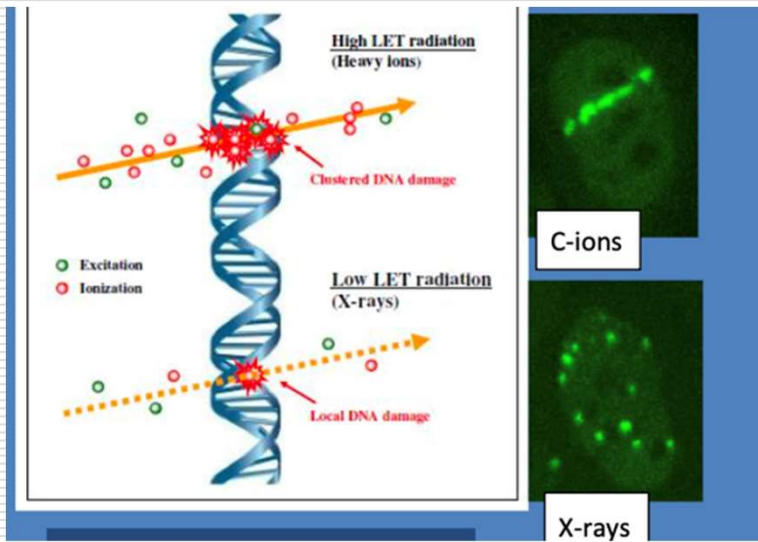

Terapia con hadrones

Alexander Helm

GSI Helmholtz Center for Heavy Ion Research, Darmstadt,
Germany

a.helm@gsi.de

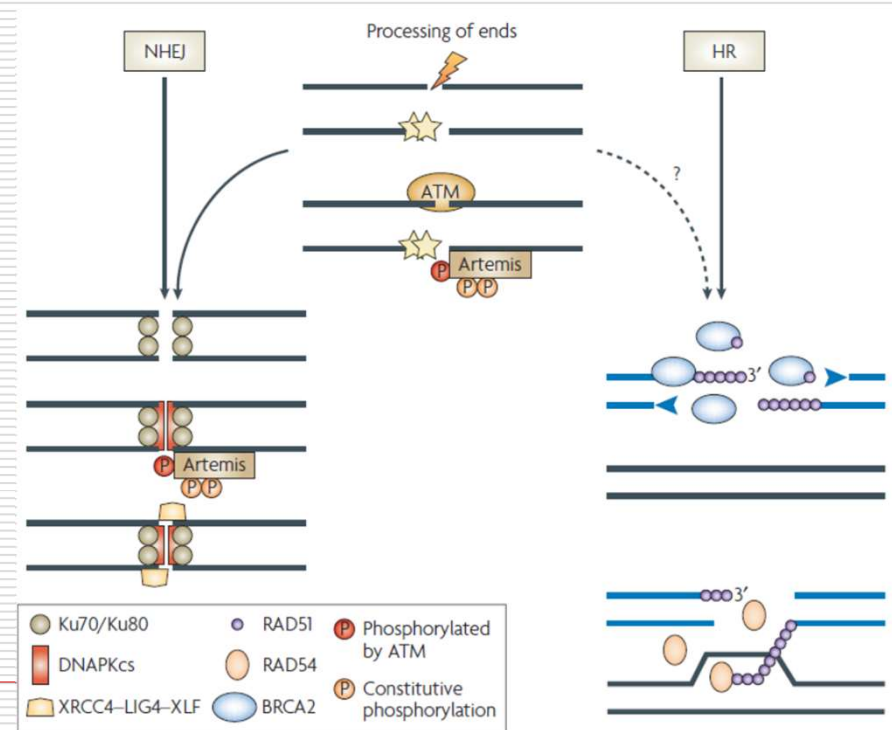
Charged particles introduce a more complex DNA damage



Carbon Ion Radiobiology

Walter Tinganelli¹, Marco Durante^{1,2}

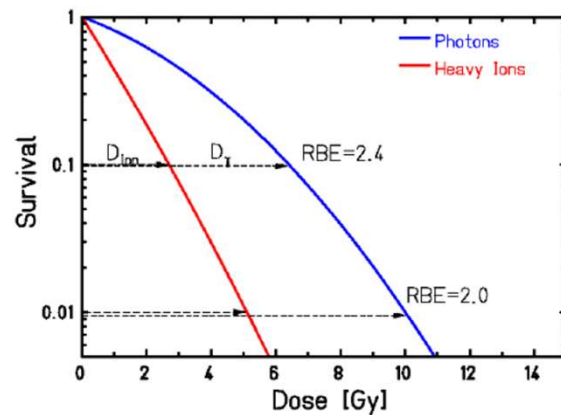
→ Increased level of cell death



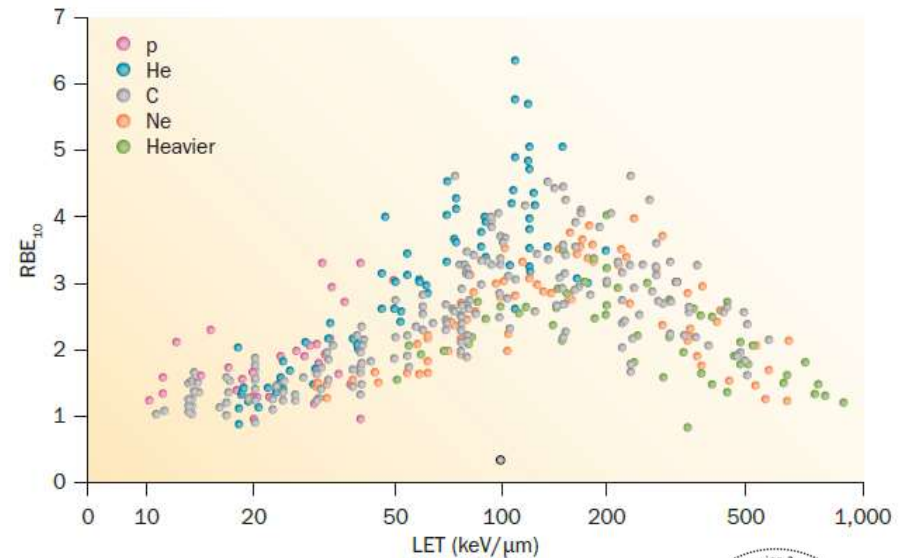
Charged particles inactivate/kill cells more effectively

Relative Biological Effectiveness

Comparison of dose values at **Isoeffect-Level!**

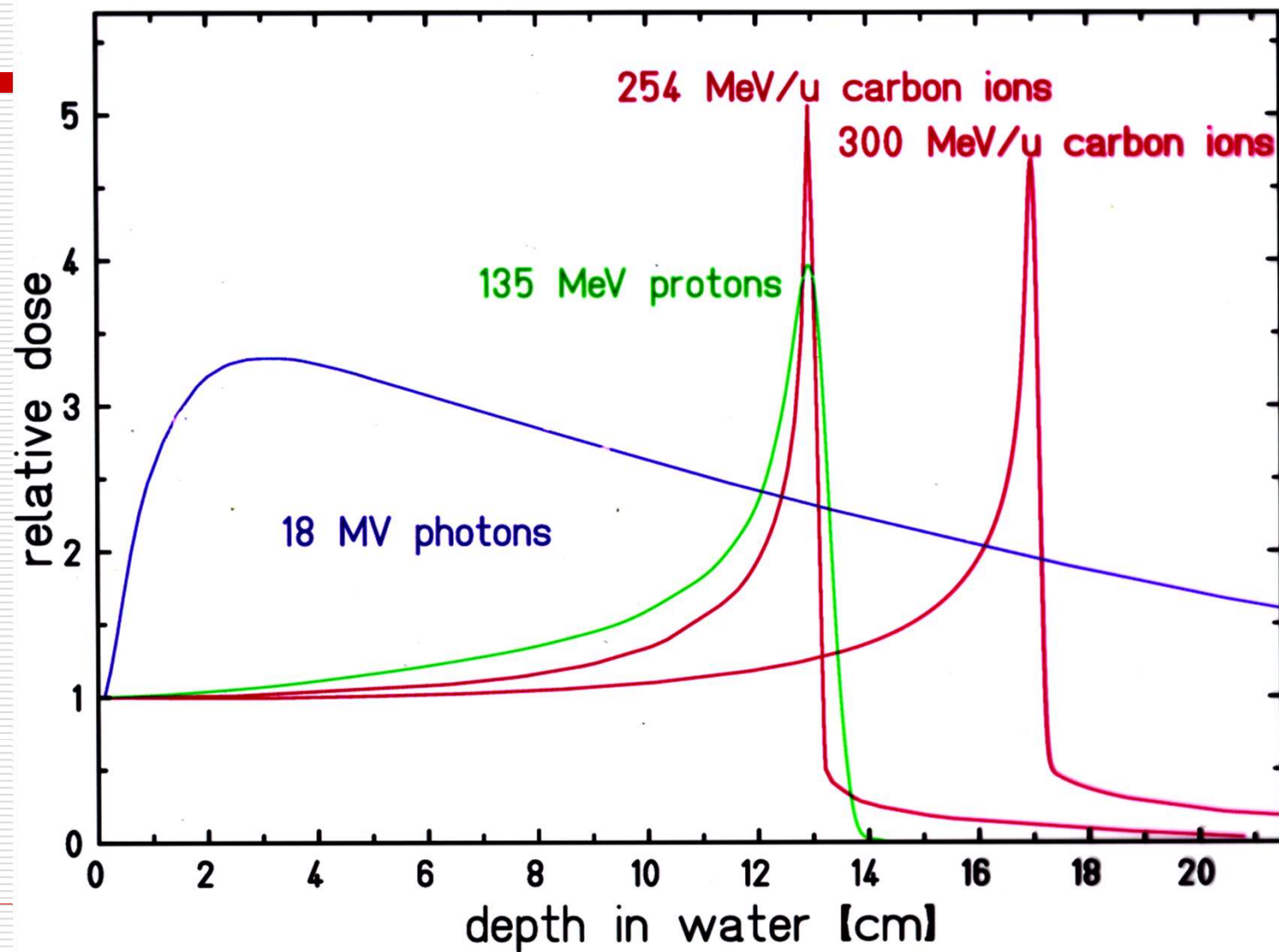


$$RBE = \frac{D_\gamma}{D_{Ion}} \Big|_{Isoeffect}$$

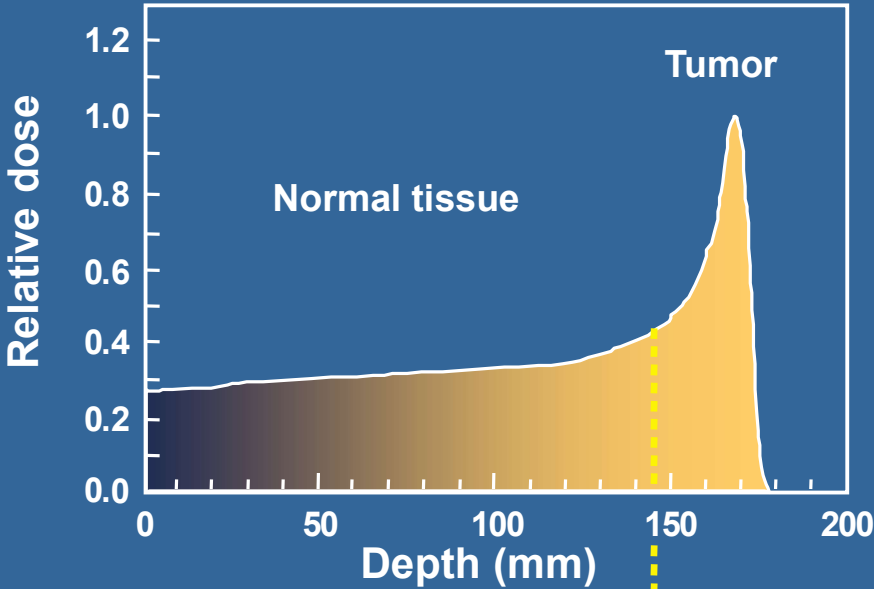


Friedrich *et al.*, *J. Radiat. Res.* 2012
PIDE database www.gsi.de/bio-pide

Depth dose distribution of various radiation modalities



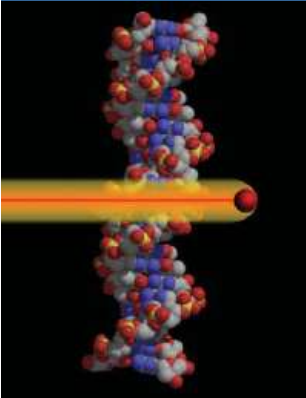
Durante & Loeffler,
Nature Rev Clin Oncol 2010



Potential advantages

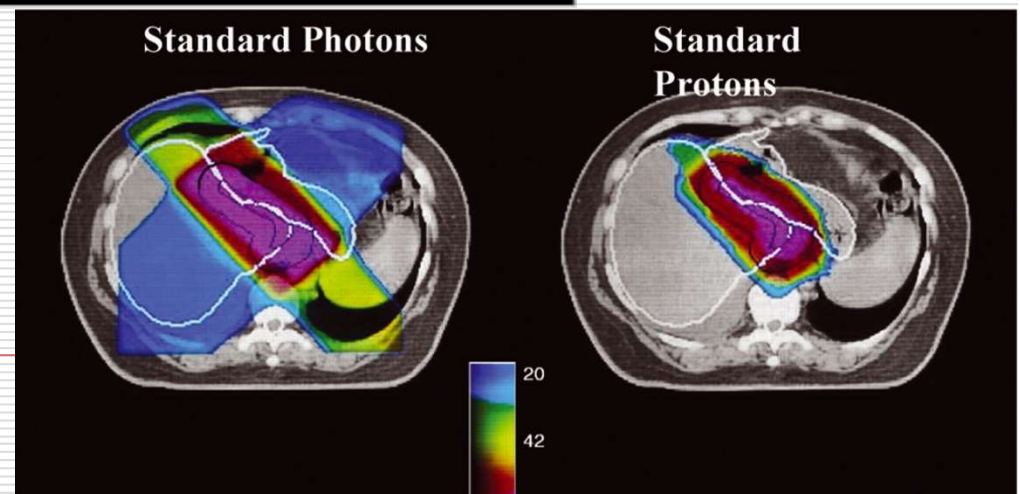
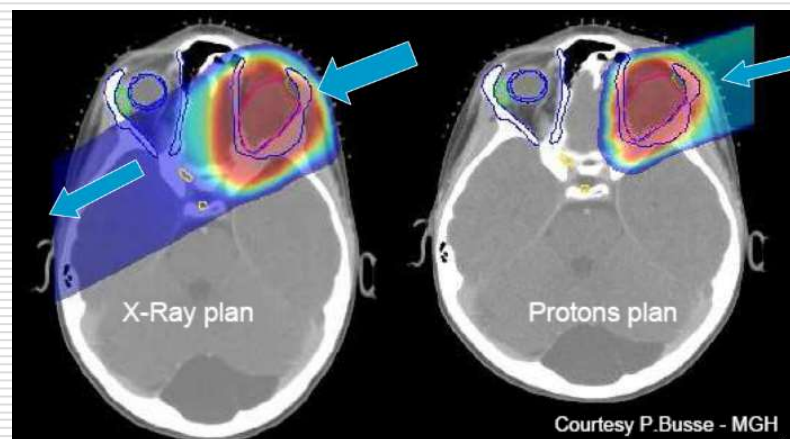
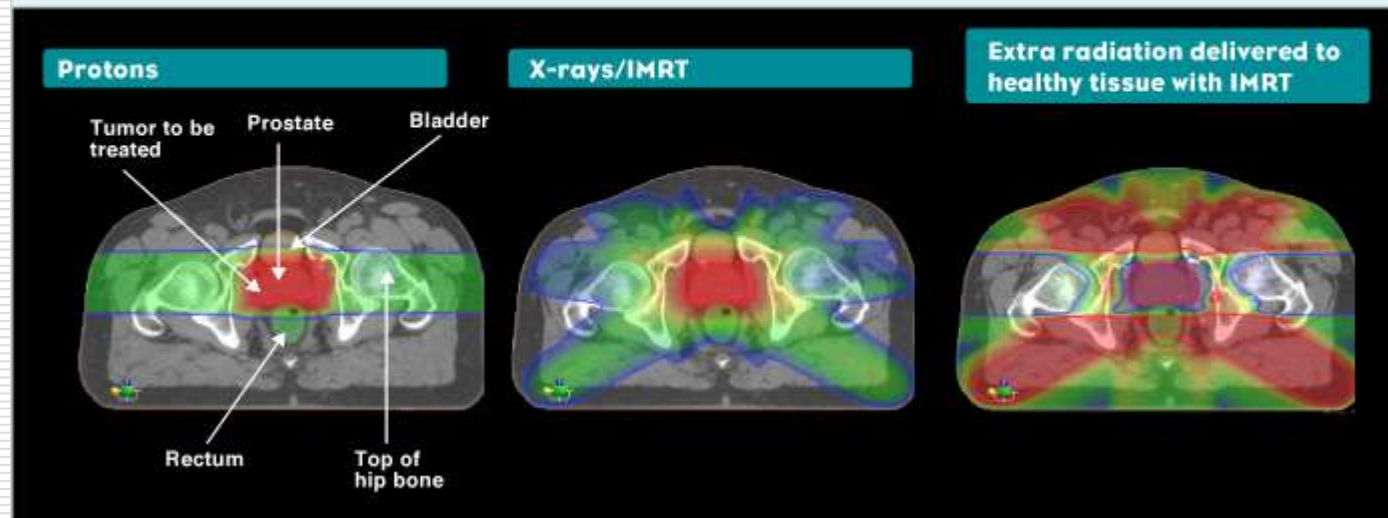
Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low
Angiogenesis	Increased	Decreased
Cell migration	Increased	Decreased

- 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

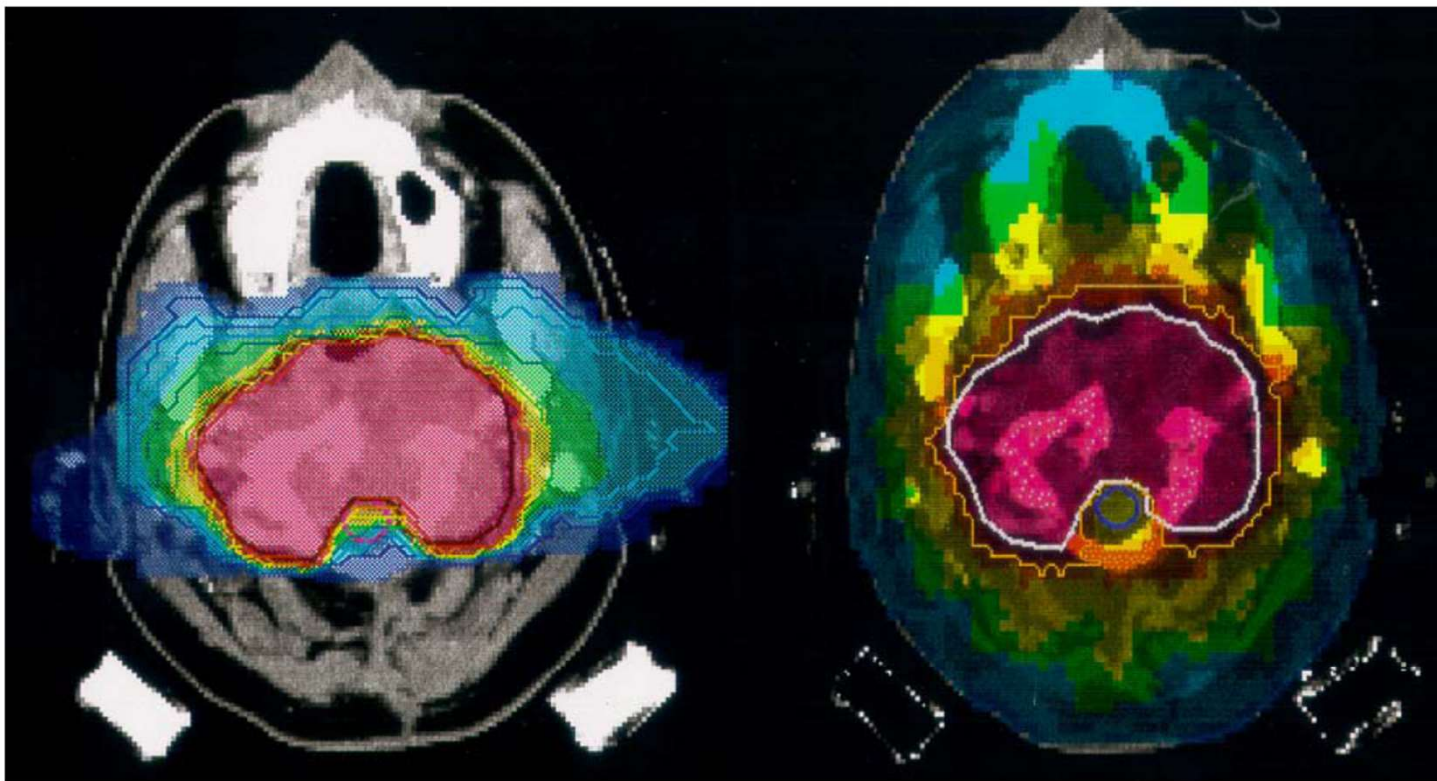


Treatment plans with protons: sparing of normal tissue, recommended especially for pediatric patients

