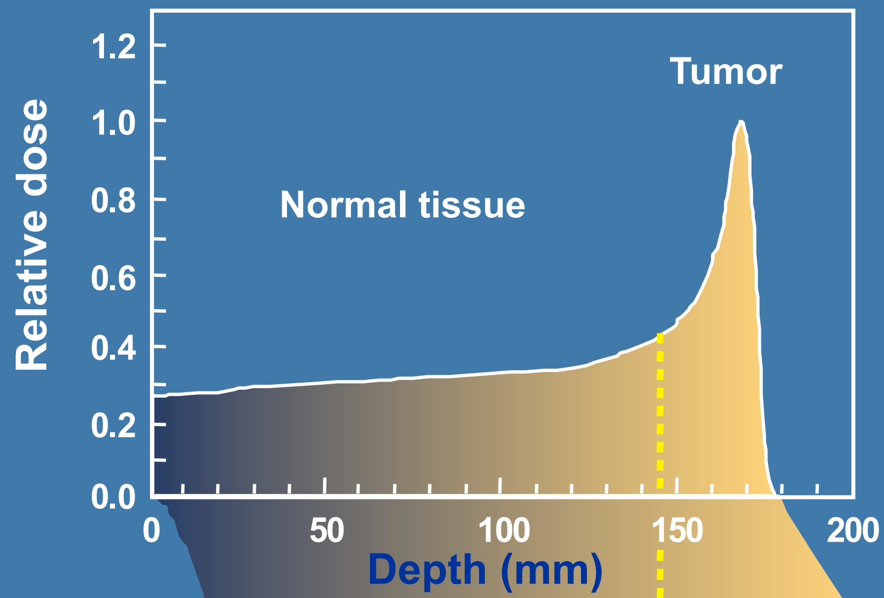
Trends in incidence/mortality in USA

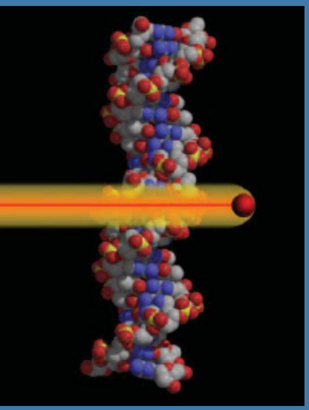


Siegel *et al., CA Cancer J. Clin.* 2012

Durante & Loeffler,

***Nature Rev Clin Oncol* 2010**



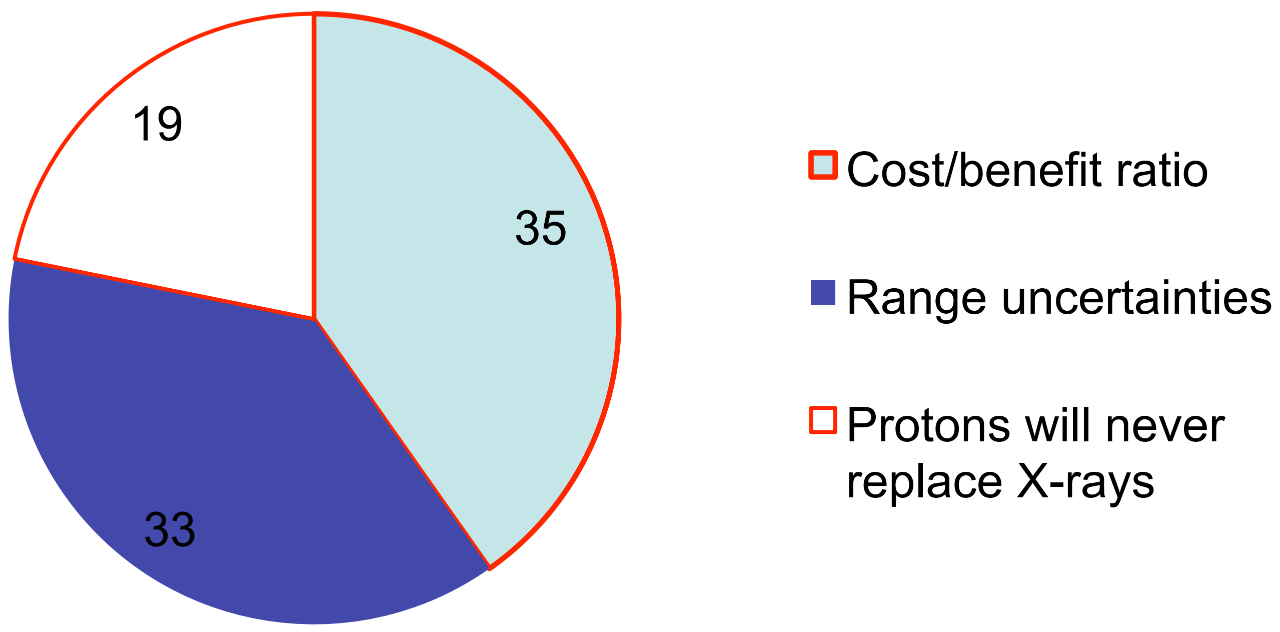


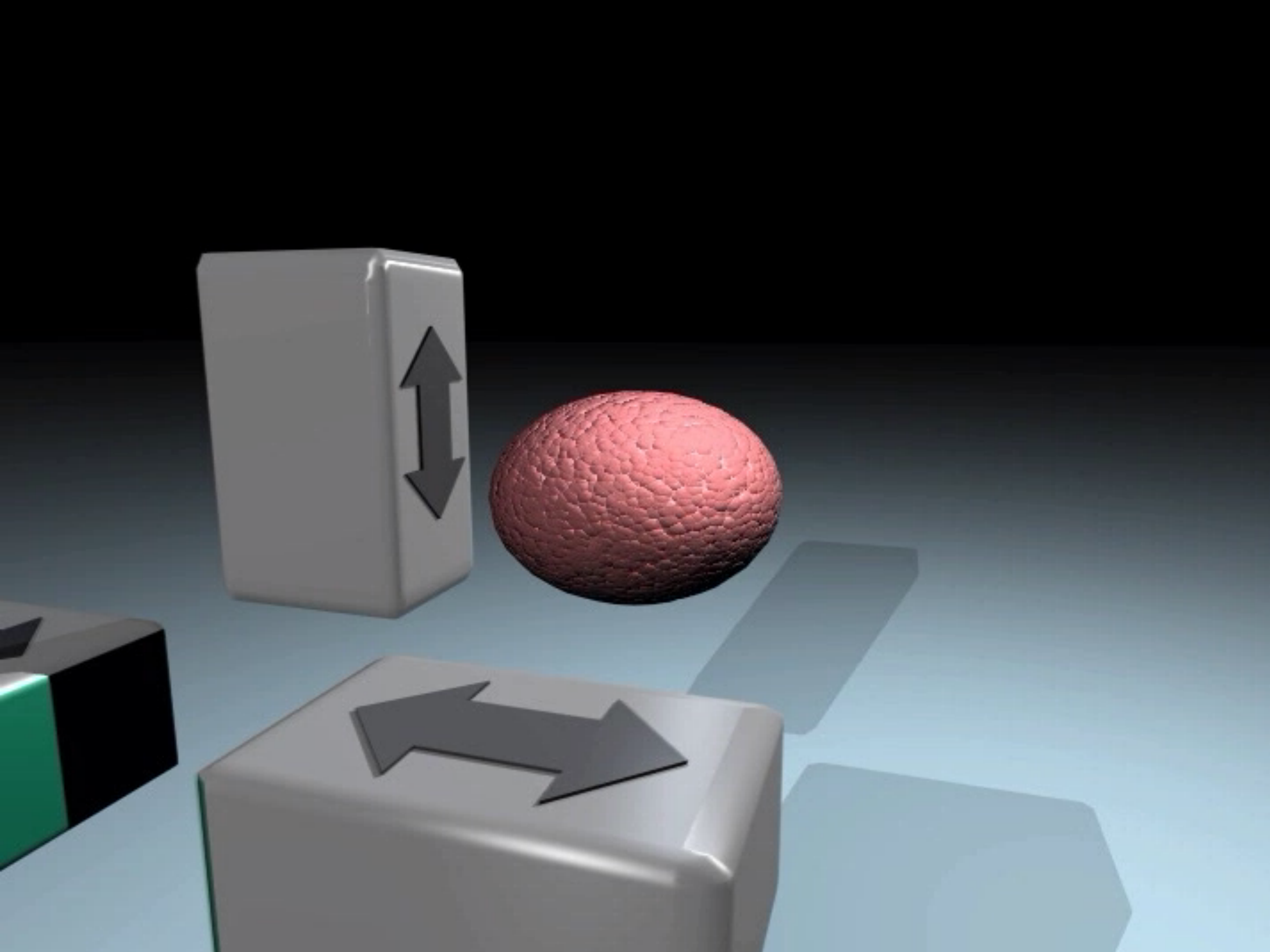
Potential advantages

Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumor cells
Cell-cycle dependence	high	low	Increased lethality in the target because cells in radioresistant (S) phase are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumor
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Cell migration	Increased	Decreased	

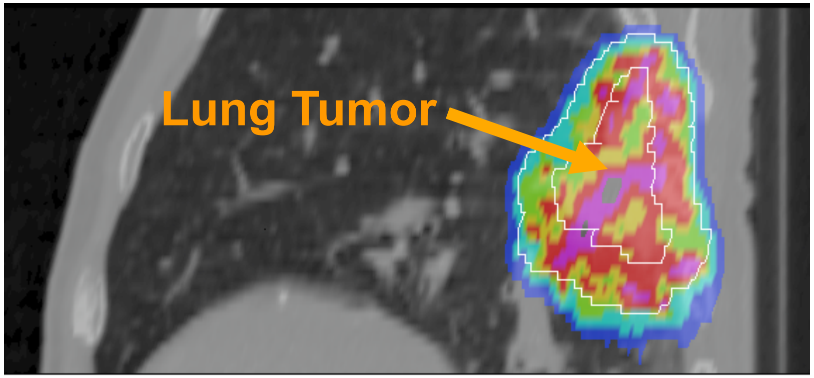
AAPM poll, August 2012

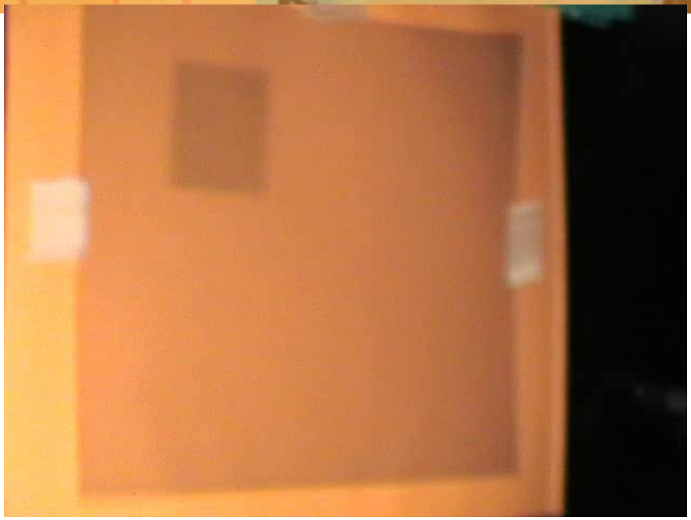
What is the main obstacle to proton therapy replacing X-rays?

