Terapia con hadrones

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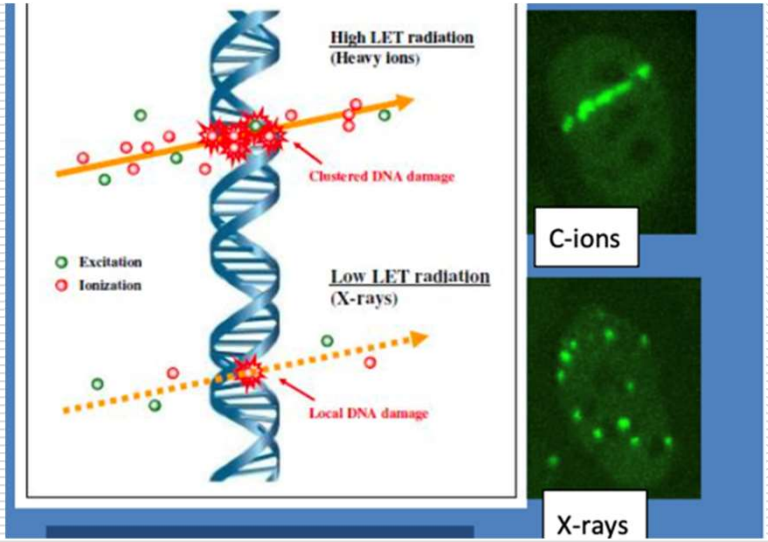
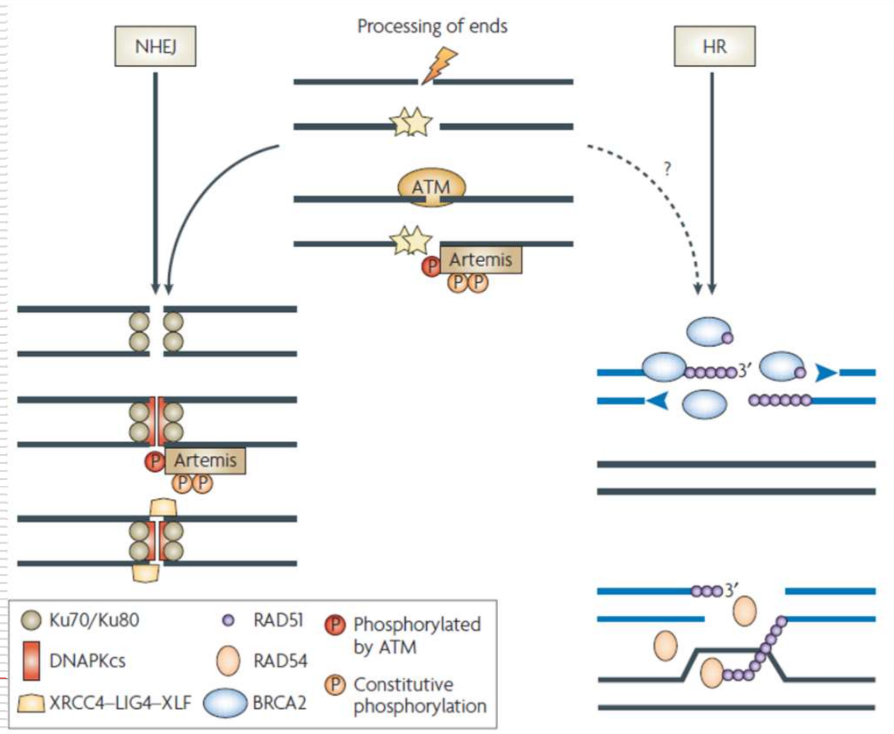
Charged particles introduce a more complex DNA damage



Carbon Ion Radiobiology

Walter Tinganelli [1], Marco Durante [1, 2]

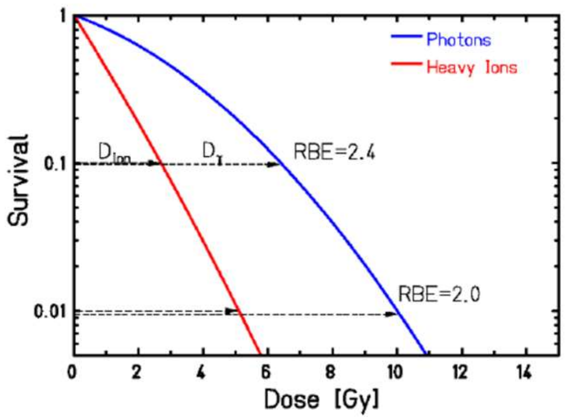


→ Increased level of cell death

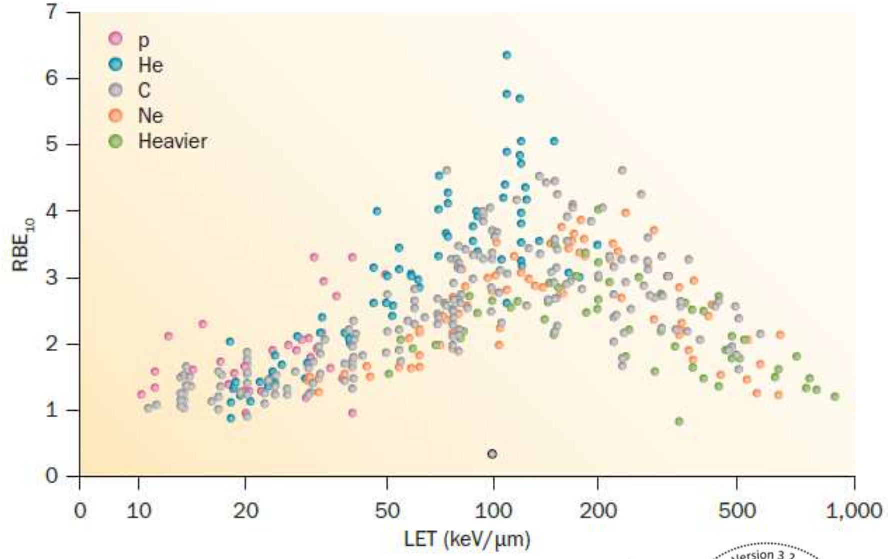
Charged particles inactivate/kill cells more effectively

Relative **B**iological **E**ffectiveness

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



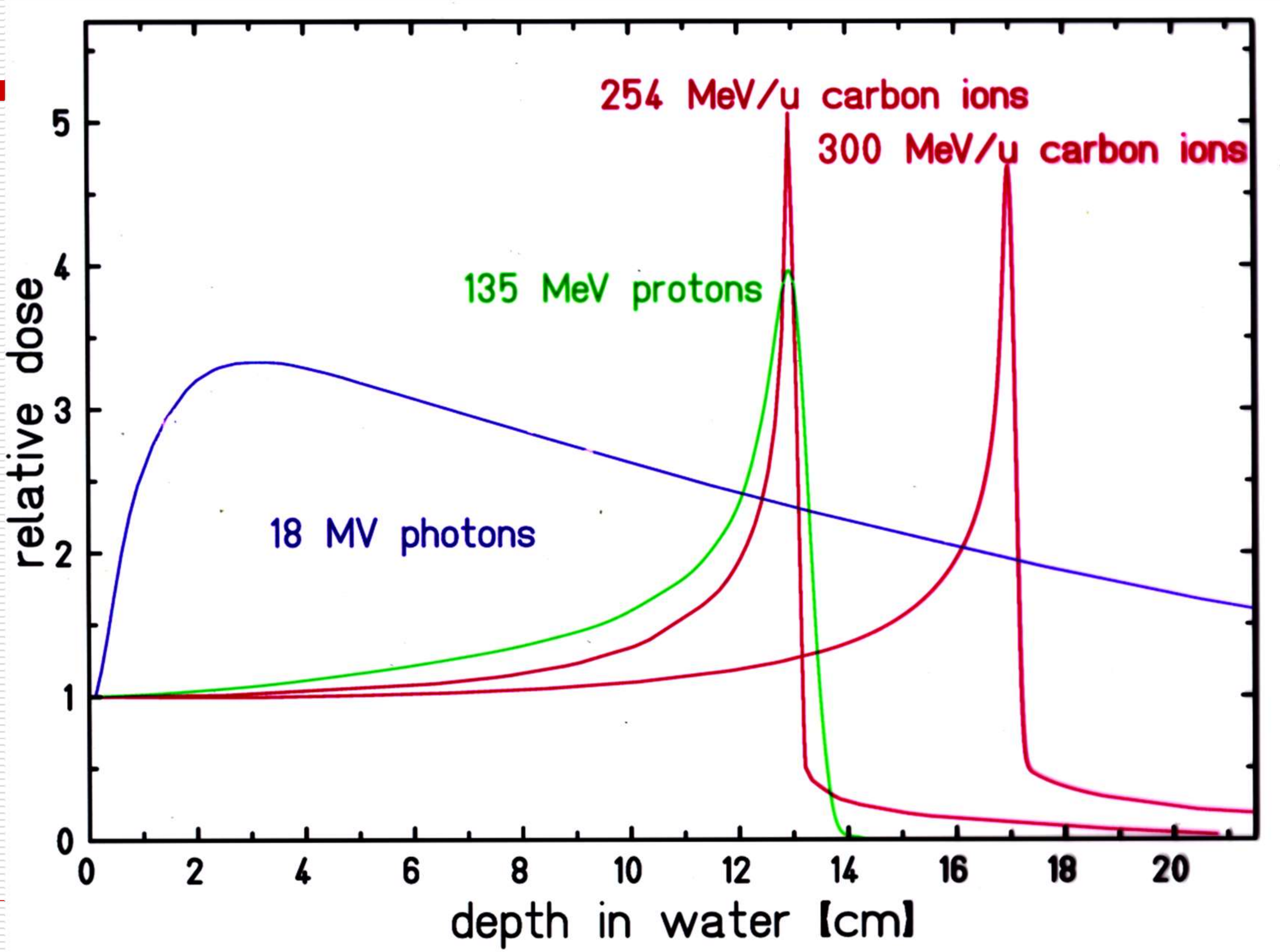
$$RBE = \frac{D_\gamma}{D_{Ion}}\Bigg|_{Isoeffect}$$



Friedrich *et al., J. Radiat. Res.* 2012

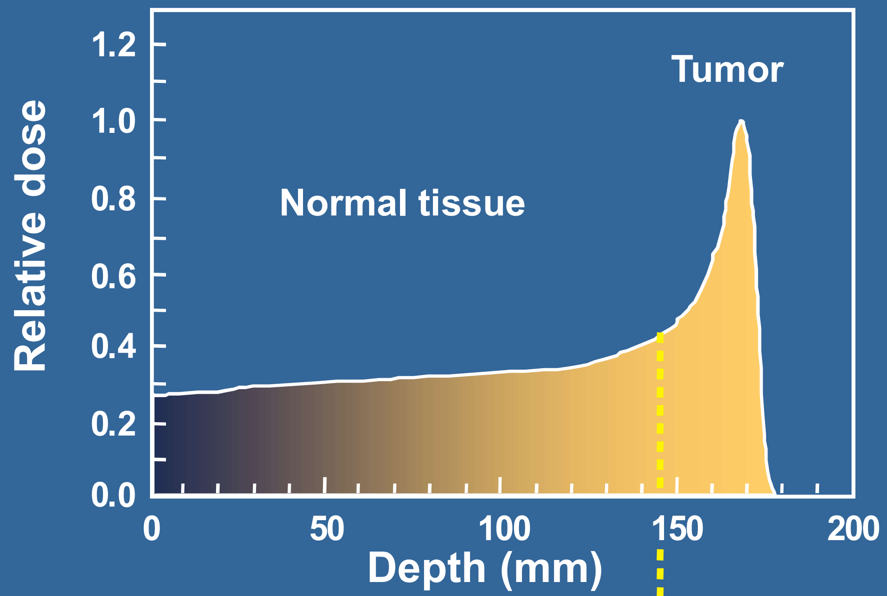
PIDE database www.gsi.de/bio-pide

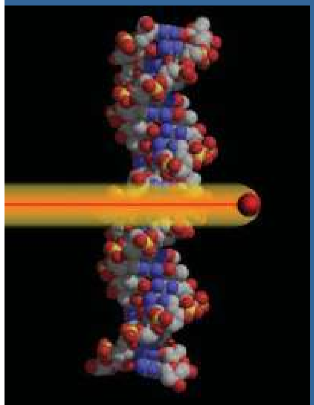
Depth dose distribution of various radiation modalities



Durante & Loeffler,

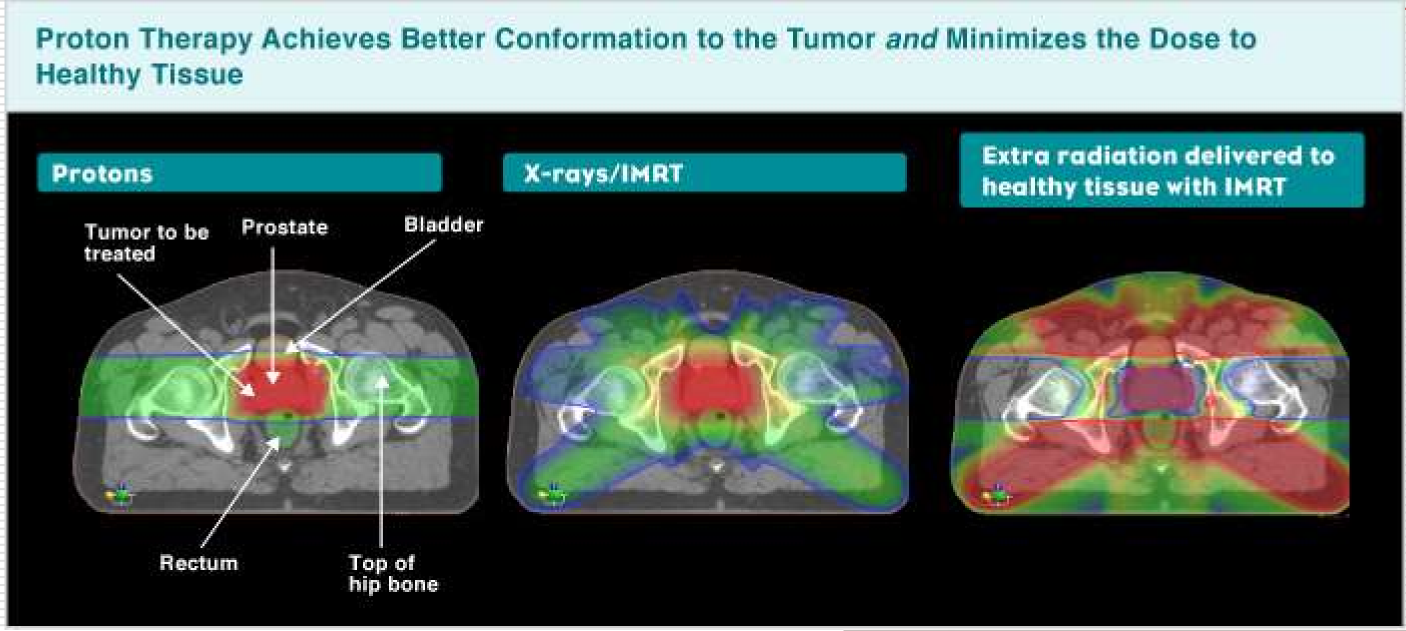
***Nature Rev Clin Oncol* 2010**

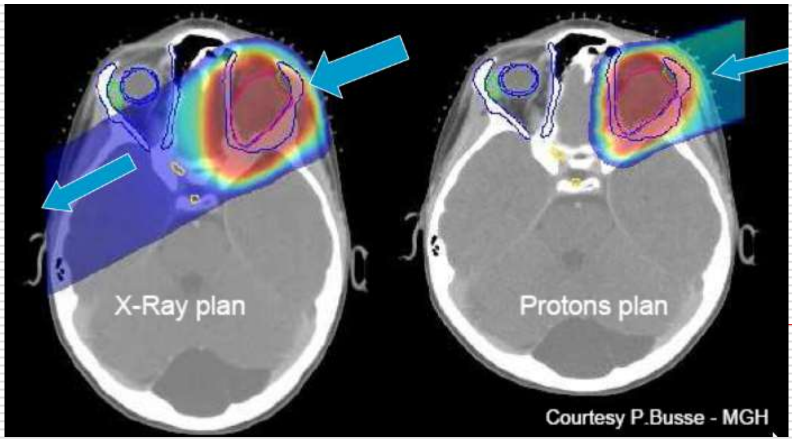


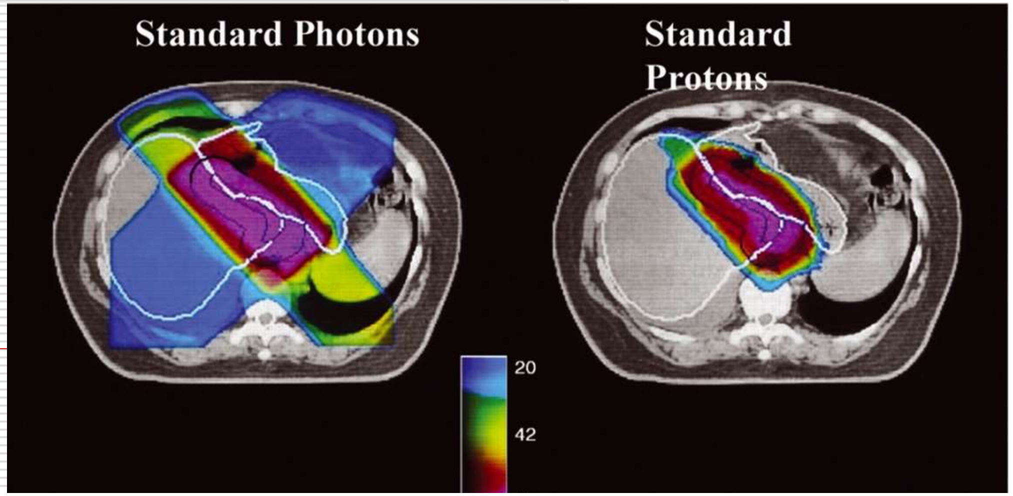


			Potential advantages
Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumor cells
Cell-cycle dependence	high	low	Increased lethality in the target because cells in radioresistant (S) 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	

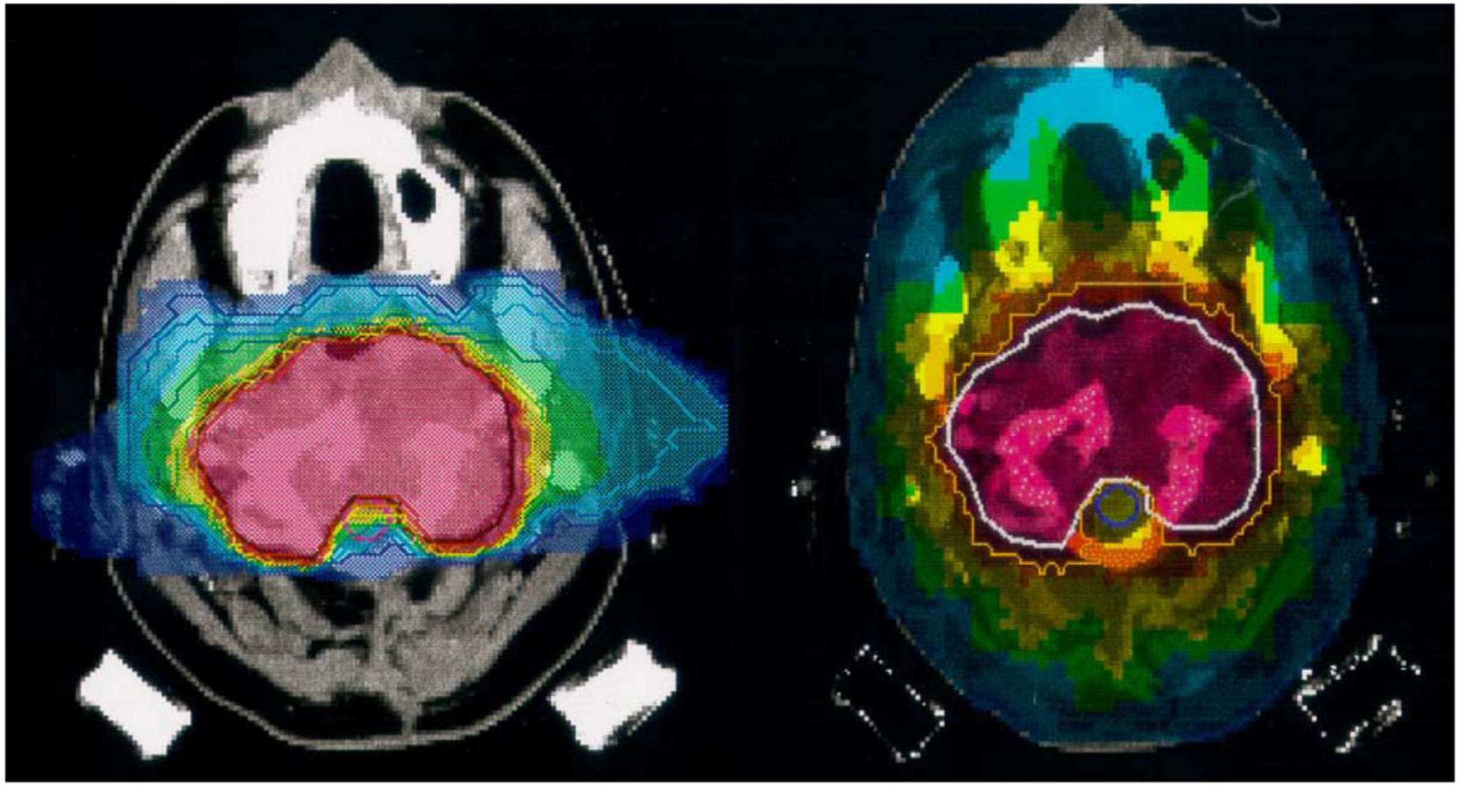
Treatment plans with protons: sparing of normal tissue, recommended especially for pediatric patients