Proton Therapy Achieves Better Conformation to the Tumor *and* Minimizes the Dose to Healthy Tissue



Treatment plans: Heavy Ion vs IMRT



C-12, 2 fields

Jäkel, Debus, Heidelberg

IMRT, 9 fields

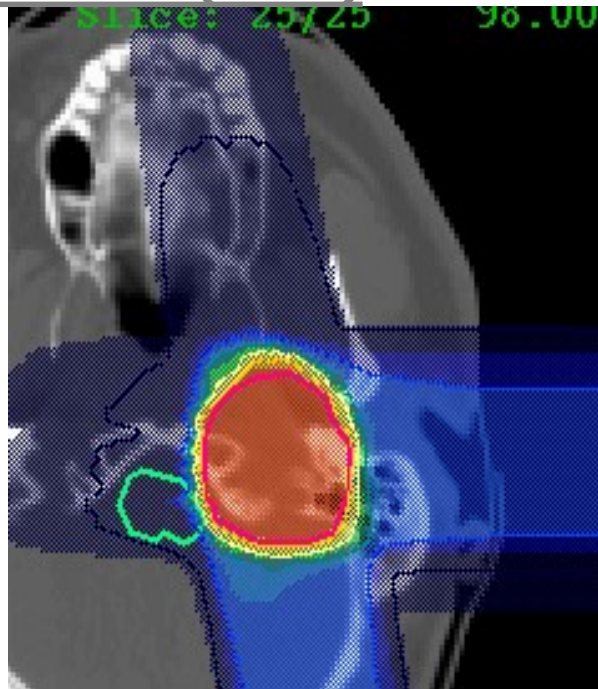
Radiation Biophysics

Carbon beam therapy

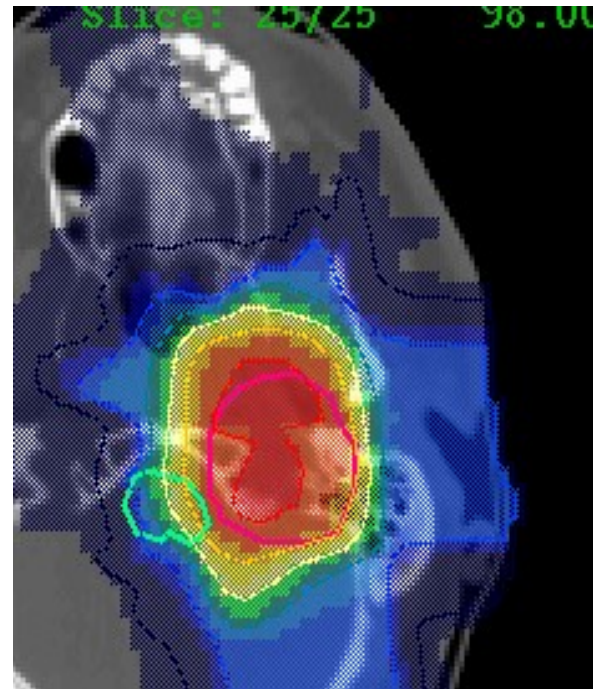


Comparison of Treatment Plans: C-ions vs. protons

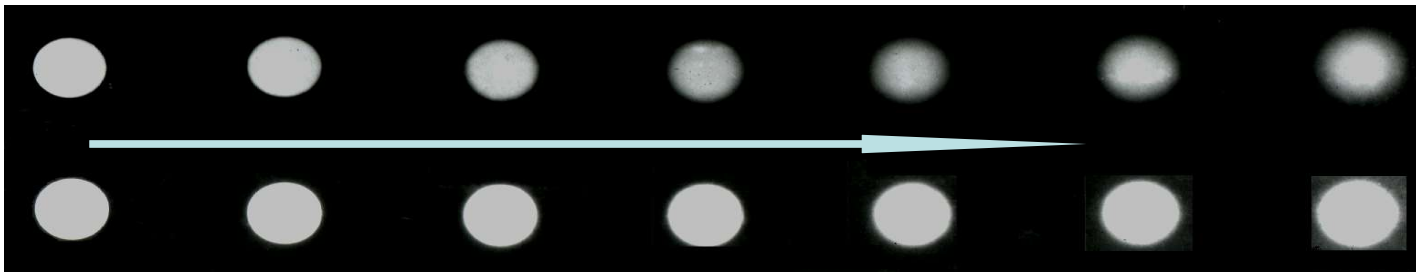
C-ions (GSI)



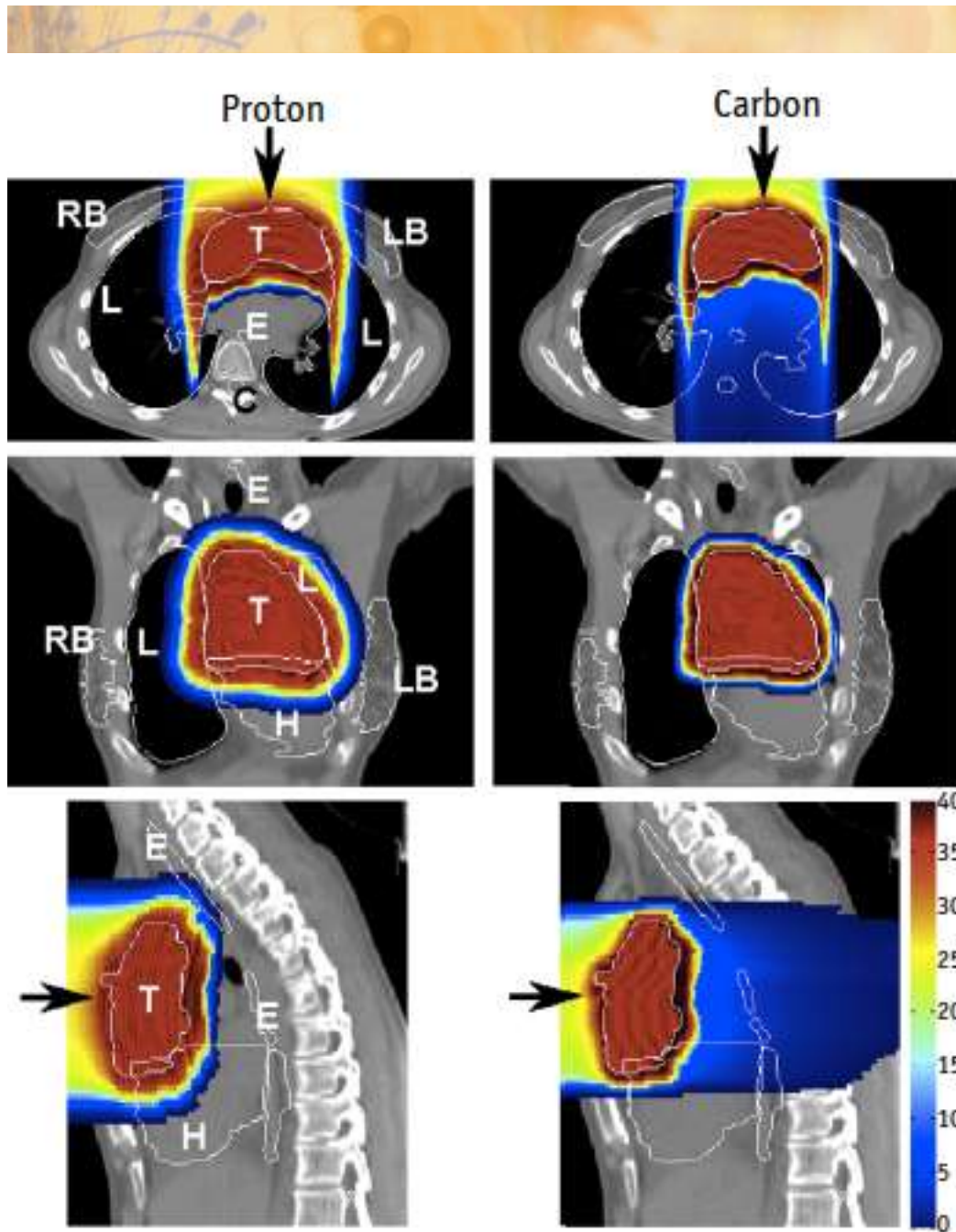
H-ions (Cape Town, SA)



H

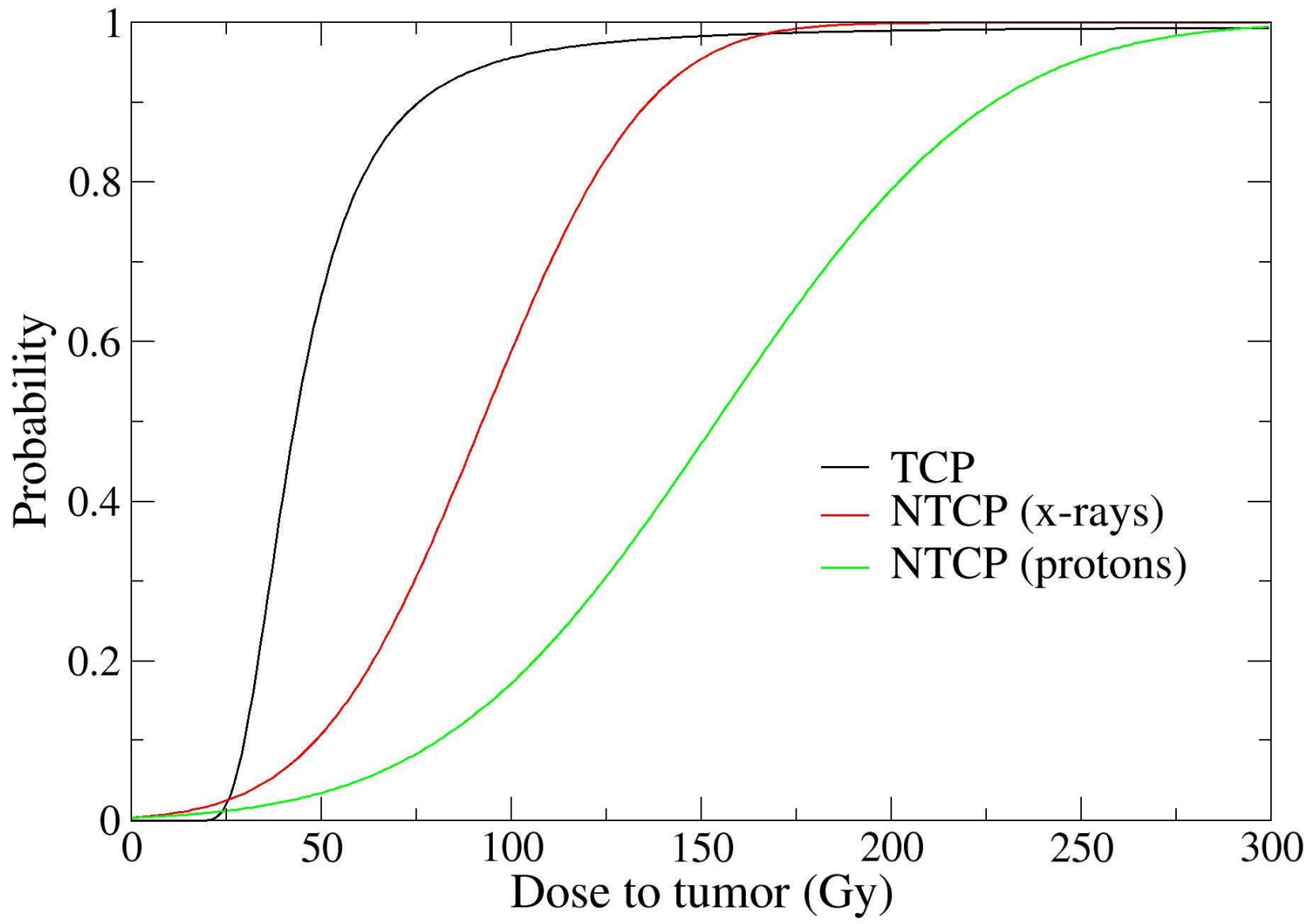


C



Hodgkin's lymphoma : protons or C-ions?

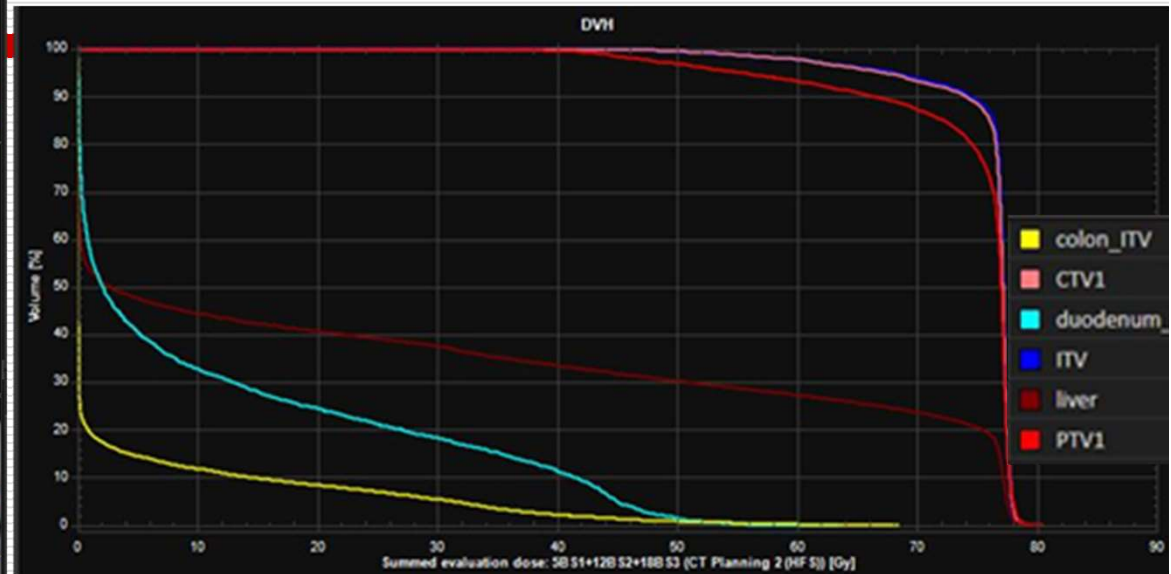
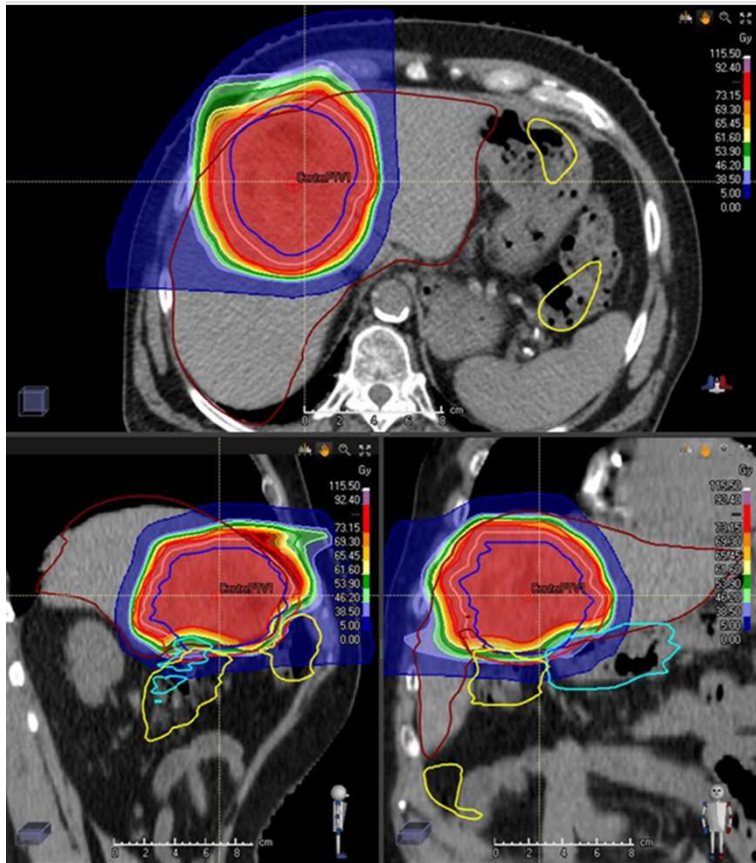
Eley et al., *Int. J. Radiat. Oncol. Biol. Phys.* 2016



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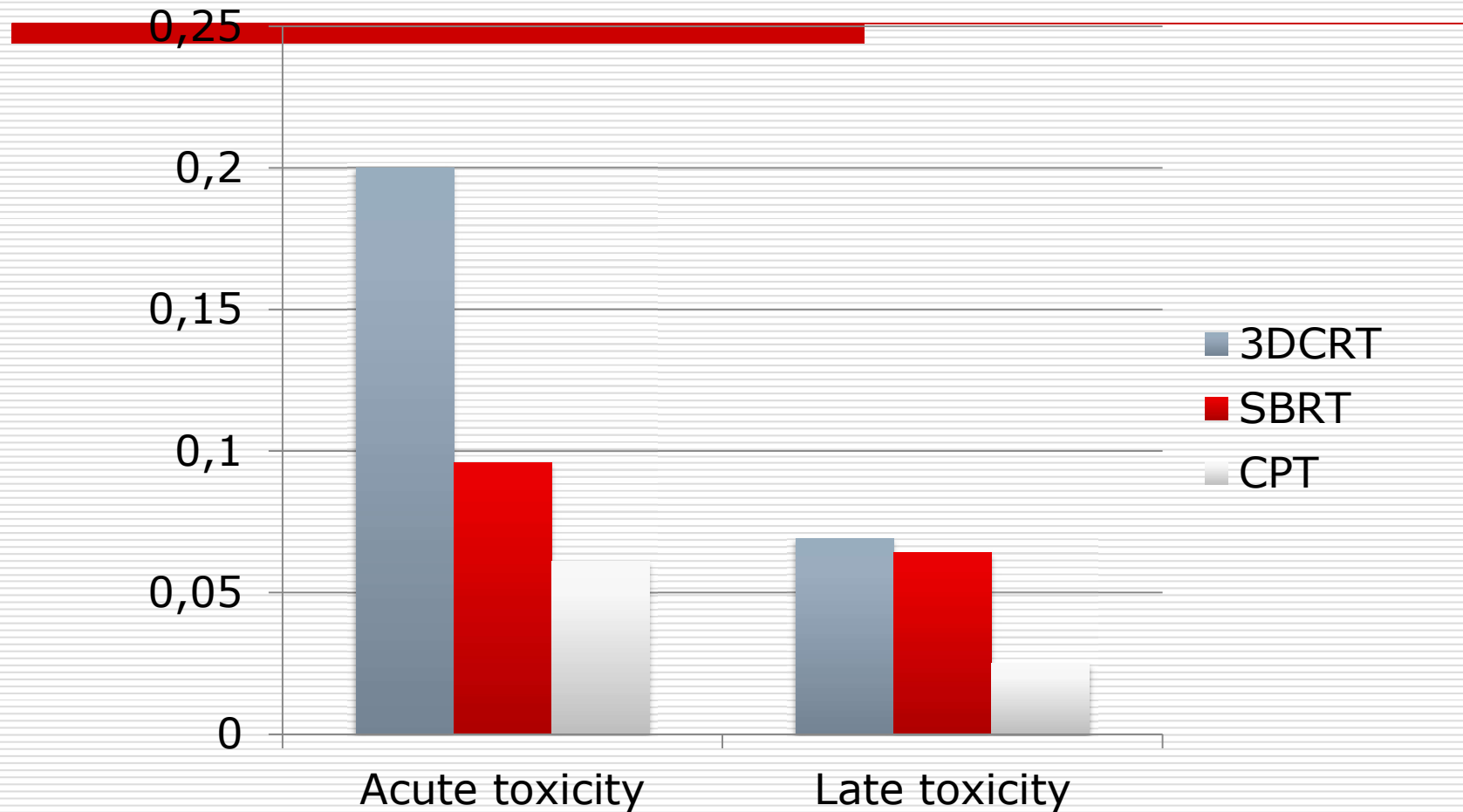
Hepatocellular carcinoma