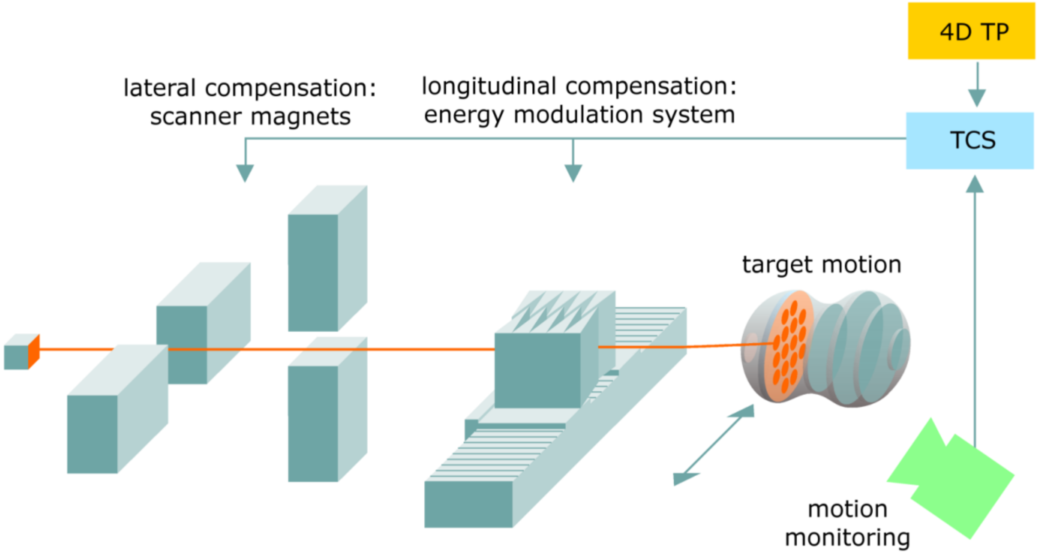


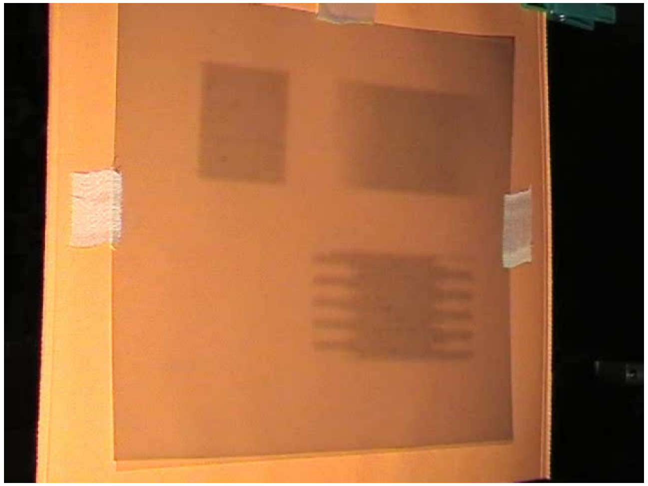


Interplay and motion mitigation techniques









Gating and rescanning already implemented in clinical environment

Tracking requires robust planning of the 4DCT data

Bert and Durante, *Phys. Med. Biol.* 2011

Range uncertainties: tumor tracking in particle therapy

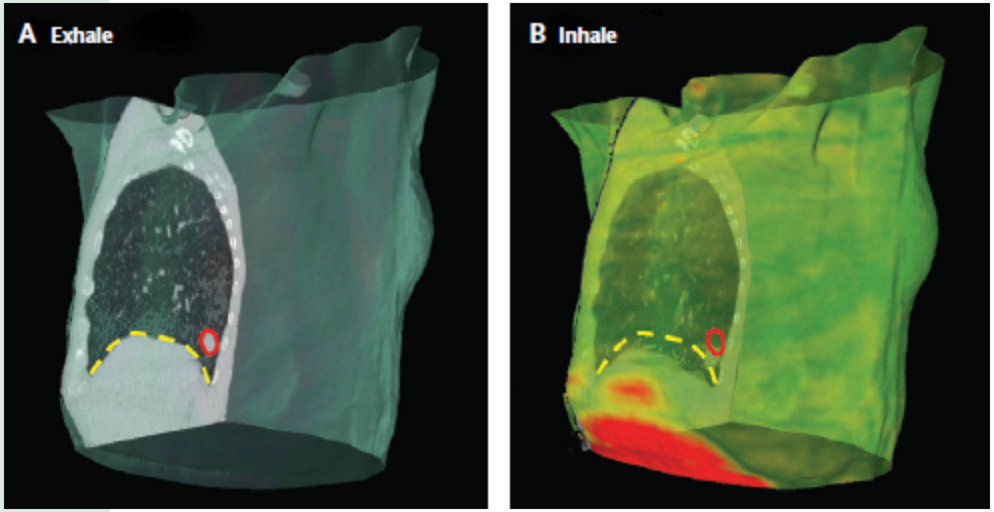
Treatment planning
- 4D CT

Motion detection
- X-ray stereo projections
- External surrogates combined with adaptive correlation models
- Soft-tissue imaging (ultrasound, MRI)
- Particle radiography

Motion tracking
- Lateral compensation (magnet steering)
- Depth compensation (moving degrader vs static degrader)

Treatment verification
- Off-line PET dosimetry
- In-beam PET dosimetry
- Prompt radiation measurement

External-internal correlation model



Riboldi *et al.*, *Lancet Oncol*. 2012

fondazione CNAO

Unproven clinical advantages of particle therapy?

- Cost/benefit is a ratio
- If €-$ (particles)< €-$ (photons) then particles would replace X-rays
- Reducing cost will require new compact and cheap accelerators and beam delivery systems (gantry)
- Improving the benefit requires more research for increasing survival, not only TCP
- Promising fields (among others): cancer stem cells, genetic background, adaptive TP, combined treatments (particle + chemo- or immuno-therapy), second cancers, noncancer diseases

Future accelerators

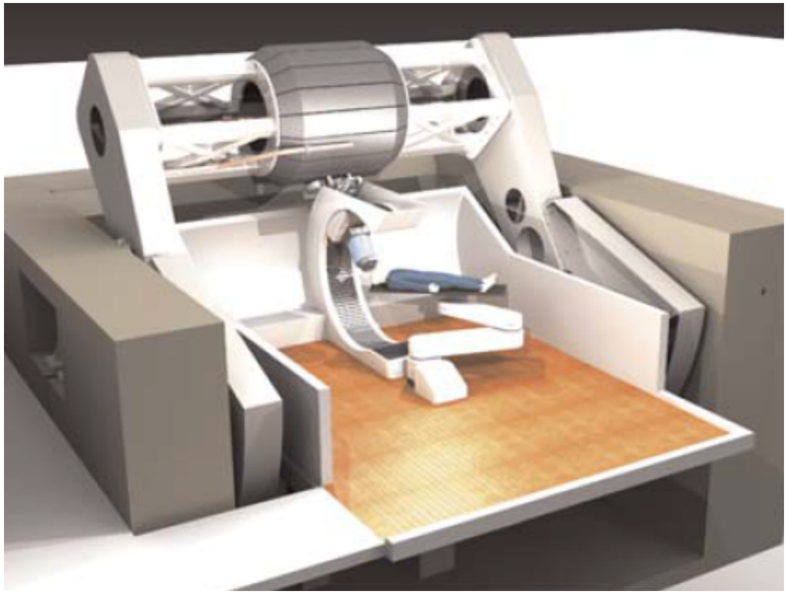
All current facilities use either a cyclotron or a synchrotron and RFQ or low-energy linacs as injectors

High-field superconducting magnets for compact, lightweight synchrocyclotrons (e.g. SRS, IBA, INFN)

Fixed-field alternating gradient (FFAG) accelerators (e.g. KEK, Japan, and RACCAM, France)

Cyclinac (TERA)

Dielectric wall accelerators (CPAC)