Treatment plans: Heavy Ion vs IMRT

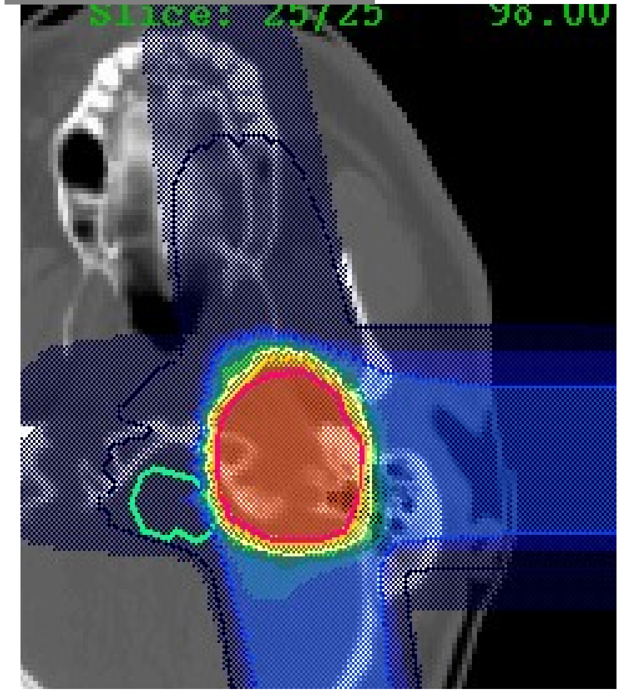


C-12, 2 fields   IMRT, 9 fields

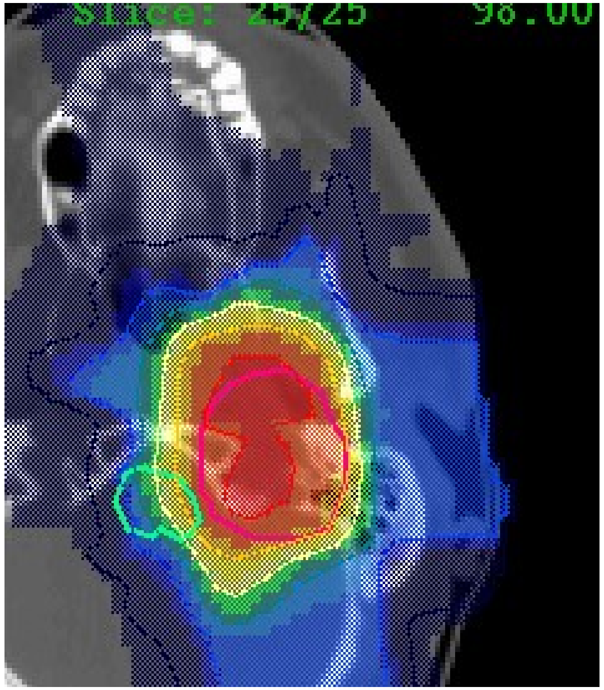
Jäkel, Debus, Heidelberg

Comparison of Treatment Plans: C-ions vs. protons

C-ions (GSI)

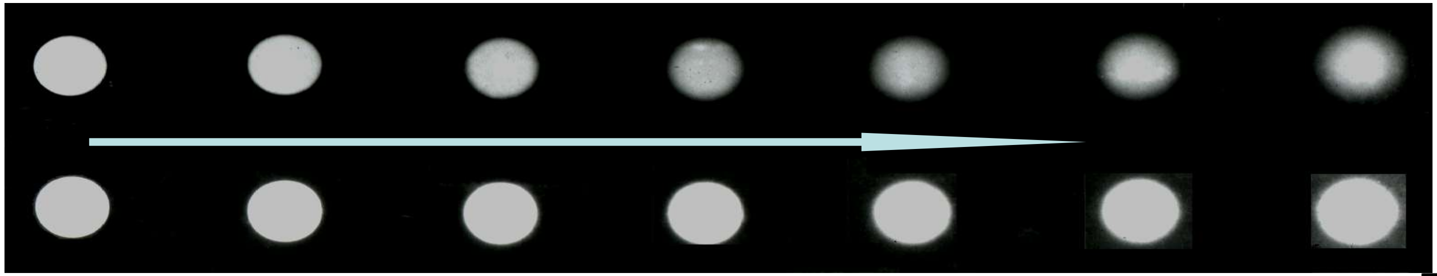


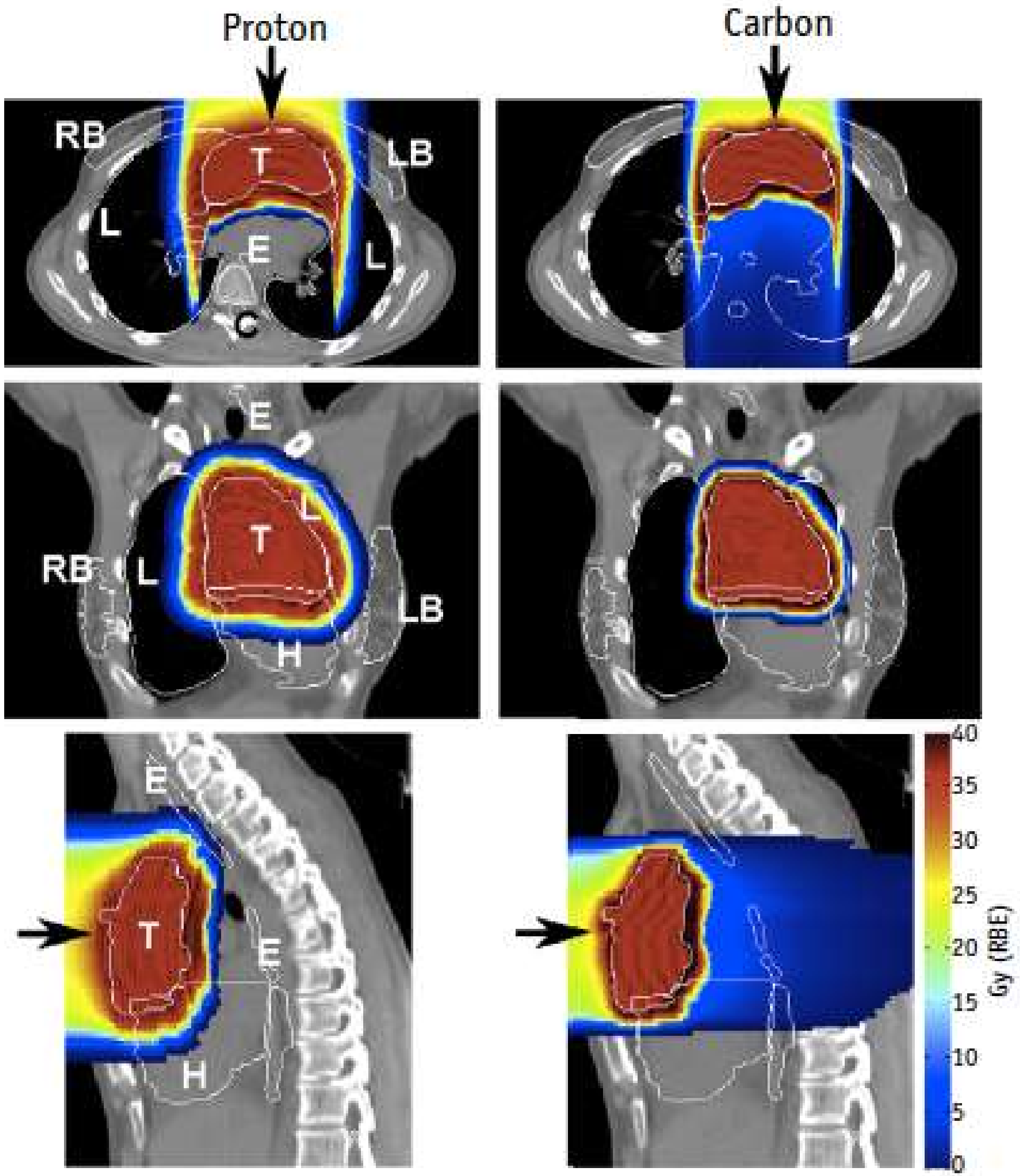
H-ions (CapeTown, SA)



H

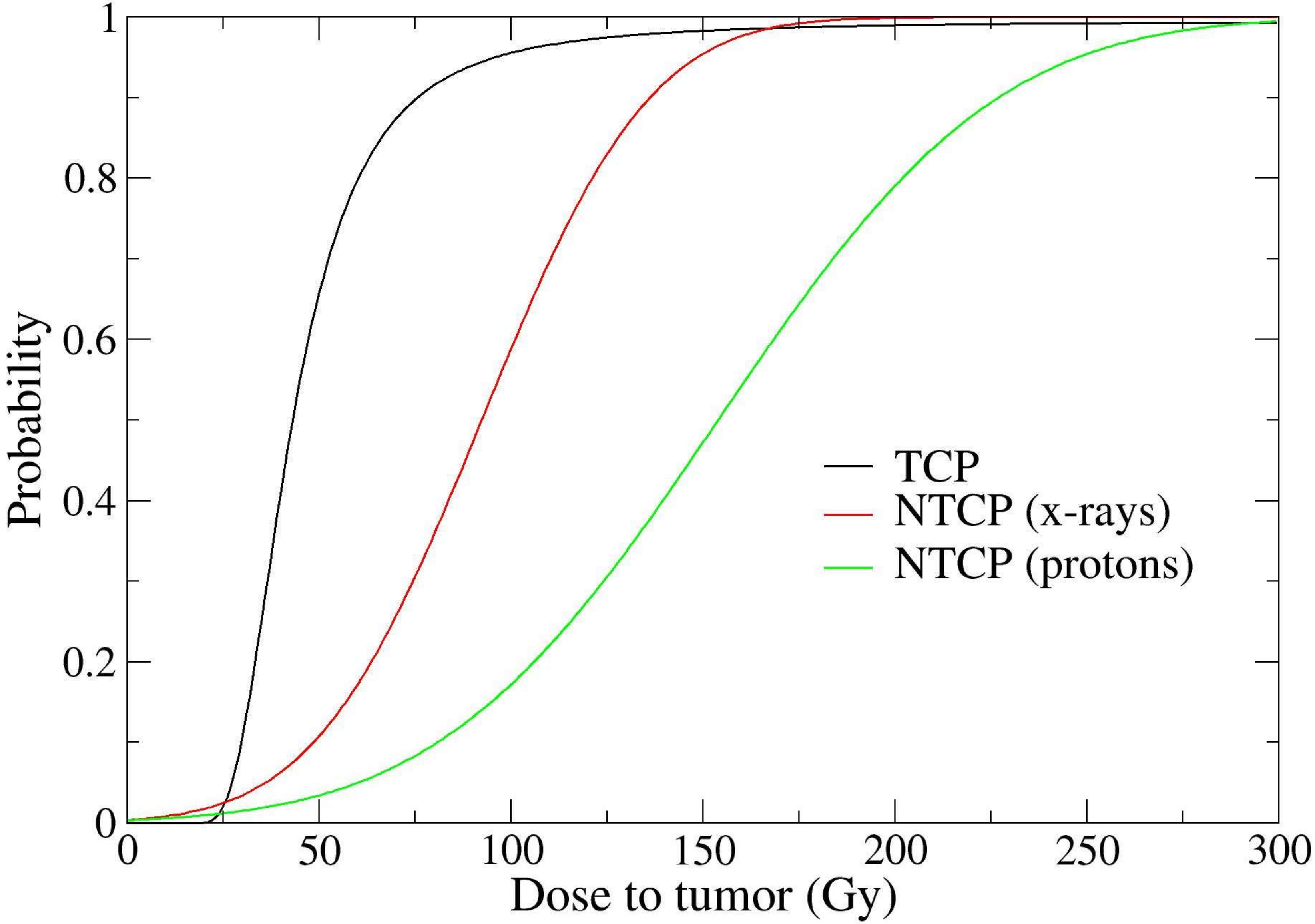
C



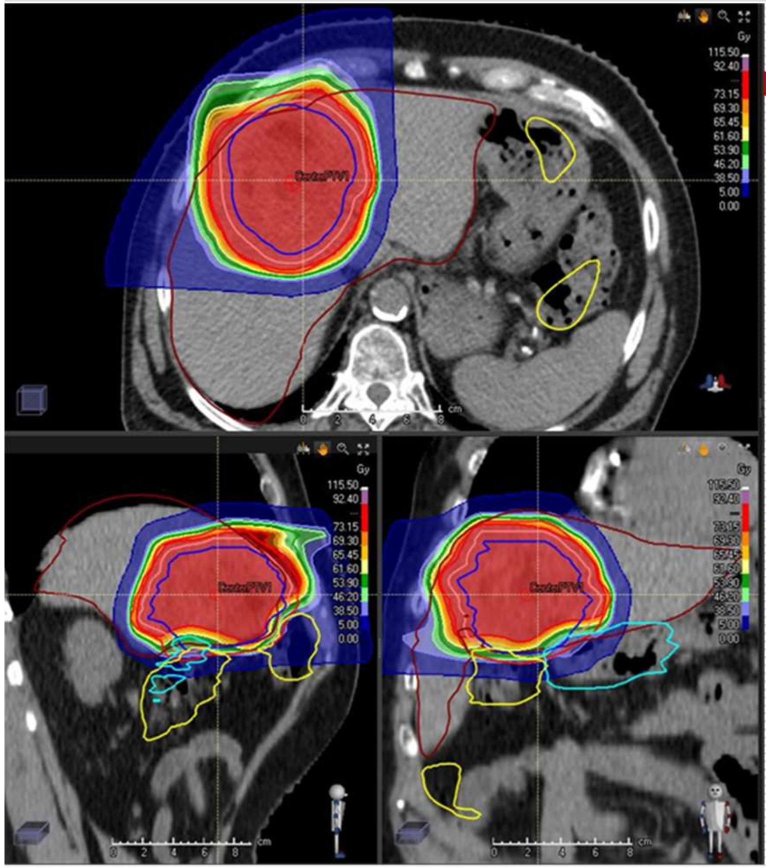


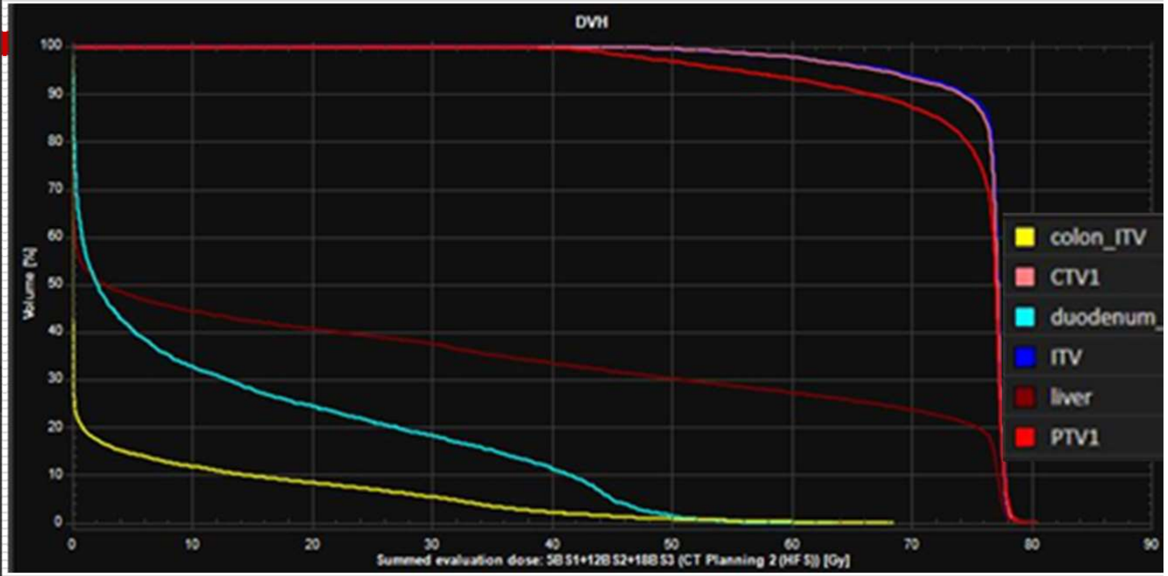
Hodgkin's lymphoma : protons or C-ions?