C-ions



~ 50% of the liver
receives ~ 0 Gy

Particle therapy in HCC

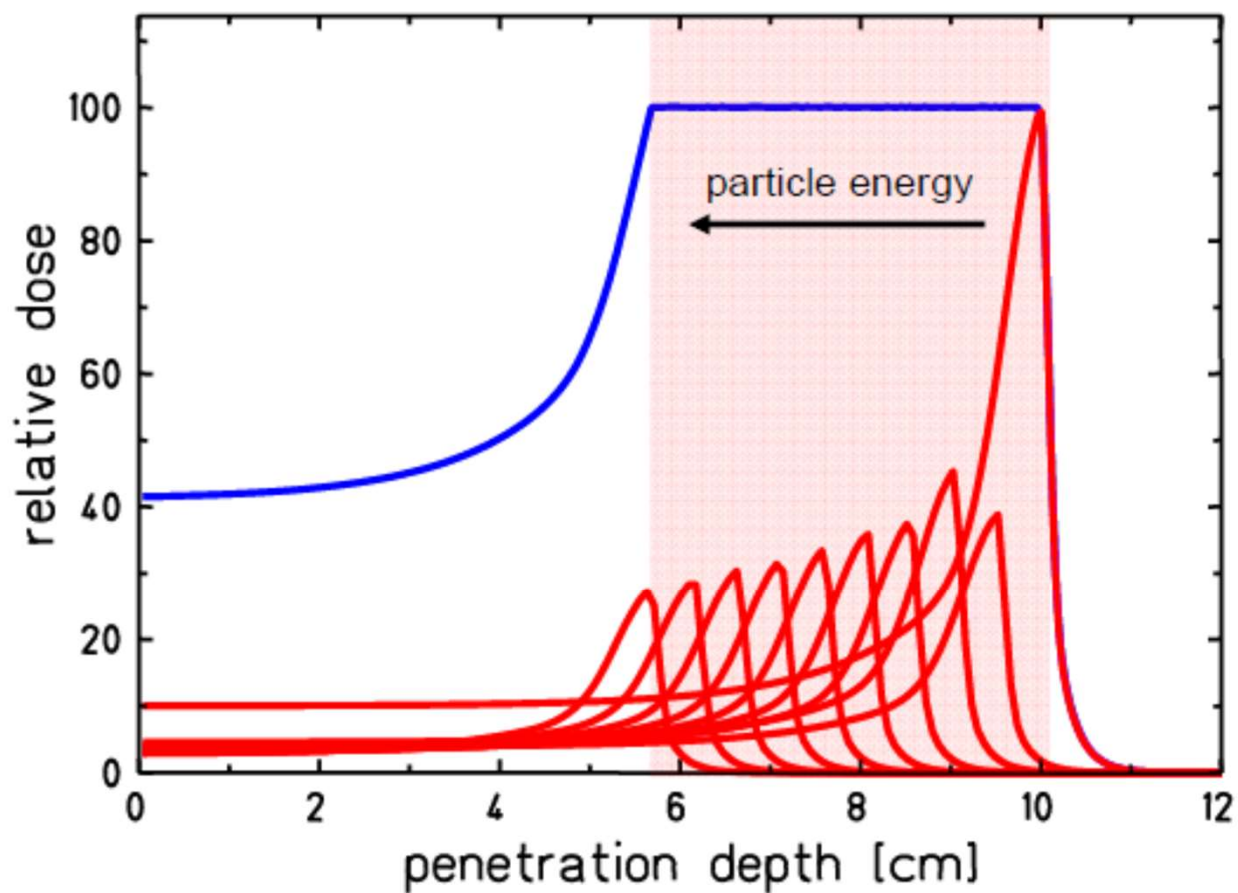




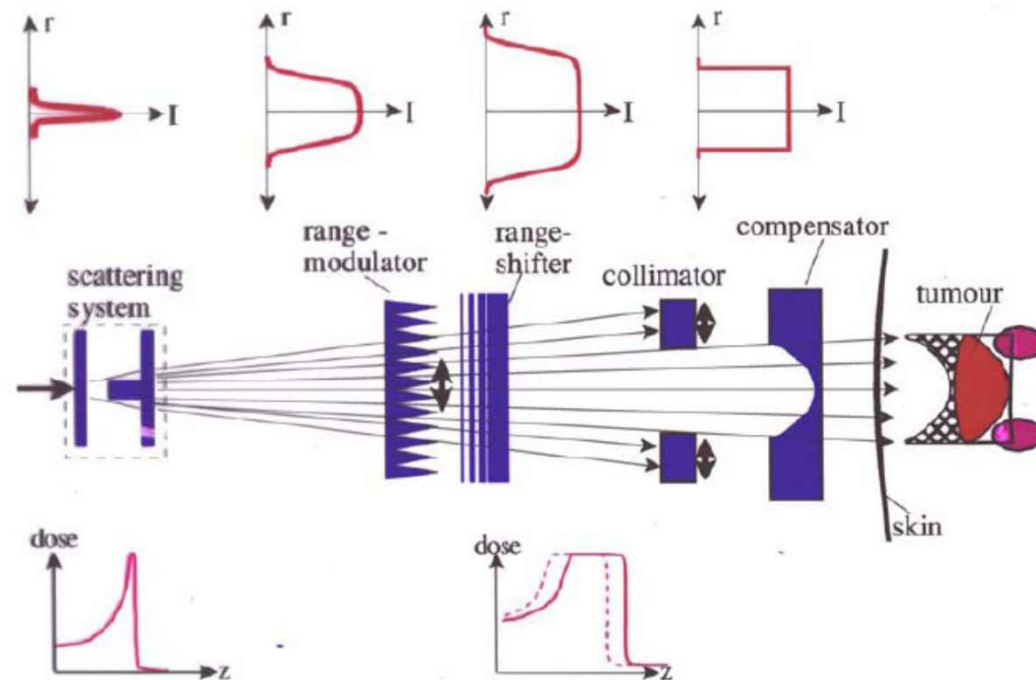
Application for therapy

- how can we irradiate a tumor volume with a particle beam?
 - lateral extension
 - longitudinal (depth) extension
- passive beam shaping
- active scanning

Longitudinal - Spread out Bragg peak



Beam shaping with passive devices



- have to be manufactured for each patient field
- fixed extension and extended Bragg peak
- missing proximal conformation

Hardware for passive beam shaping

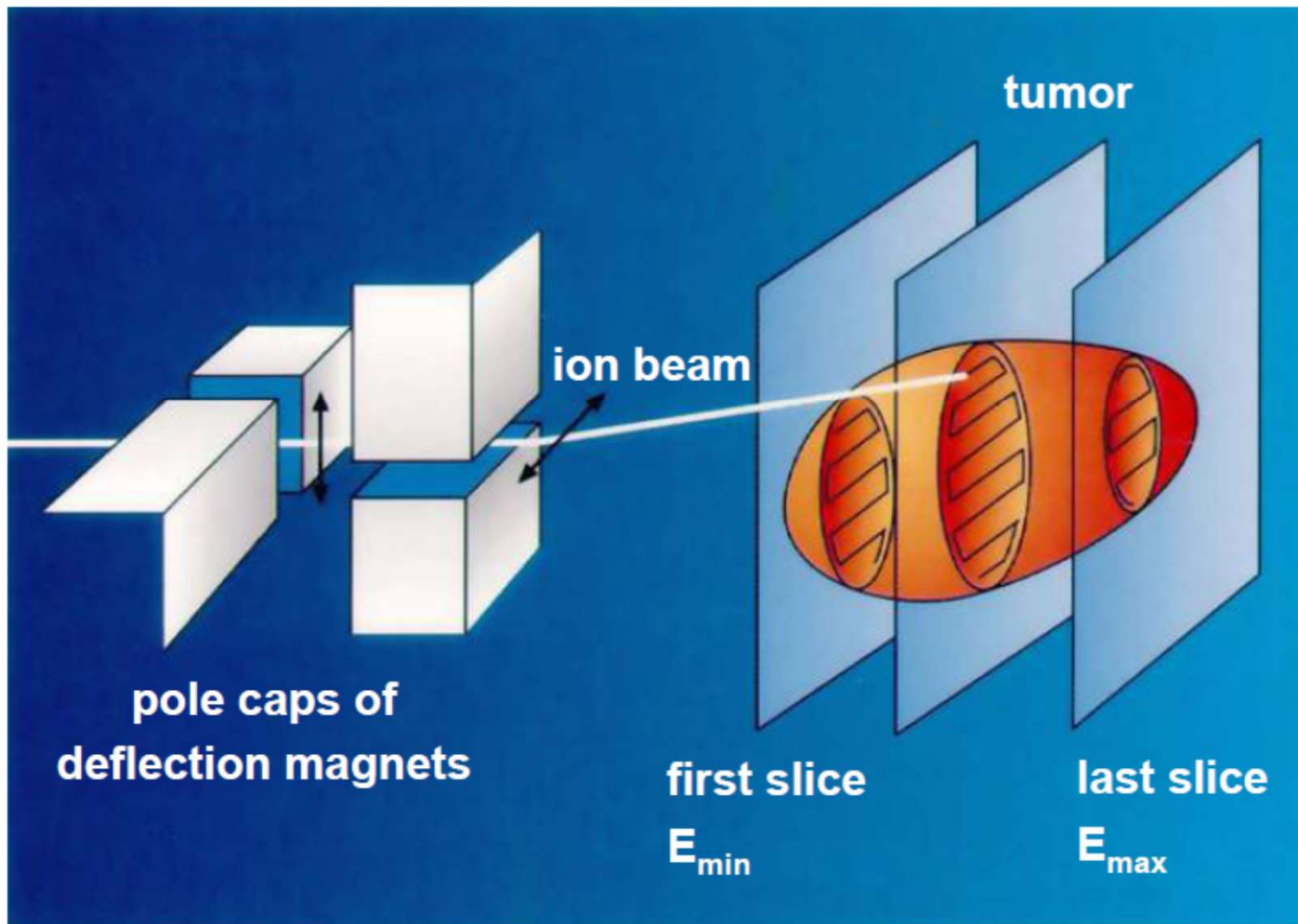


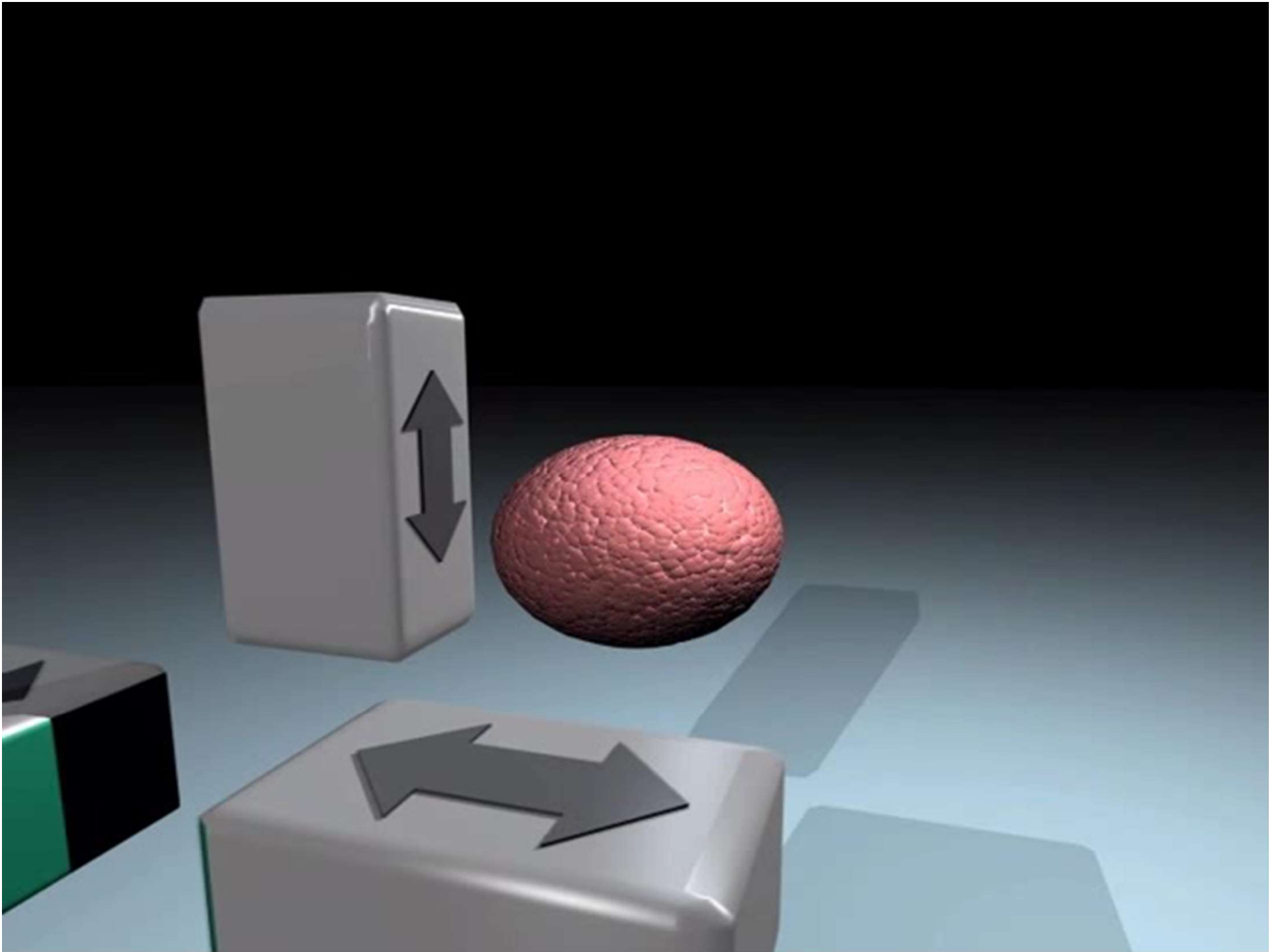
Collimator



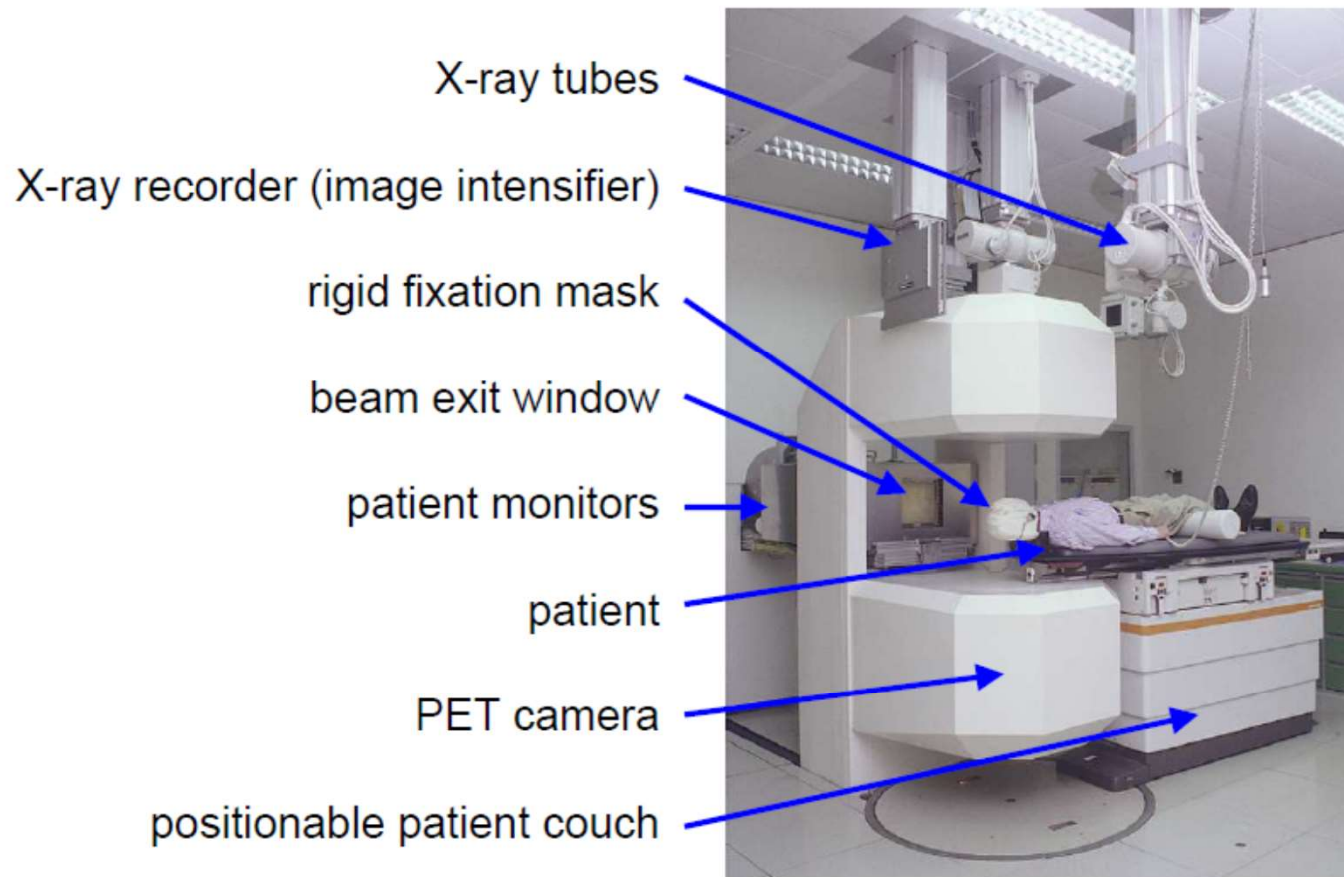
Compensator

Active scanning - Rasterscan system





Experimental Therapy Room: Cave M



Detectors in particle therapy

Detectors used to monitor the beam



Large area Parallel plate Ionization Chamber

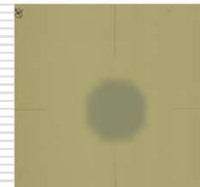
Used to count the beam particles

Multiwire Ionization chambers
Used to check the beam position during the irradiation

Detectors used to verify the irradiation



Small volume ionization chambers used to measure the dose at the target position.



GadChromic Films
Visualization the irradiation field.
Can measure the dose but not very accurate.