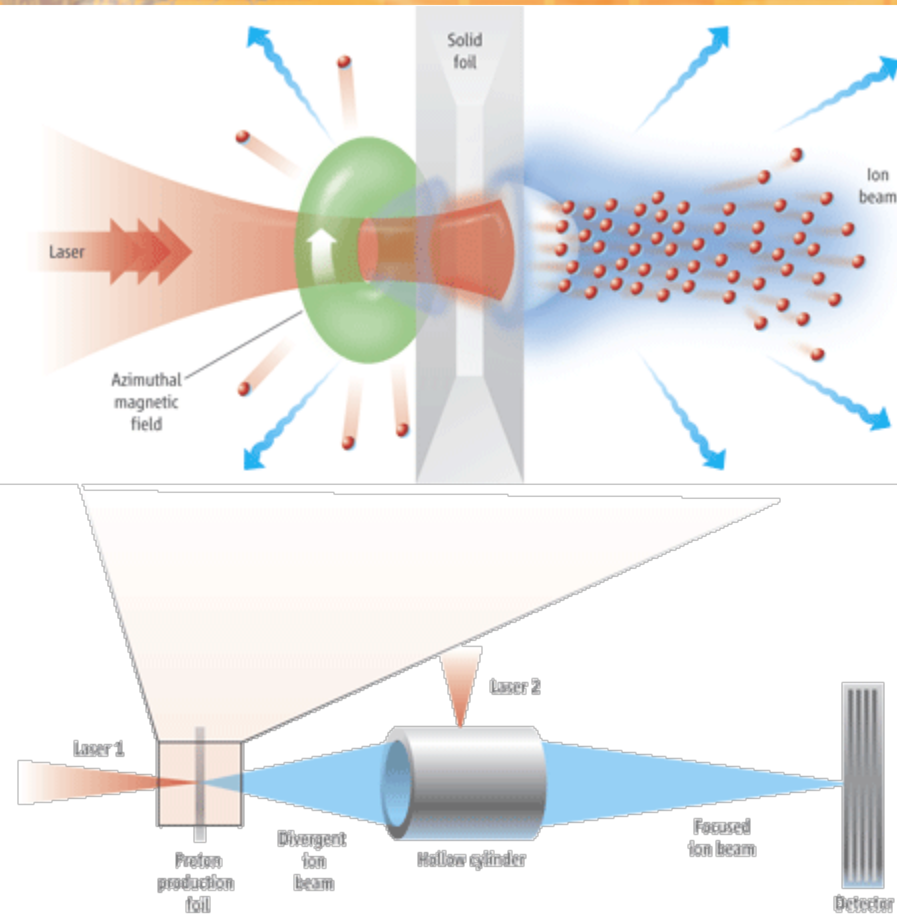


Still Rivers single-room protontherapy unit

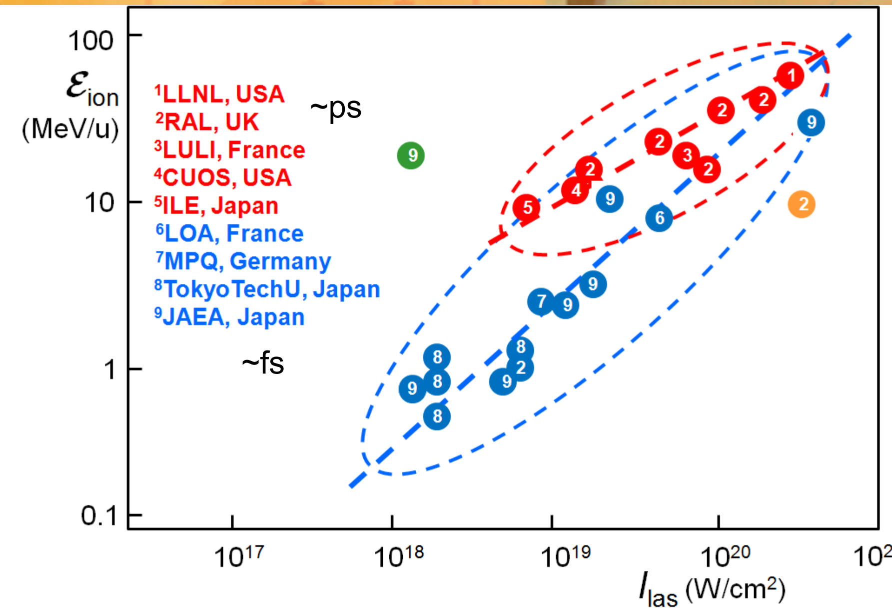
IBA-C400

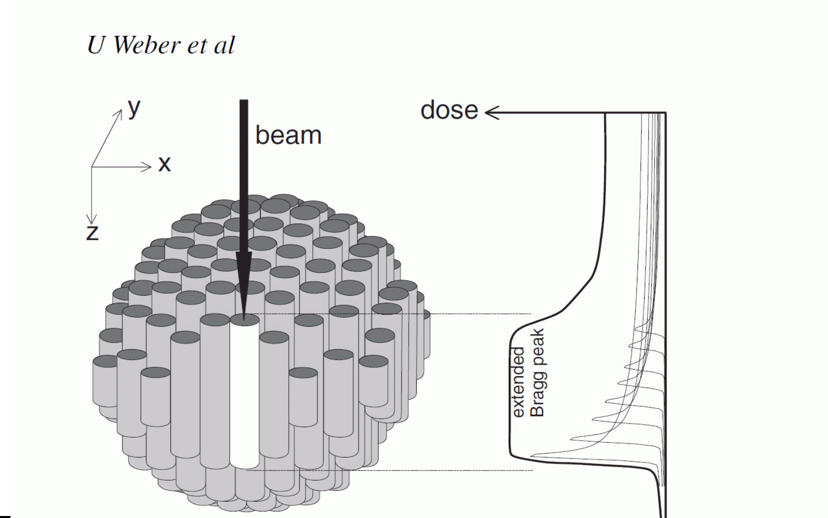
M.Silari, *Radiat. Prot. Dosim*. 2011

Laser-driven particle accelerators



Toncian et al., *Science* 2006

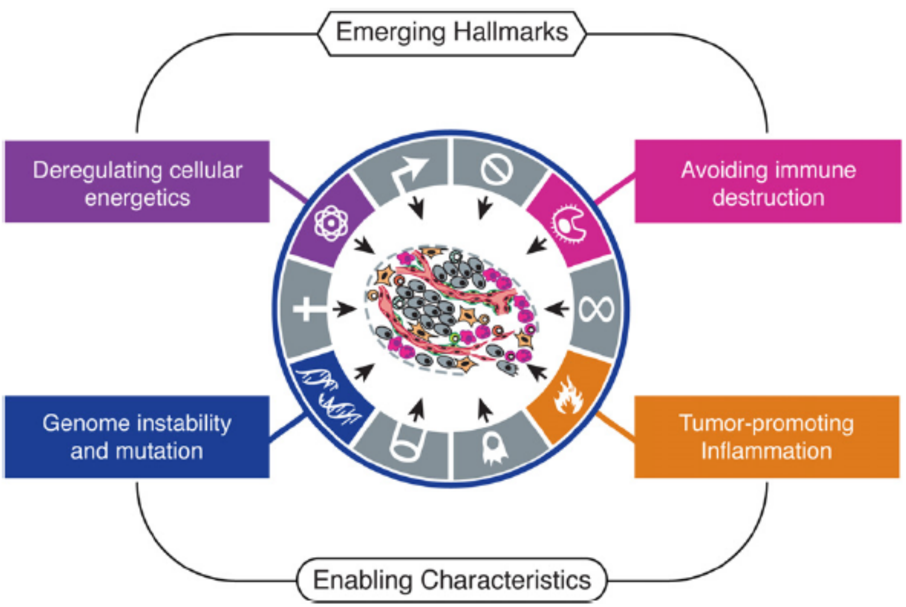


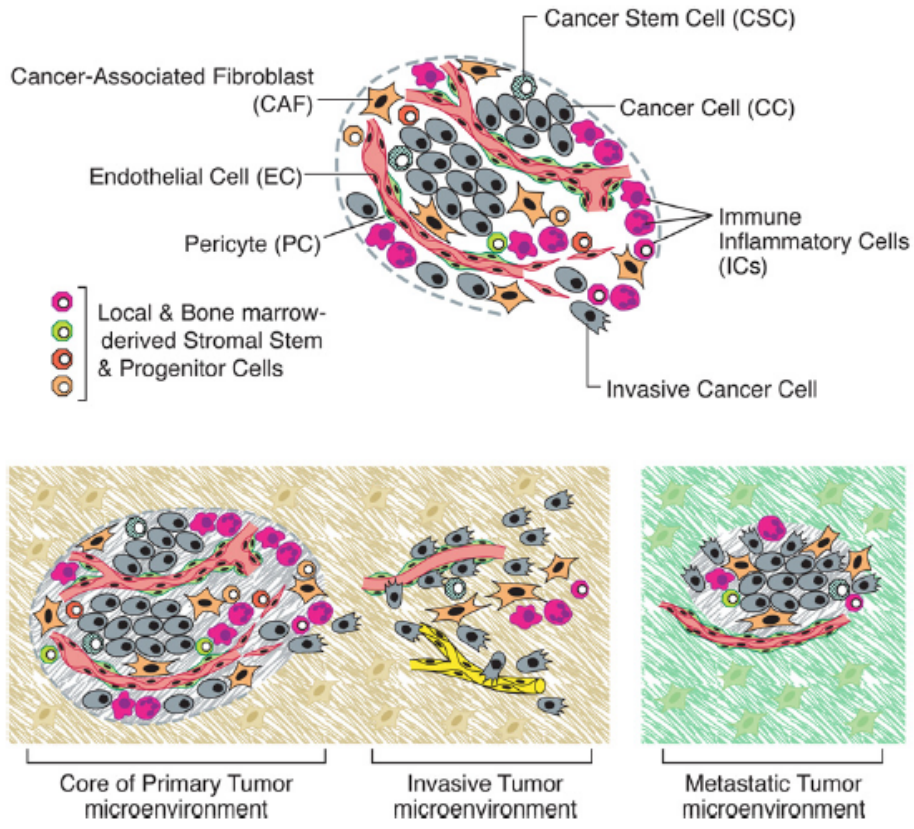


courtesy of S.D.Kraft & G. Kraft

Future research trends in particle radiobiology

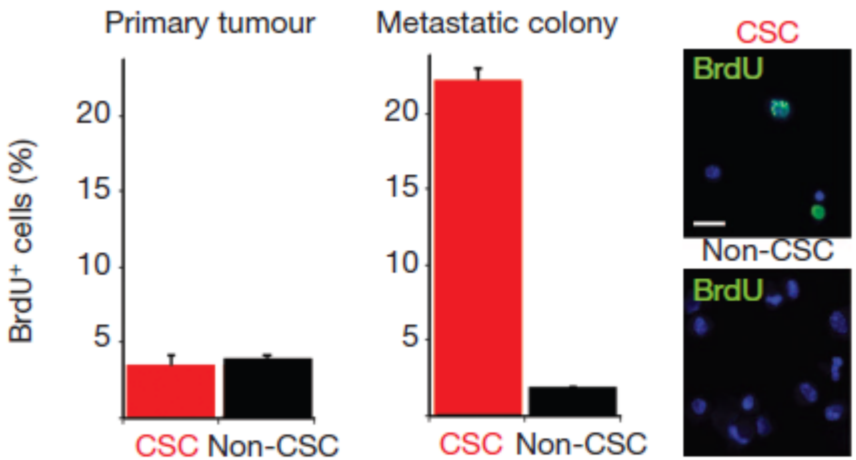
Even if novel technologies may increase the TCP, can radiotherapy significantly reduce mortality?

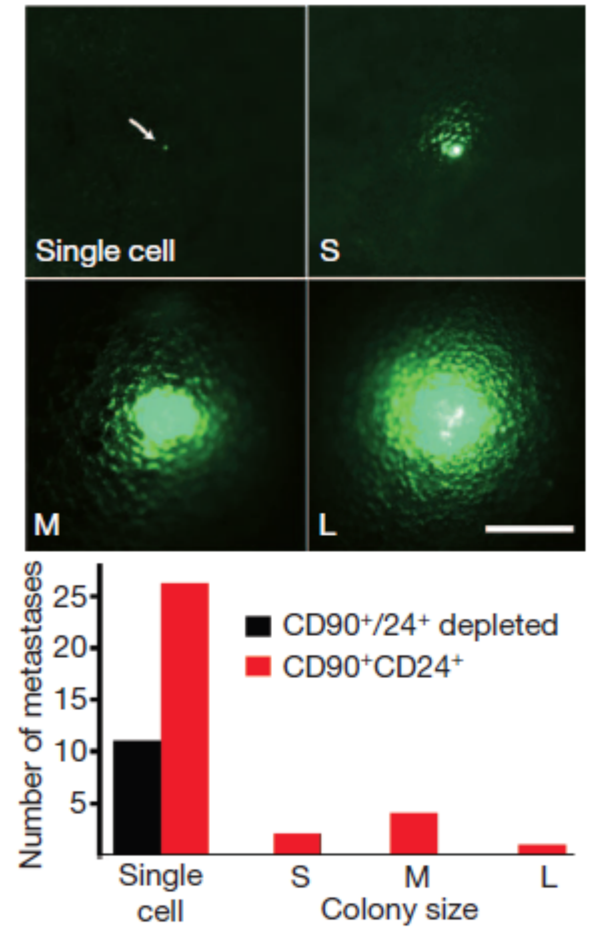




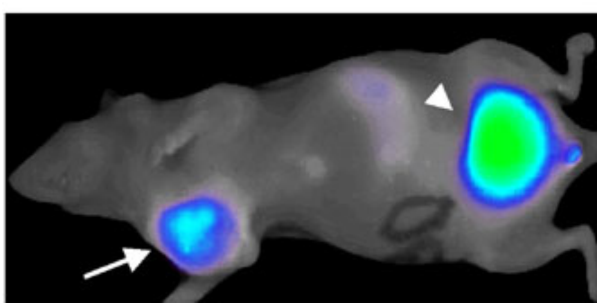
Hanahan & Weinberg, *Cell* 2012

CSCs form metastatic colonization and stromal niche signals is required for expansion