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


1
0.8
0.6
0.4
0.2
0
Probability
0
50
100
150
200
250
300
Dose to tumor (Gy)
TCP
NTCP (x-rays)
NTCP (protons)

Hepatocellular carcinoma
C-ions



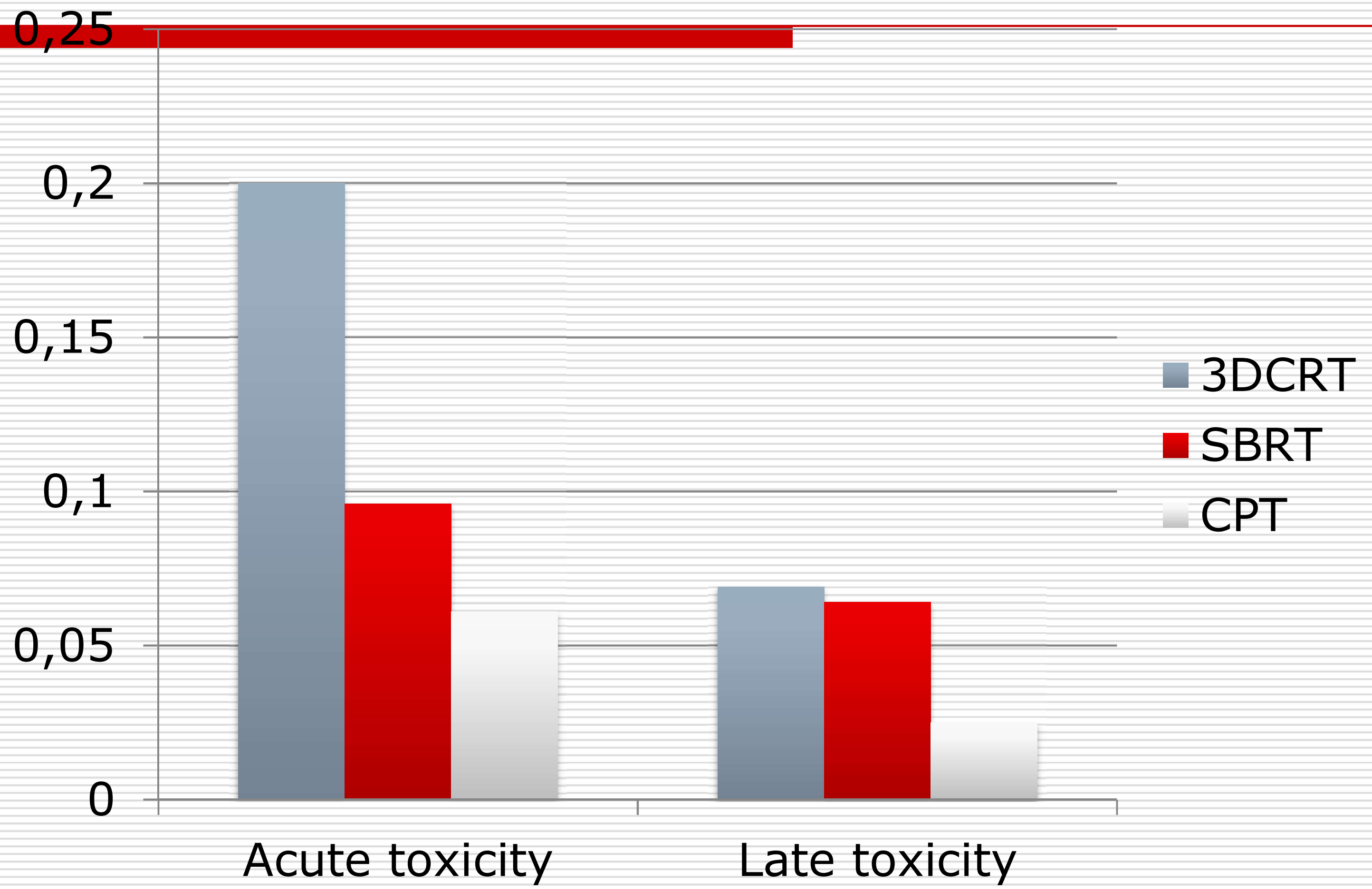


~ 50% of the liver receives ~ 0 Gy

MedAustron

Courtesy of Piero Fossati

Particle therapy in HCC



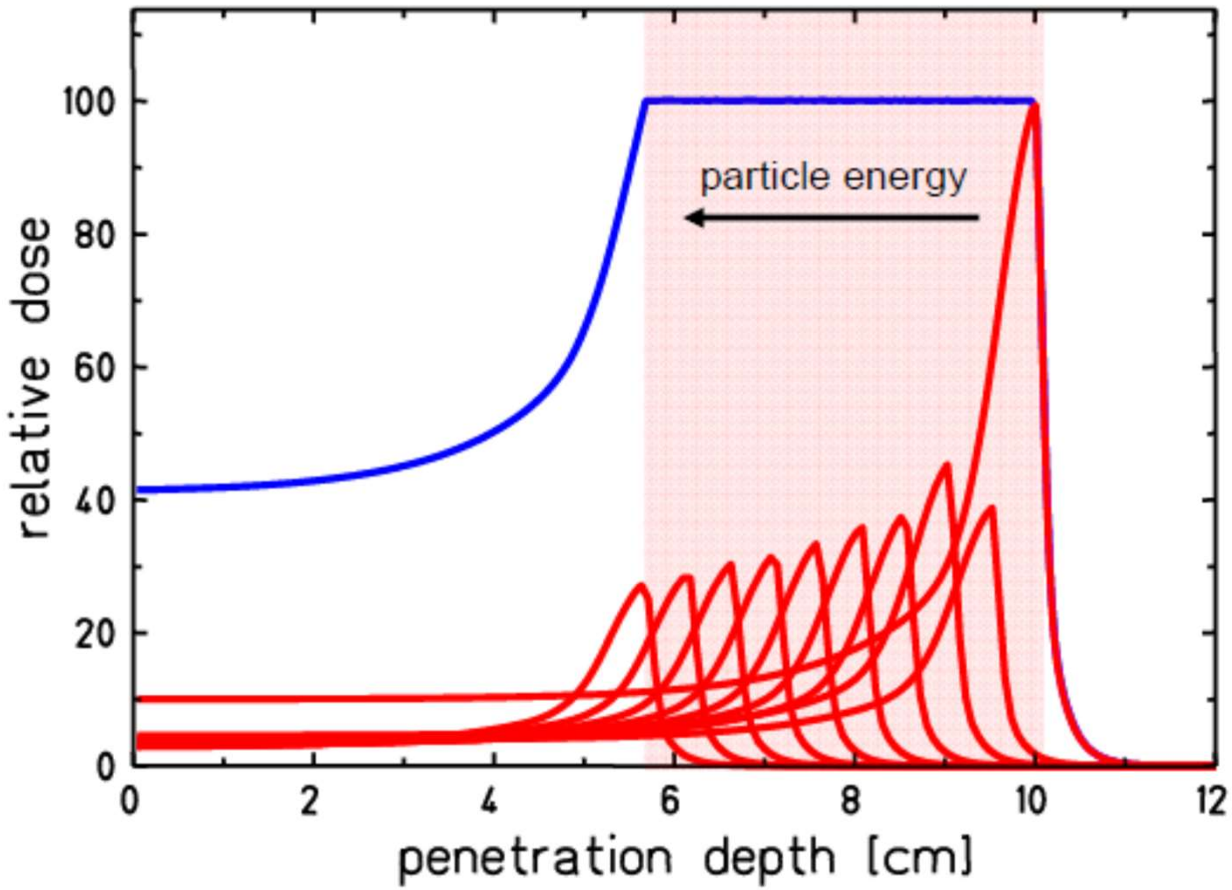
Durante, *Ann. Transl. Med.* 2016

Application for therapy

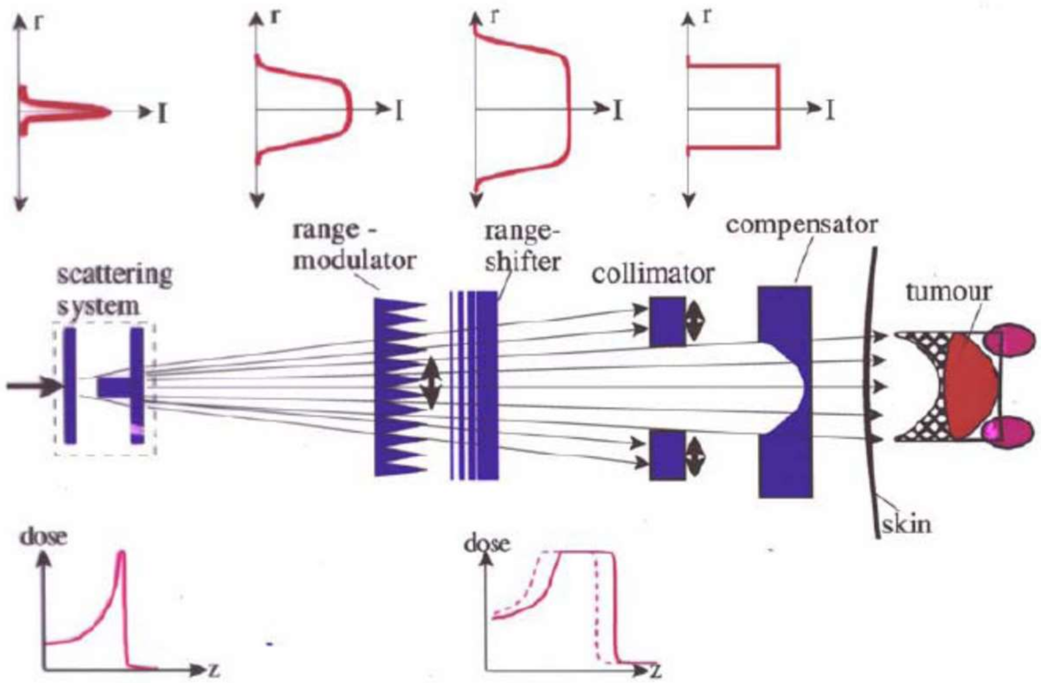
- how can we irradiate a tumor volume with a particle beam?
  - lateral extension
  - longitudinal (depht) extension

- passive beam shaping
- active scanning

Longitudinal - Spread out Bragg peak



Beam shaping with passive devices



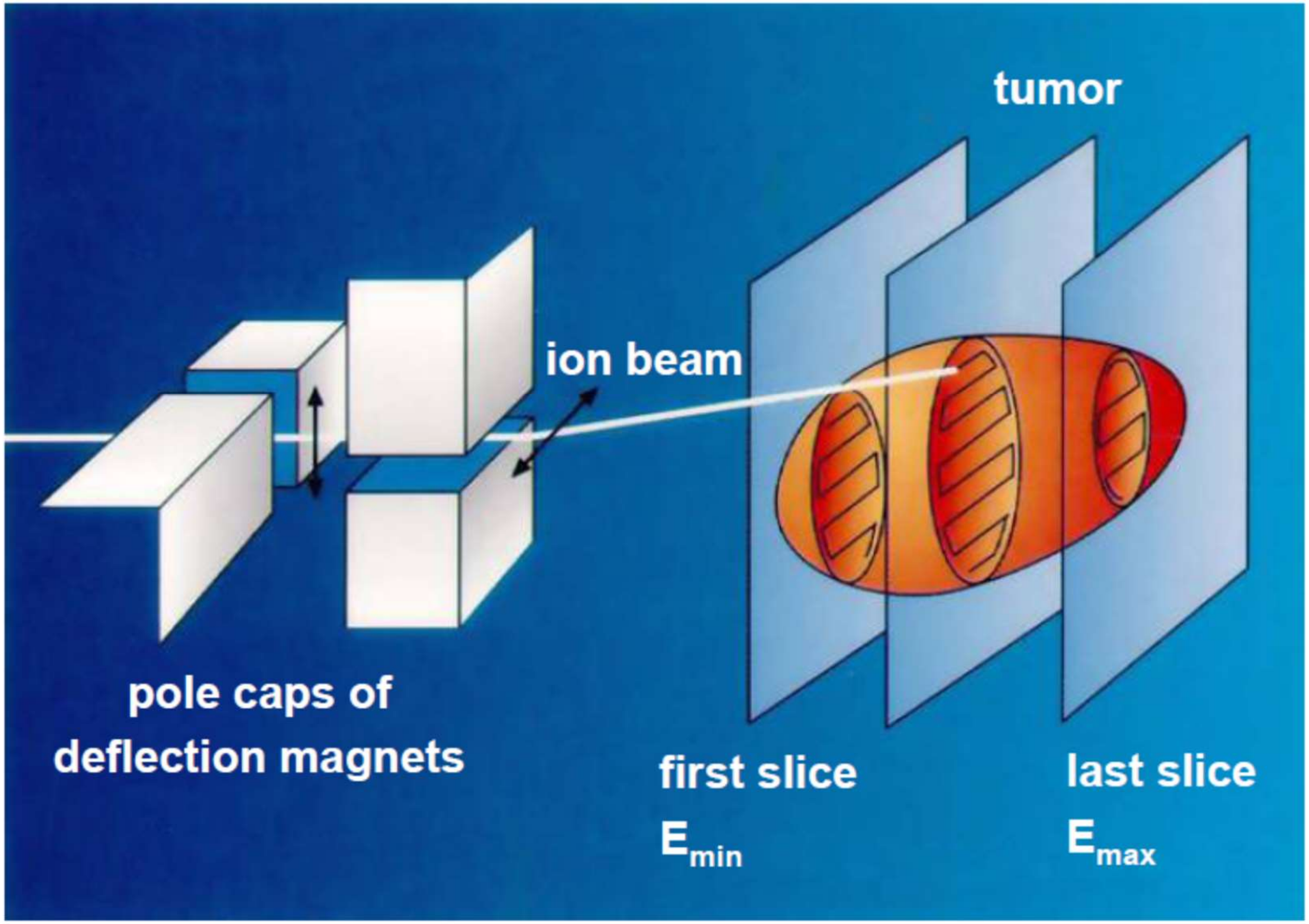
- have to be manufactured for each patient field
- fixed extension and extended Bragg peak
- missing proximal conformation

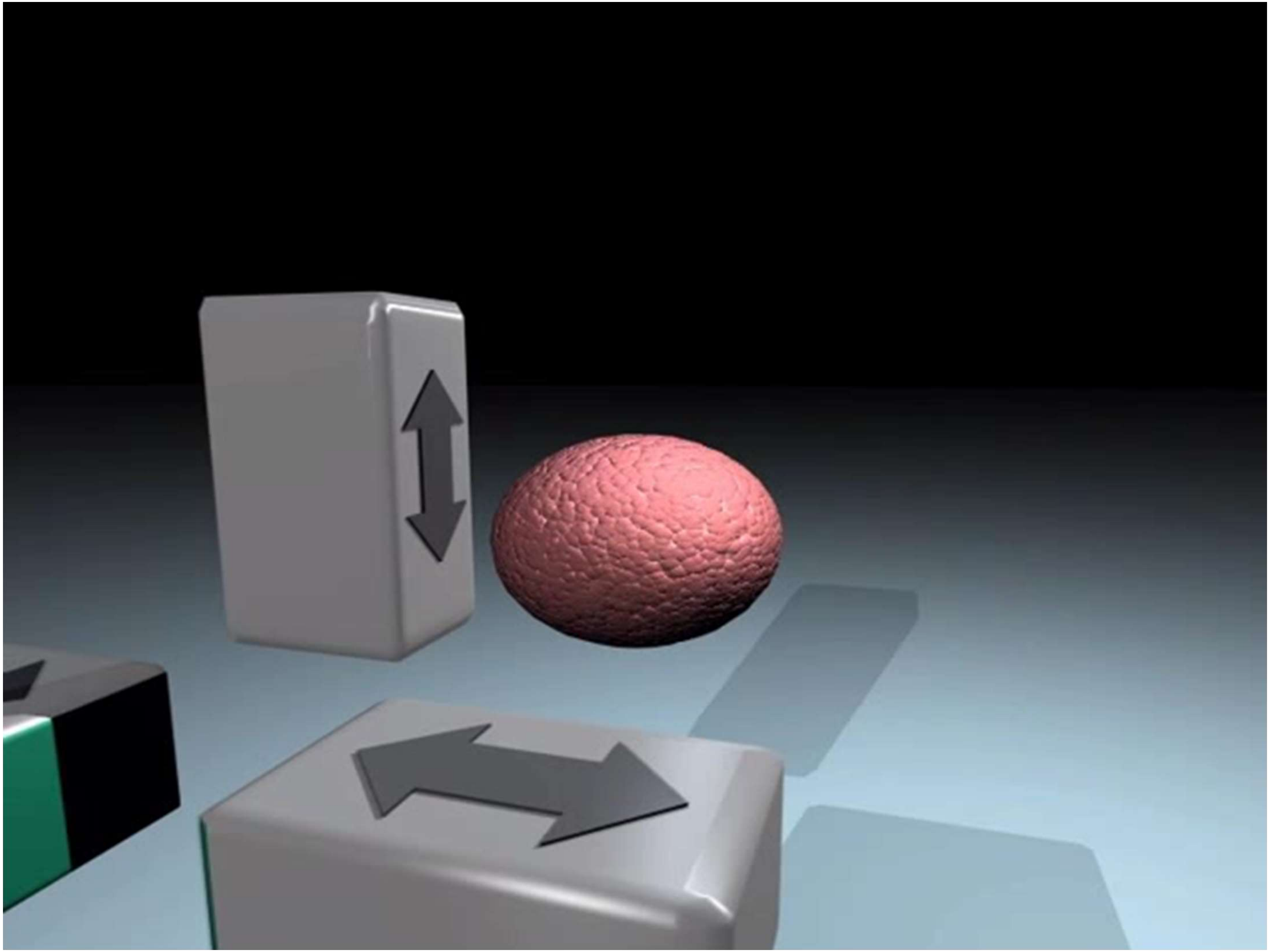
Hardware for passive beam shaping

Collimator

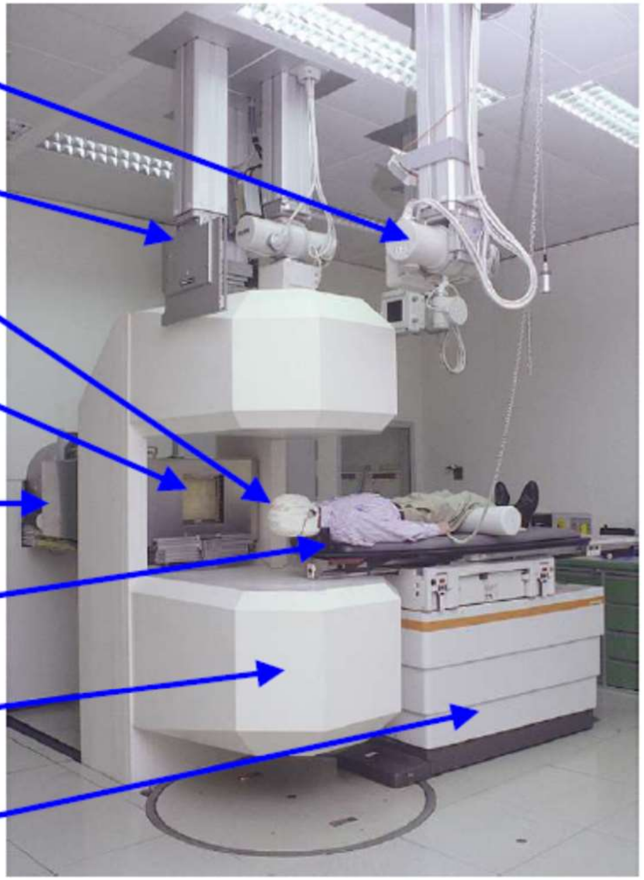
Compensator

Active scanning - Rasterscan system





Experimental Therapy Room: Cave M



Detectors in particle therapy

Detectors used to monitor the beam

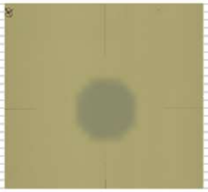
Large area Parallel plate Ionization Chamber

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.



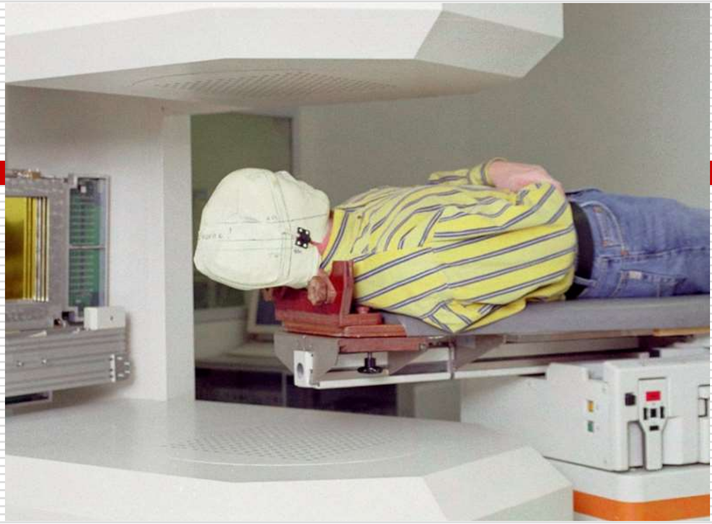
GadChromic Films
Visualization the irradiation field.
Can measure the dose but not very accurate.

