Nuclear physics in particle therapy

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Istituto Nazionale di Fisica Nucleare

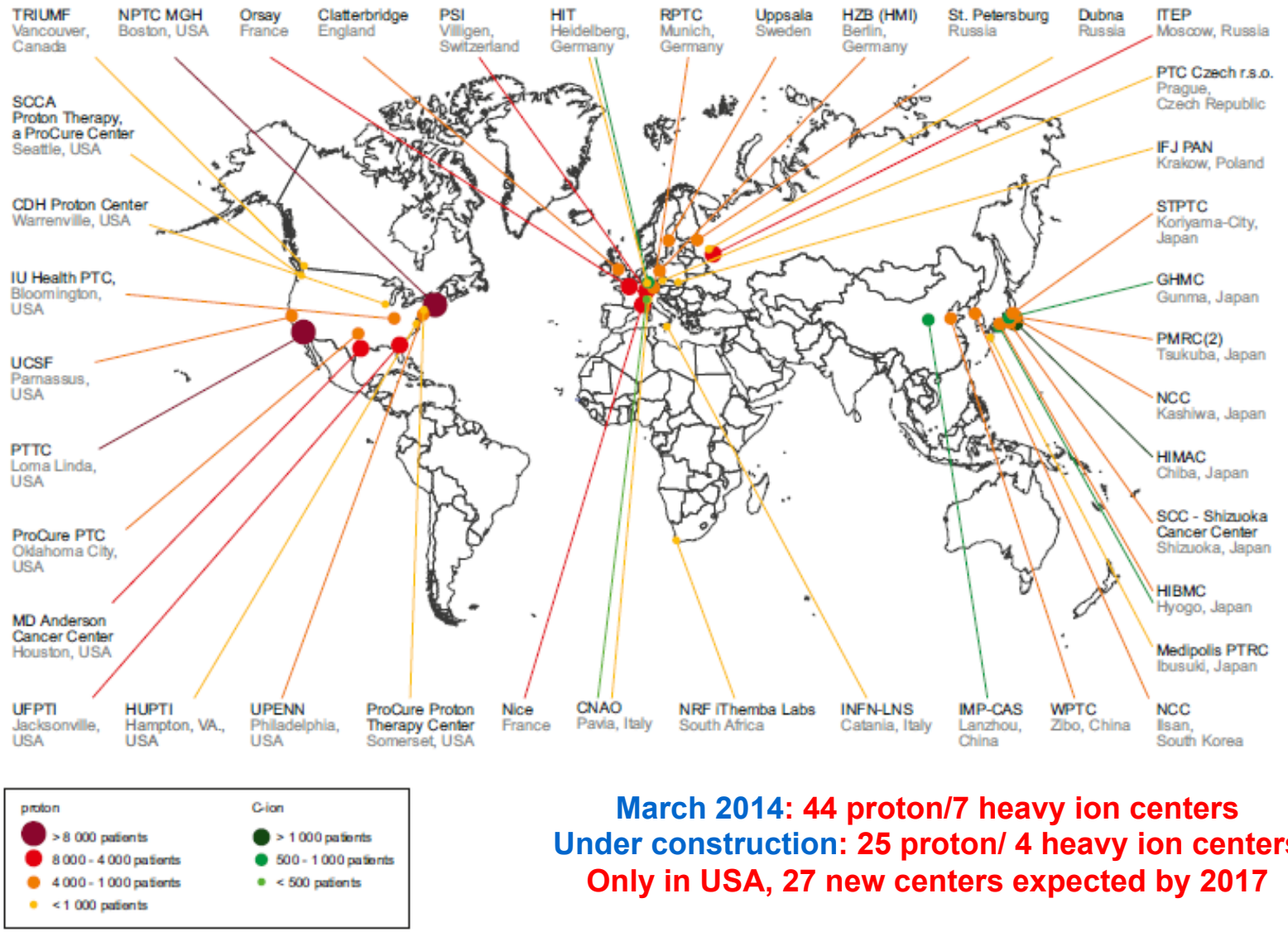
INFN Piano Triennale 2015-2017

FAIR

TECHNISCHE UNIVERSITÄT DARMSTADT

FIAS Frankfurt Institute for Advanced Studies

GSI



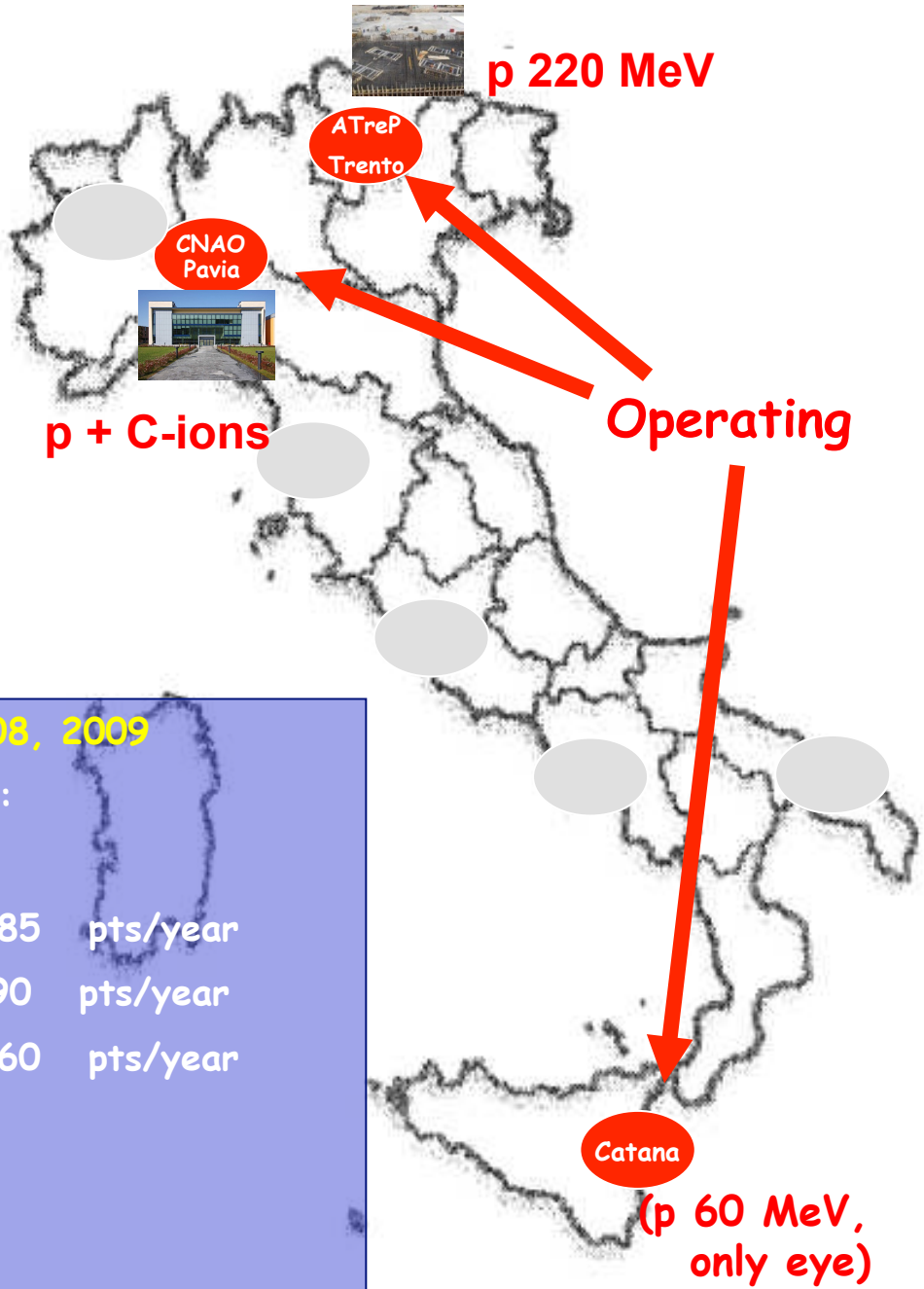
March 2014: 44 proton/7 heavy ion centers
Under construction: 25 proton/ 4 heavy ion centers