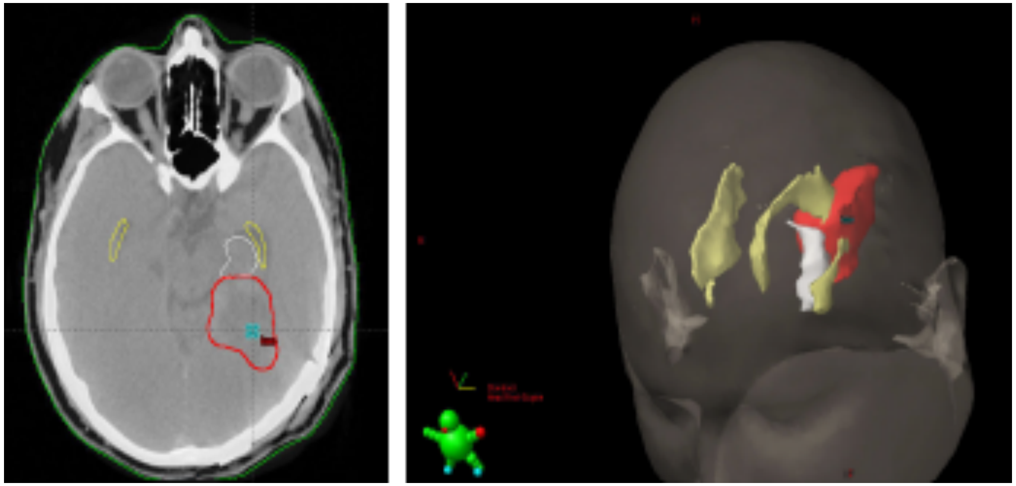
MMTV-PyMT mouse breast cancer model



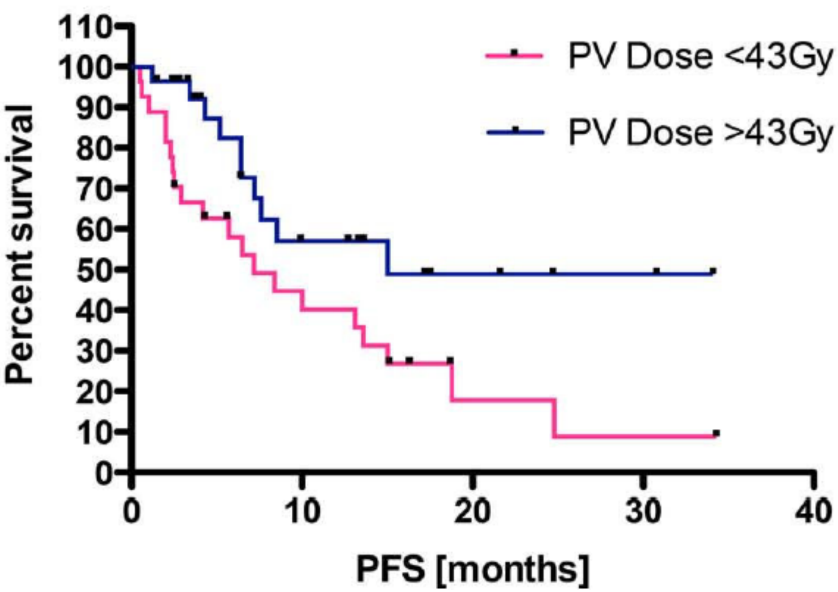
Malanchi *et al.*, *Nature* 2012

ISREC @EPFL
INSTITUT SUISSE DE RECHERCHE EXPÉRIMENTALE SUR LE CANCER

CSCs-targeted therapy in glioblastoma



Red=GTV
Yellow= PV (periventricular region)
White=hyppocampal formation



Evans *et al., BMC Cancer* 2010

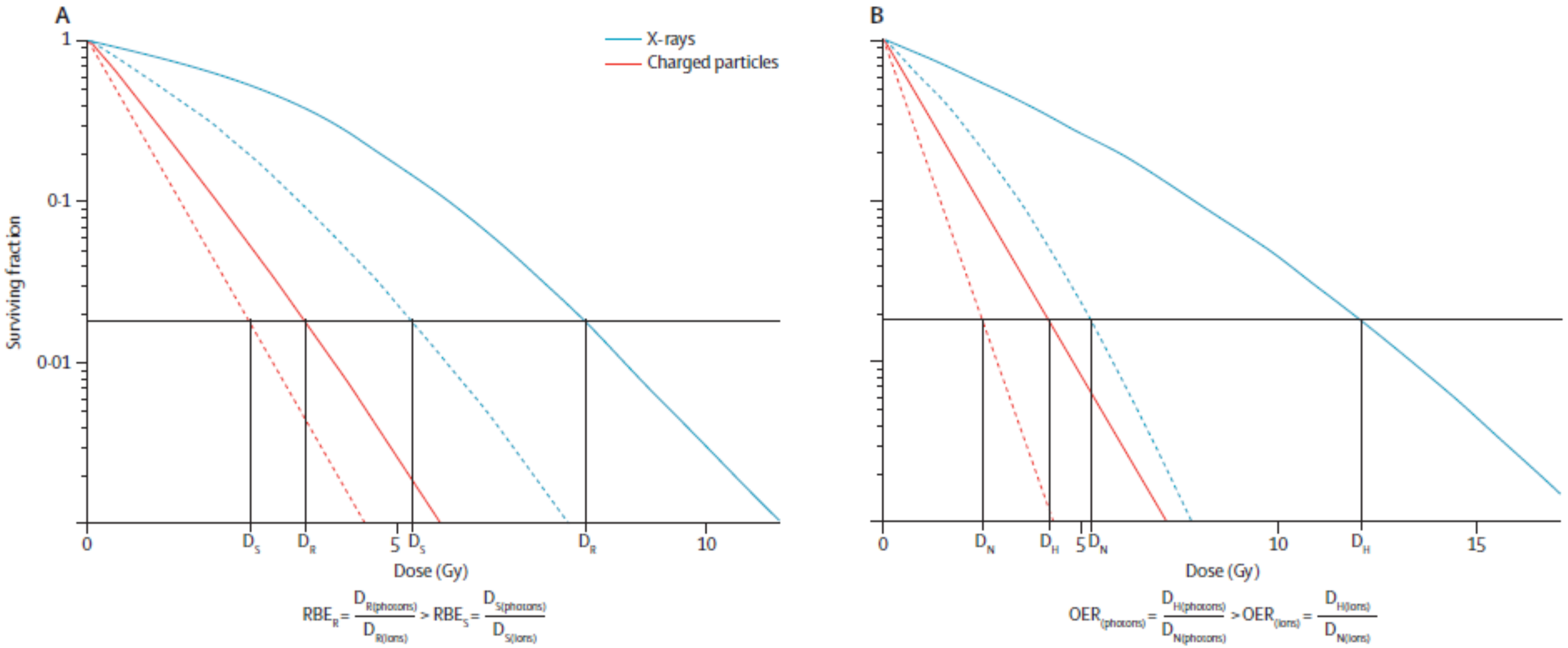
J Neurooncol (2012) 109:195–203
DOI 10.1007/s11060-012-0887-3

CLINICAL STUDY

Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma?

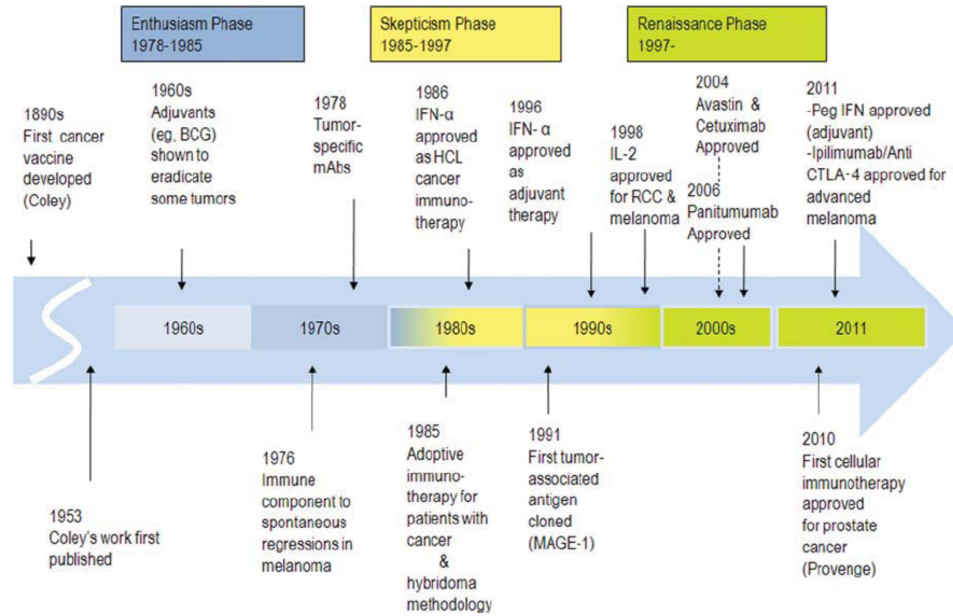
Increasing mean dose to the ipsilateral SVZ leads to improved OAS

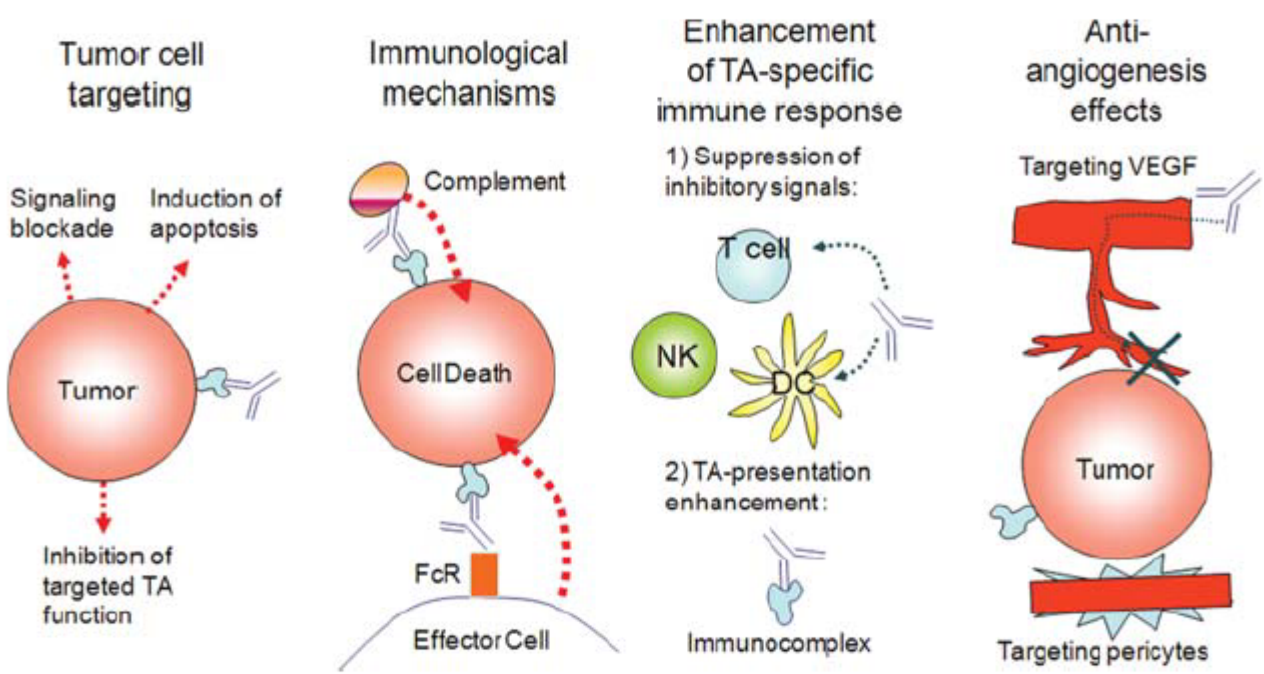
Heavy ions against CSCs



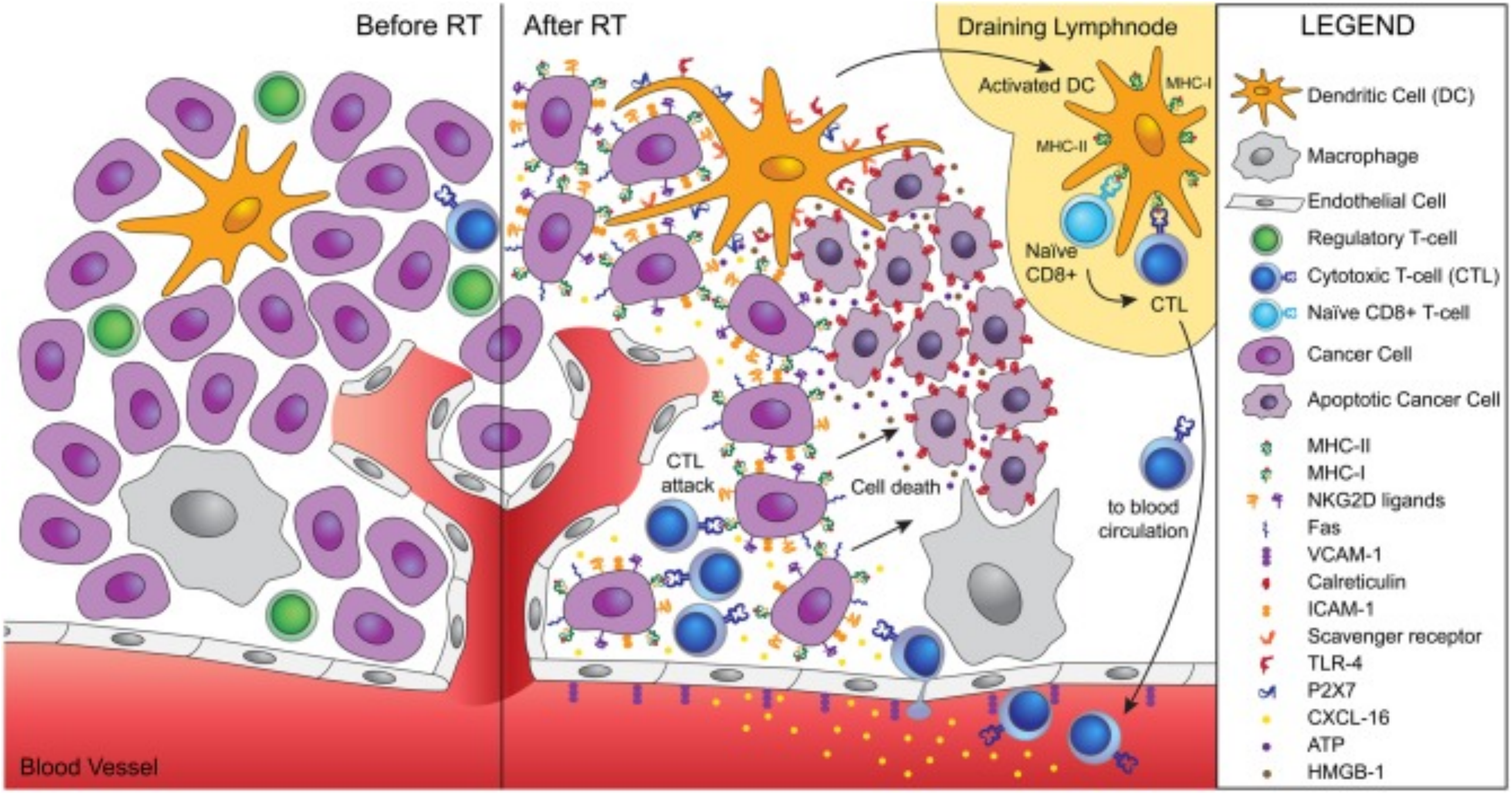
Pignalosa & Durante, *Lancet Oncol*. 2012

Cancer immunoediting and immunotherapy: solution of the cancer problem?