Typical Set up and instrumentation for particle therapy application

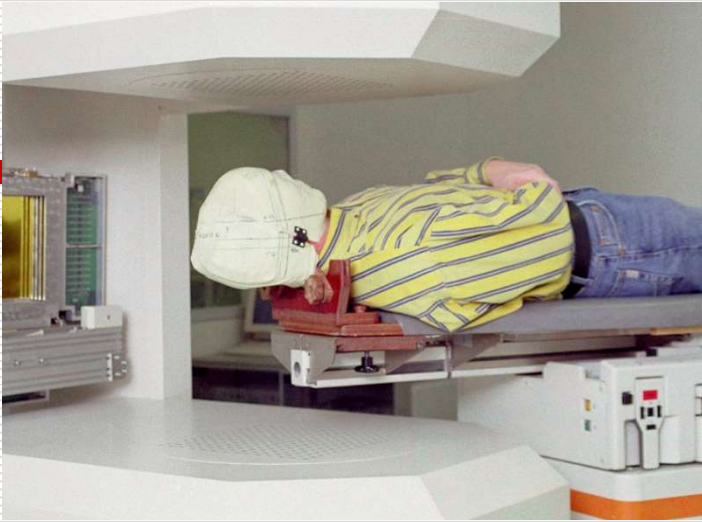
Water phantom
you can equip it with different detectors and measure in water



Measure Bragg the depth dose distribution in water



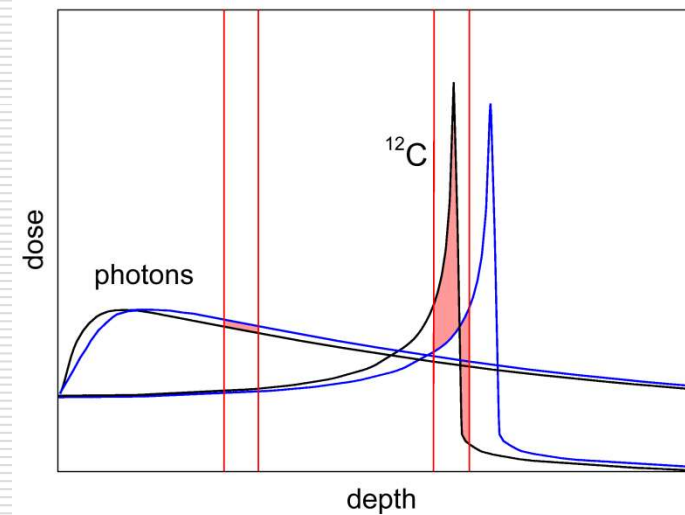
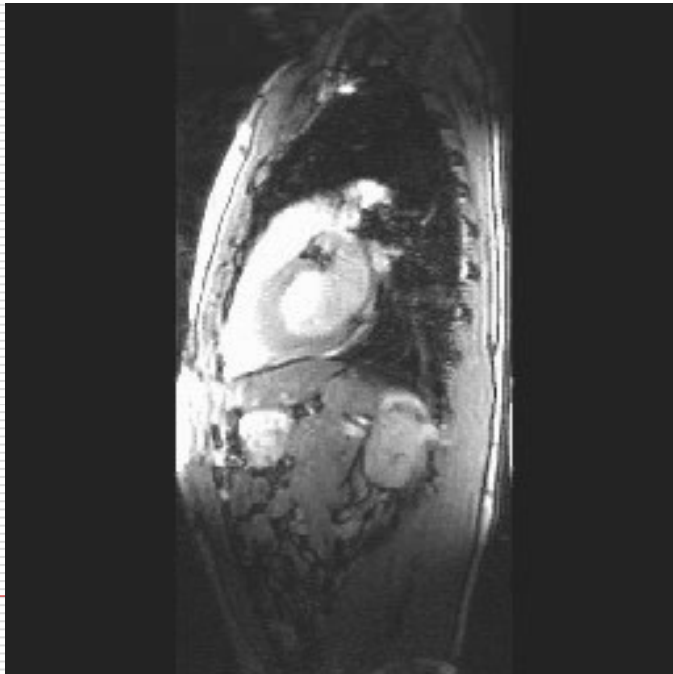
Range uncertainty



precision of stereotactic fixation:

1mm in the head to

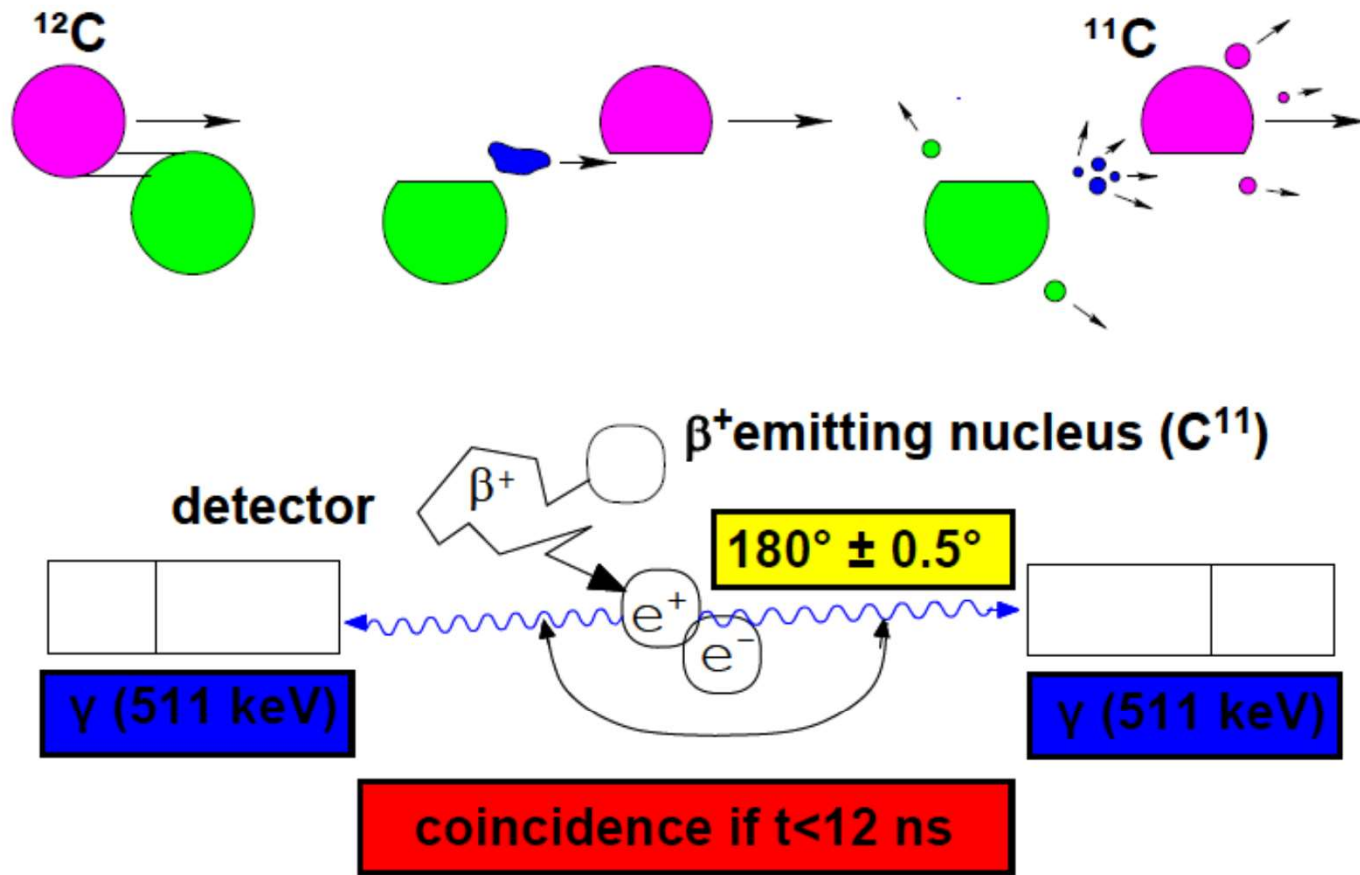
3mm in the pelvic region

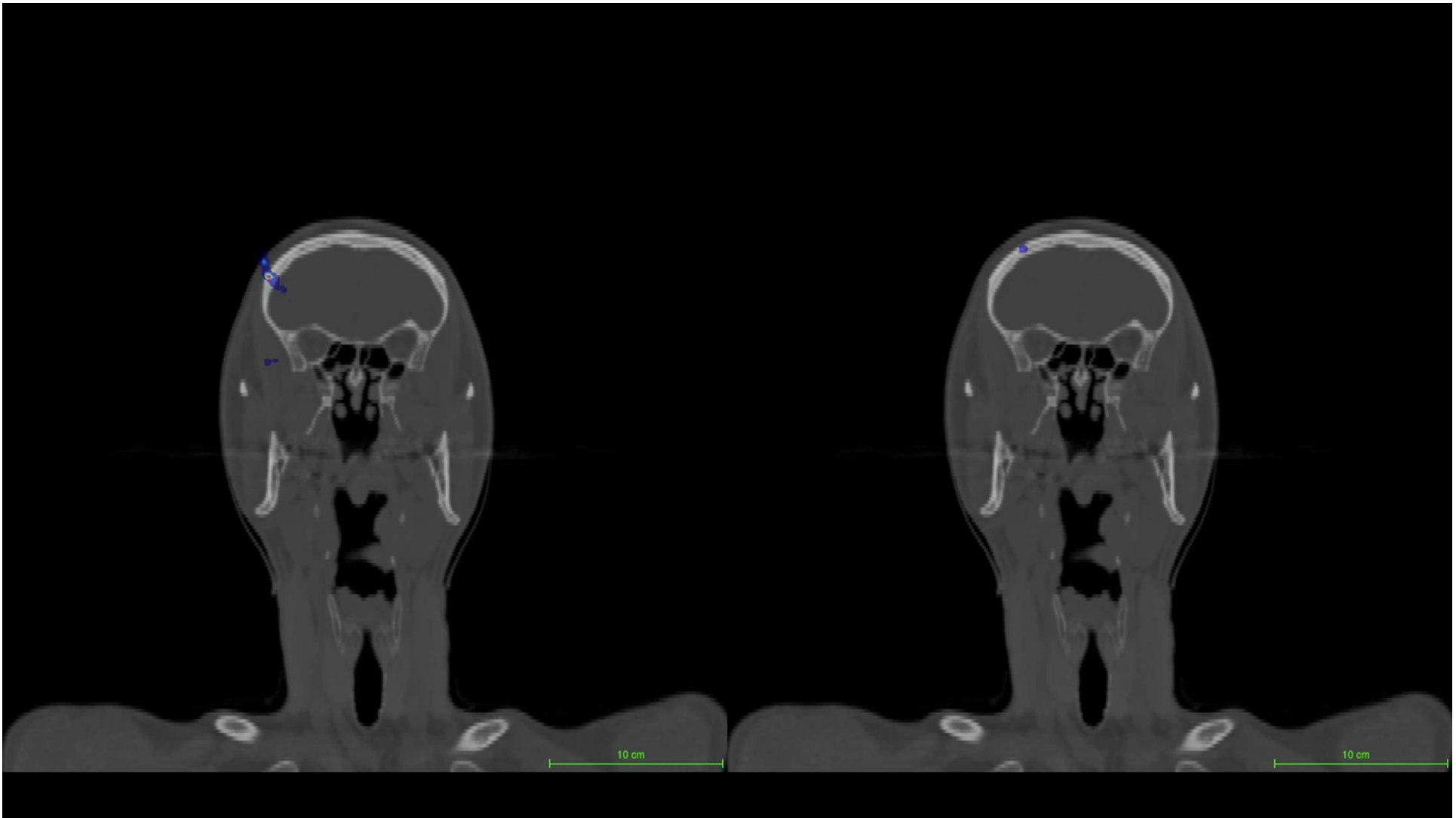


for ions: variations in radiological path length extremely important

not feasible for regions with internal motion
(e.g. respiration in thorax and abdomen)

Positron Emission Tomography (PET)





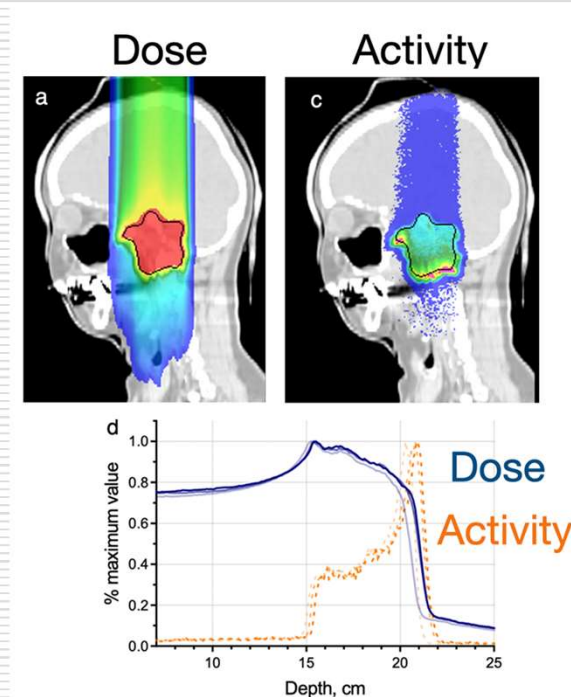
Tackling range uncertainties in particle therapy

Online range monitoring is one of the bigger challenges in particle therapy

PET (Positron emitter tomography) is one of the most promising techniques for Charged particles.

RIBs (e.g. $^{10,11}\text{C}$) give a PET signal at the Bragg peak position.

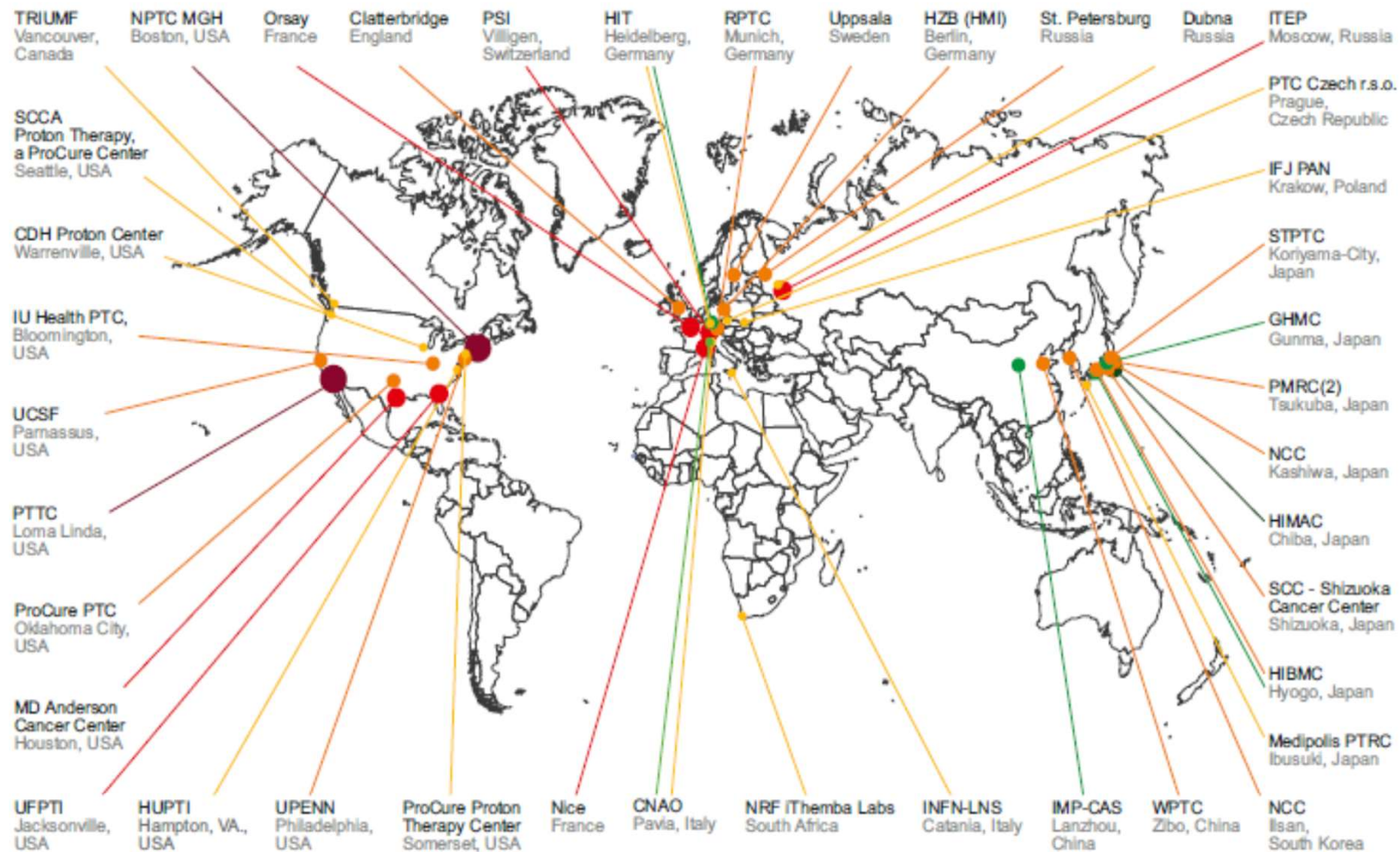
Improved count rate and dose activity match compared to the stable ions



Sokol et al. Sci Rep 2022



Biomedical Applications of Radioactive ion Beams (PI Marco Durante)



NuPECC report „Nuclear Physics in Medicine“, 2014



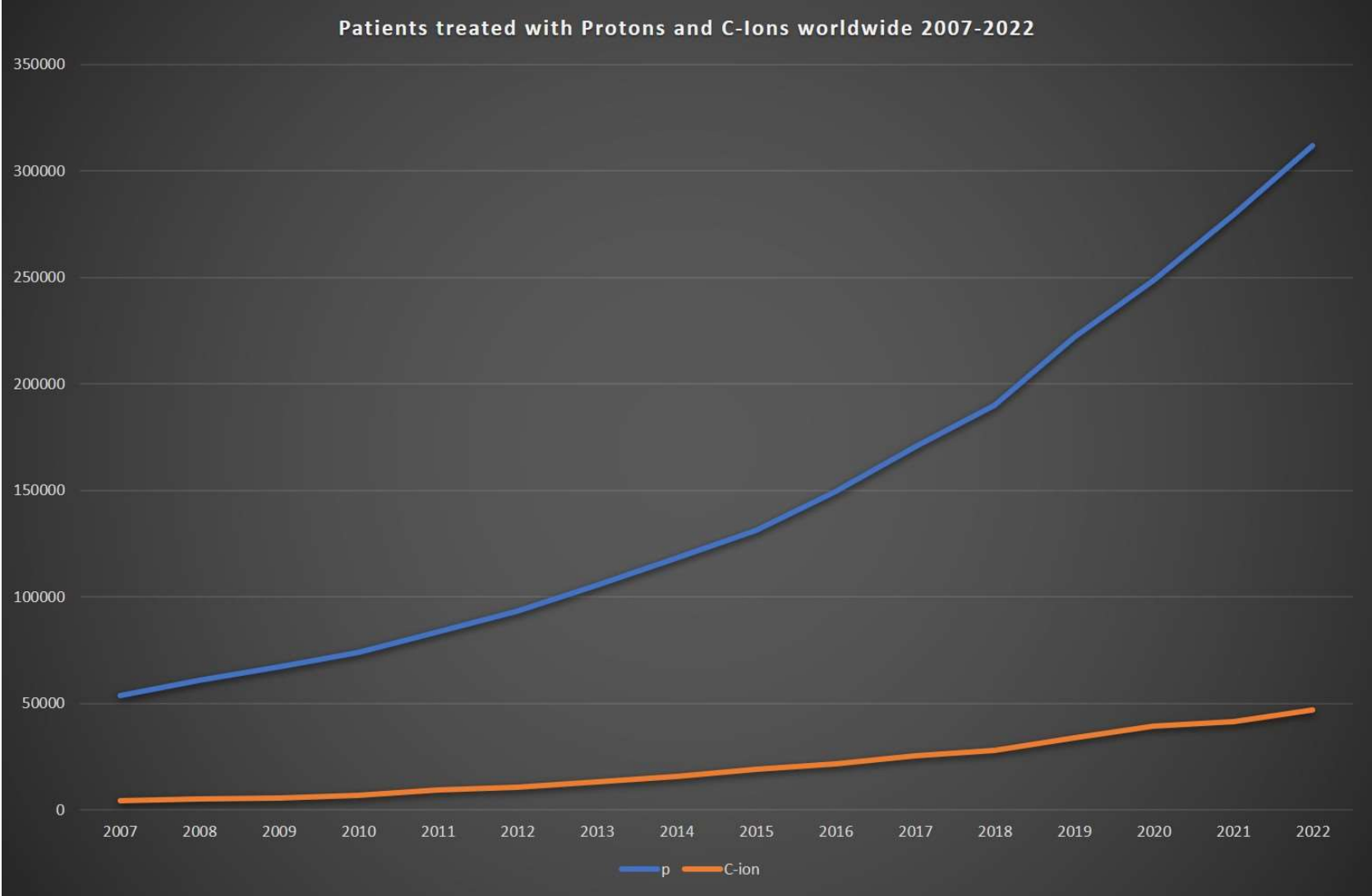
Existing centers (March 2024): >100 proton/13 heavy ion centers