Typical Set up and instrumentation for particle therapy application

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

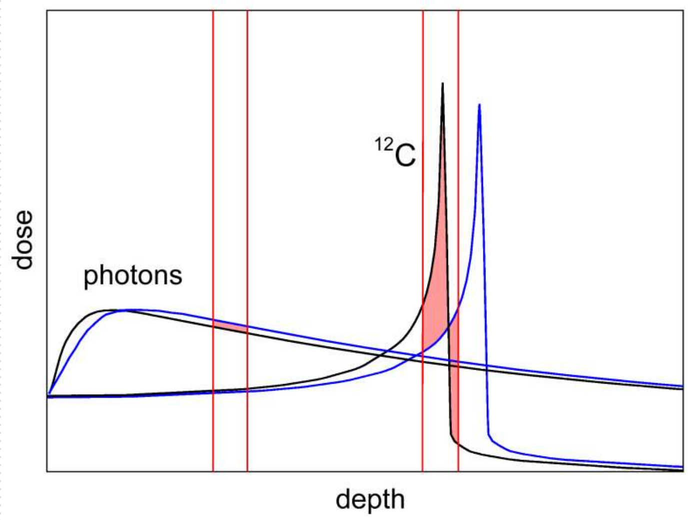
Measure Bragg the depth dose distribution in water

Range uncertainty

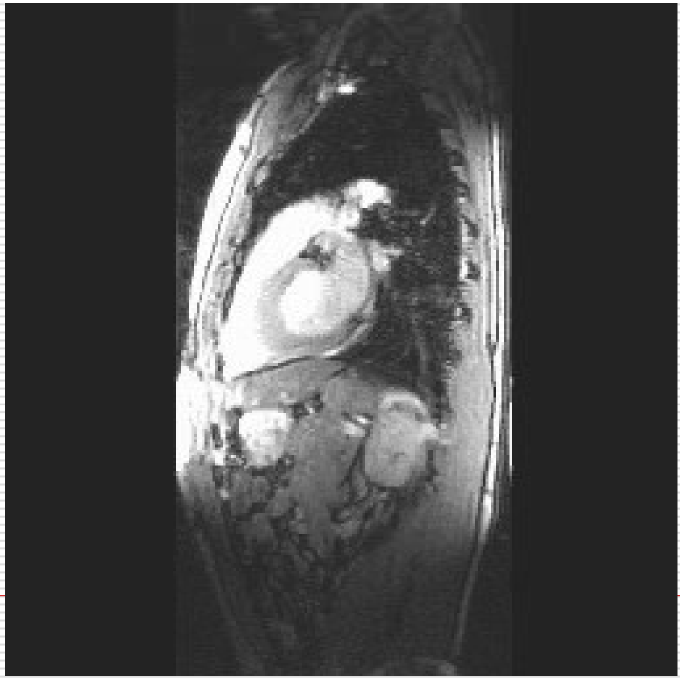


precision of stereotactic fixation:

1mm in the head to
3mm in the pelvic region

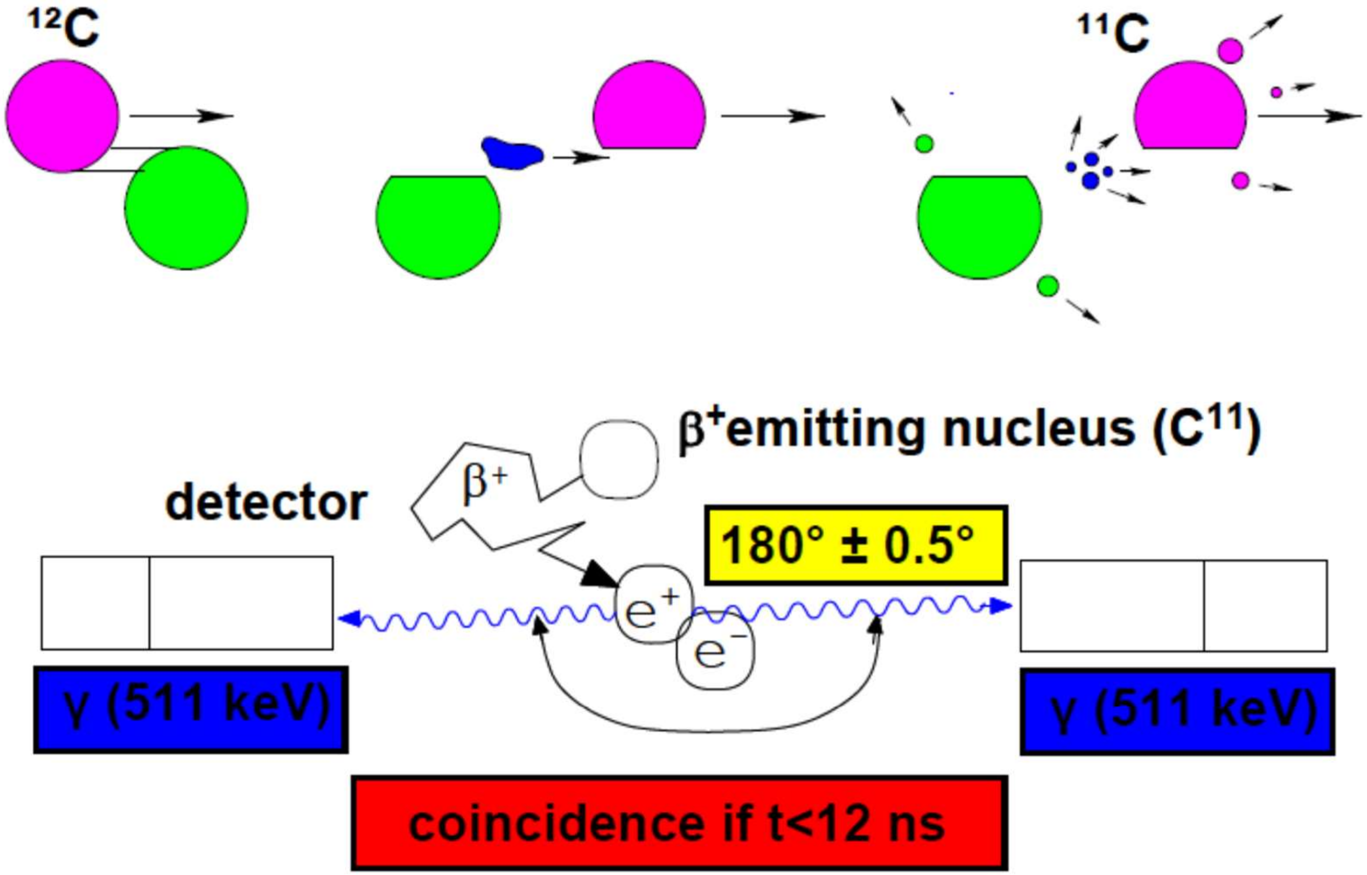


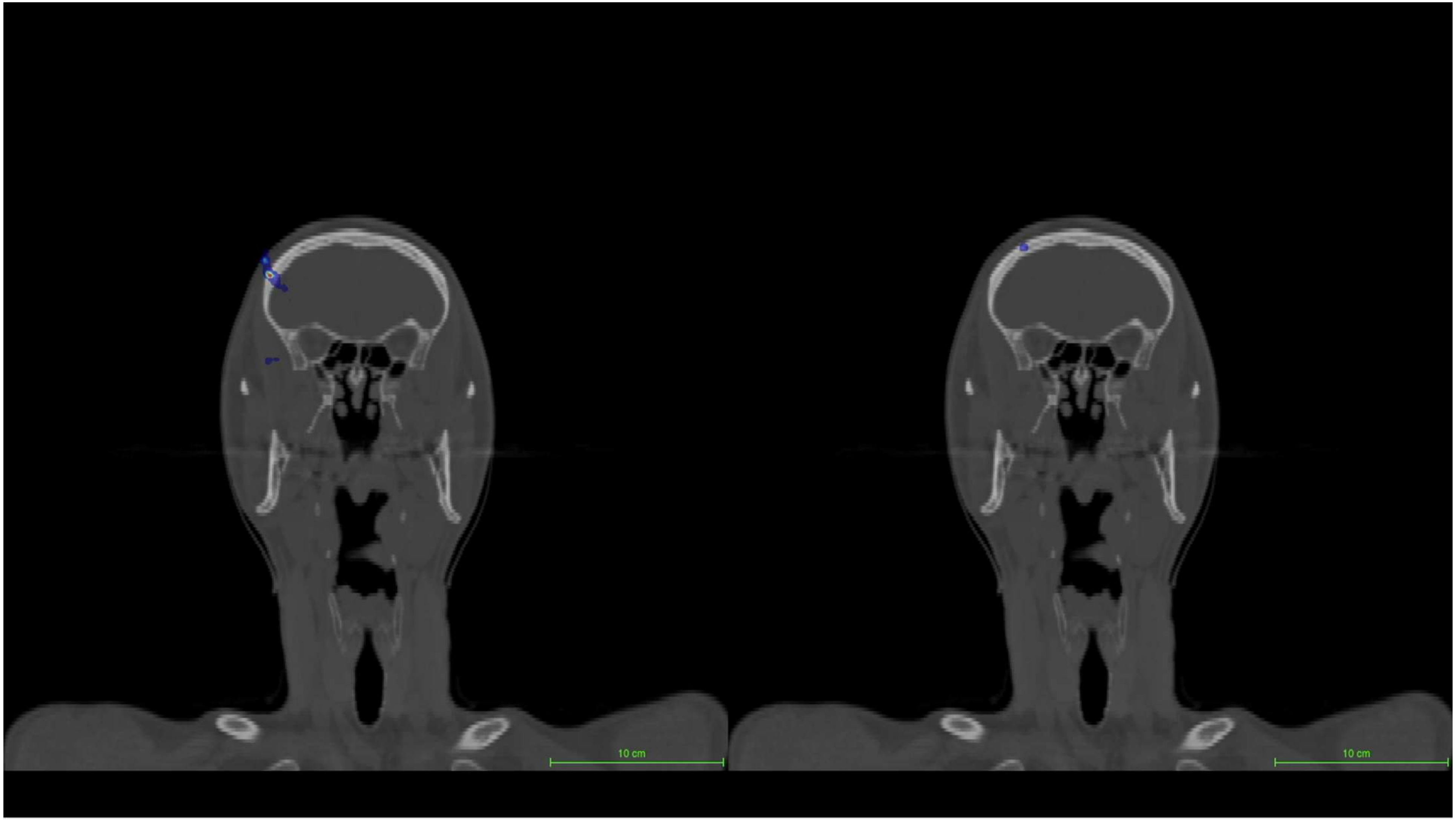
for ions: variations in radiological path length extremely important



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

Positron Emission Tomography (PET)





10 cm
10 cm

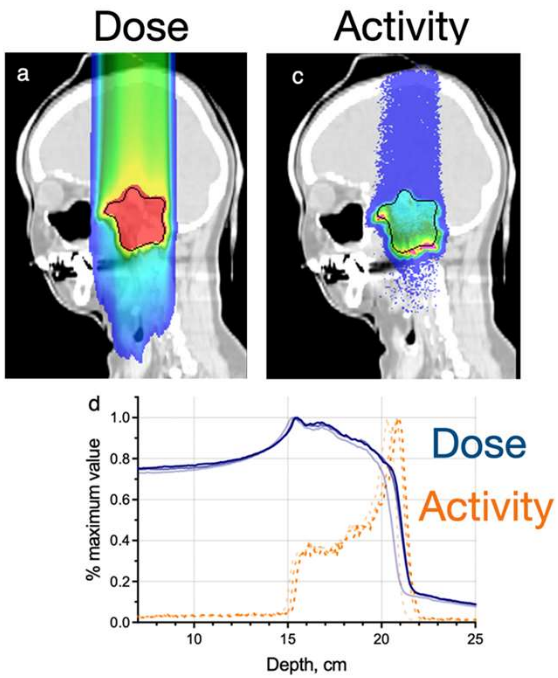
Tackling range uncertainties in particle therapy

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. $^{10,11}C$) give a PET signal at the Bragg peak position.

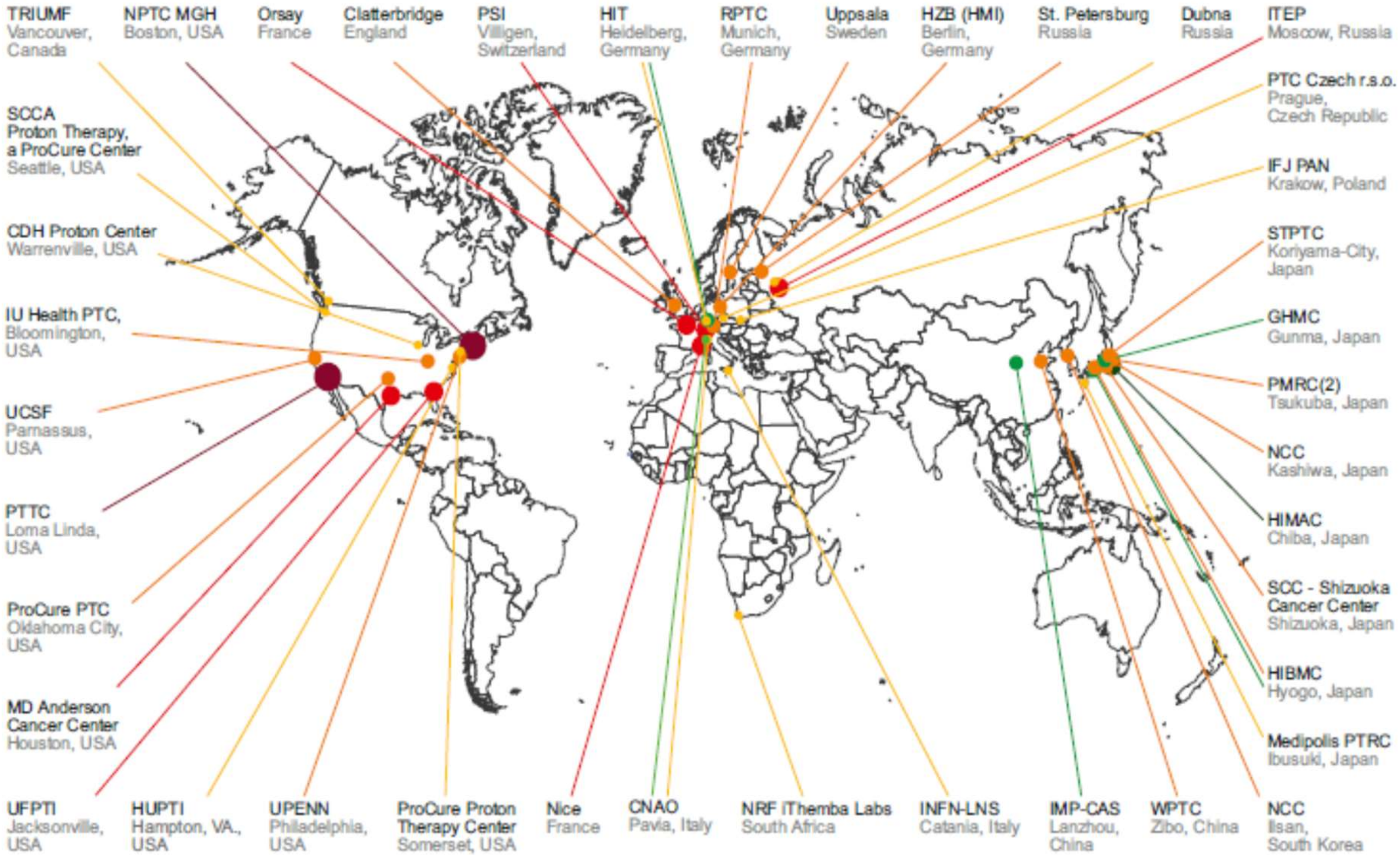
Improved count rate and dose activity match compared to the stable ions



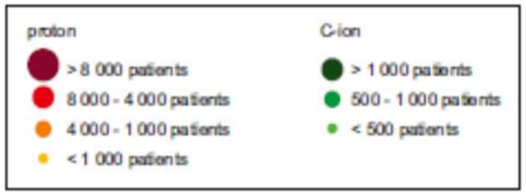
Sokol et al. Sci Rep 2022

B · A · R · B

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

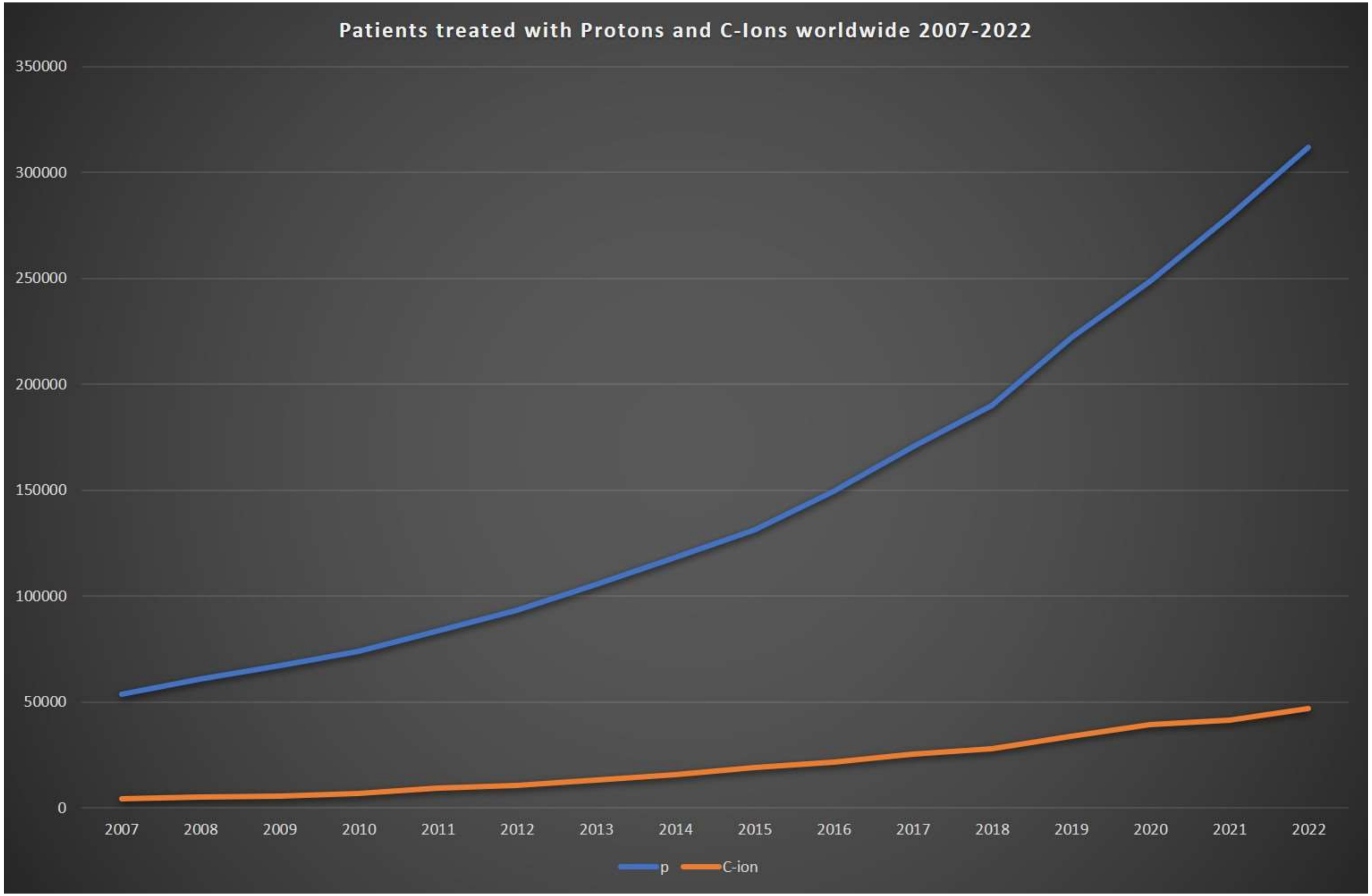
Under construction: 28 proton/ 5 heavy ion centers