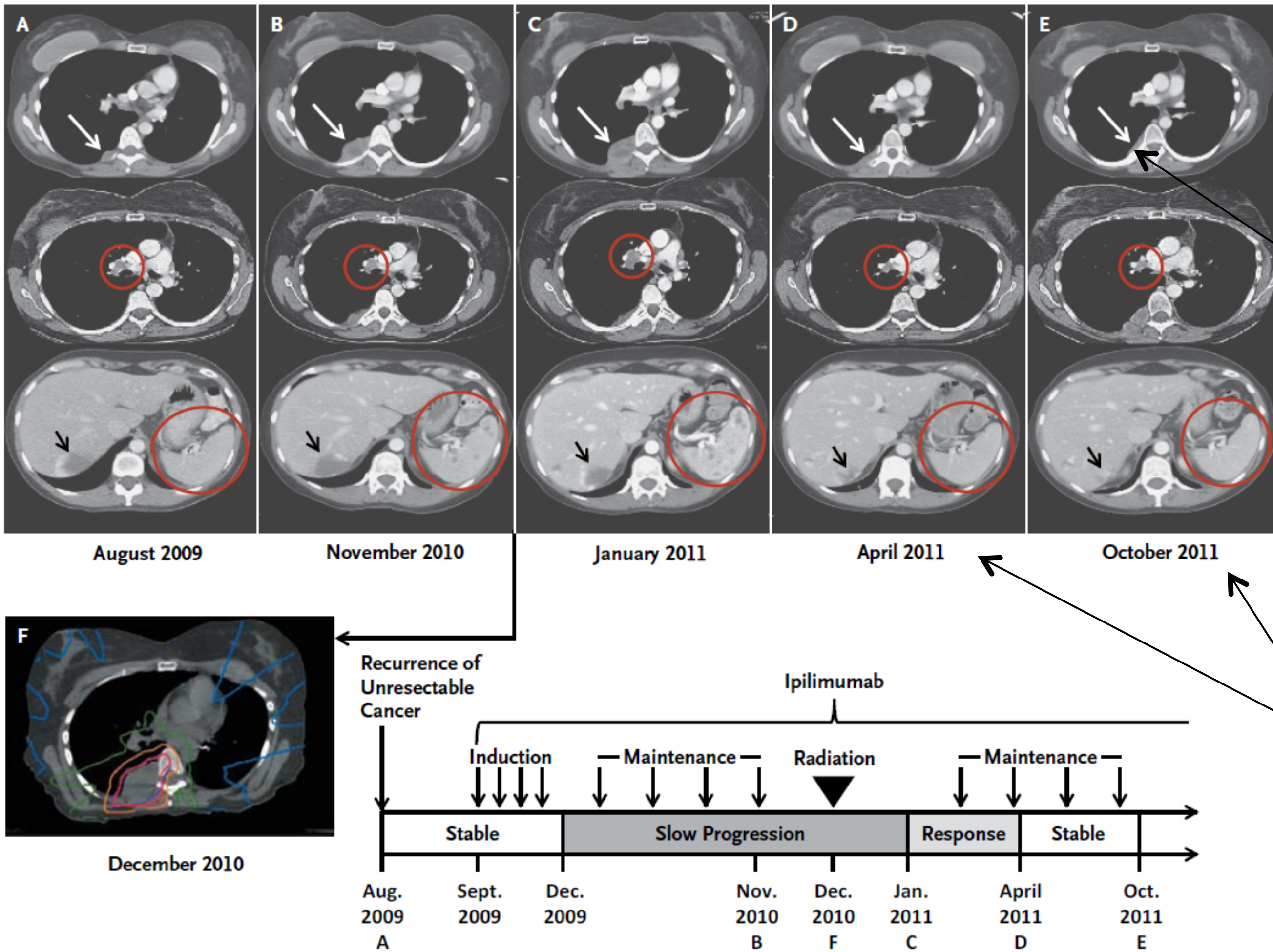
Kirkwood *et al.*, *CA Cancer J. Clin*. 2012



Ionizing radiation acts as a modifier of the tumor microenvironment converting the tumor into an *in situ* vaccine. Radiation induces an immunogenic cell death of tumor cells characterized by calreticulin translocation to the surface of dying cells, and release of HMGB-1 and ATP. Calreticulin allows uptake of dying cells by dendritic cells via scavenger receptor(s). Activated dendritic cells migrate to the draining lymph node, where they activate naïve T cells specific for tumor antigens. Activated CD8 T cells acquire effector functions and traffic to the tumor guided by radiation-induced chemokines. Tumor infiltration by CTLs is facilitated by radiation-induced upregulation of VCAM-1 on the vascular endothelium. Tumor cells killed by CTLs become a source of antigens for cross-presentation, thus fueling the process.

Formenti & Demaria, *Lancet Oncol*. 2009

Radiation and immune response: a patient with metastatic melanoma treated by monoclonal antibody (Ipilimumab) and 28 Gy/3f IMRT

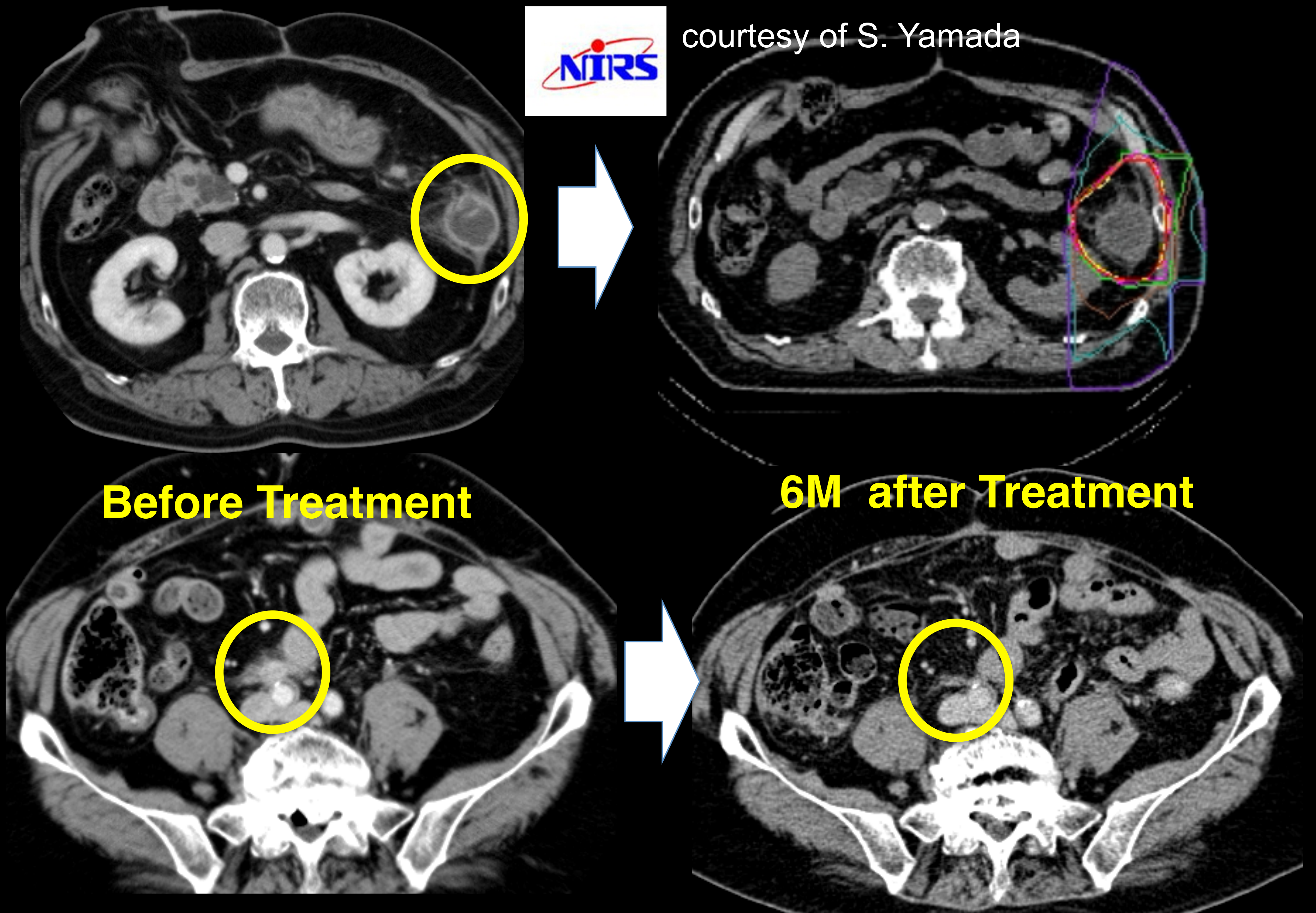


Regression of the targeted pleral-based paraspinal mass

Abscopal regression in right hilar lymph node (1 Gy) and spleen (2 cGy)

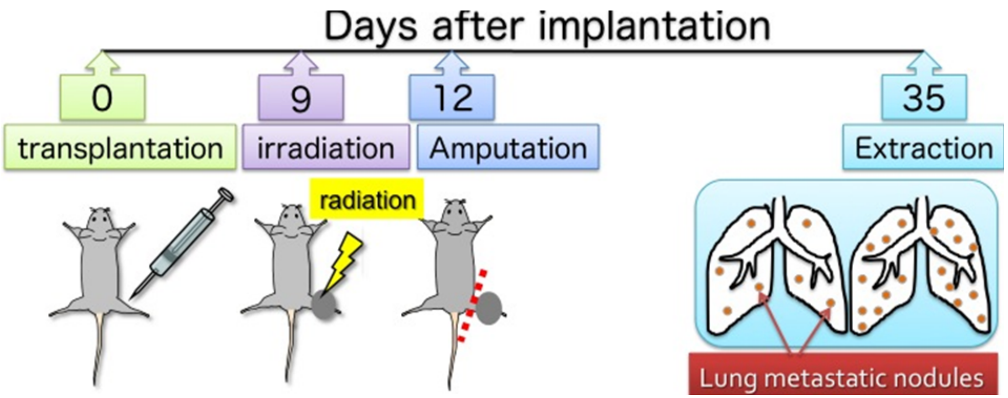
Postow *et al., N. Eng. J. Med*. 2012

Abscopal regression of a para-aortic lymph node metastasis from a resected sigmoid colon cancer and 73.6GyE/16fr to abdominal metastasis