Under construction: 28 proton/ 5 heavy ion centers

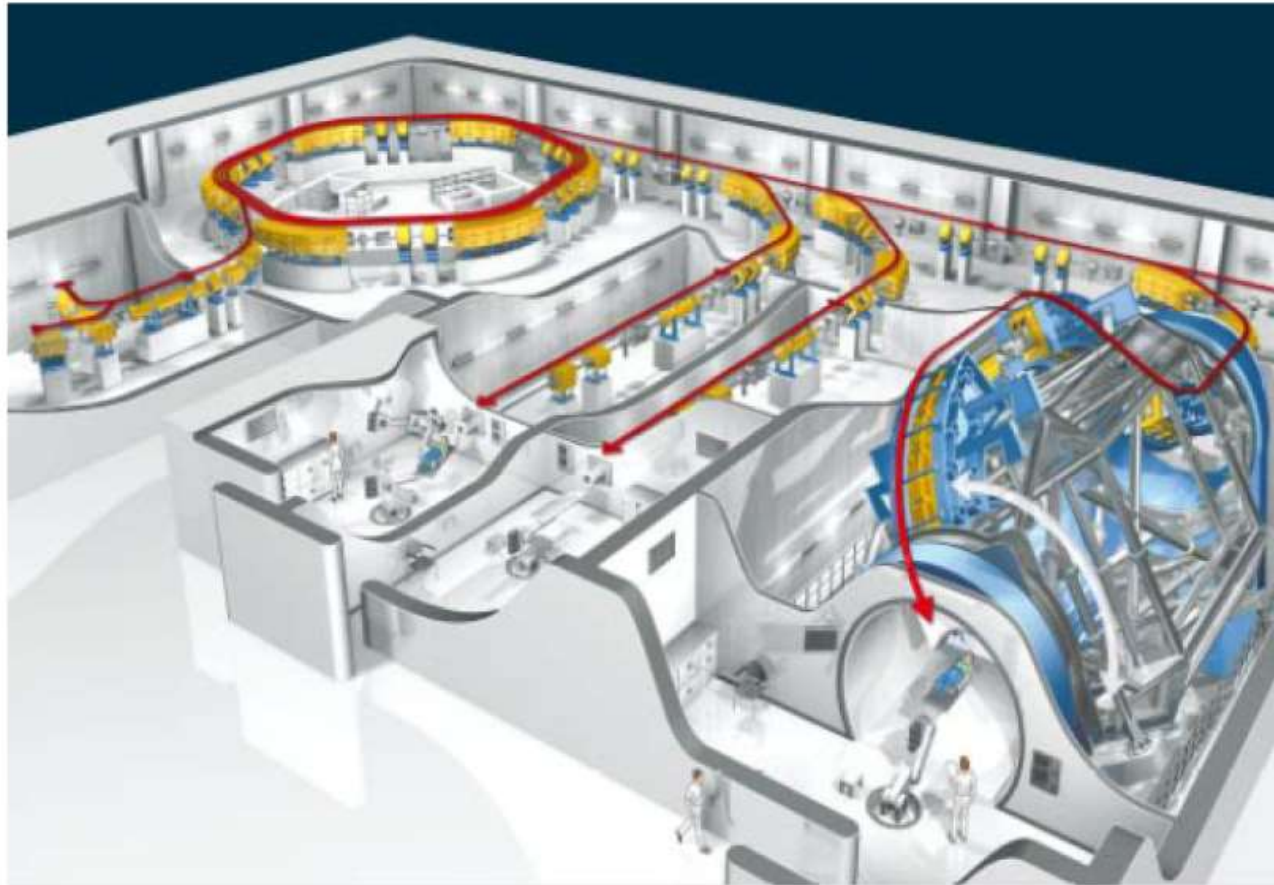
Mayo Clinics in USA 1 heavy ion center by 2025+

10+ proton centers to be built in Spain (by 2026+)

Patients treated with particle therapy worldwide (as of 2022)



Heidelberg Ion Beam Therapy



Radiation Biophysics

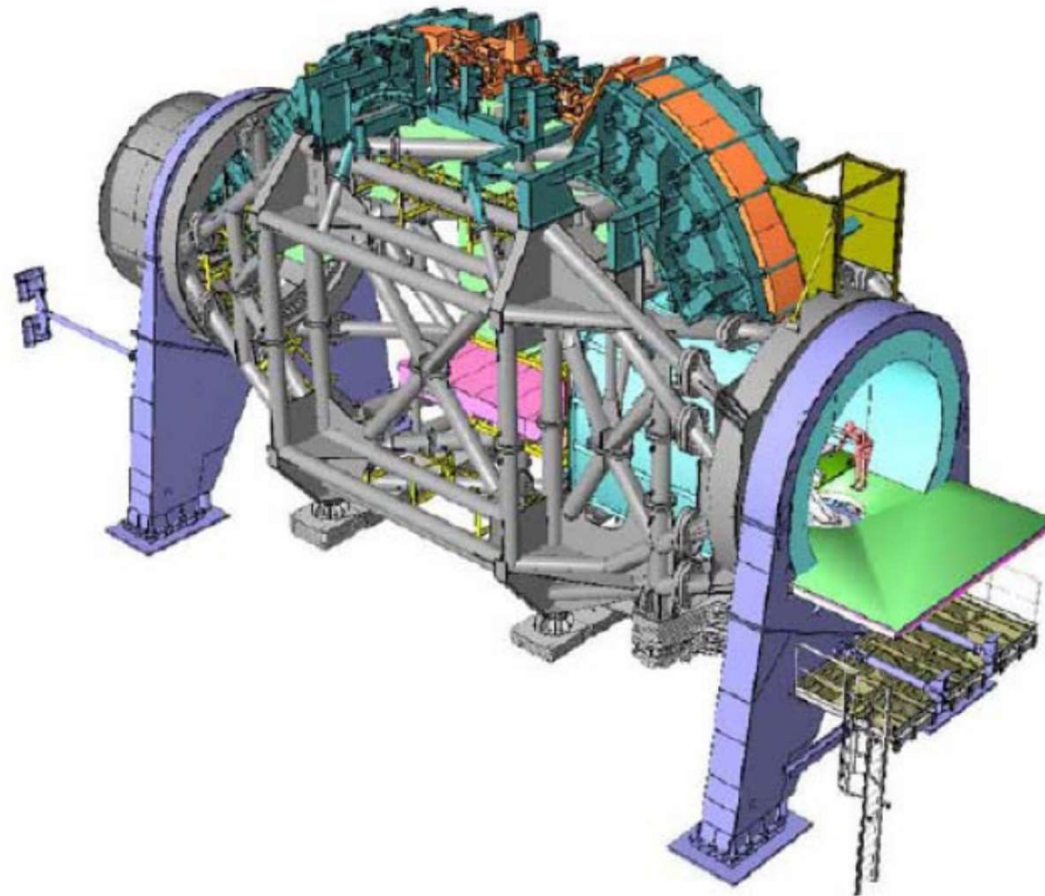
Carbon beam therapy



1st patient treated: November 2009



Gantry @ HIT



total weight: 670t

length: 22m

diameter: 14m

precision at

isocenter: ~1mm

CNAO: National Centre for Oncological Hadrontherapy Pavia, Italy



MedAustron- milestones and status



Milestones	Dates
Start of the construction	02/2011
Building ready	10/2012
1st beam in treatment room	06/2014
Horizontal beam commissioned	06/2015
Start of clinical operation	12/2015
Full clinical operation	2020

Particle therapy clinics

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

Proton Beam Therapy for Breast Cancer

About 200,000 new cases per year in U.S

Most affected at the most productive part of life

Most patients survive (> 2 millions survivors)

Most diagnosed at early stage

Majority receives radiation

“Horror” stories from side effects of radiation
leads many women to choose mastectomy
over BCT

Distribution of Coronary Artery Stenosis After Radiation for Breast Cancer

Nilsson, C. Blomqvist et al. JCO 30(4) 380-386; 2012



UPPSALA
UNIVERSITET

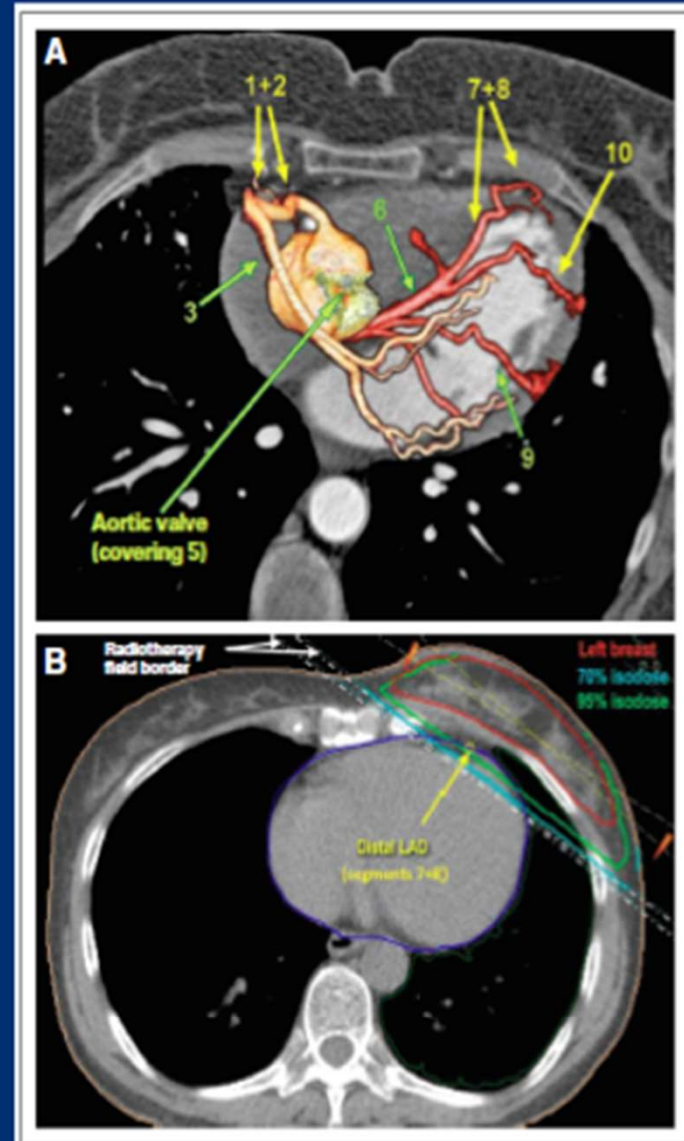
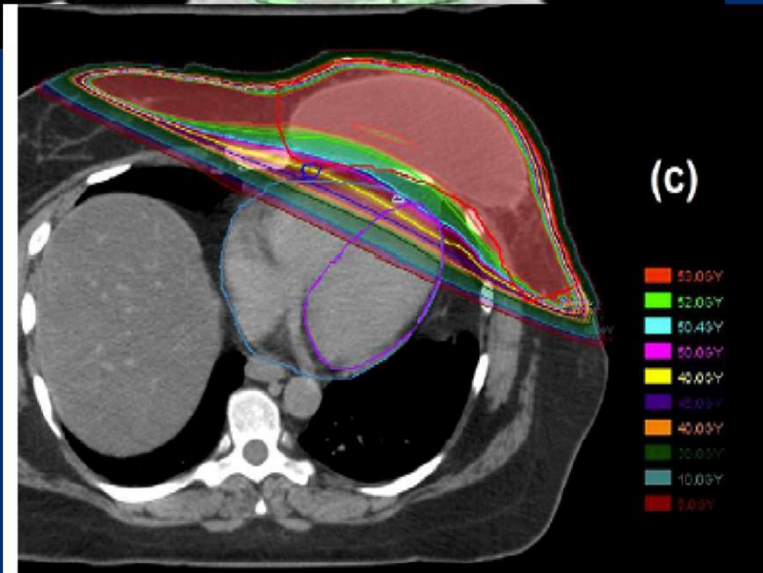
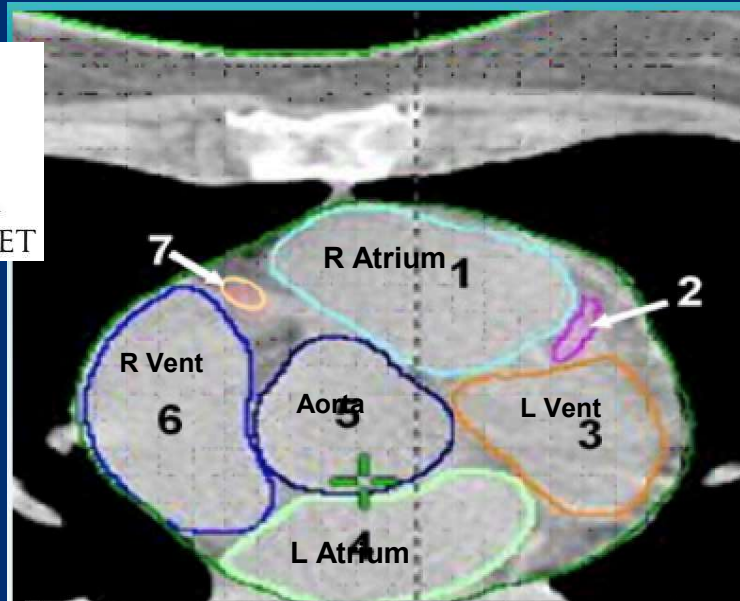
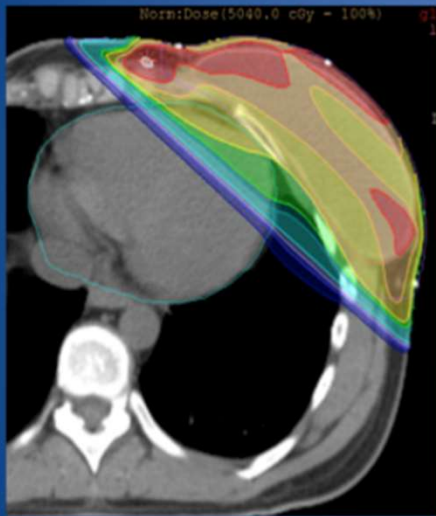


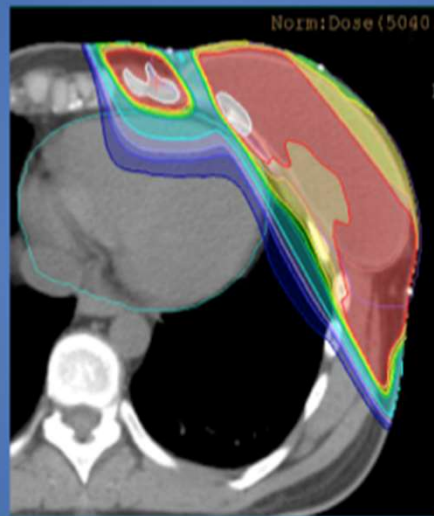
Fig 2. (A) Coronary angiogram superimposed on computed tomography (CT) of heart illustrating anatomy of coronary arteries with branches of right coronary artery (orange) and left circumflex and left anterior descending (LAD) arteries (red); numbered arrows indicate segments. (B) CT dose-planned left tangential breast irradiation showing distal LAD (yellow circle) and radiation fields.

Post-mastectomy radiotherapy for left-side breast with or without immediate reconstruction

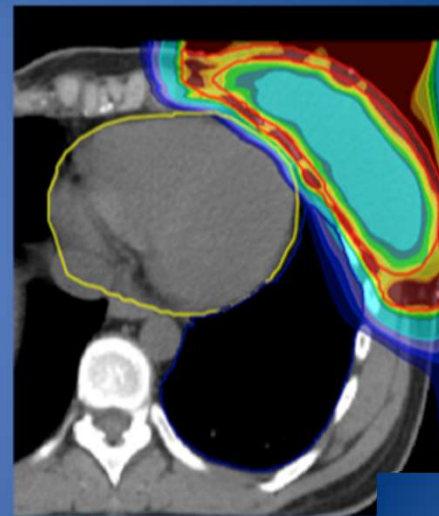
Protons with implants



Photons



Photon/Electron



Proton(IMPT)



Bilateral Nipple Sparing Mastectomy with Implants



End of RT

4 weeks after RT

8 weeks after RT

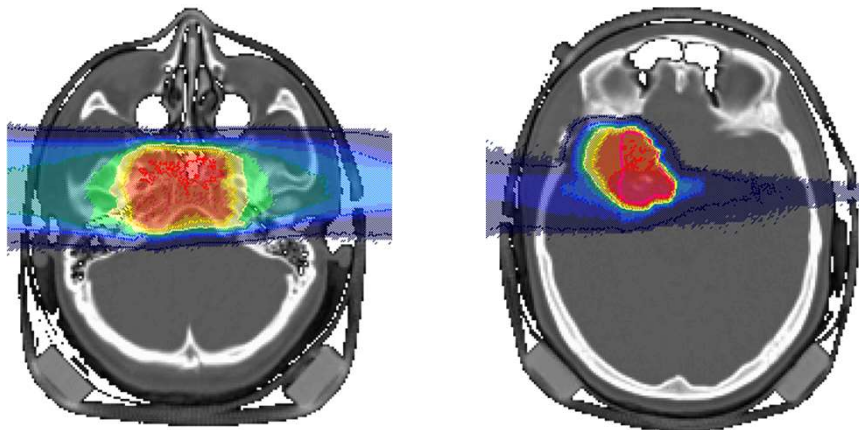
MacDonald et al, *Int J Rad Onc Bio Phys*, 1-7, 2013

Clinical results

- Patient: 23 years old
- Diagnosis: Chondrosarcoma
- Subtotal surgery
- Postoperative radiation therapy: 60 Gye
- 3 fields with 20 fraction