Mayo Clinics in USA 1 heavy ion center by 2025+

PTCOG Homepage March 2024

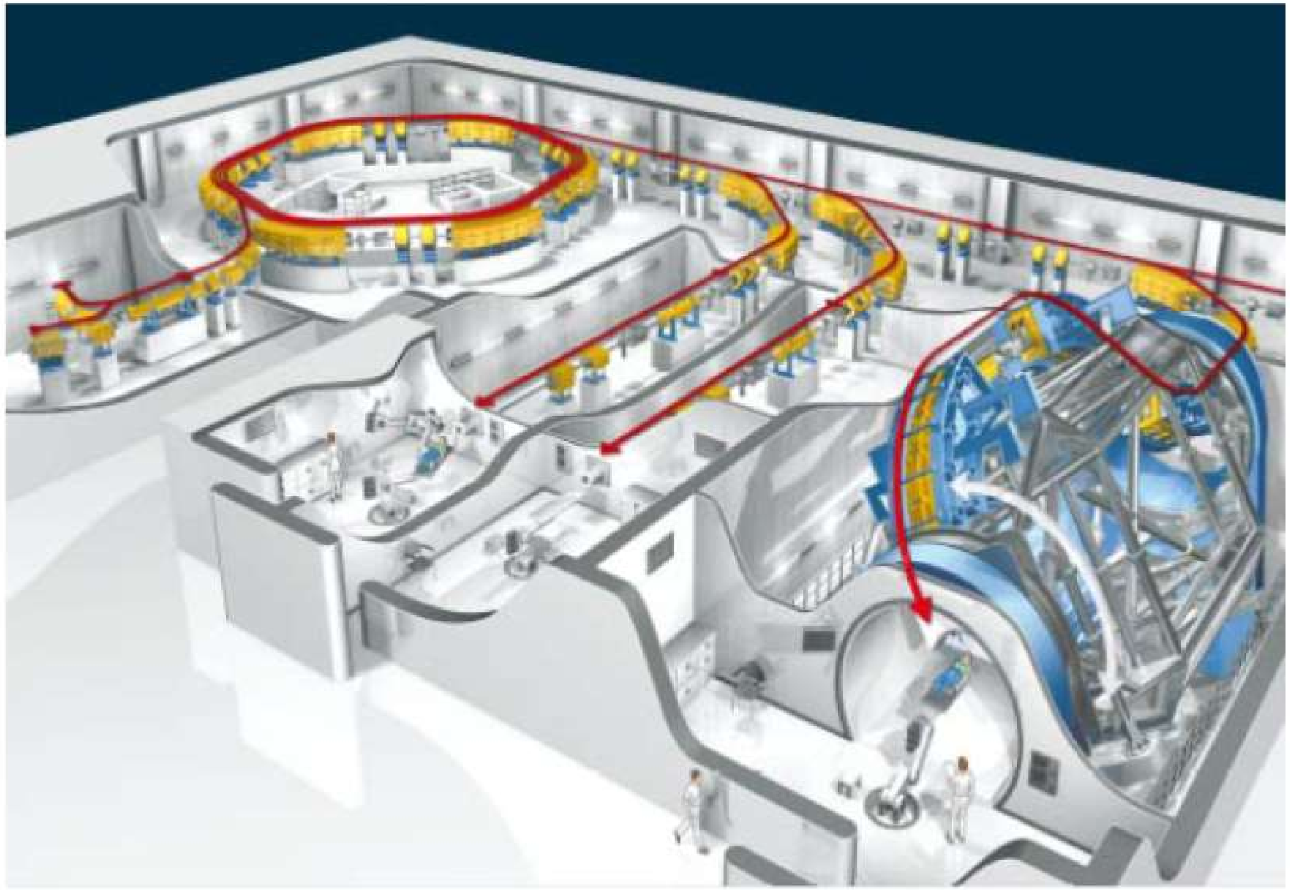
10+ proton centers to be built in Spain (by 2026+)

Patients treated with particle therapy worldwide (as of 2022)



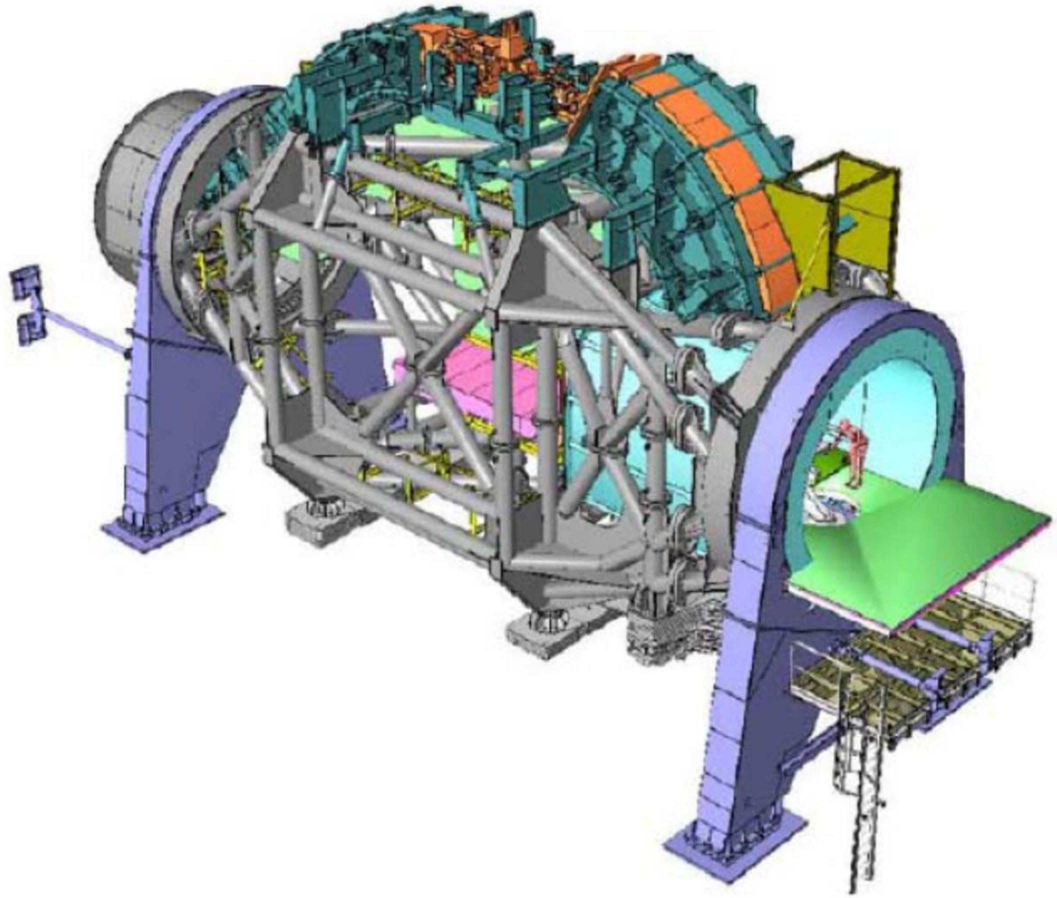
PTCOG Homepage March 2024

Heidelberg Ion 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

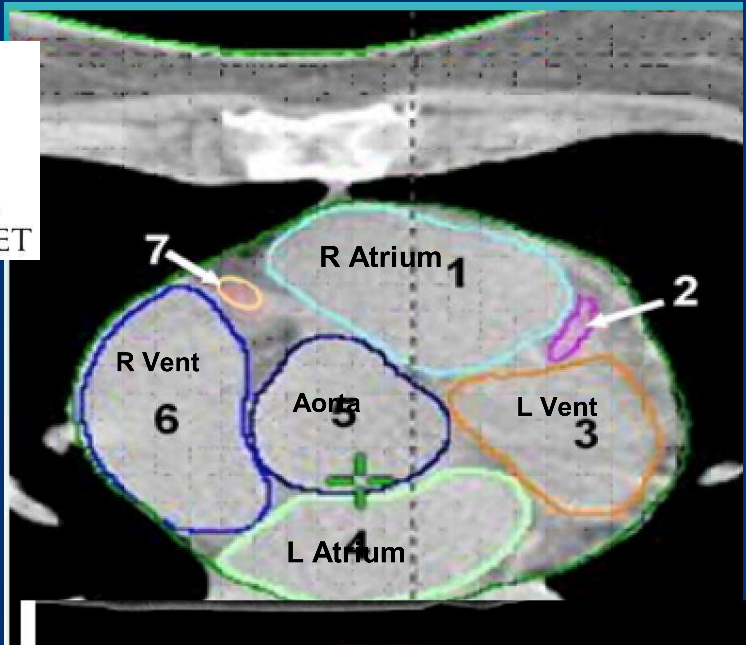
Majority receives radiation

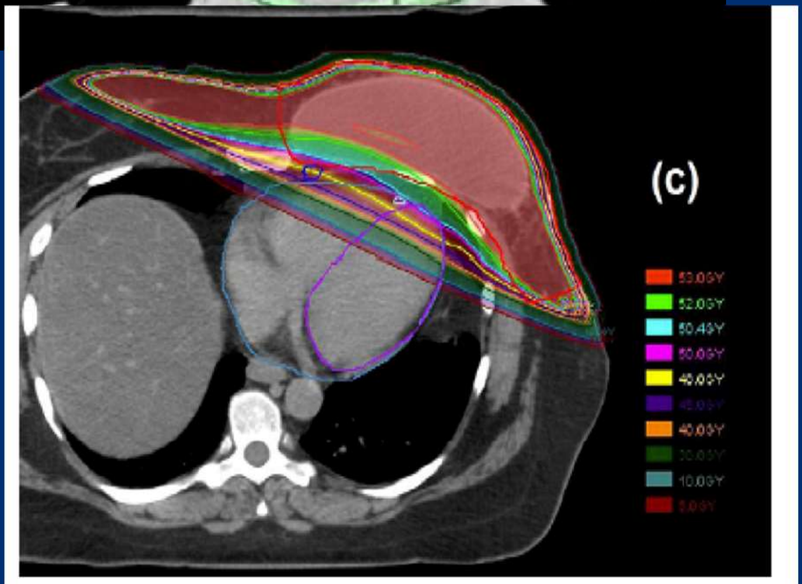
“Horror” stories from side effects of radiation leads many women to choose mastectomy over BCT

Distribution of Coronary Artery Stenosis After Radiation for Breast CancerG.

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

UPPSALA UNIVERSITET





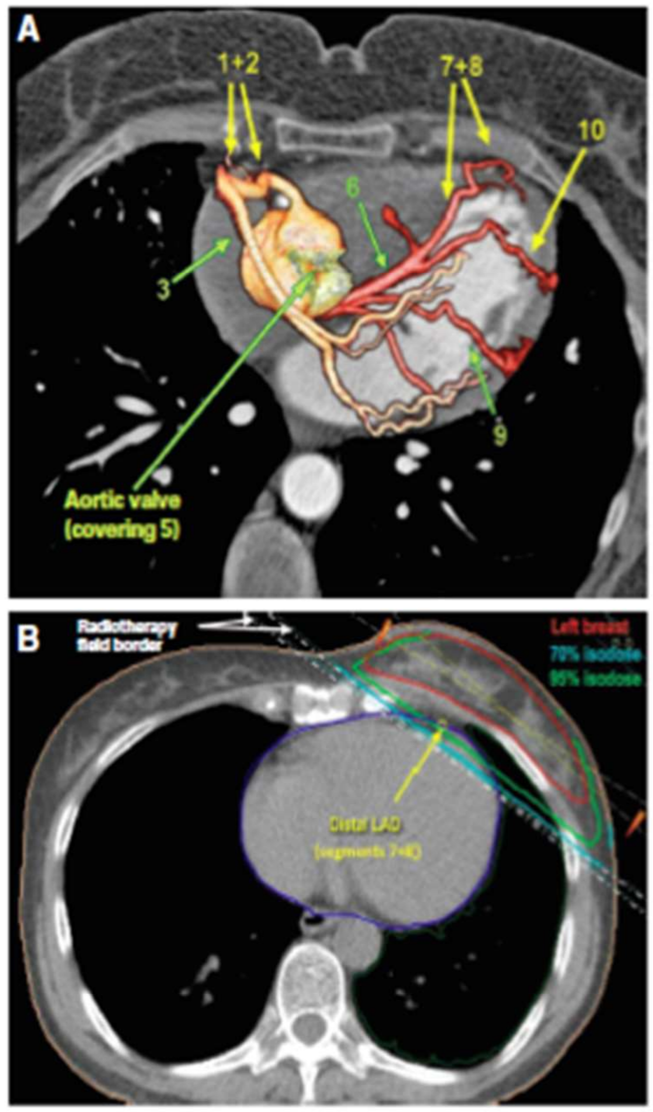
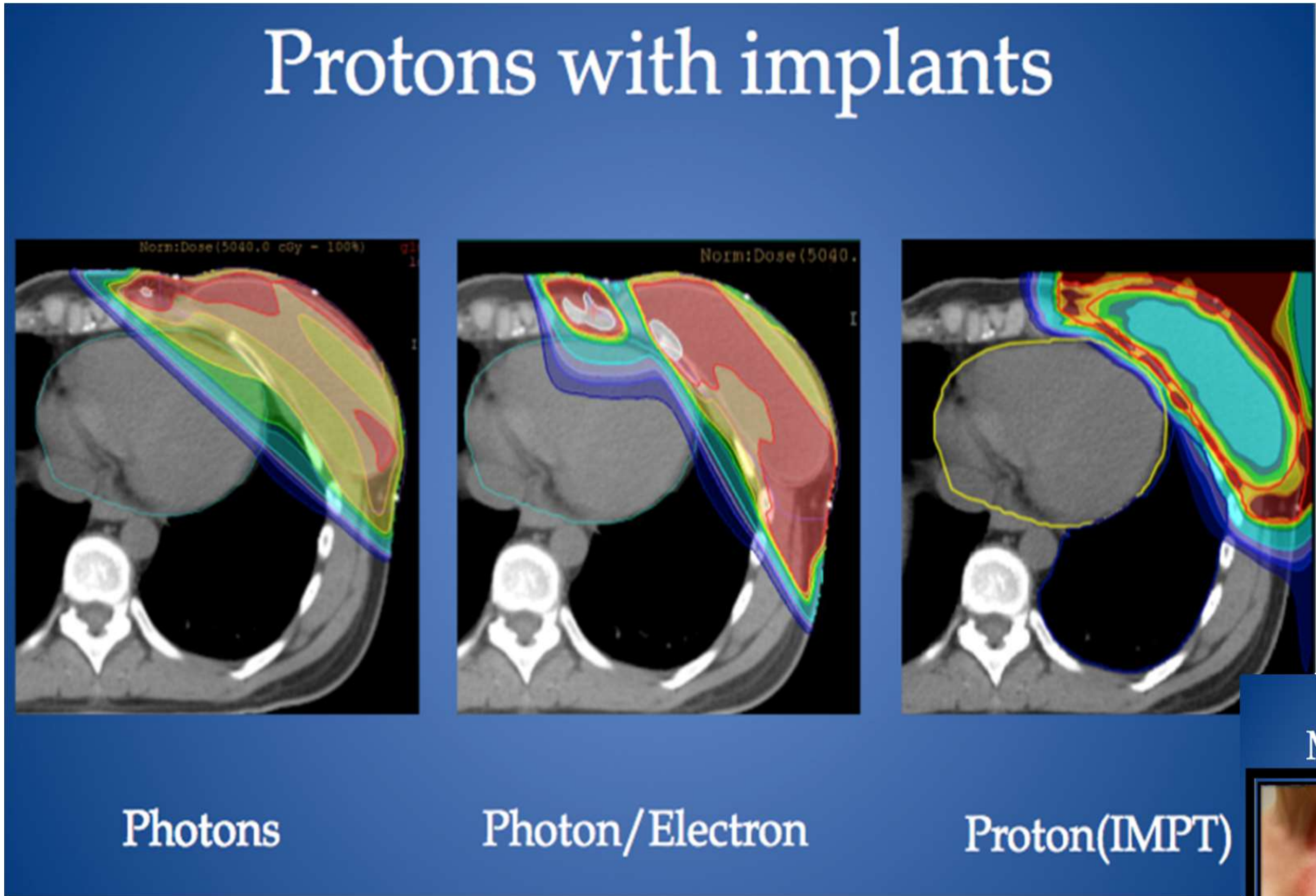


Fig 2. (A) Coronary angiogram superimposed on computed tomography (CT) of heart illustrating anatomy of coronary arteries with branches of right coronary artery (orange) and left circumflex and left anterior descending (LAD) arteries (red); numbered arrows indicate segments. (B) CT dose-planned left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

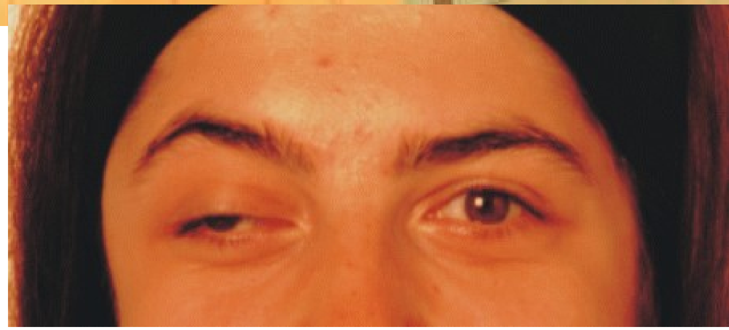
Post-mastectomy radiotherapy for left-side breast with or without immediate reconstruction



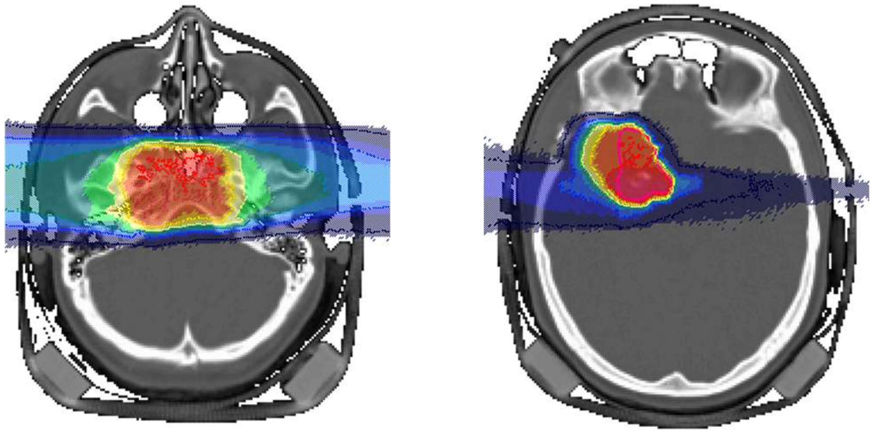
MacDonald et al, *Int J Rad Onc Bio Phys*, 1-7, 2013

Clinical results

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



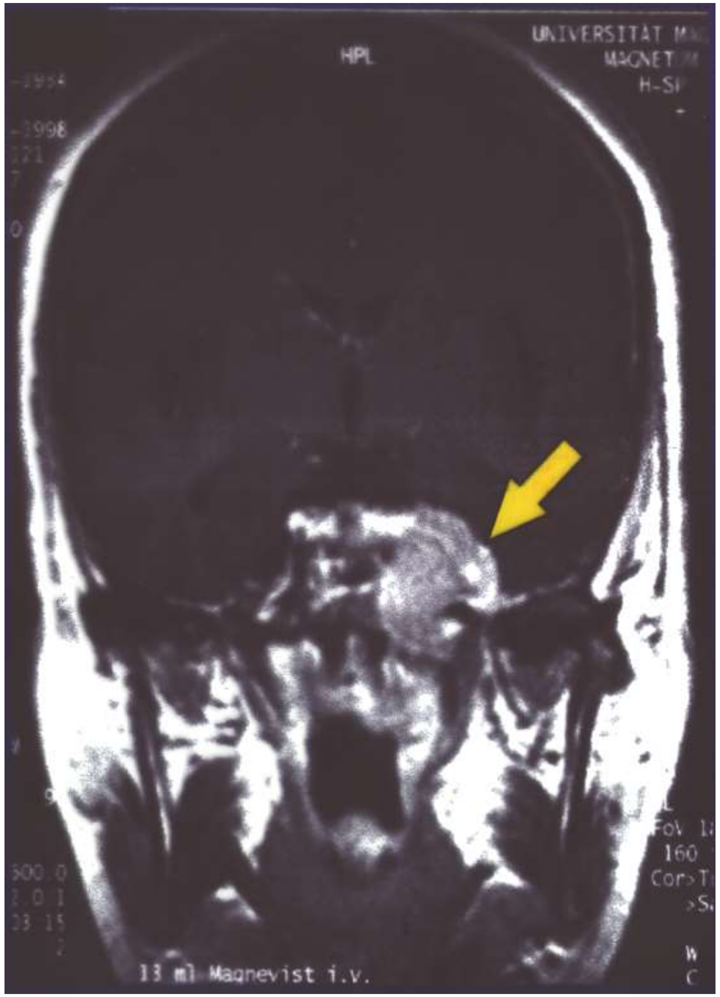
vor Bestrahlung



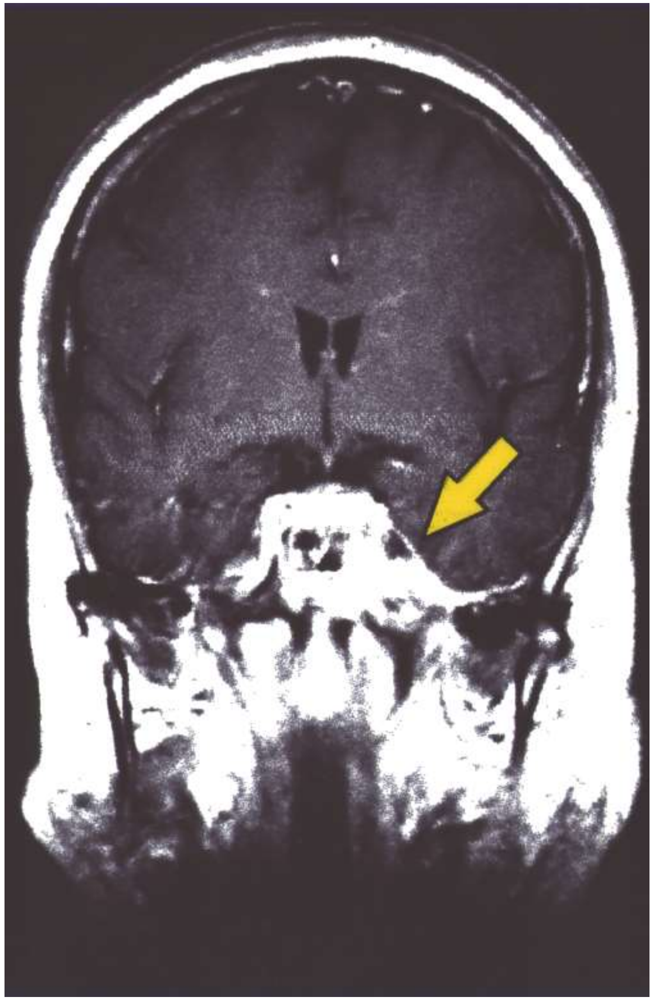
6 Weeks after carbon tfeatment with a dose of 60 Gye

D.Schulz-Ertner et al.