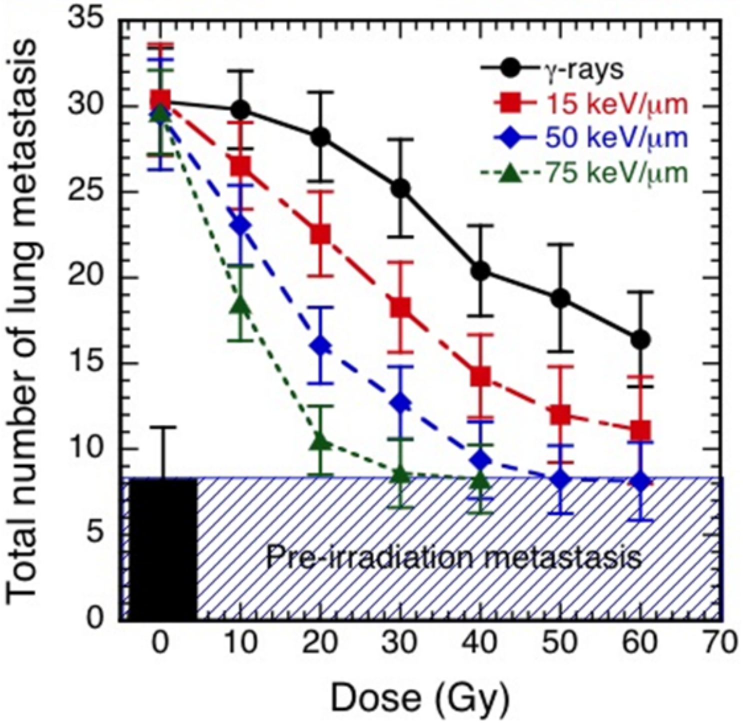


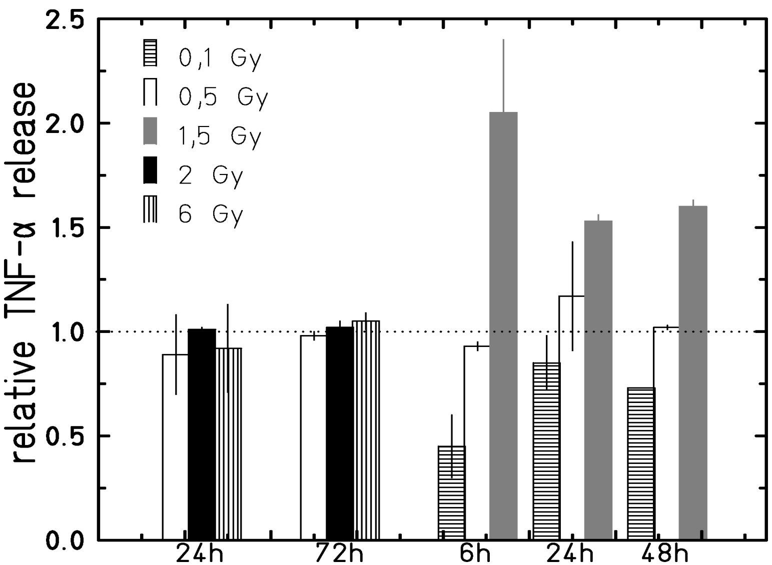
Heavy ion induced immune response

GSI/NIRS IOL project



Courtesy of Y. Matsumoto & Y. Furusawa

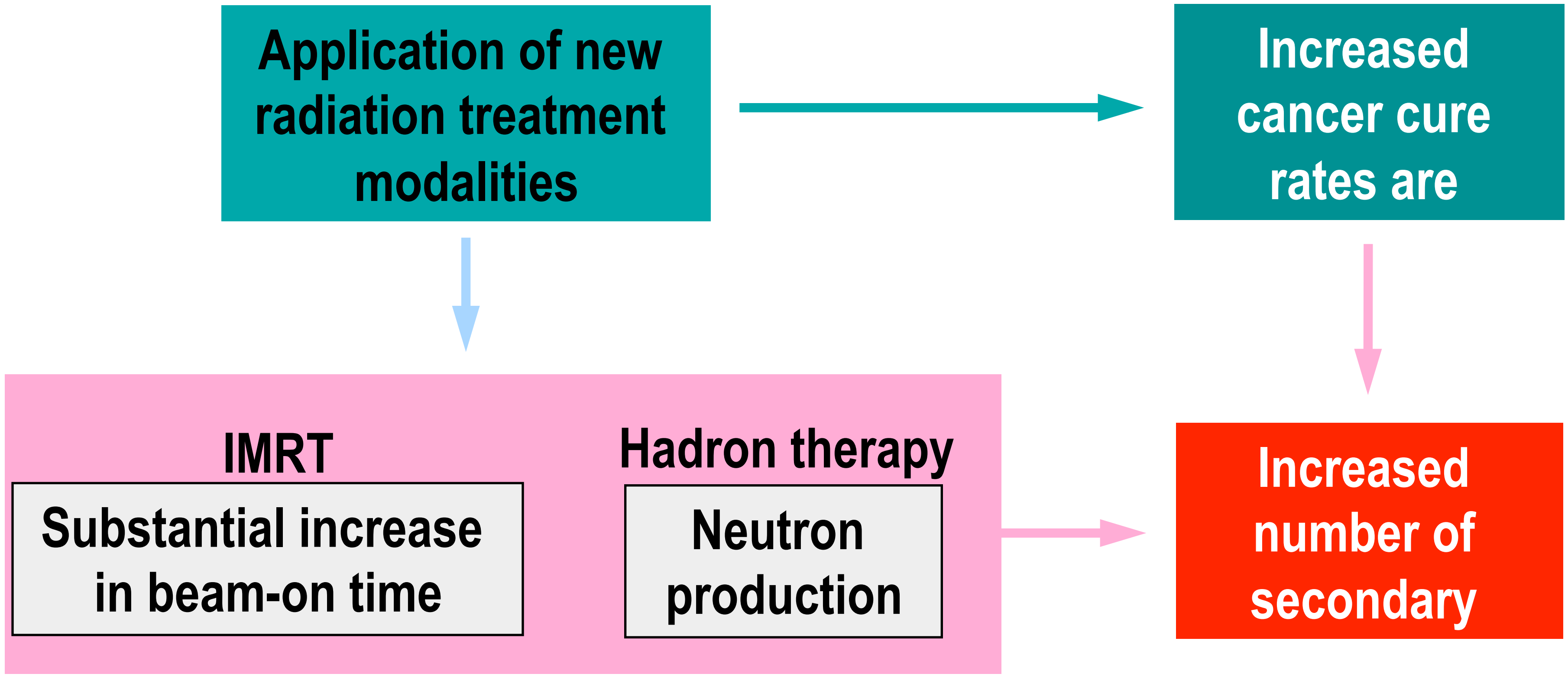




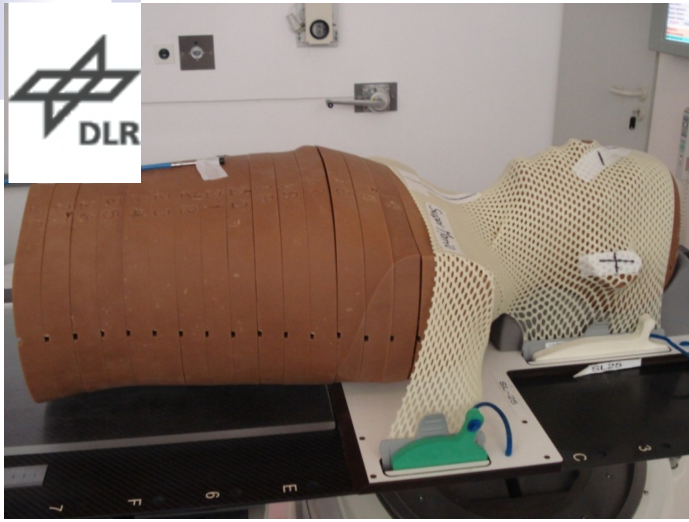
TNF-α release in primary human lymphocytes 24h after X-ray or ^{14}N-ions exposure, +lipopolysaccharide (LPS) endotoxin (1μg/ml)

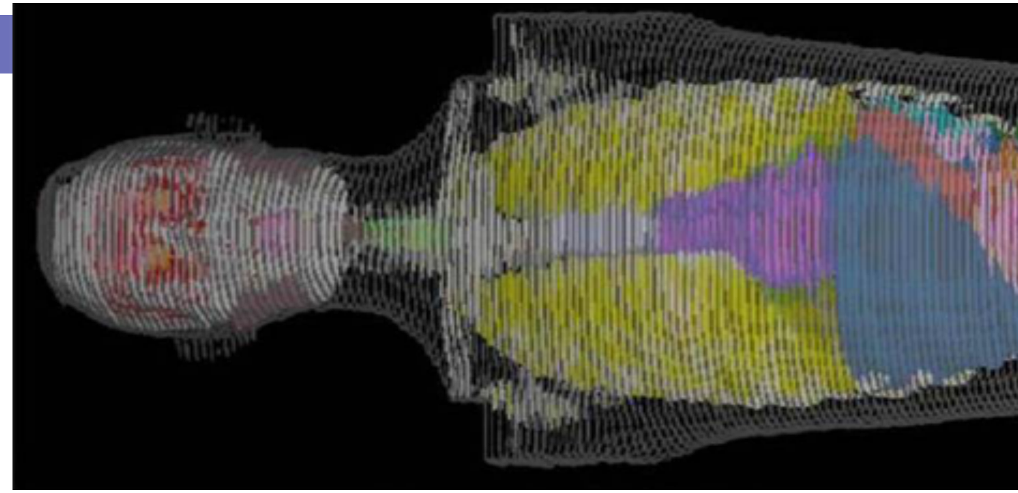
Jonas Klinger Ph.D. thesis, TU Darmstadt 2012

Second malignant neoplasias (SMN)

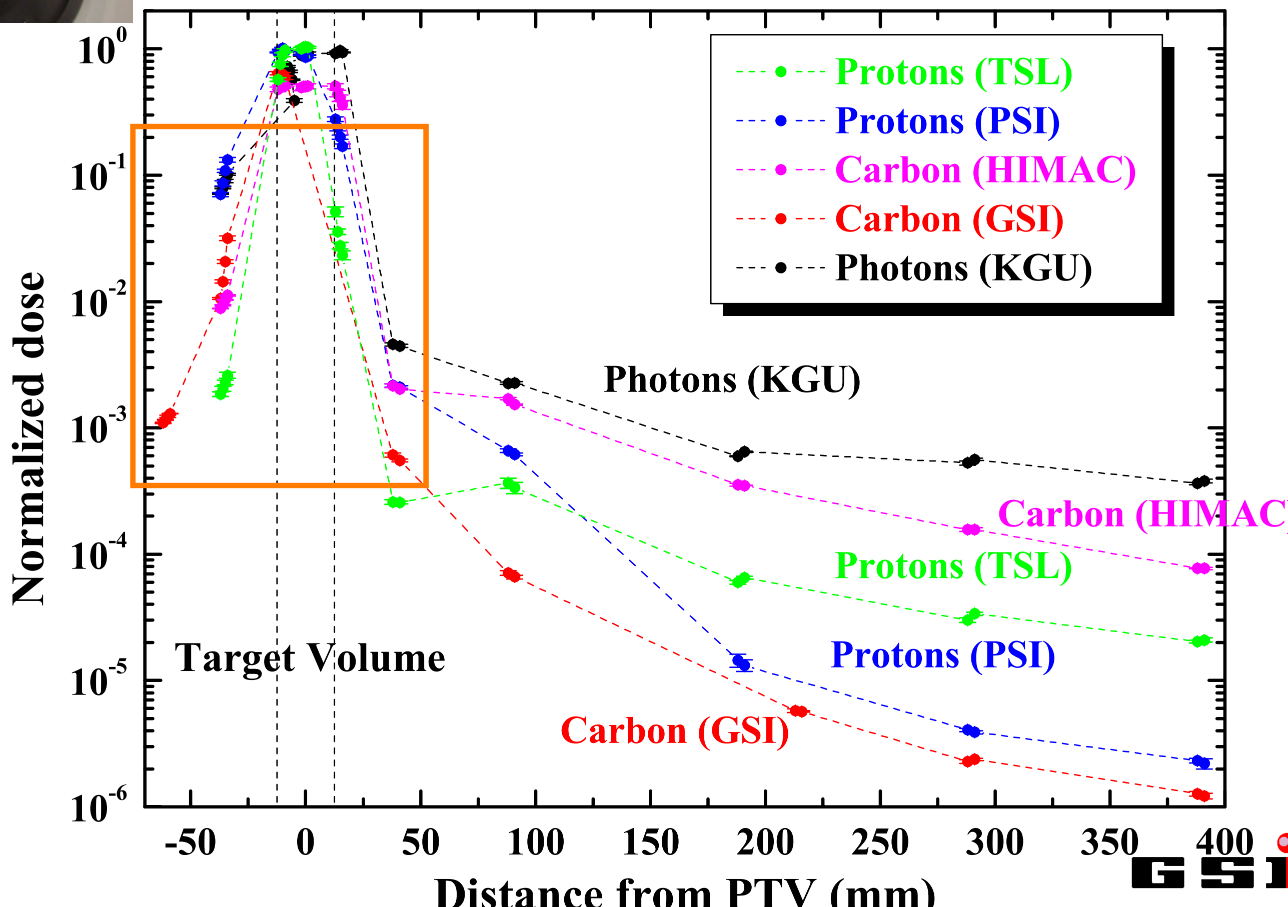


- Childhood cancer is 1% of cancer diagnosis, but 1st cause of disease-realted death in children
- Most common pediatric tumors are leukemia (34%) and CNS tumors (27%)
- Survival rate is now over 80%, but the incidence of SMN is close to 20%
- Most common SMN are breast, CNS, bone, soft tissue, AML





- *Highest out-of-field dose for photons*
- *Higher lateral dose for passive modulation than scanning delivery*
- *Higher lateral dose for protons than carbon ions*
- *Collimator produces sharper field edges*



La Tessa *et al. Radiother. Oncol.* 2012

In patient dosimetry (uterus dose for a pregnant woman)

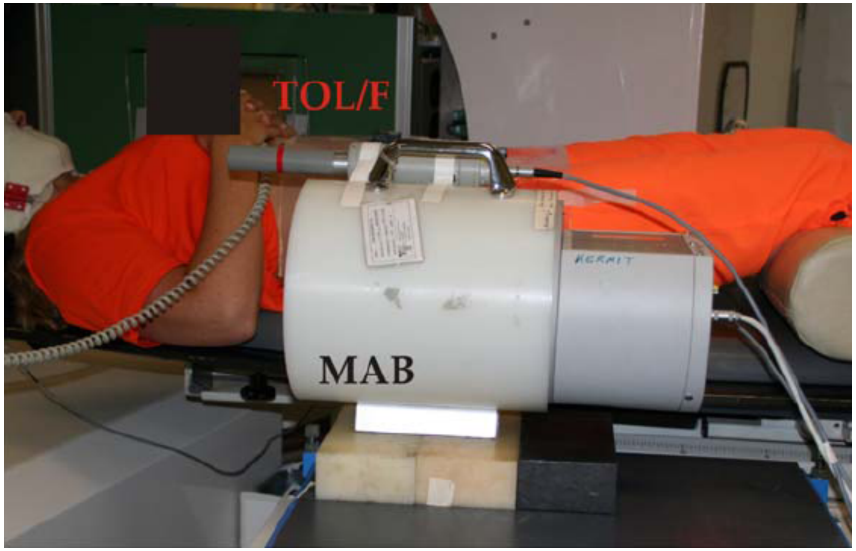


TABLE 1

Measured doses in the pelvic region during the treatment.

	Photon dose (μSv/fraction)	Neutron dose (μSv/fraction)	No. of fractions	Total dose (μSv)
Normal field	3.0[a]	1.4	15	66
Boost field	2.2[b]	1.0	5	16
Total treatment			20	82

[a] Calculated assuming a factor of 1.4 between normal and boost fields as in neutron dose.
[b] Measured by the TOL/F gamma dose rate meter. The passive thermoluminescence dosimeter films did not measure any significant dose above the normal background.