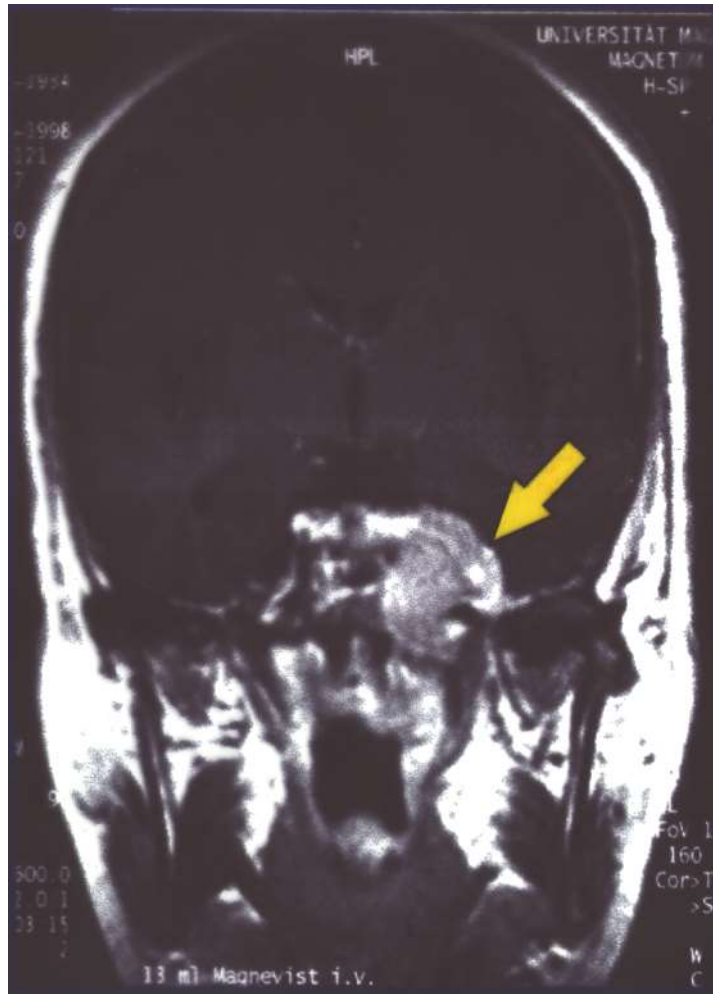


vor Bestrahlung

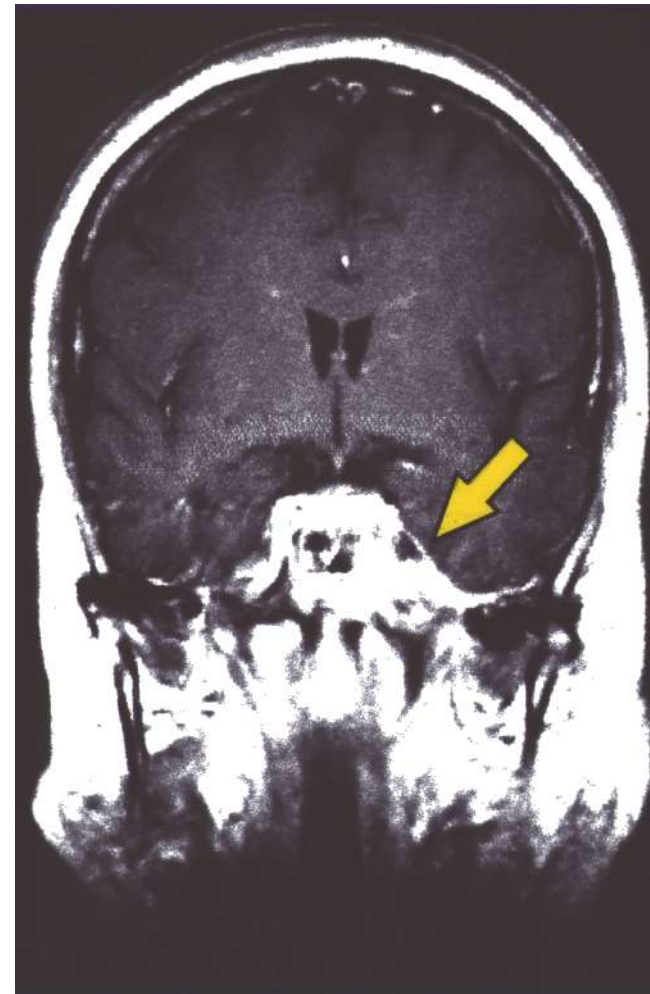


6 Weeks after carbon treatment with a dose of 60 Gye

Adenocystic Carcinoma combined photons and C12-Boost

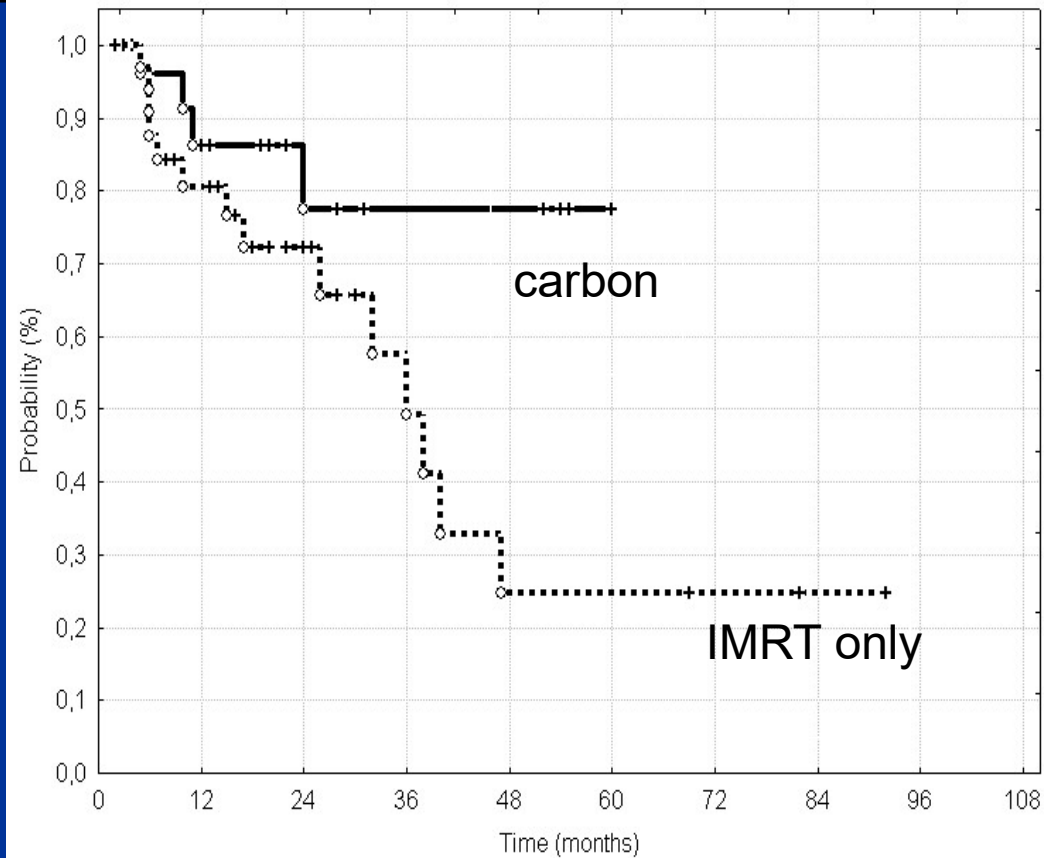


Prior RT



6 weeks after RT

Adenoidcystic carcinomas: Photon-IMRT with and without carbon boost

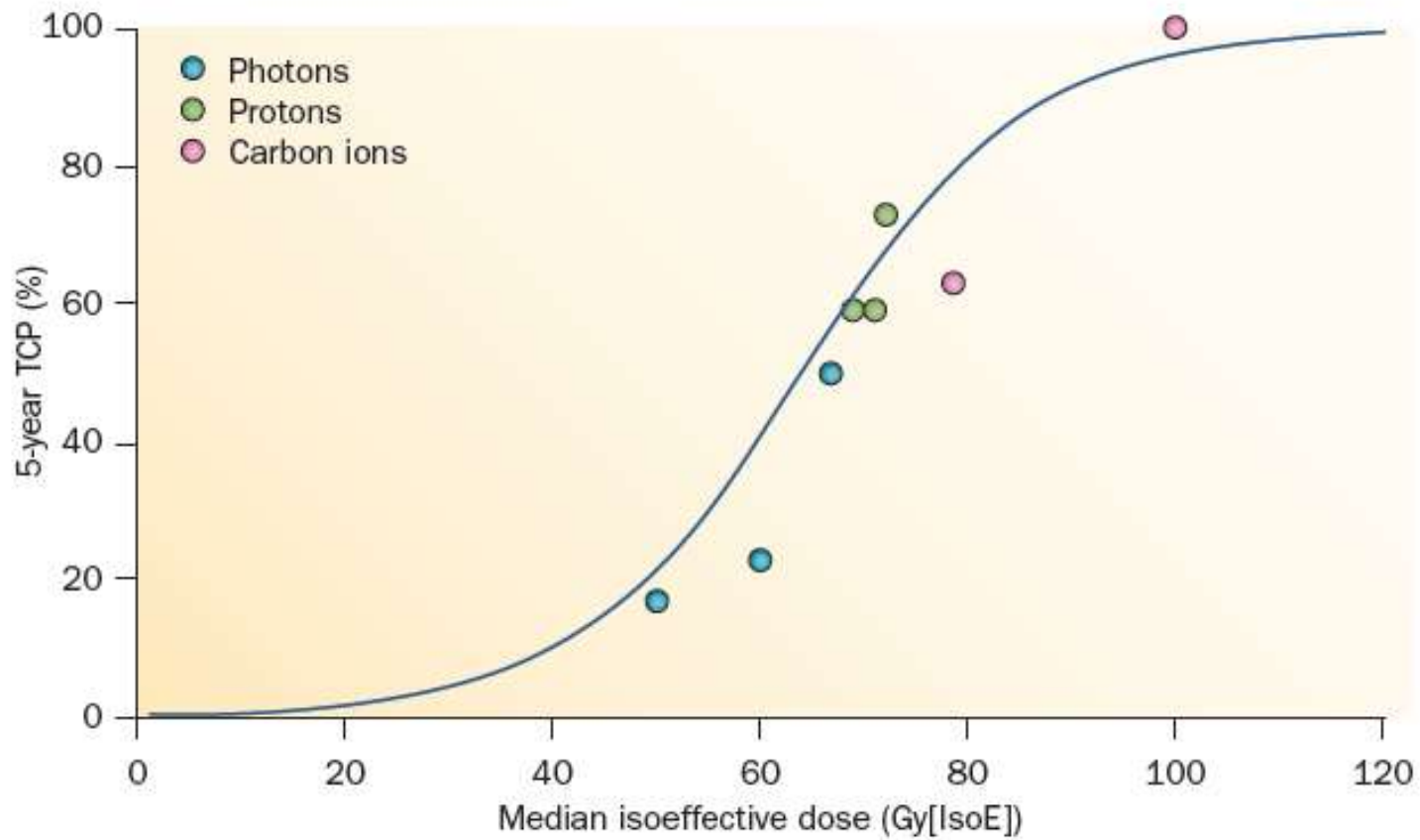


Tumor control

[Schulz-Ertner, Cancer 2005]

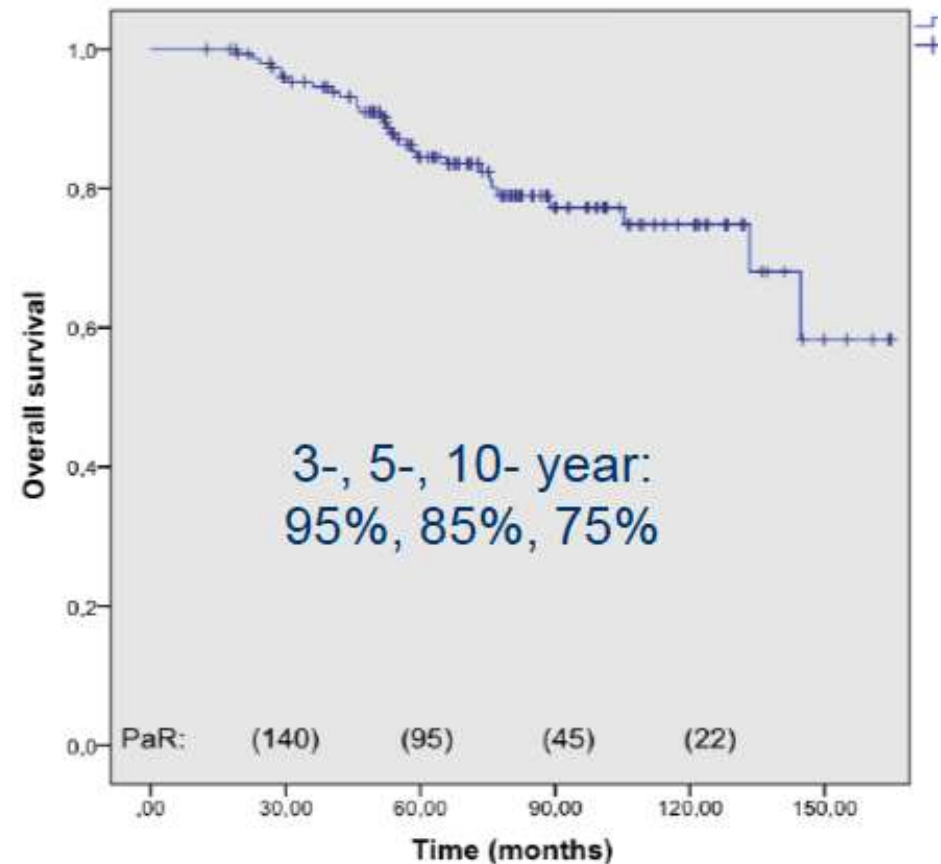
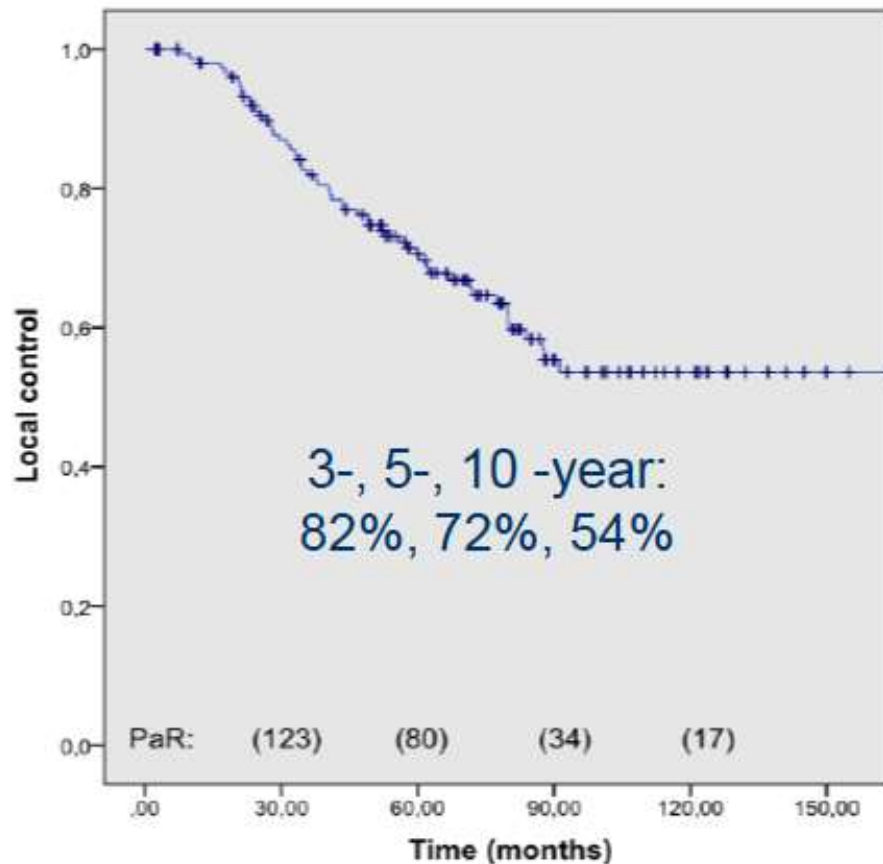


Skull-base chordoma



Loeffler & Durante, *Nat. Rev. Clin. Oncol.* 2013

Long-term results of the chordoma patients treated at GSI



Universitätsklinikum Heidelberg | Heidelberger Ionenstrahl Therapiezentrum



courtesy of Jürgen Debus



HEIDELBERG
UNIVERSITY
HOSPITAL



The NIRS experience



Clinical experiences have demonstrated that C-ion RT is effective in such regions as the **head and neck, skull base, lung, liver, prostate, bone and soft tissues, and pelvic recurrence of rectal cancer**, as well as for histological types including **adenocarcinoma, adenoid cystic carcinoma, malignant melanoma and various types of sarcomas**, against which photon therapy are less effective. Furthermore, when compared with photon and proton RT, **a significant reduction of overall treatment time and fractions** has been accomplished without enhancing toxicities.

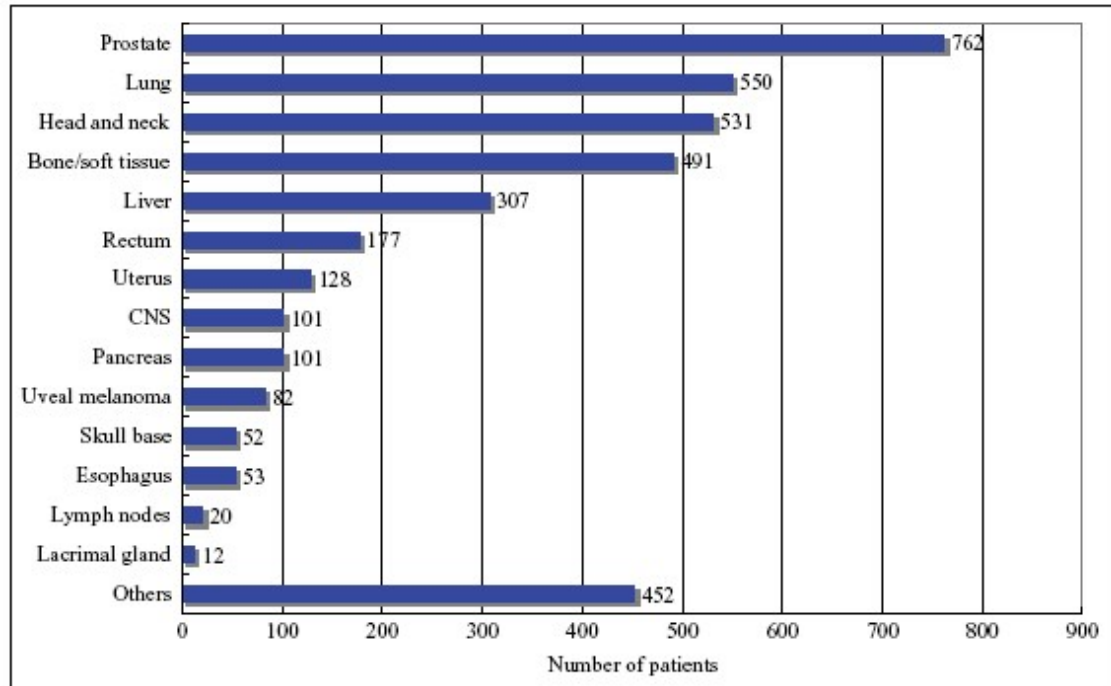
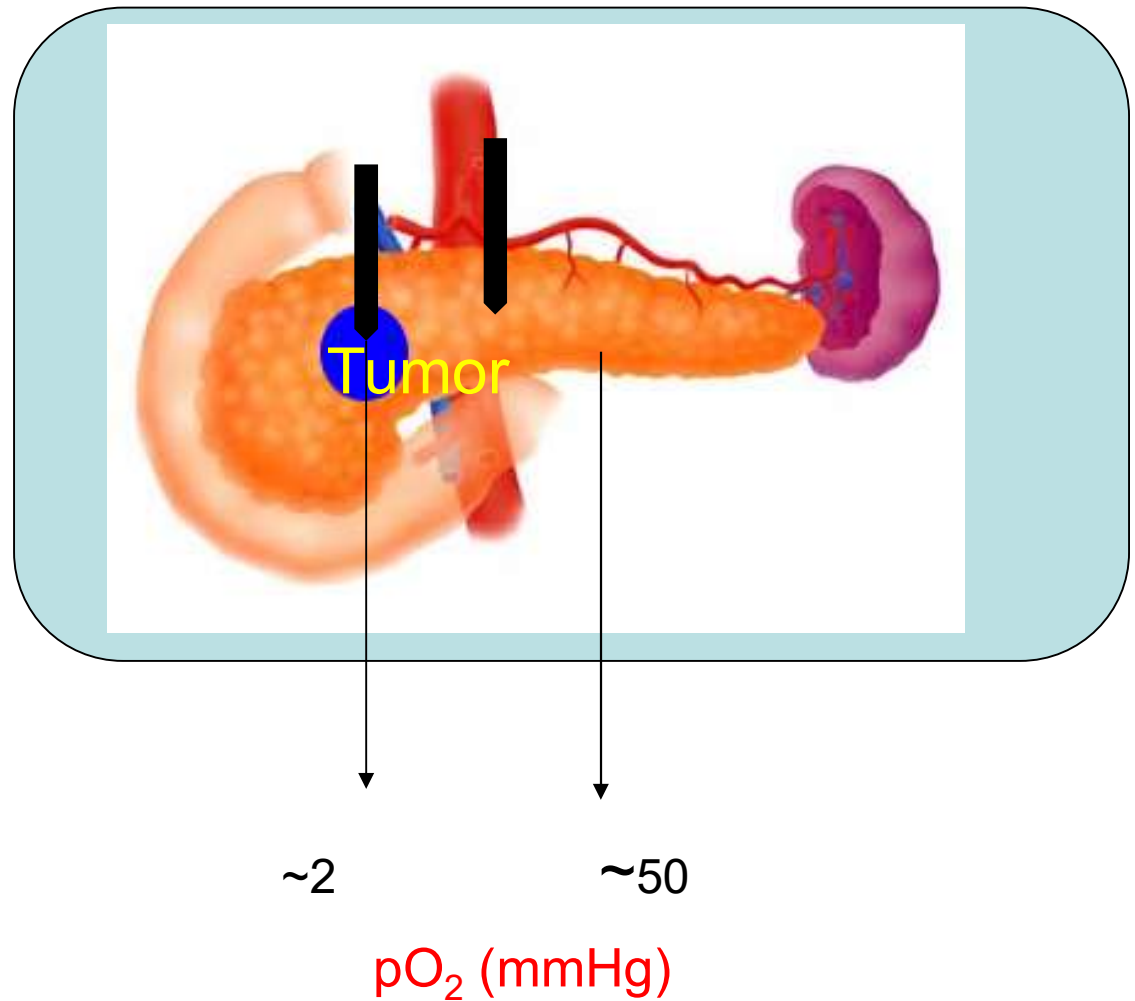


Figure 1. Number of patients, with a variety of tumors enrolled at NIRS for C-ion RT.

[NIRS annual report 2008, Tsujii et al.](#)

A recent application: pancreas cancer

- Pancreatic cancer ranks as the fifth leading cause of cancer related death in the world.
- 95% are adenocarcinomas
- Approximately 34,000 patients die from pancreatic cancer per year in USA.
- The 5 year survival rate of pancreatic cancer patients is no more than 10% and its average survival time after diagnosis is only 9 months.
- Even after curative resection, 5 year survival rate is only 12%.