Adenocystic Carcinoma
combined photons and C12-Boost

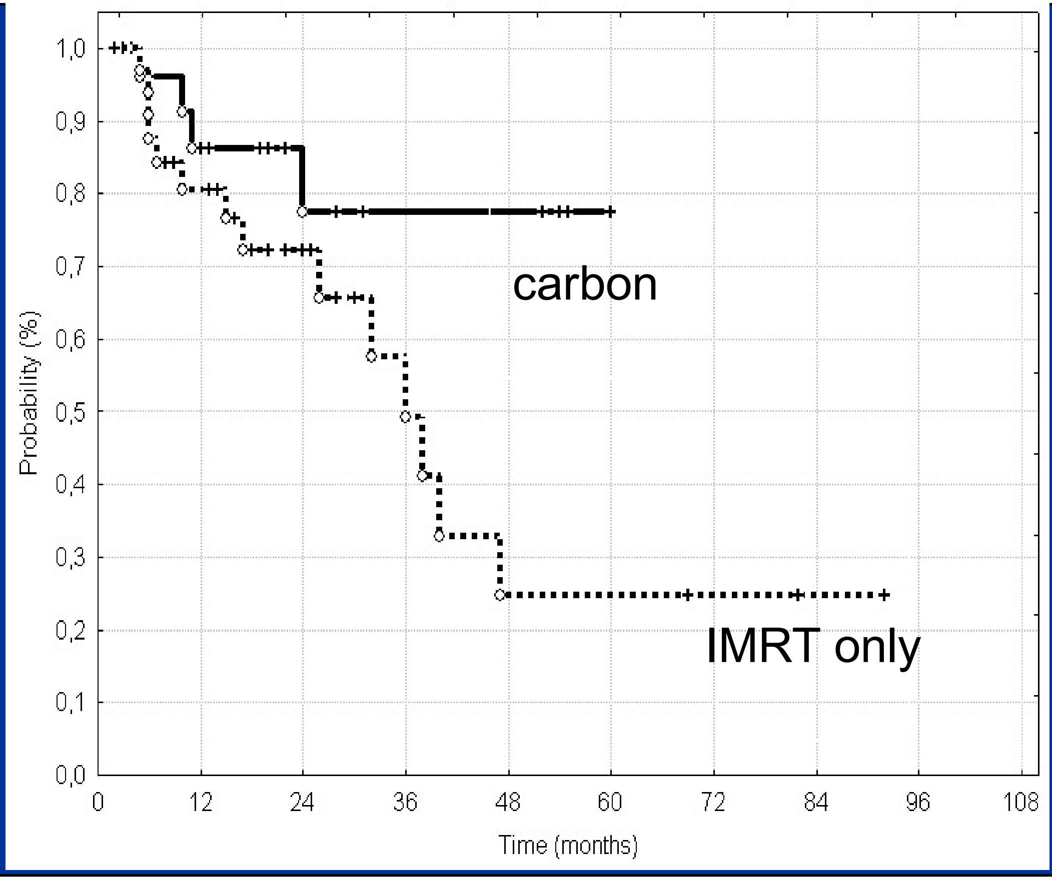


Prior RT



6 weeks after RT

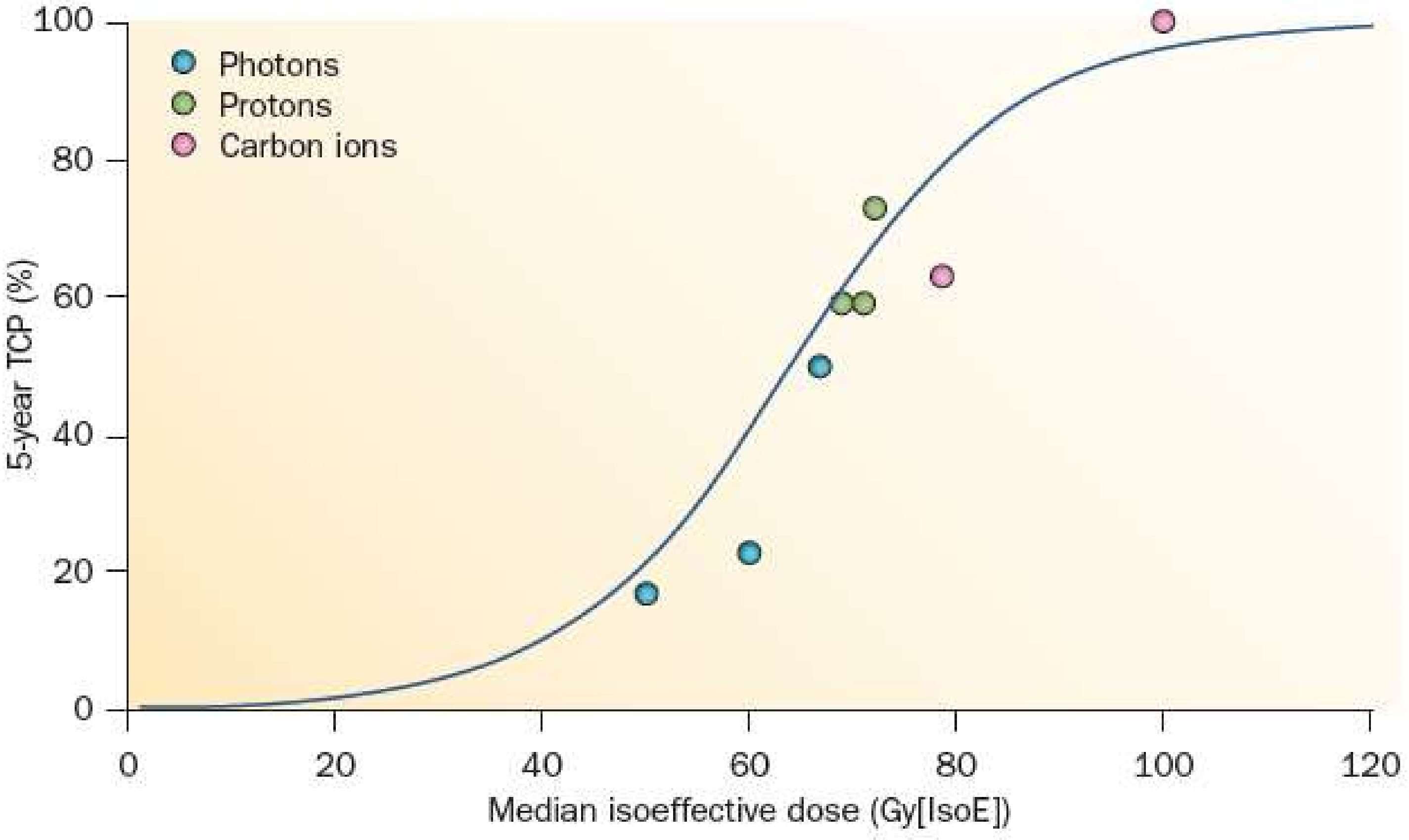
Adenoidcystic carcinomas: Photon-IMRT with and without carbon boost



Tumor control

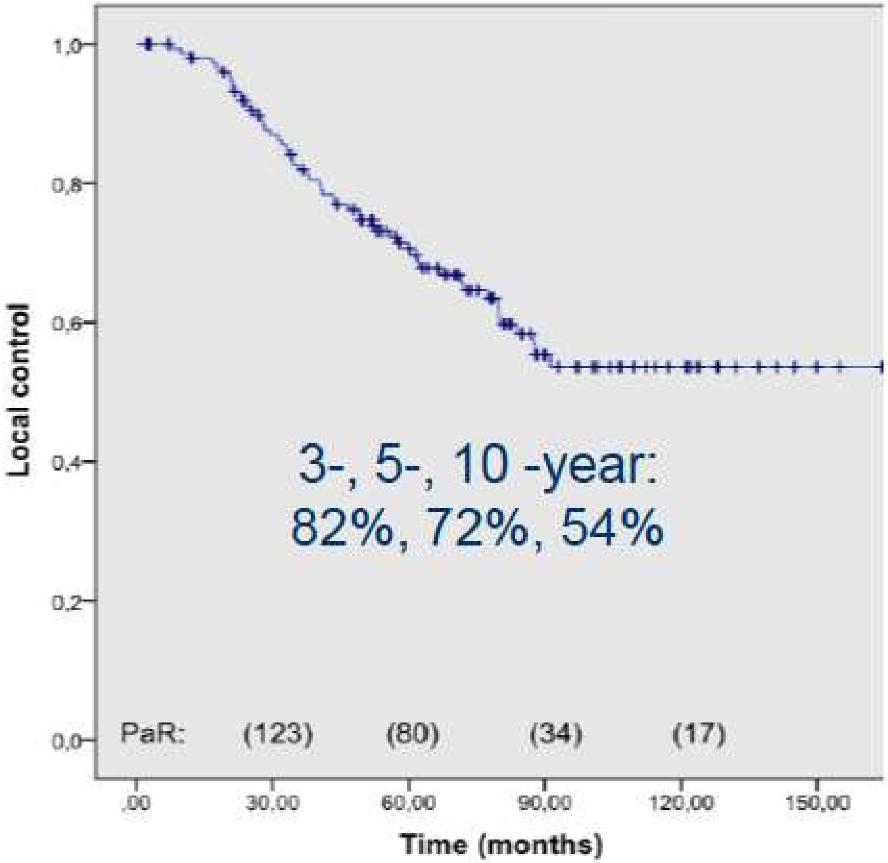
[Schulz-Ertner, Cancer 2005]

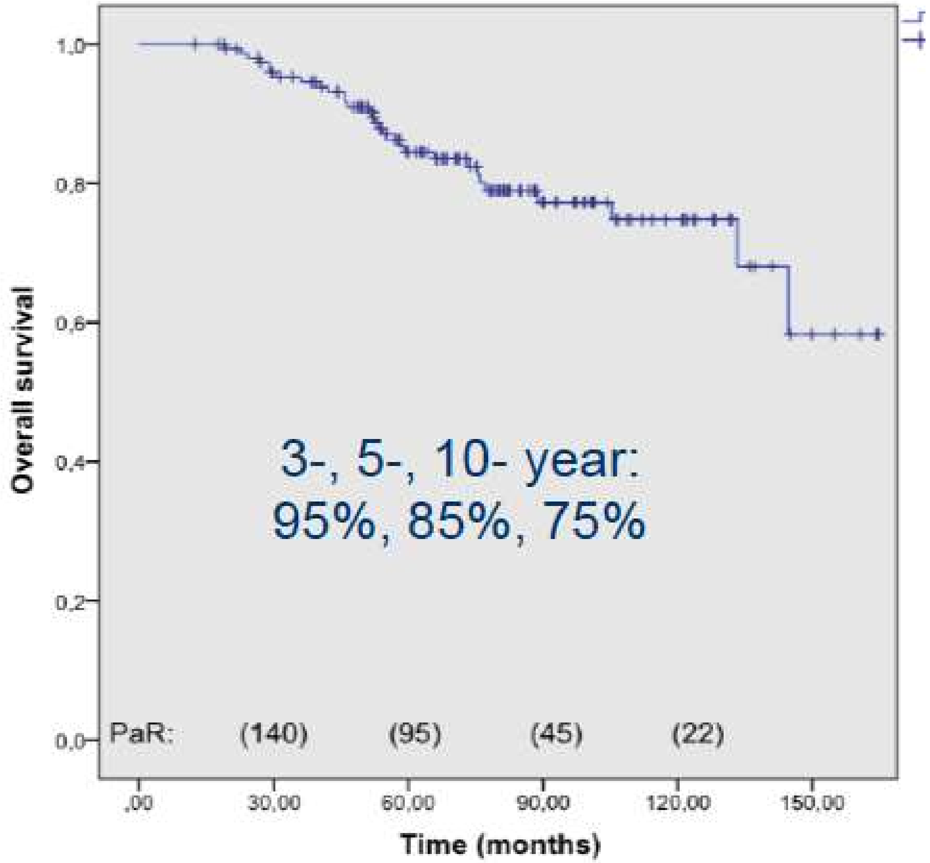
Skull-base chordoma



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

Long-term results of the chordoma patients treated at GSI





courtesy of Jürgen Debus

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.

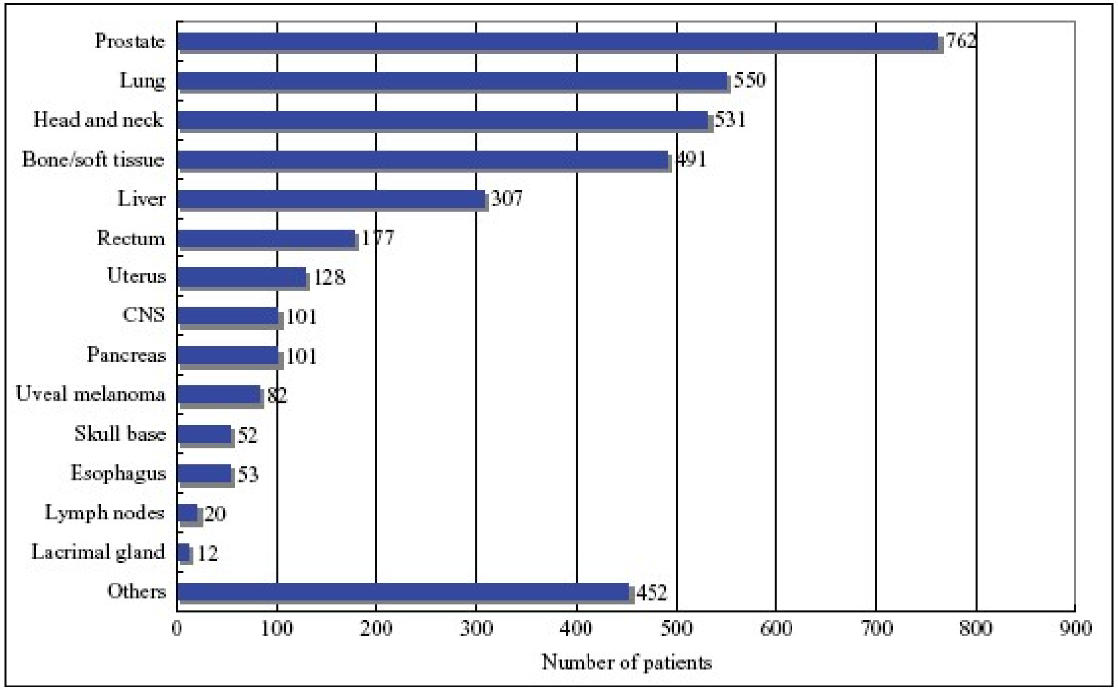
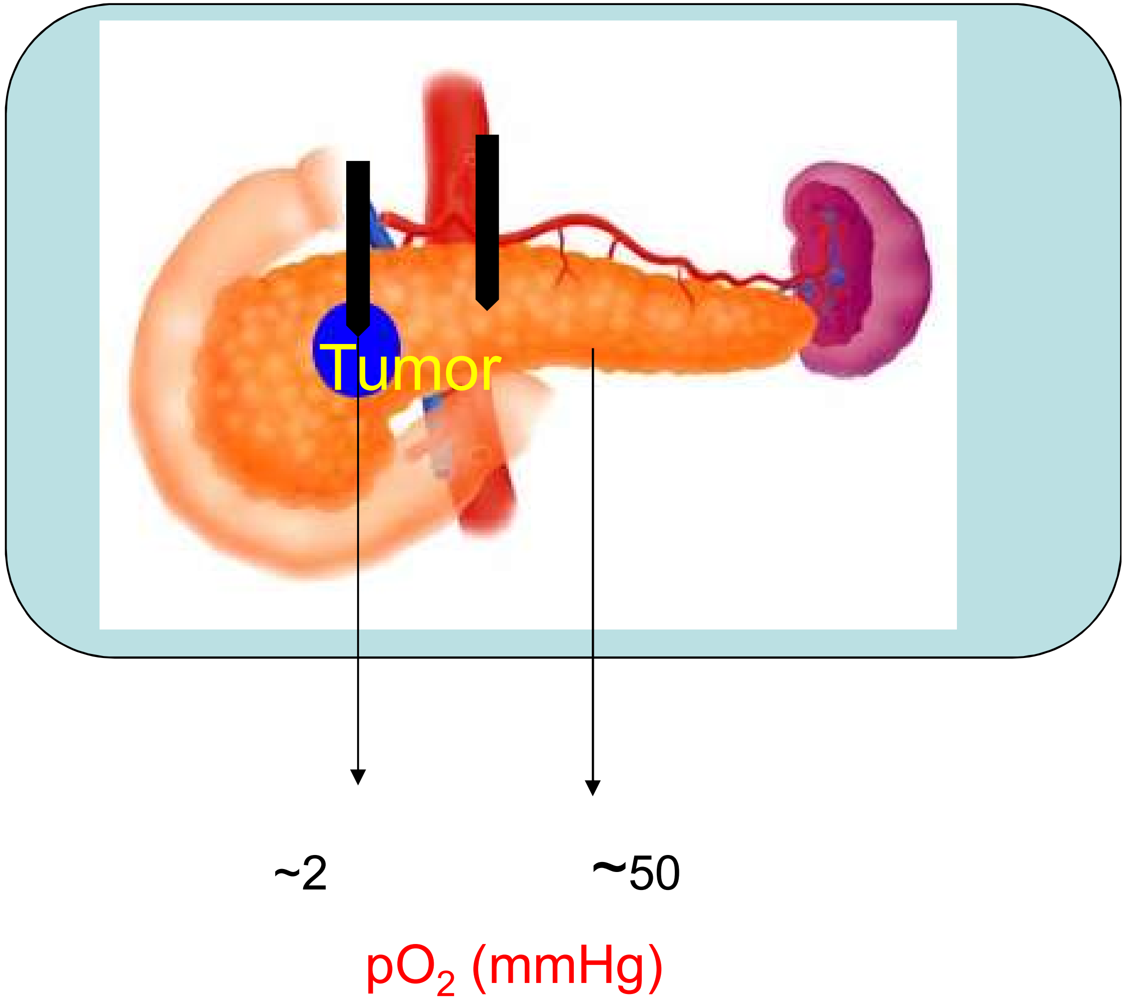


Figure 1. Number of patients, with a variety of tumors enrolled at NIRS for C-ion RT.

NIRS annual report 2008, Tsujii et al.