Münter. Heavy ion radiotherapy during pregnancy. Fertil Steril 2010.

Total dose < 0.3 mSv

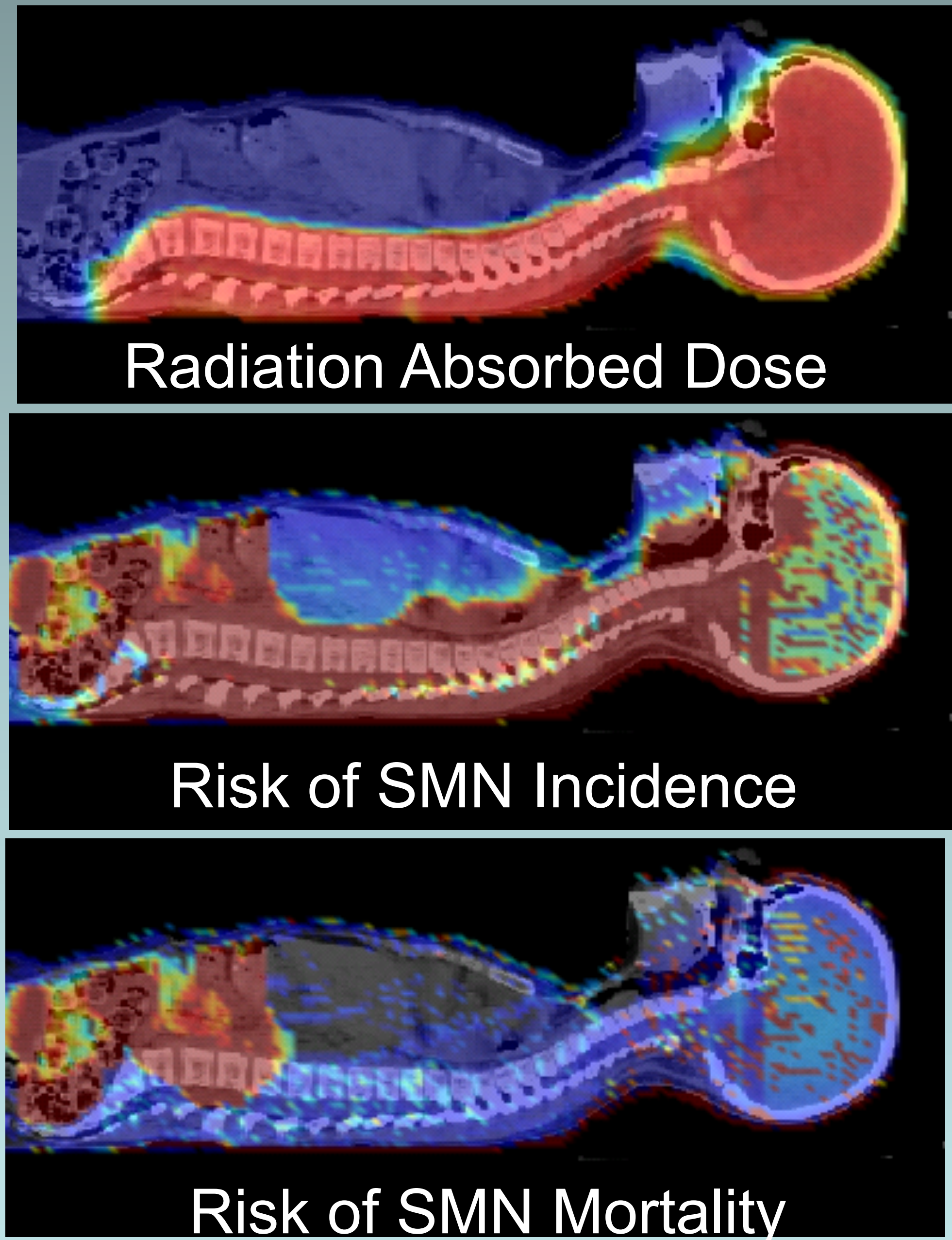
Very low stray radiation

reduced risk of secondary cancers or teratogen effects

Münter *et al., Fertil Steril.* 2010

GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Secondary Malignant Neoplasms (SMN) in particle therapy



Comparison of relative radiation dose distribution with the corresponding relative risk distribution for radiogenic second cancer incidence and mortality. This 9-year old girl received craniospinal irradiation for medulloblastoma using passively scattered proton beams. The color scale illustrates the difference for absorbed dose, incidence and mortality cancer risk in different organs.

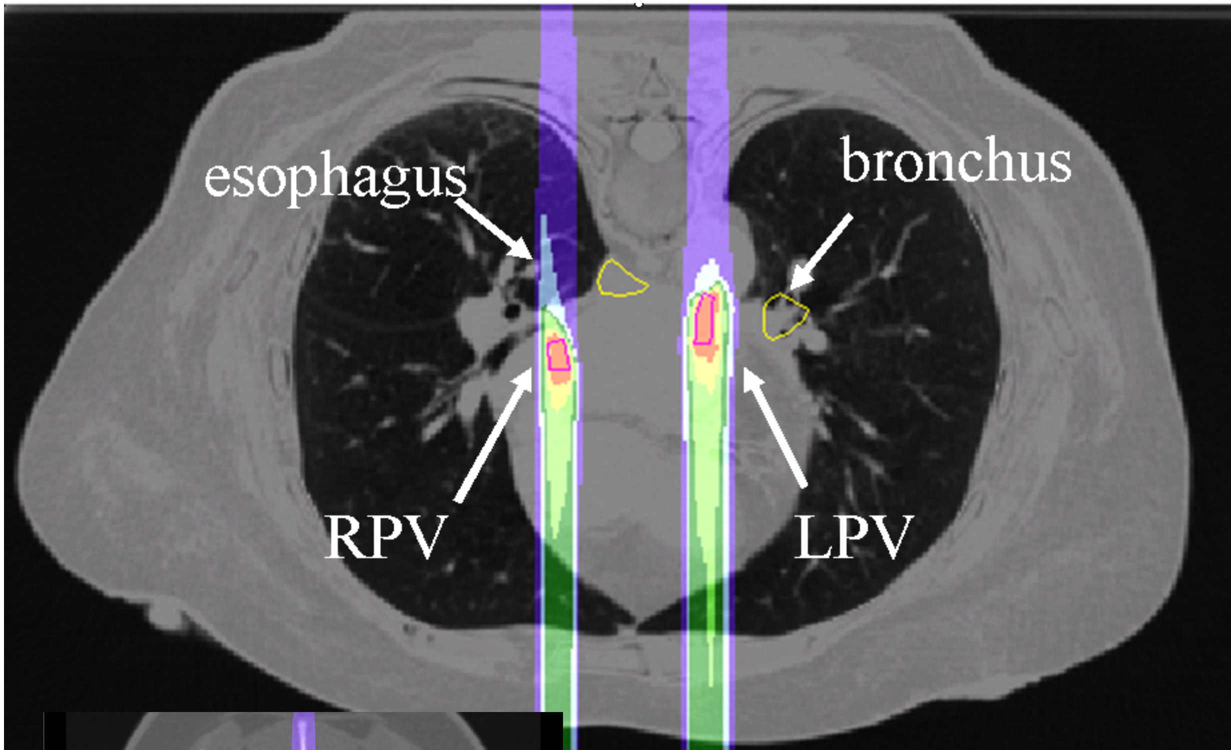
Newhauser & Durante,

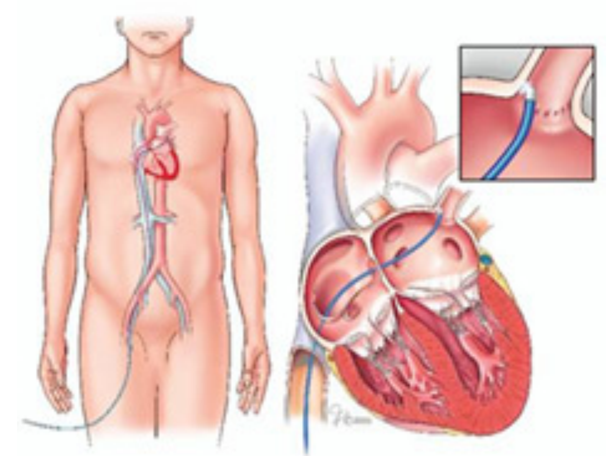
Nature Rev. Cancer 2011

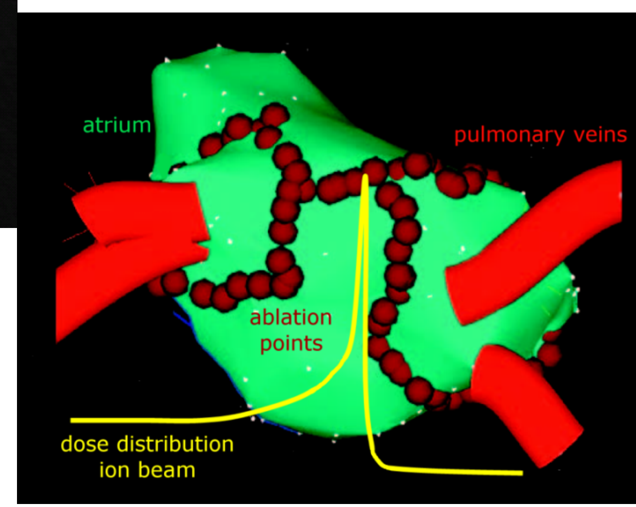
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

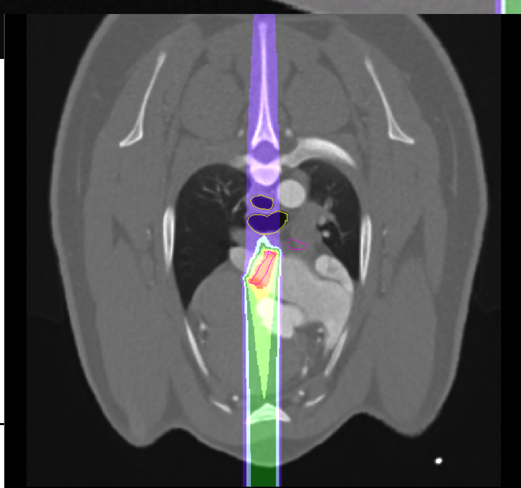
GSI

Noncancer diseases: 5D-TP for atrial fibrillations









C-ion TP by Anna Constantinescu

Bert *et al.*, *Med. Phys*. 2012

A challenge for ENLIGHT towards Horizon 20/20

- ENLIGHT: a successfull example of scientifc network and lobbying with EU for funding
- Many facilities available in Europe in future years, both clinical (HIT, CNAO, MedAustron) and research centers (GSI →FAIR, GANIL→ARCHADE, CERN→LEIR), but research in the field may be severely underfunded
- Main challenge of ENLIGHT will be to attract collaborations and funding (Horizon 20/20 but also ESF, ERC etc.) for innovative technologies and clinical radiobiology research projects
- Can ENLIGHT act similarly to MELODI (radiation protection→ DoReMi funded in FP7 EURATOM) for particle therapy/medical physics as a NoE in Horizon 20/20?

ENLIGHT

MELODI

Biophysics Department

M. Durante (Director)

G. Kraft (Helmholtz Professor)

G. Taucher-Scholz (DNA damage)

S. Ritter (Stem cells)

C. Fournier (Late effects)

W. Kraft-Weyrather (Clinical radiobiology)

M. Scholz (Biophysical modelling)

M. Krämer (Treatment planning)

C. Bert (Moving targets)

C. La Tessa (Dosimetry)

Thank you very much!