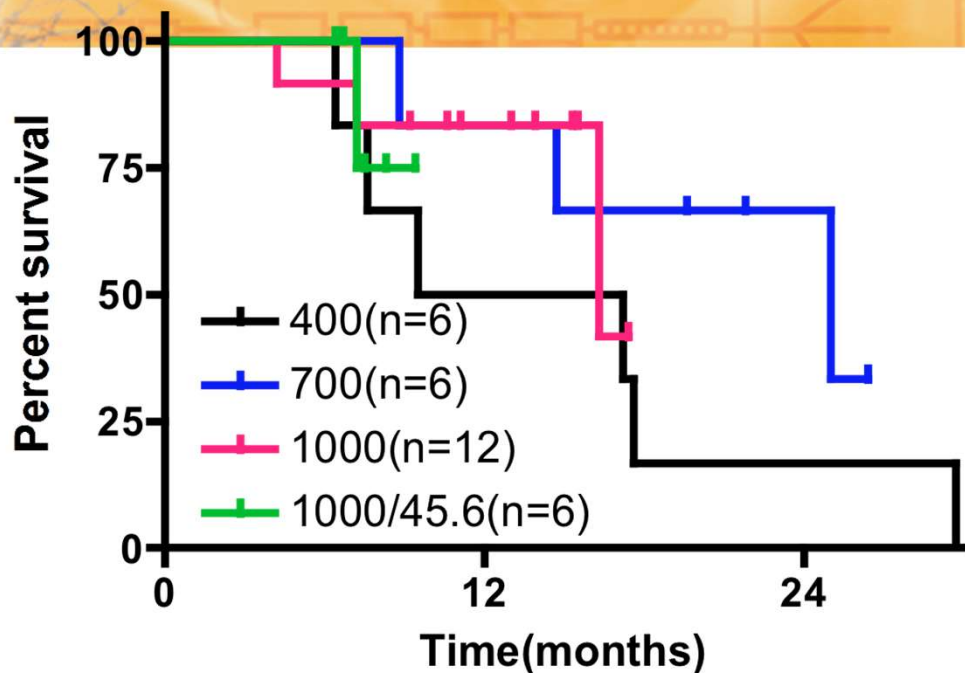




Survival Rates

Courtesy of Dr. Shigeru Yamada, NIRS

Combination of Gemcitabine and Carbon-ion therapy



	1y-OS
43.2GyE+400mg/m ²	50%
43.2GyE+700mg/m ²	83%
43.2GyE+1000mg/m ²	83%
45.6GyE+1000mg/m ²	----

	Year	n	Treatment	Survival		MST(m)
				12m	24m	
ECOG ¹⁾	2008	34	GEM+RT(50.4 Gy)	50%	12%	11.0
		37	GEM	32%	4%	9.2
NIRS		30	GEM+CIRT	74%	44%	17.4



1) ASCO2008 Patric J. Loehrer Senior

Selected research topics at GSI



New ions

Cancer stem cells

Hypofractionation

FLASH

Combined treatments

Radiogenomics

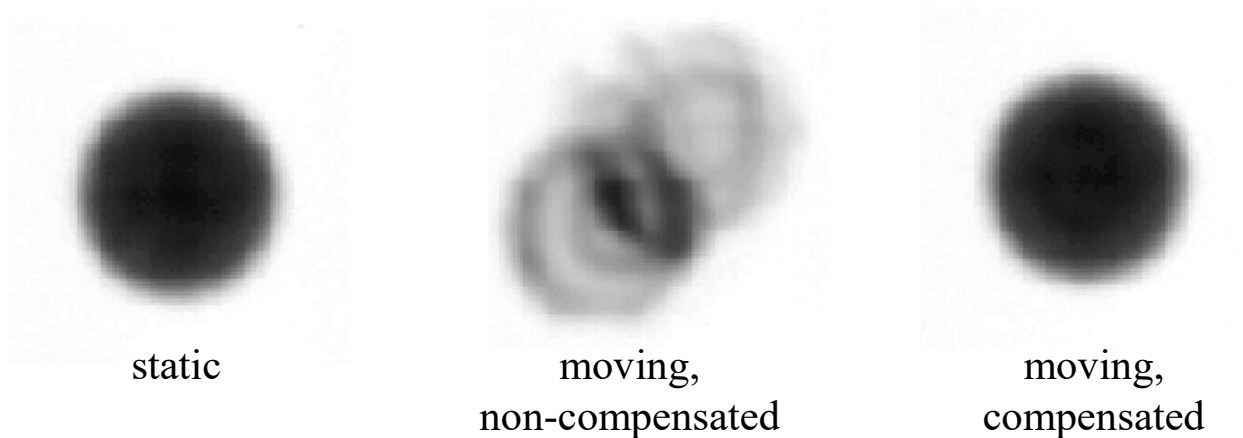
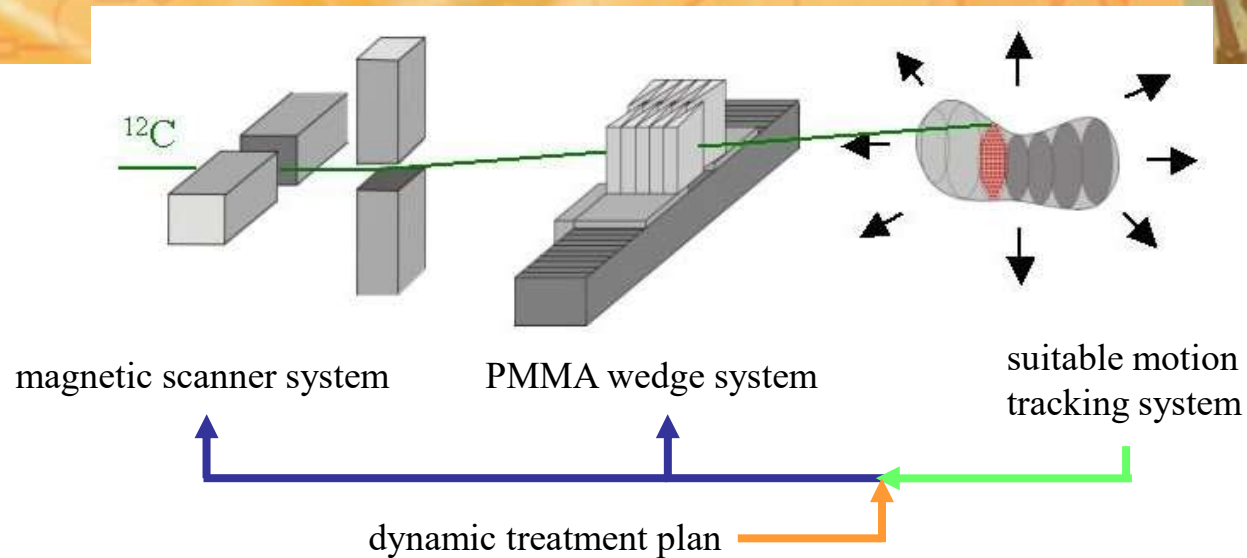
Biomarkers

Intra-tumoral
heterogeneity (hypoxia)

Noncancer diseases

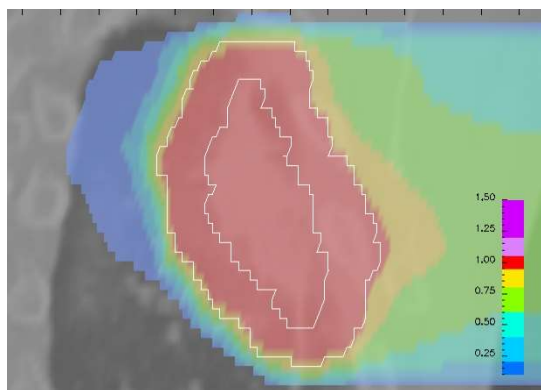
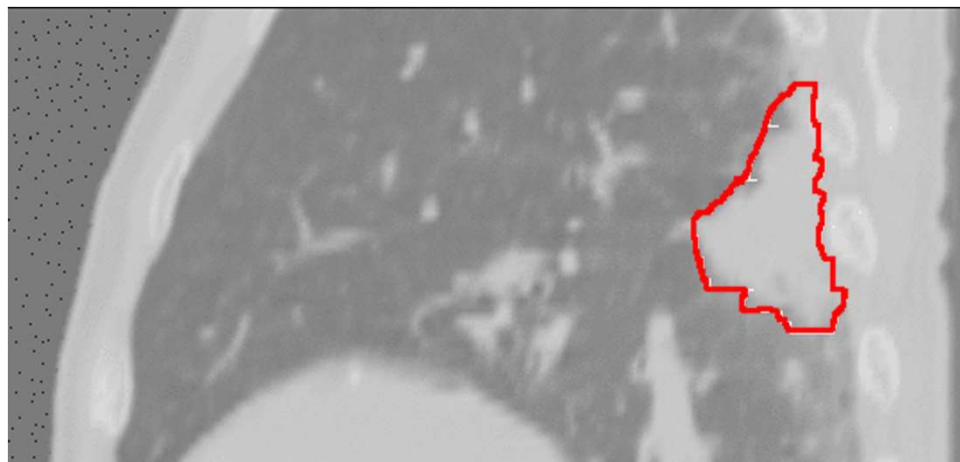
Second cancers

3D online motion compensation (3D-OMC)

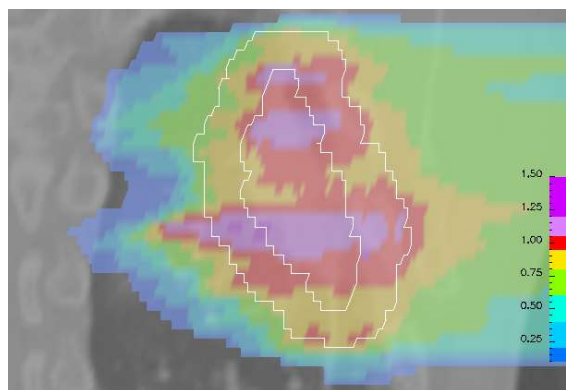


➤ real-time, highest precision

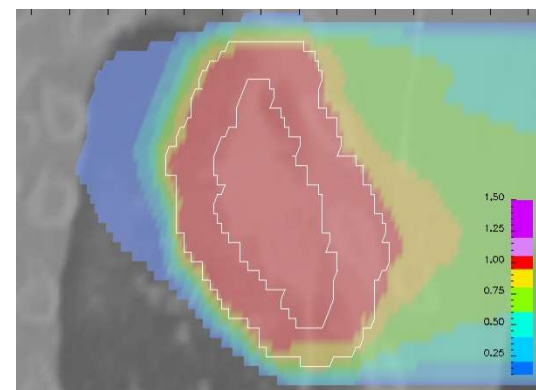
Influence of target motion



static



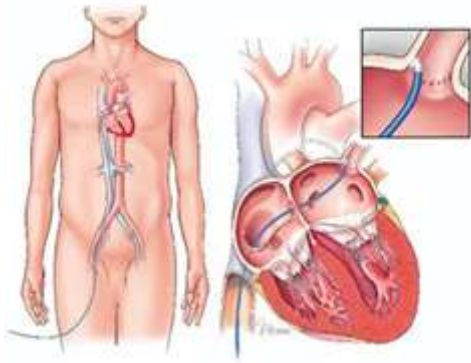
not compensated



compensated

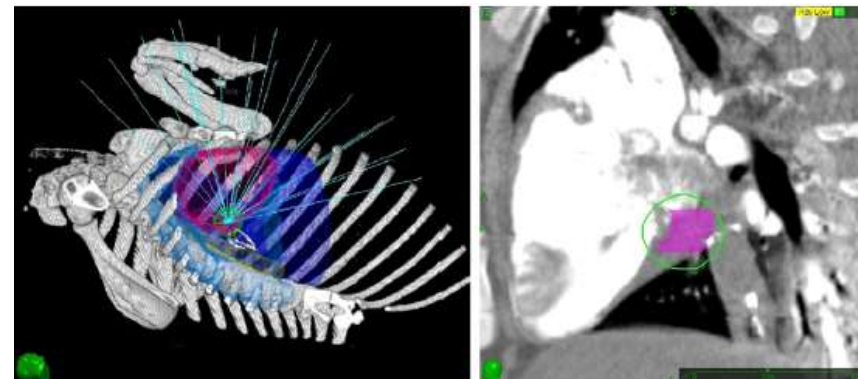
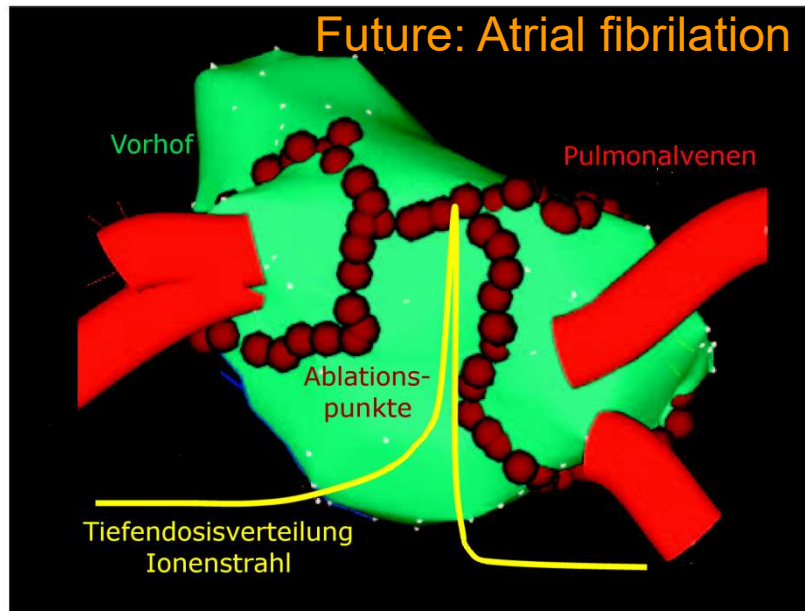
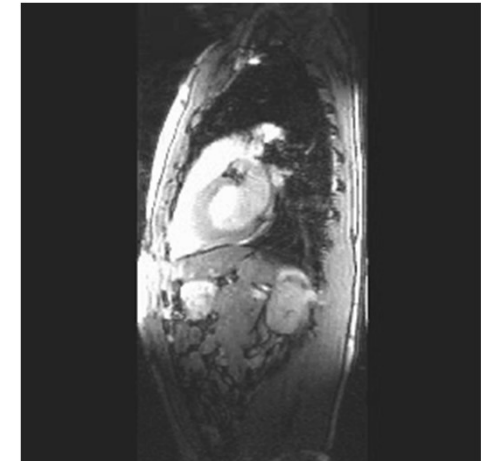
Bert & Durante, Phys. Med. Biol. 2011 $T=6.0s$, $\Phi=270^\circ$

Treatment of noncancer diseases: cardiac arrhythmias?



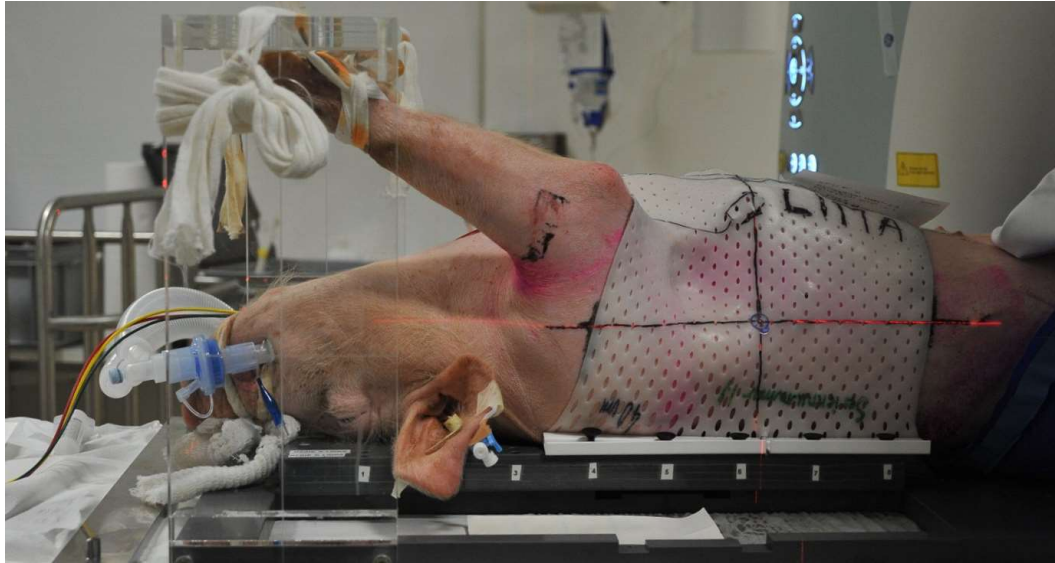
- Atrial fibrillation affects about 5% of middle-aged population and is associated with high risk of stroke and death

- Catheter ablation of pulmonary vein is the current non-pharmacological solution (75% of success, severe complications in 6% of the patients)



- CyberHeart: cardiac lesion induced by a Cyberknife (*Heart Rhythm.*, June 2010)

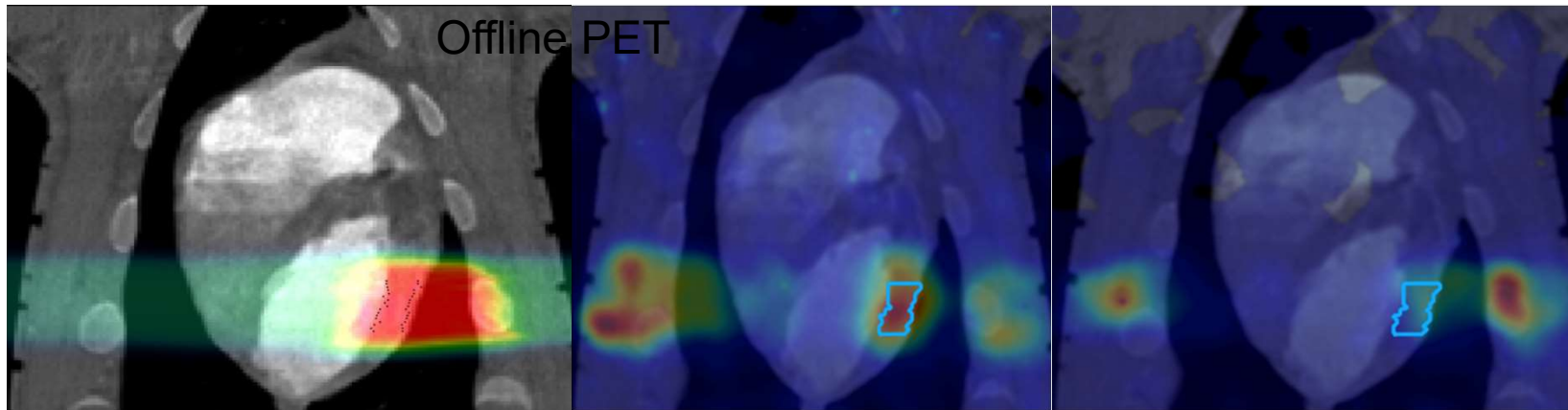
Noninvasive treatment of ventricular fibrillation by C-ions