A recent application: pancreas cancer

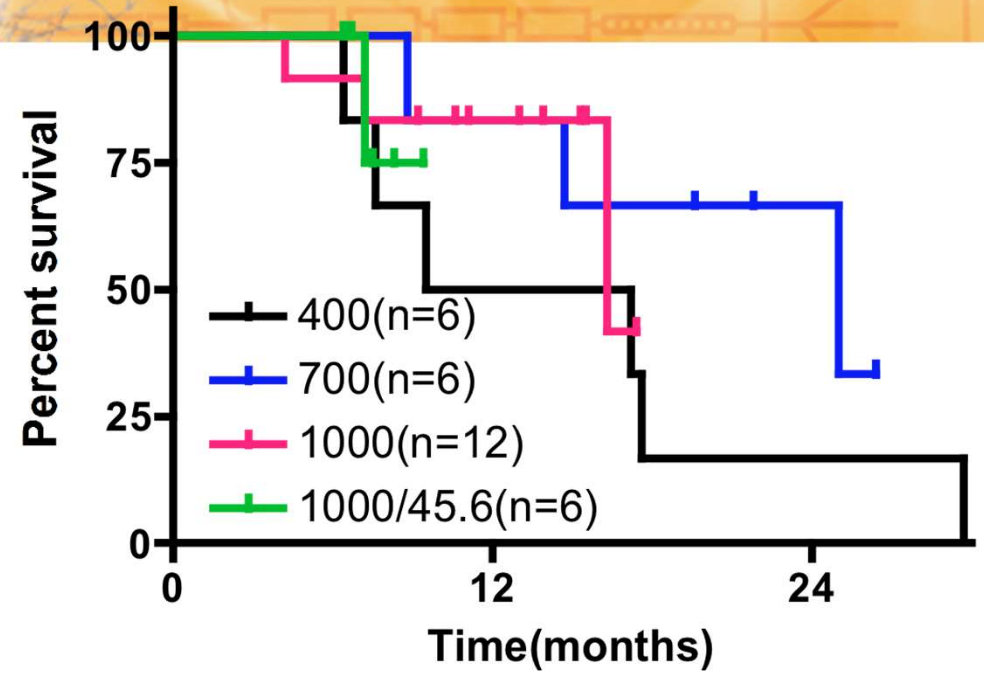
•Pancreatic cancer ranks as the fifth leading cause of cancer related death in the world.
•95% are adenocarcinomas
•Approximately 34,000 patients die from pancreatic cancer per year in USA.
•The 5 year survival rate of pancreatic cancer patients is no more than 10% and its average survival time after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

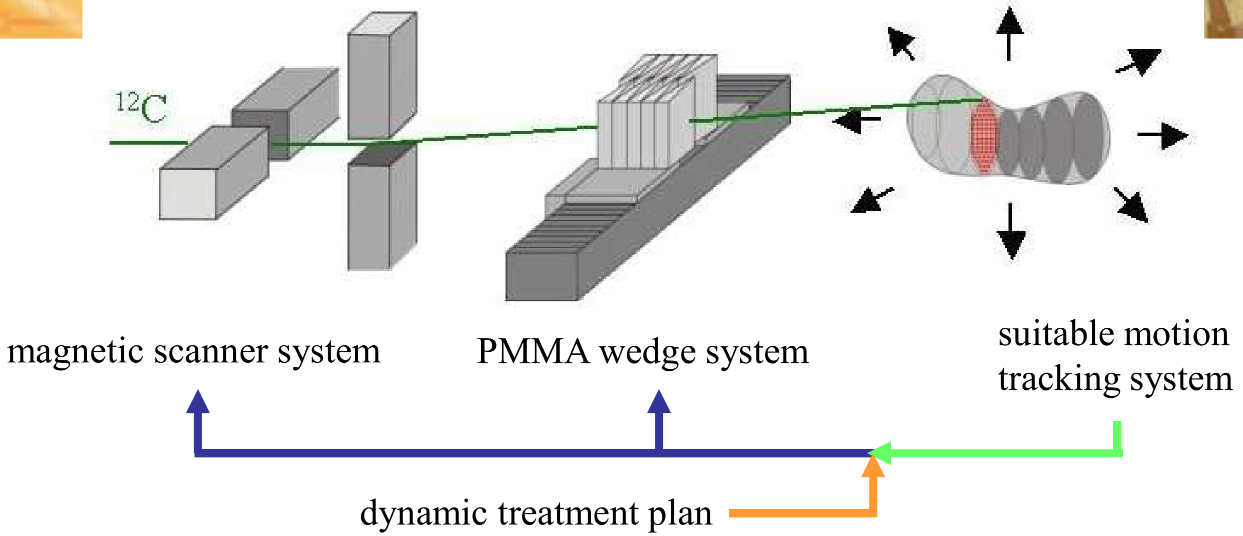
Biomarkers

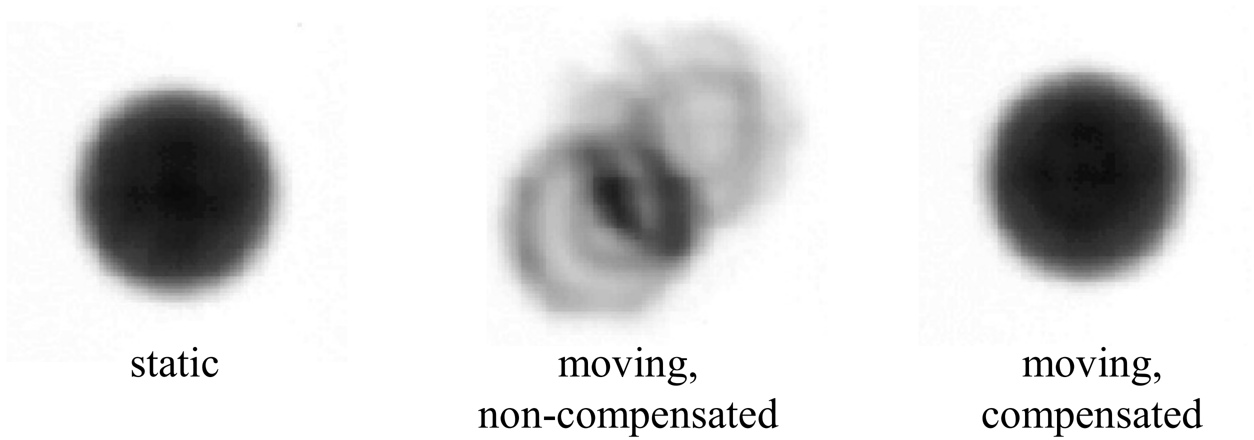
Intra-tumoral heterogeneity (hypoxia)

Noncancer diseases

Second cancers

3D online motion compensation (3D-OMC)

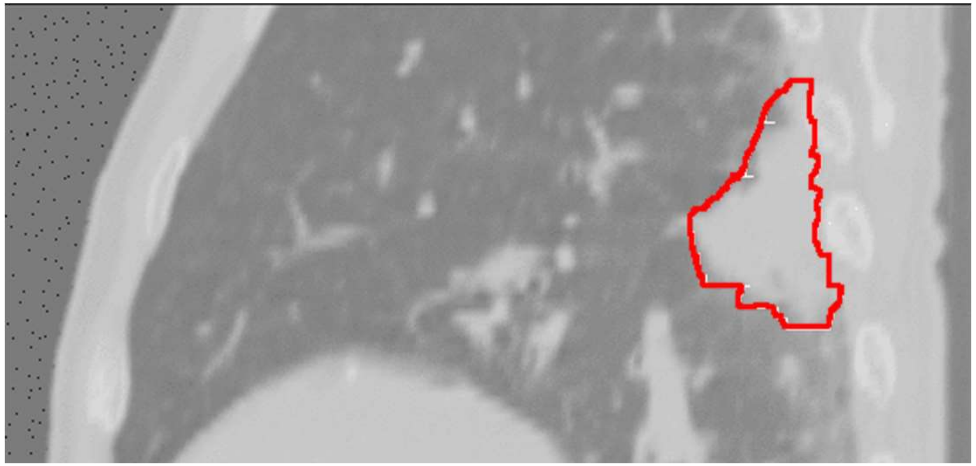


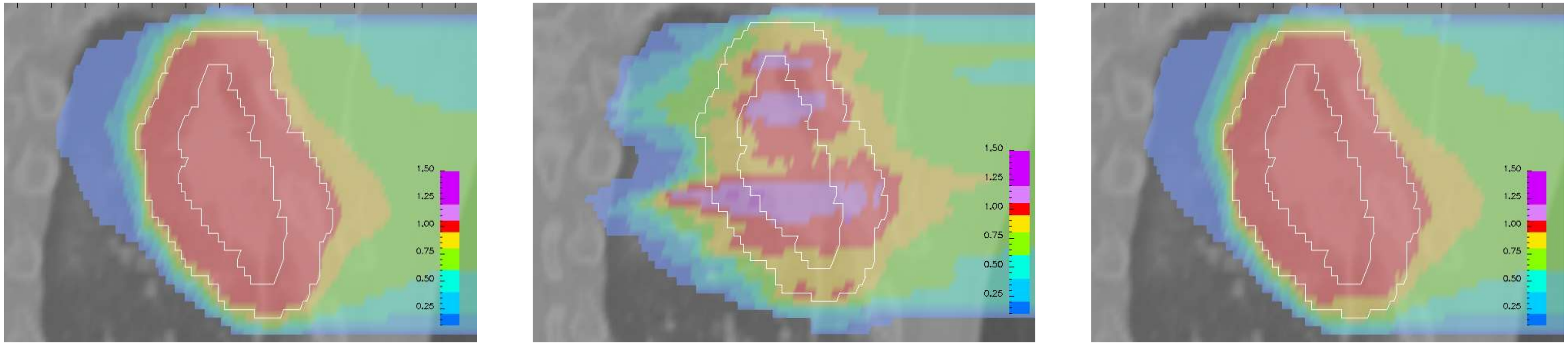


➢ real-time, highest precision

Bert & Durante Phys. Med. Biol. 2011

Influence of target motion

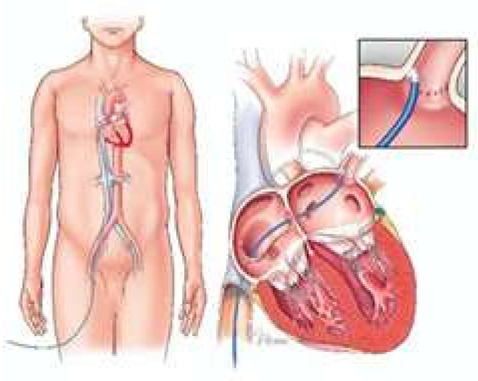




static | not compensated | compensated

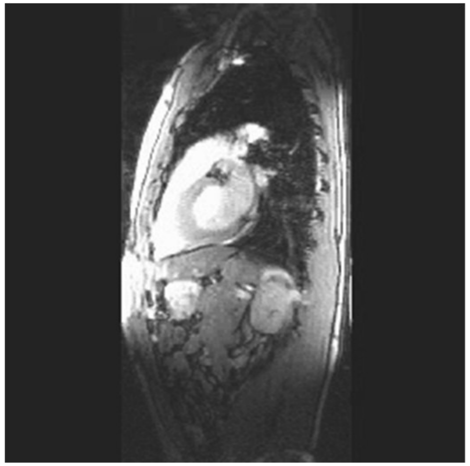
Bert & Durante, Phys. Med. Biol. 2011 $T=6.0s, \Phi=270^o$

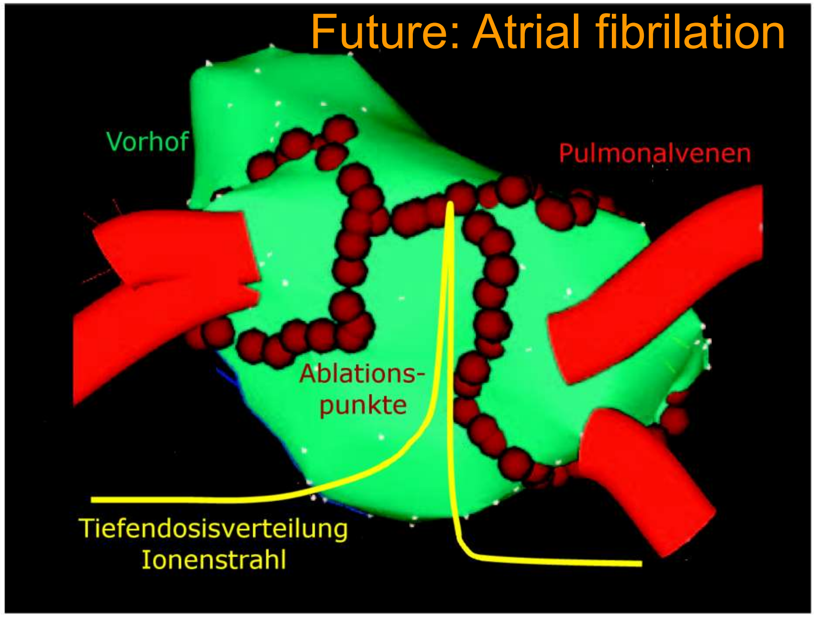
Treatment of noncancer diseases: cardiac arrhythmias?

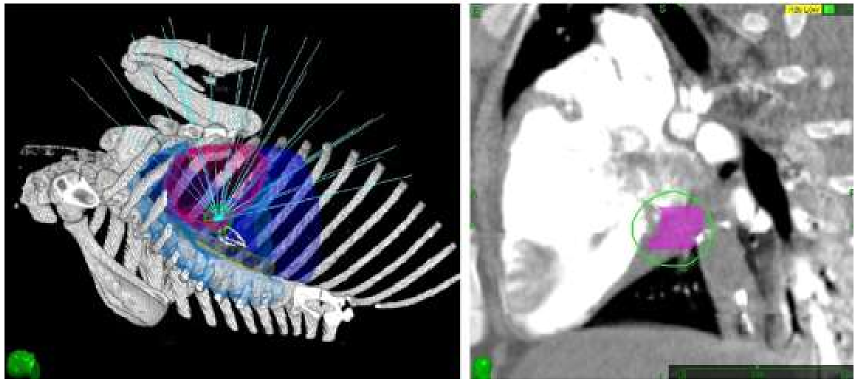


- Atrial fibrillation affects about 5% of middle-aged population and is associated with high risk of stroke and death

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

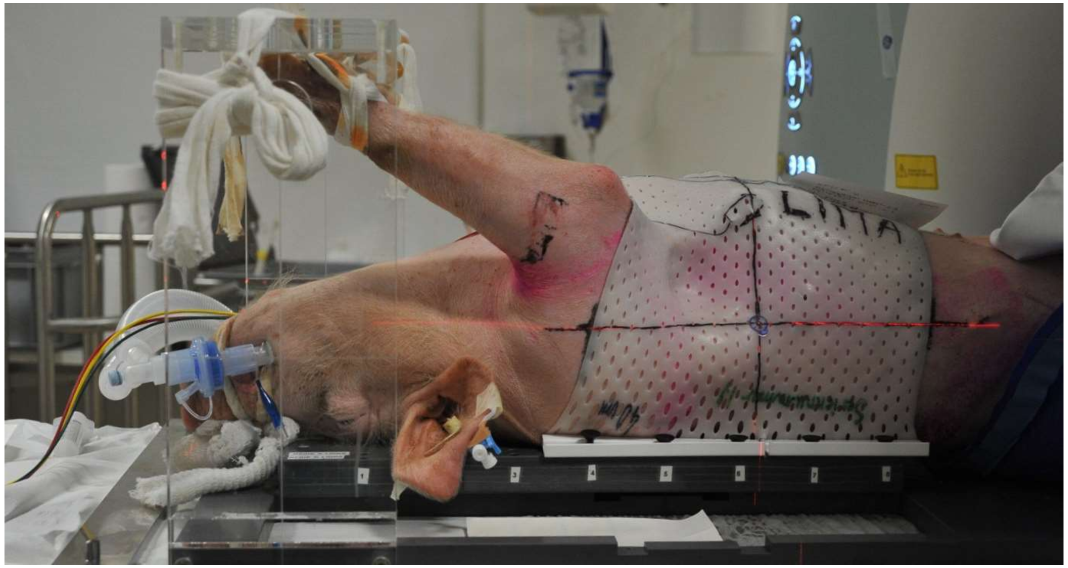






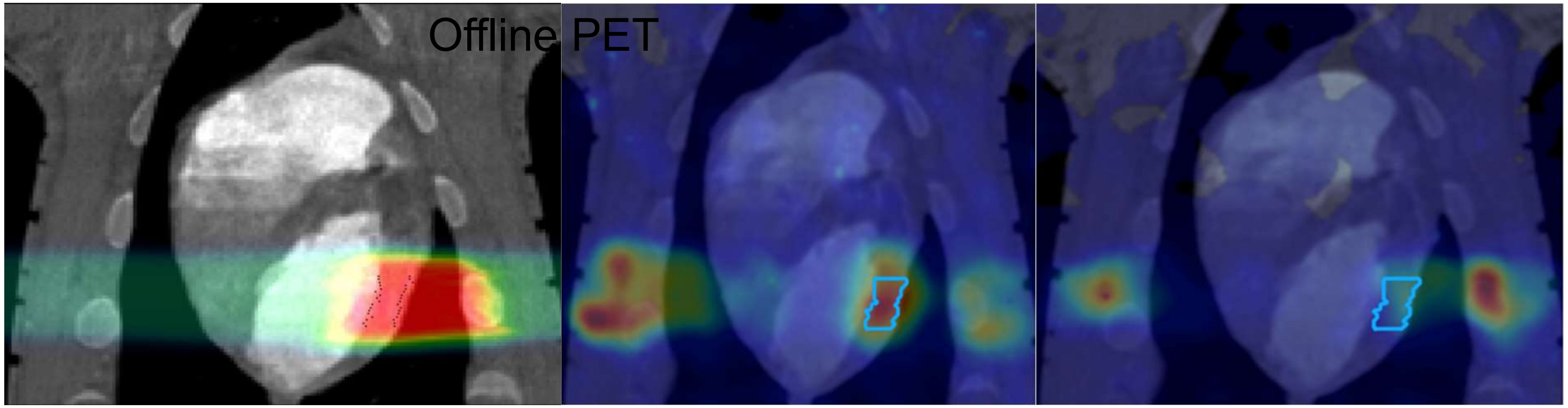
- CyberHeart: cardiac lesion induced by a Cyberknife (*Heart Rhythm*., June 2010)