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

Additional slides

Cancer incidence/mortality in USA

Estimated New Cases*

			Males	Females		
Prostate	241,740	29%		Breast	226,870	29%
Lung & bronchus	116,470	14%		Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%		Colon & rectum	70,040	9%
Urinary bladder	55,600	7%		Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%		Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%		Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%		Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%		Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%		Ovary	22,280	3%
Pancreas	22,090	3%		Pancreas	21,830	3%
All Sites	**848,170**	**100%**		**All Sites**	**790,740**	**100%**

Estimated Deaths

			Males	Females		
Lung & bronchus	87,750	29%		Lung & bronchus	72,590	26%
Prostate	28,170	9%		Breast	39,510	14%
Colon & rectum	26,470	9%		Colon & rectum	25,220	9%
Pancreas	18,850	6%		Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%		Ovary	15,500	6%
Leukemia	13,500	4%		Leukemia	10,040	4%
Esophagus	12,040	4%		Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%		Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%		Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%		Brain & other nervous system	5,980	2%
All Sites	**301,820**	**100%**		**All Sites**	**275,370**	**100%**

Siegel *et al., CA Cancer J. Clin.* 2012

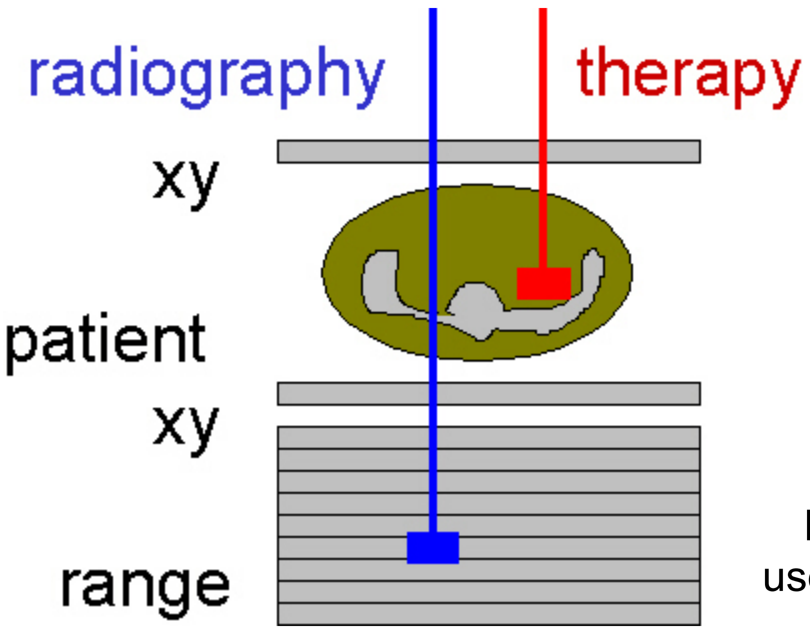
Particle radiography

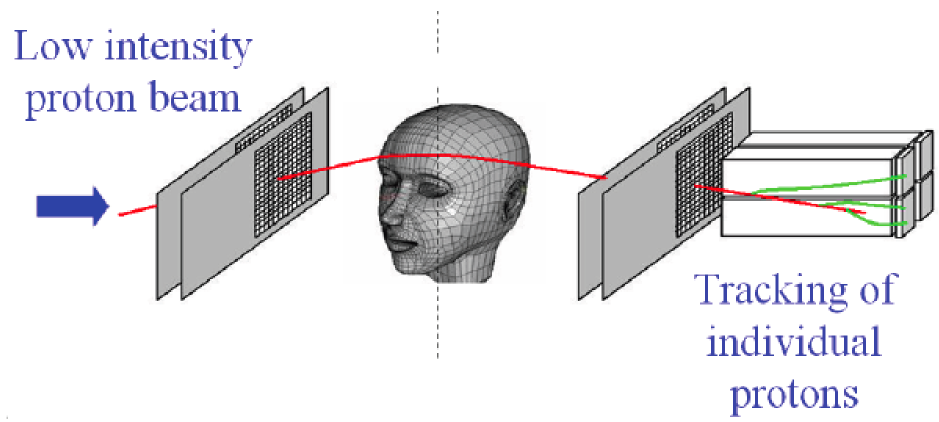
Proton radiography of a RANDO phantom head at PSI, Switzerland

PAUL SCHERRER INSTITUT

PSI

Proton radiography using <u>marginal range radiography</u> is currently under study for quality control in several protontherapy centers

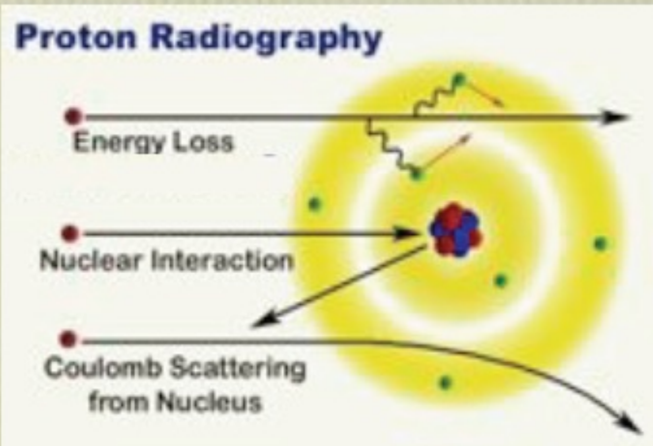




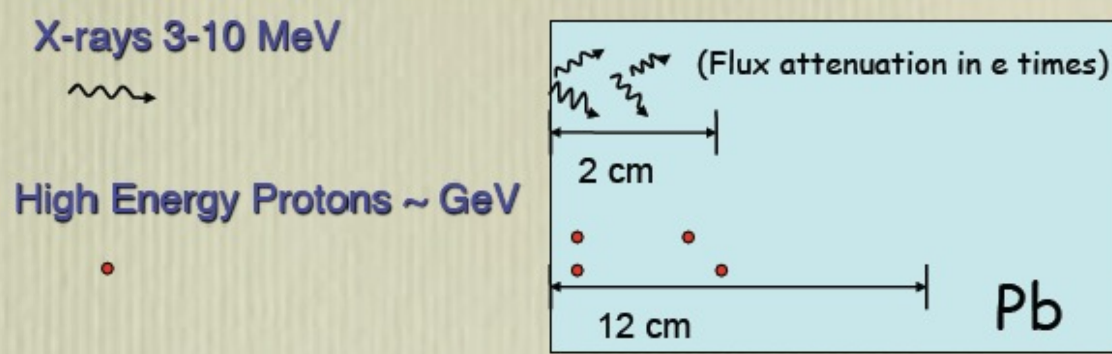
New single-particle ultrafast detectors can be used for imaging based on scattering (courtesy of J. Seco & H. Paganetti, MGH/Harvard)

Proton Radiography Basics

Courtesy of D. Varentsov



X-rays and protons ranges in matter



Protons Image Blurring due to MCS

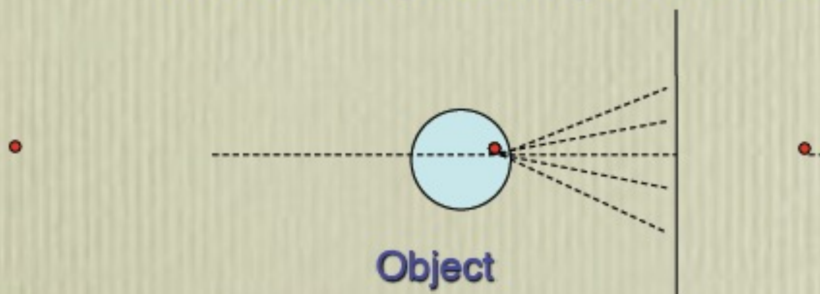
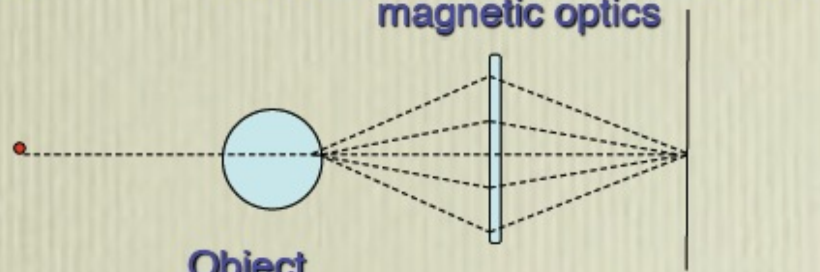
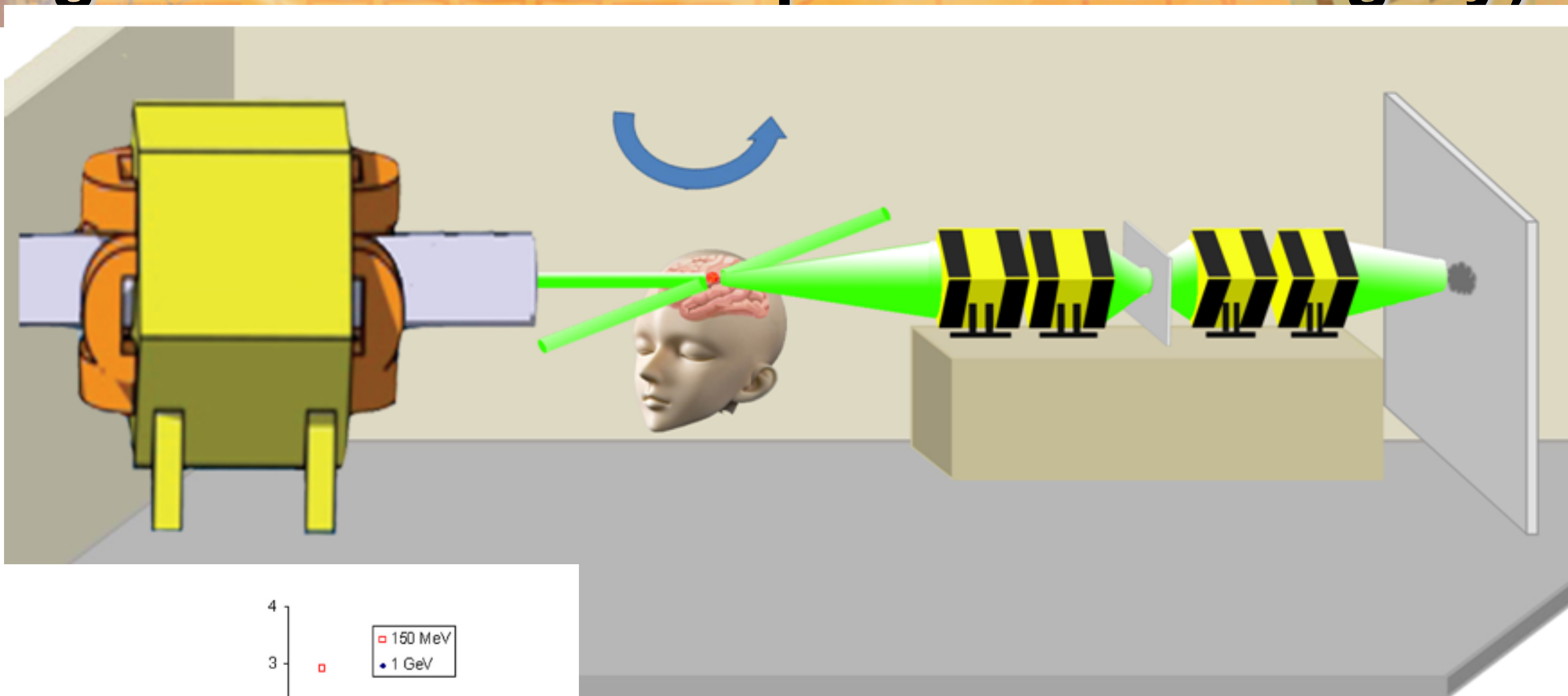


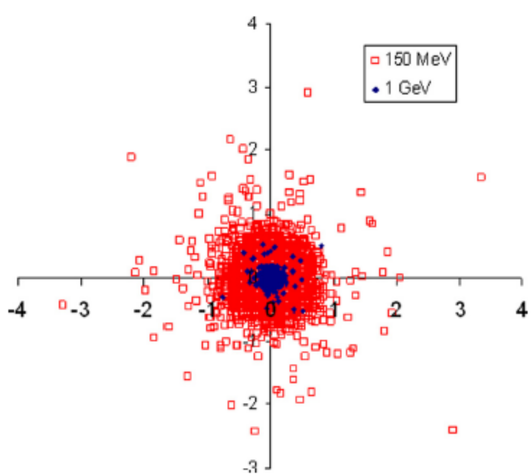
Image Blurring compensation with magnetic optics



A. M. Koehler, *et al.* *Science* **160**, 303 (1968);
J. A. Cookson Naturwissenschaften 61, 184—191 (1974)
C.L. Morris, J.D. Zumbro, Overview of proton radiography—concepts and techniques, Technical Report LA-UR-97-4172, Los Alamos National Laboratory, 1997.

Relativistic proton theranostics (image-guided stereotactic proton radiosurgery)





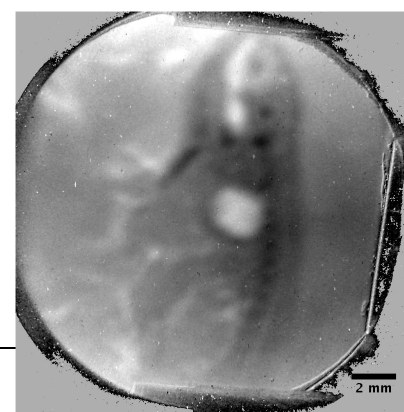


Image of a zebrafish obtained with 800 MeV protons at ITEP (Moscow, Russia)

GSI

Durante & Stöcker, *J. Phys*. 2012