Planned dose

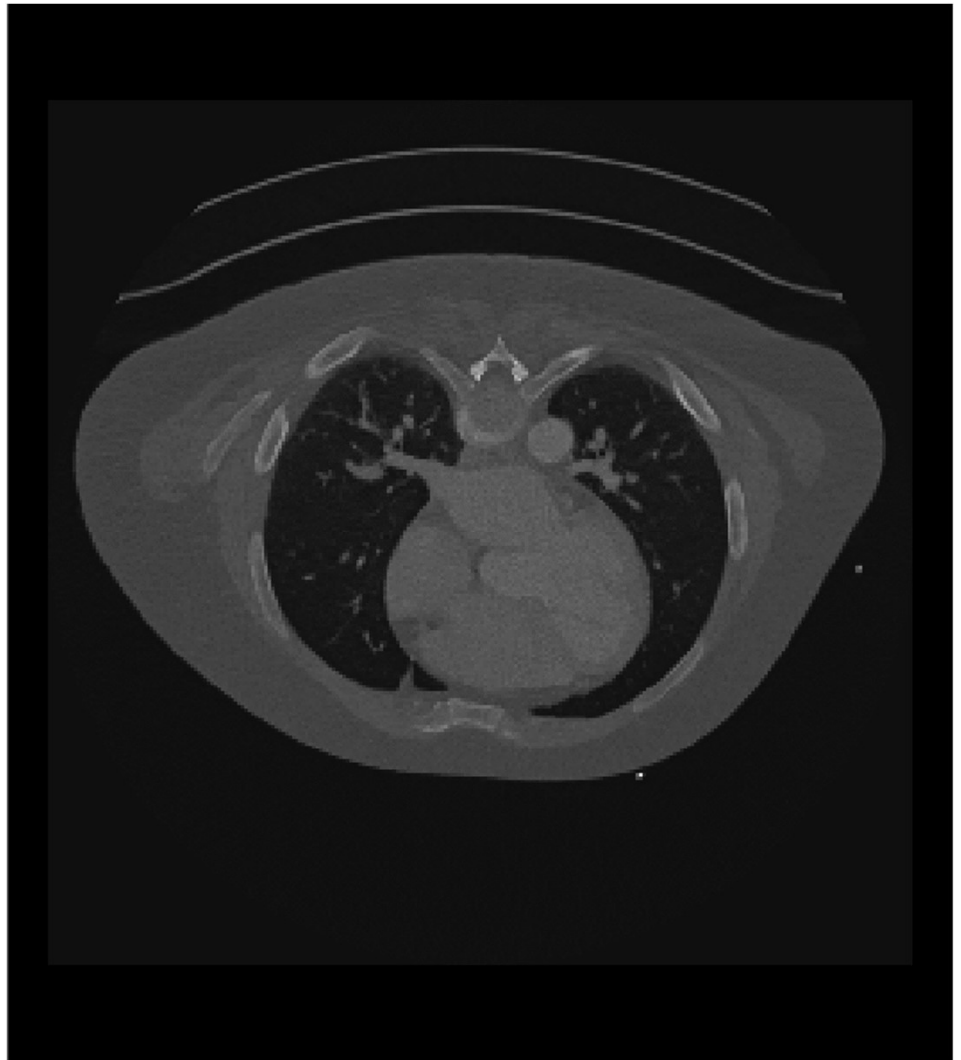
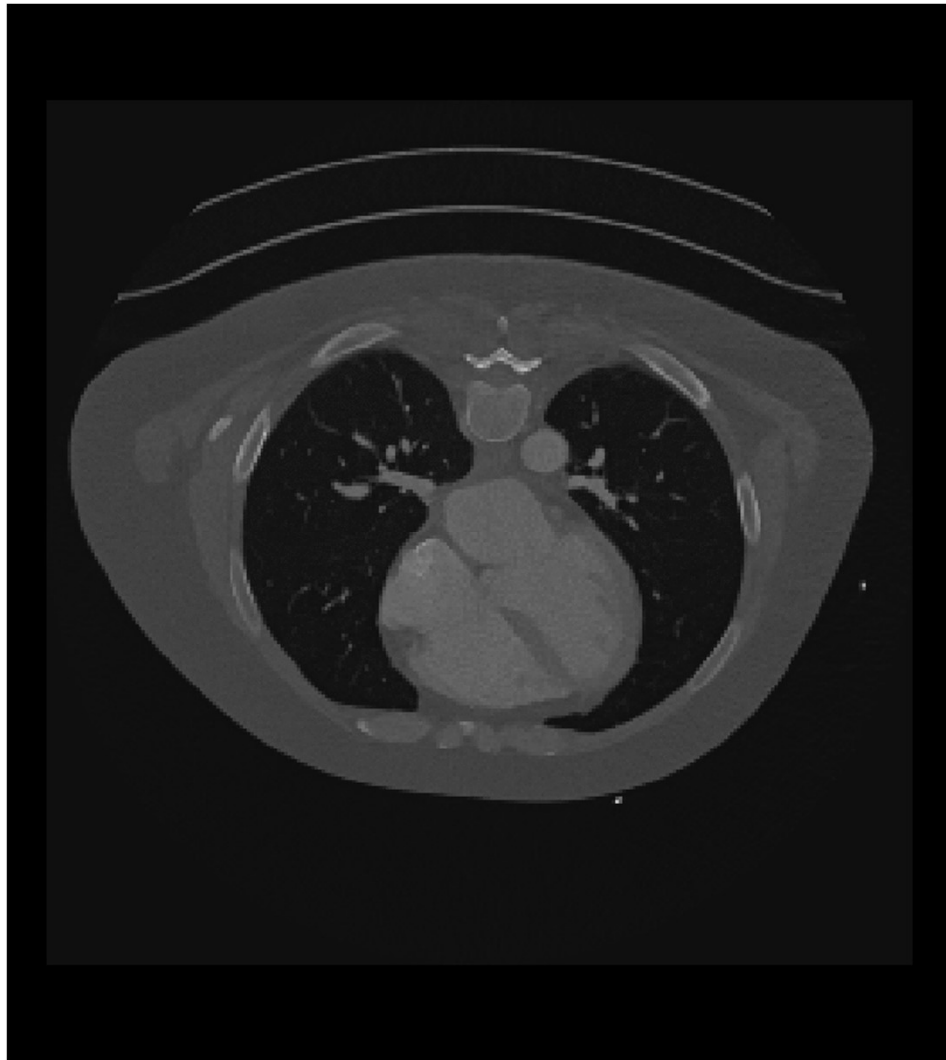


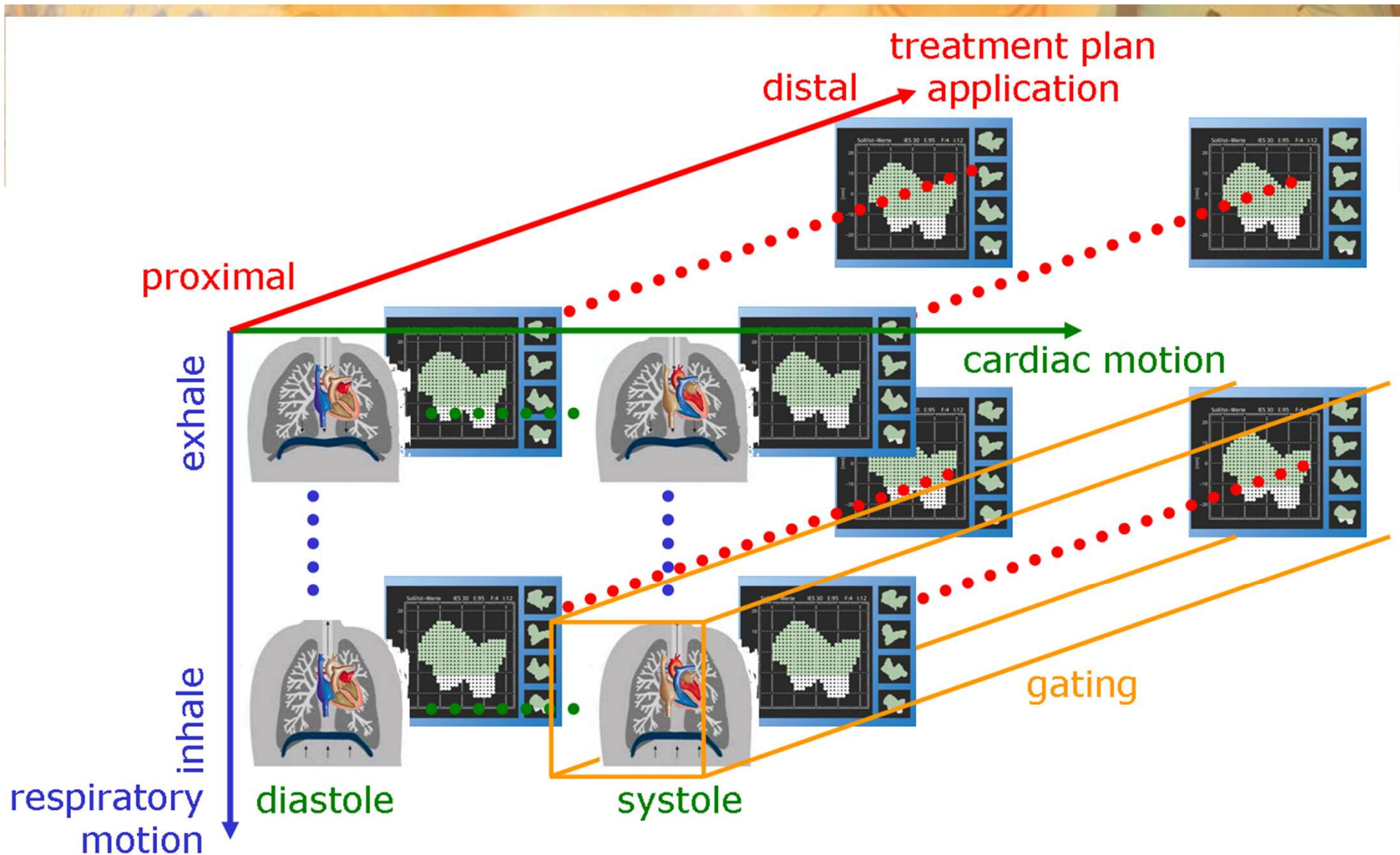
In-beam PET



Lehmann *et al.*, *Sci. Rep.* 2016; Rapp *et al.*, *Sci. Rep.* 2019

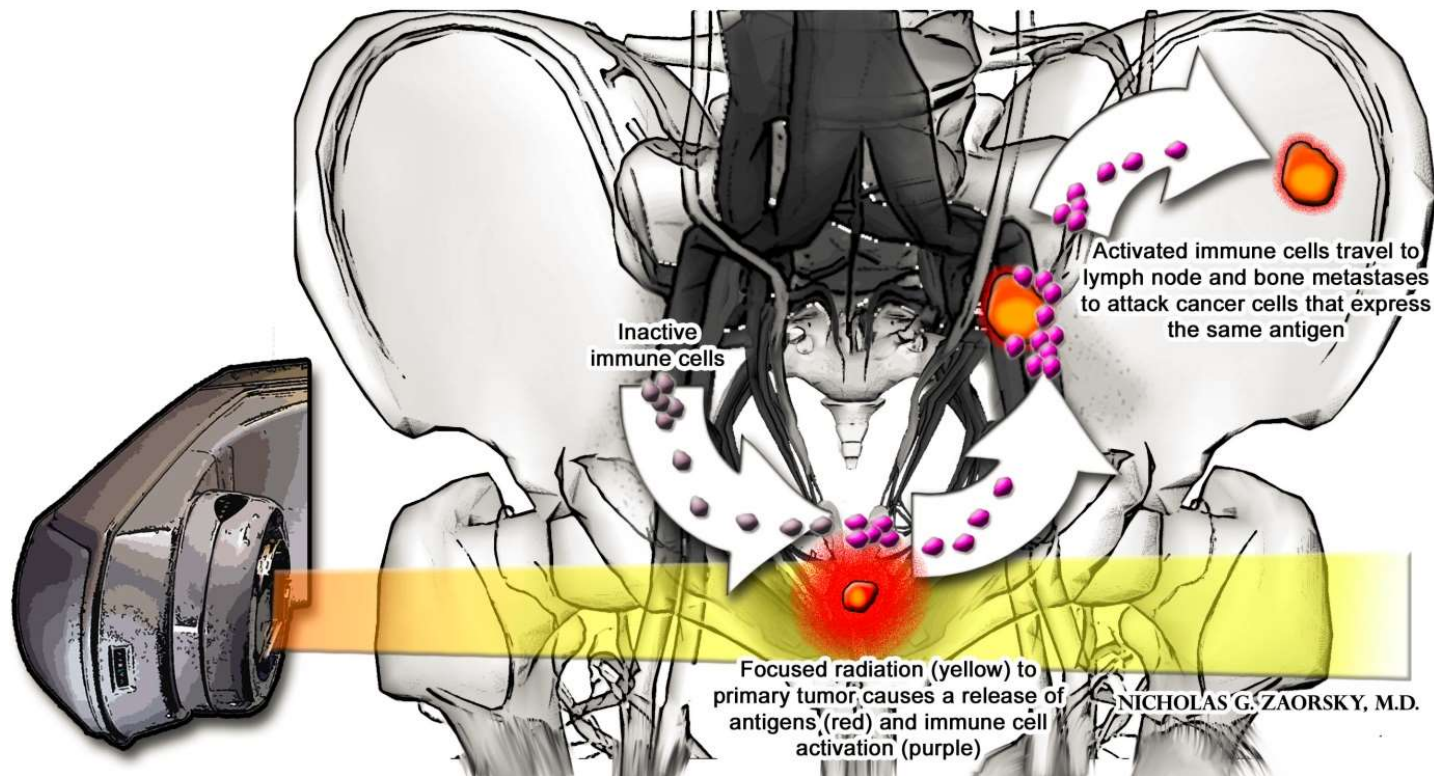
Mayo Clinics: 5D CT





Particle 5D-TP (Bert *et al.*, *Med. Phys.* 2012)

Abscopal effect – radiation-induced, immunogenic inactivation of metastases



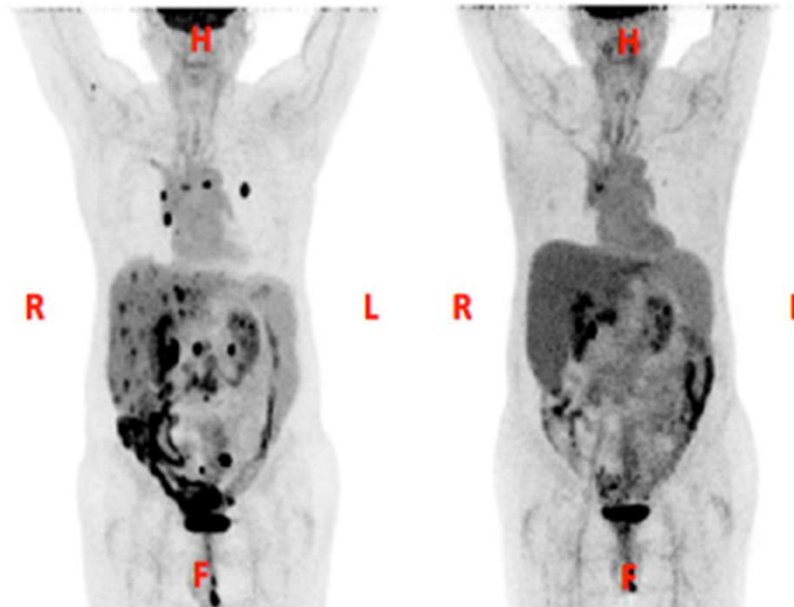
Combining RT and checkpoint inhibitors

NSCLC progressing after 3 lines of chemo
and chest RT: Multiple lung, bone
and liver metastasis

Courtesy of Silvia Formenti



**Weill Cornell
Medicine**



August 2012 PET/CT January 2013 PET/CT

RT to one liver met 6 Gy X 5 (TD 30 GY)
Ipilimumab, 3 mg/Kg, after first RT q3 weeks, X 4 cycles

Particle therapy and immunotherapy

Does Heavy Ion Therapy Work Through the Immune System?

Marco Durante, PhD,^{*} David J. Brenner, PhD,[†]
and Silvia C. Formenti, MD[‡]

^{}Trento Institute for Fundamental Physics and Applications-National Institute for Nuclear Physics, University of Trento, Trento, Italy; [†]Center for Radiological Research, Columbia University Medical Center, New York, New York; and [‡]Department of Radiation Oncology, Weill Cornell Medical College, New York, New York*

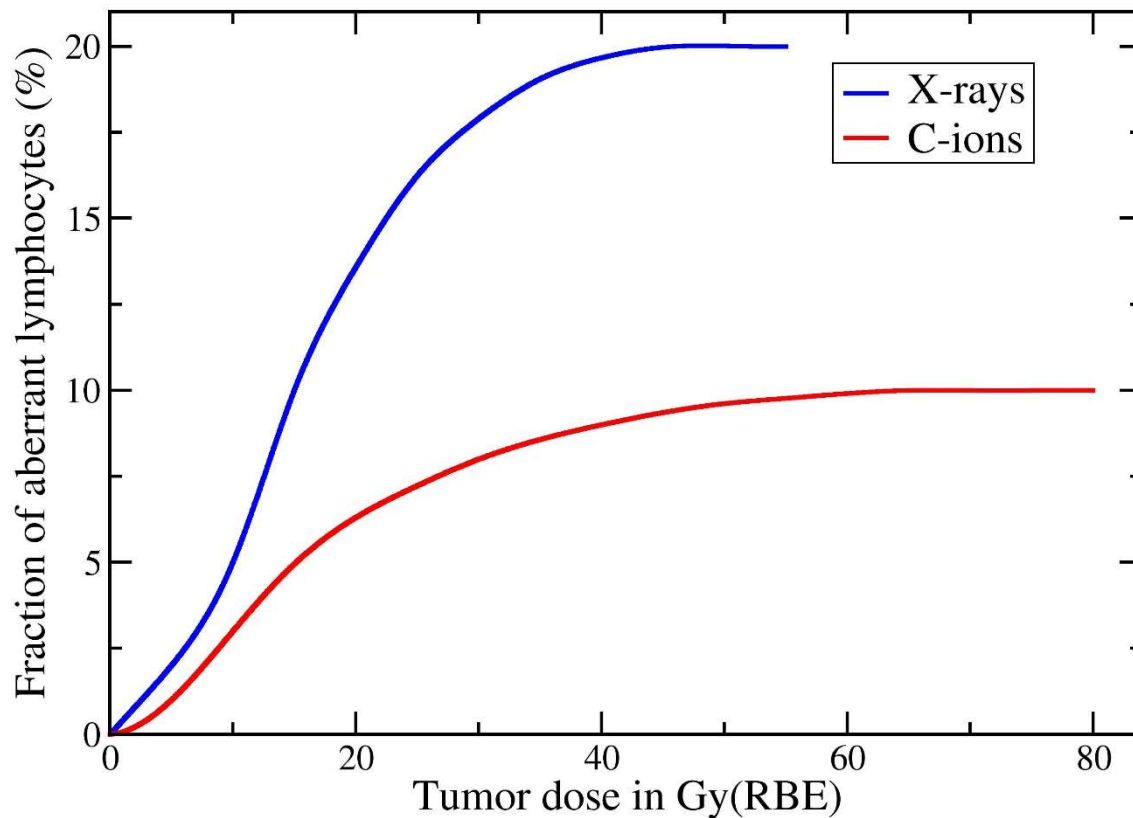
Received Aug 10, 2016, and in revised form Aug 21, 2016. Accepted for publication Aug 25, 2016.

➔ matter of ongoing discussion in literature

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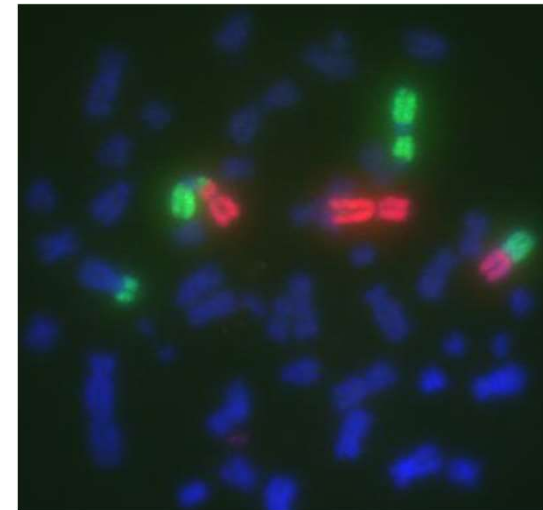
www.redjournal.org

Advantages of particle RT for the immune system



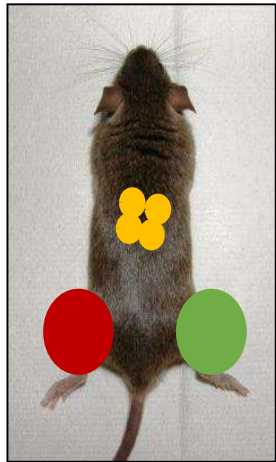
Reduced integral dose of carbon ion therapy to healthy tissue

Result: circulating blood lymphocytes are better spared and are available for an efficient immune response



Durante et al., *Int. J. Radiat. Oncol. Biol. Phys.* 2000

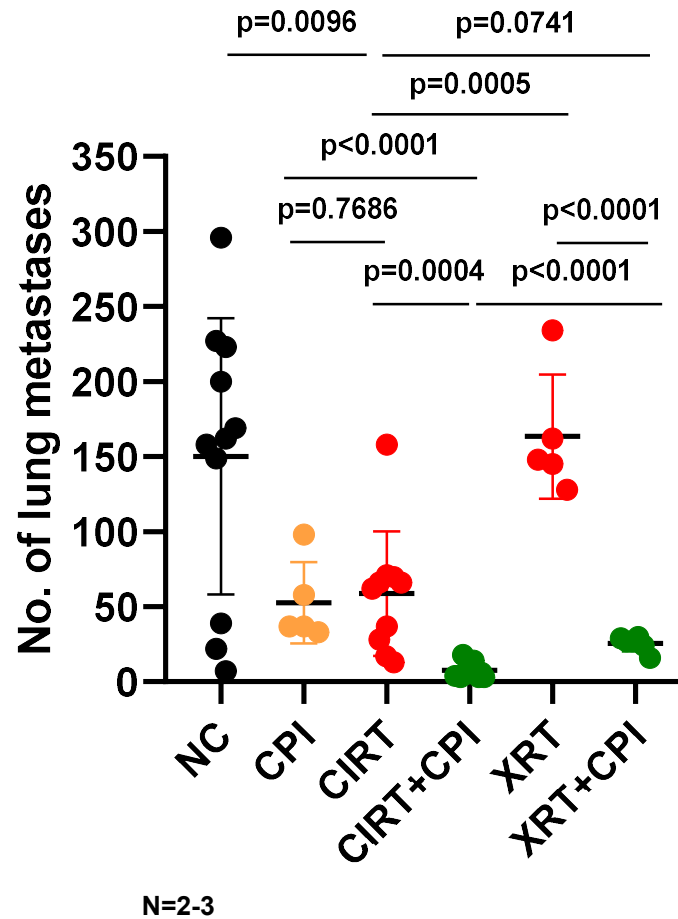
Reduction of lung metastases



CIRT+CPI

Negative control

Assessment of superficial nodules after fixation in Bouin's solution



NC = negative control
 CPI = check point inhibitors only
 CIRT = C-ions only, 10 Gy
 XRT = photons, 10 Gy