Noninvasive treatment of ventricular fibrillation by C-ions



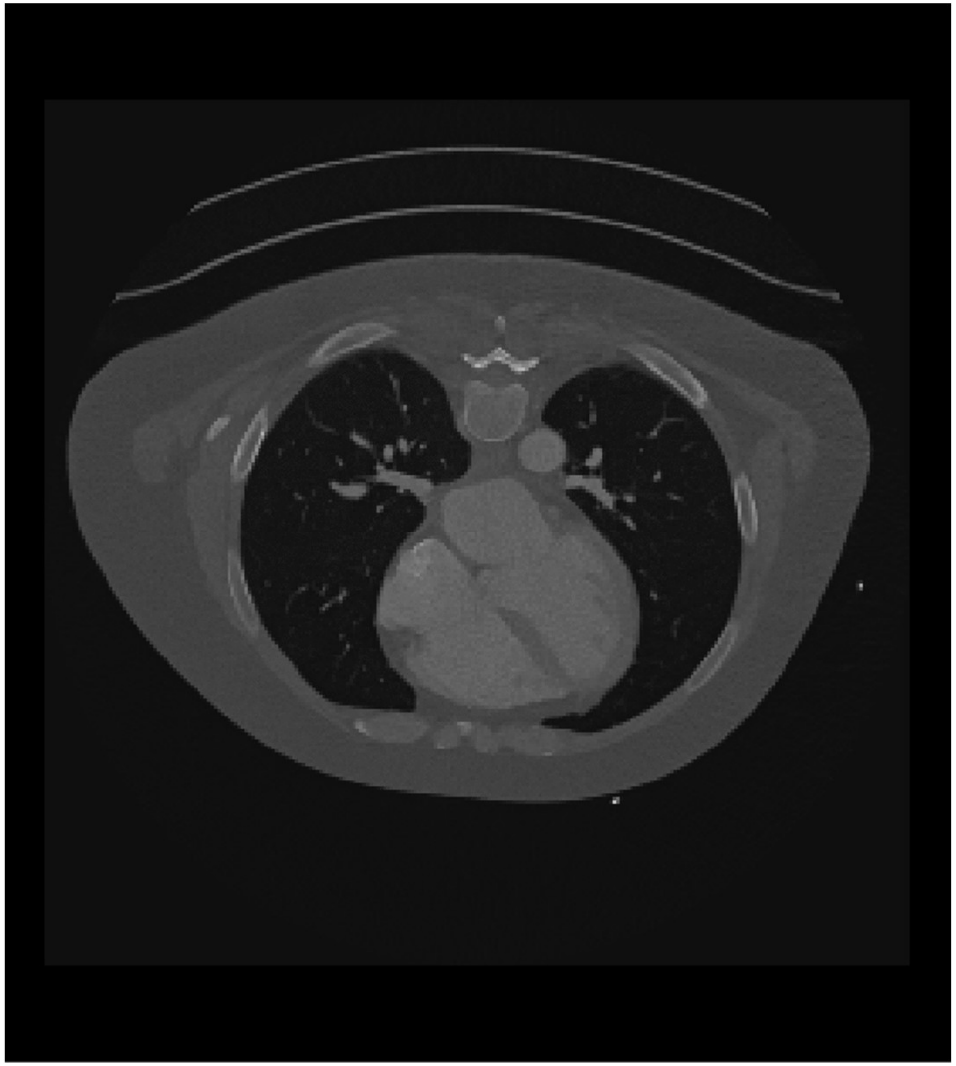
Planned dose In-beam PET

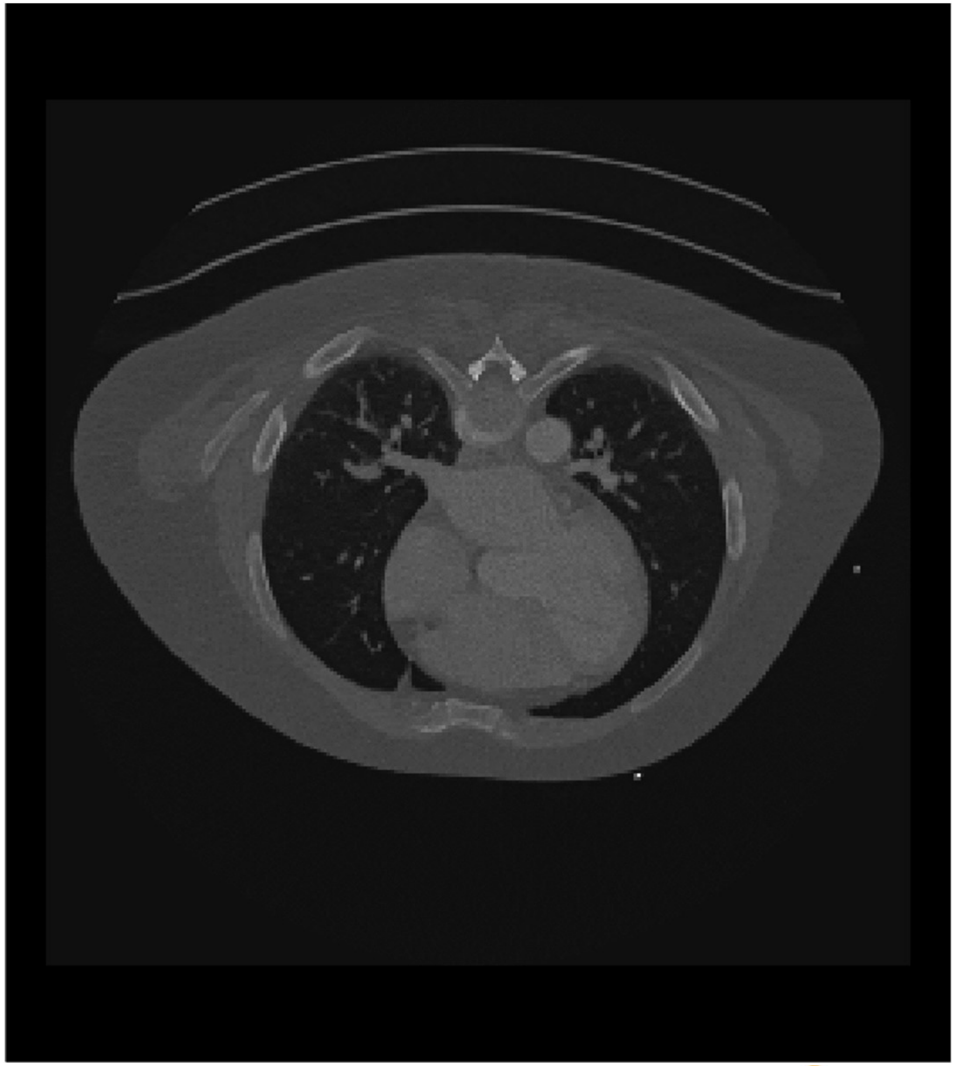
Offline PET

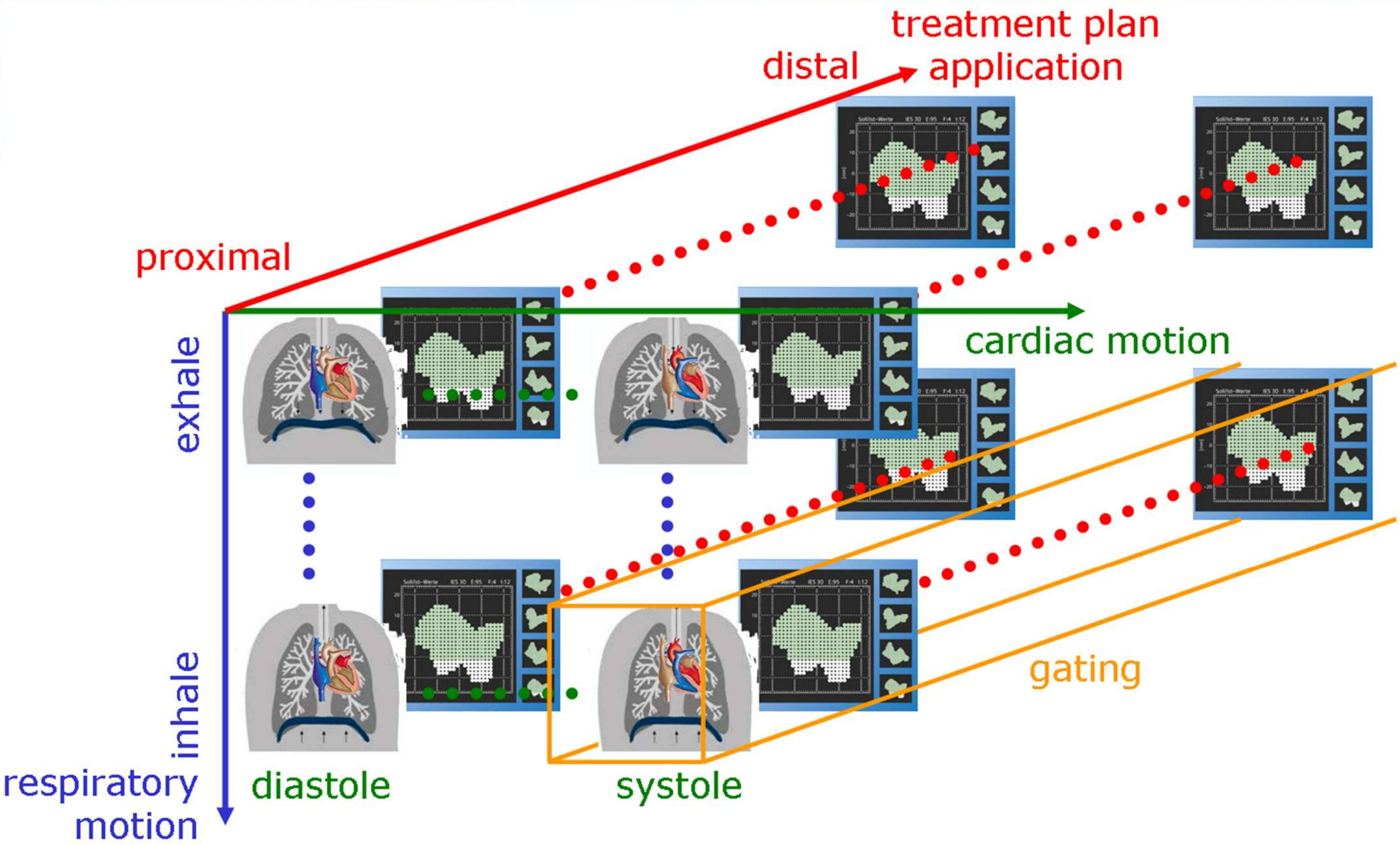


Lehmann *et al., Sci. Rep*. 2016; Rapp *et al., Sci. Rep*. 2019

Mayo Clinics: 5D CT

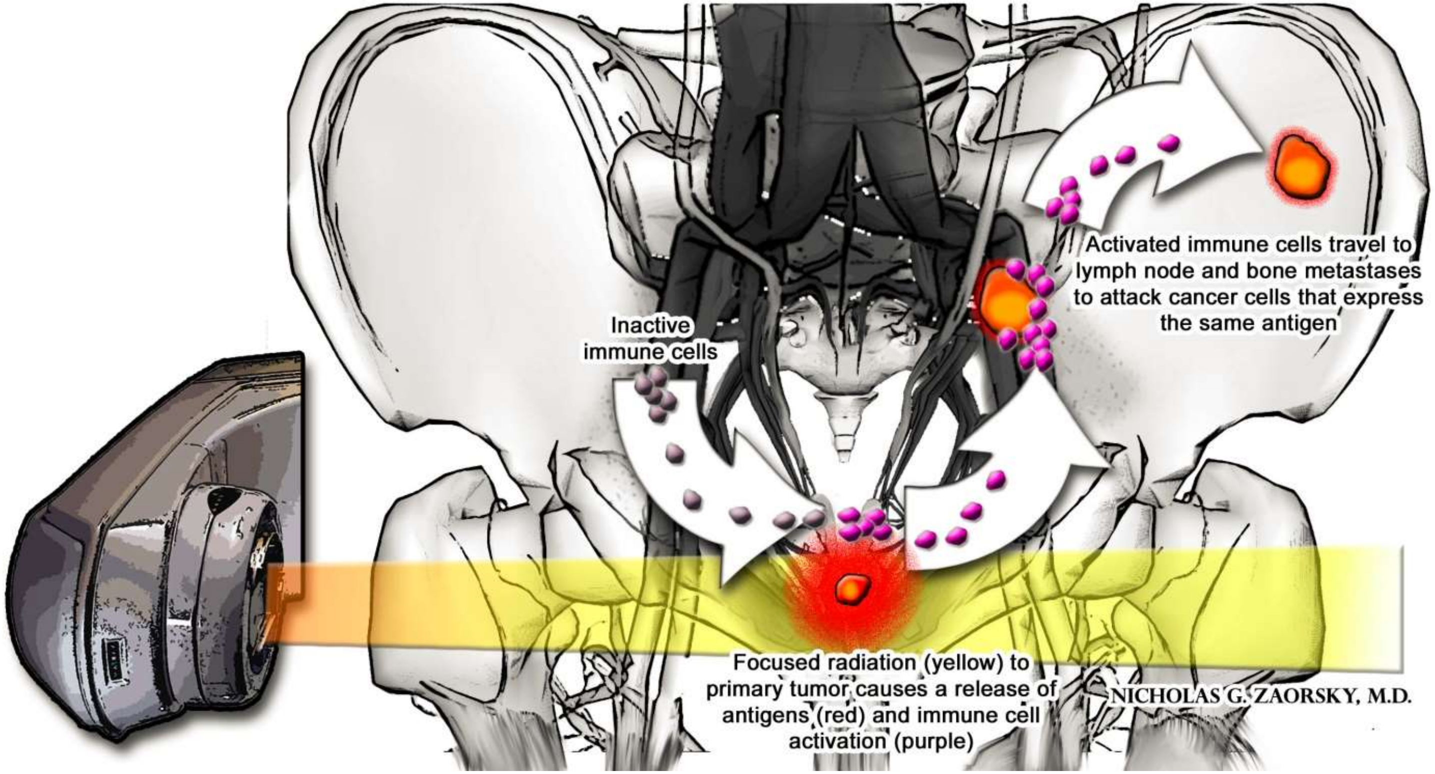






Particle 5D-TP (Bert *et al., Med. Phys*. 2012)

Abscopal effect – radiation-induced, immunogenic inactivation of metastases

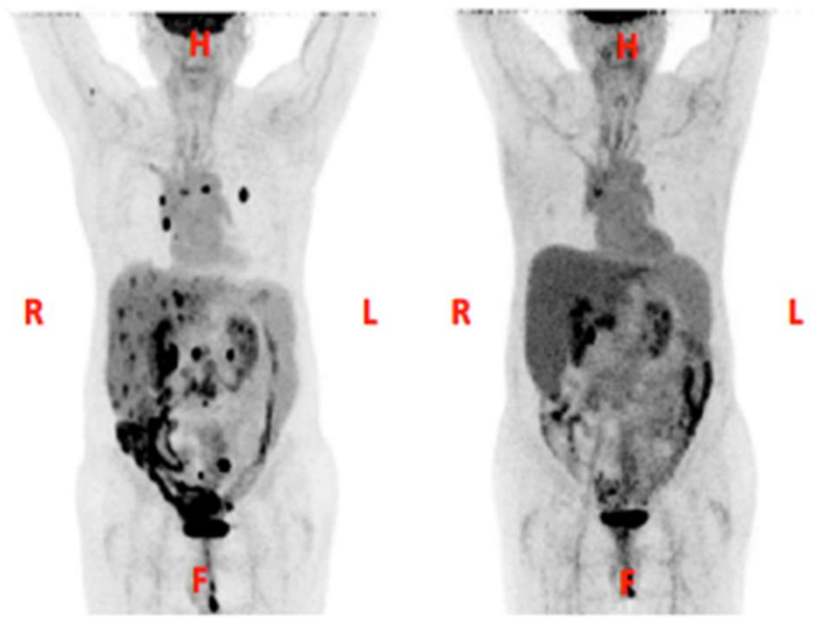


Combining RT and checkpoint inhibitors

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

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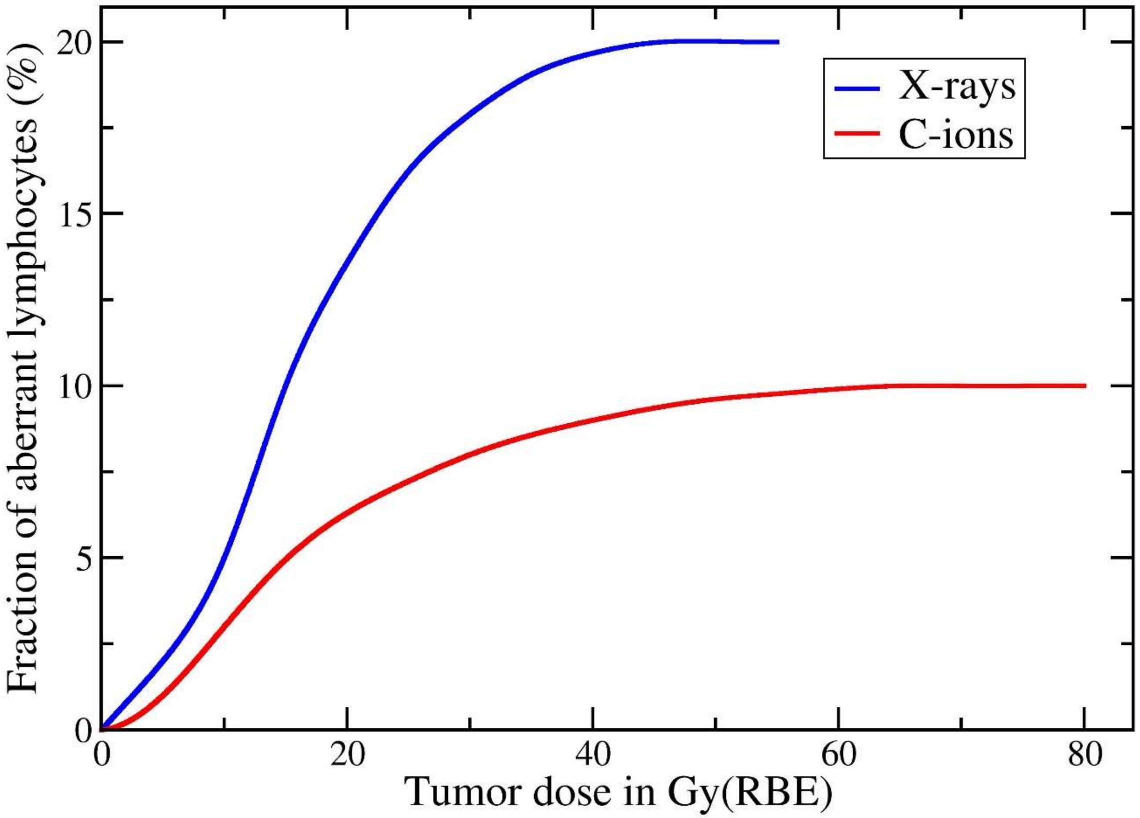
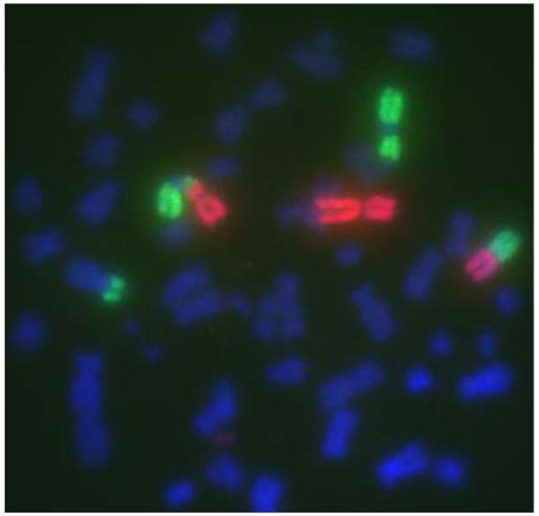
→ **matter of ongoing discussion in literature**

Advantages of particle RT for the immune system



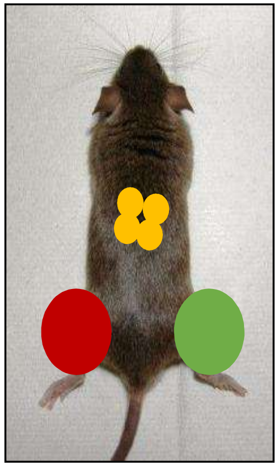
Reduced integral dose of carbon ion therapy to healthy tissue

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

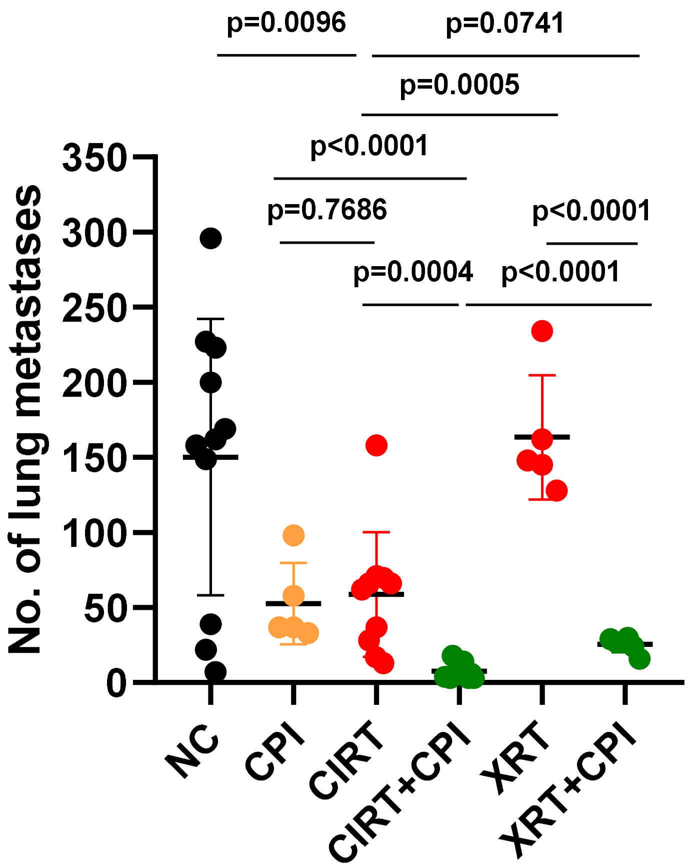


Durante et al., *Int. J. Radiat. Oncol. Biol. Phys*. 2000

Reduction of lung metastases



Assessment of superficial nodules after fixation in Bouin's solution



N=2-3

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