Only in USA, 27 new centers expected by 2017

NuPECC report „Nuclear Physics in Medicine“, 2014
Available online www.nupecc.org

ITALIAN NETWORK FOR HADRONTHERAPY

EXISTING 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

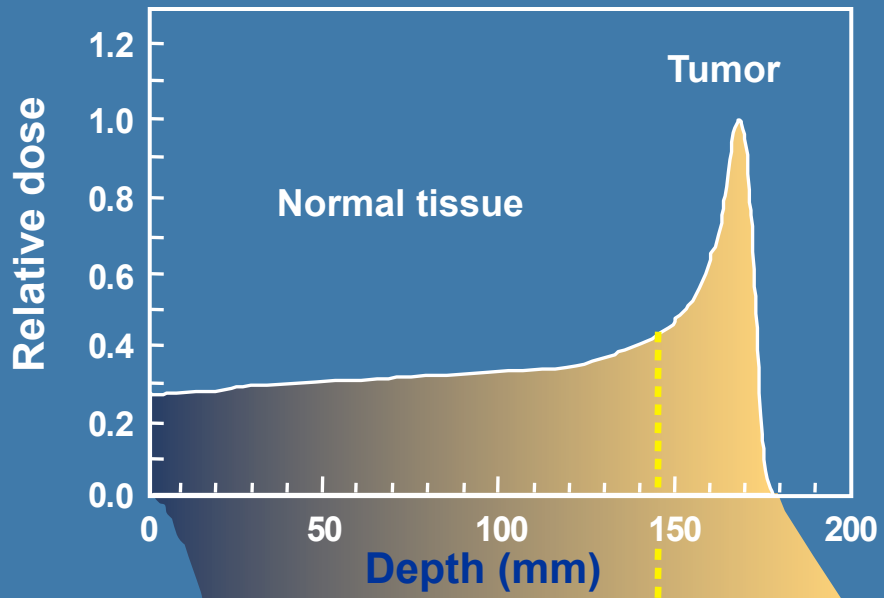
Conclusions of AIRO:

1 centre for ions

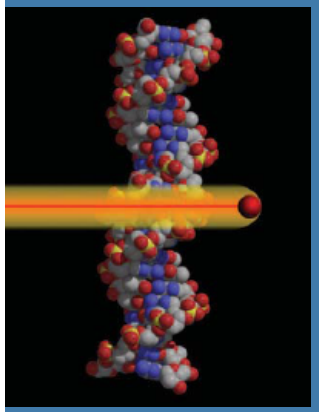
4-5 centres for protons

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

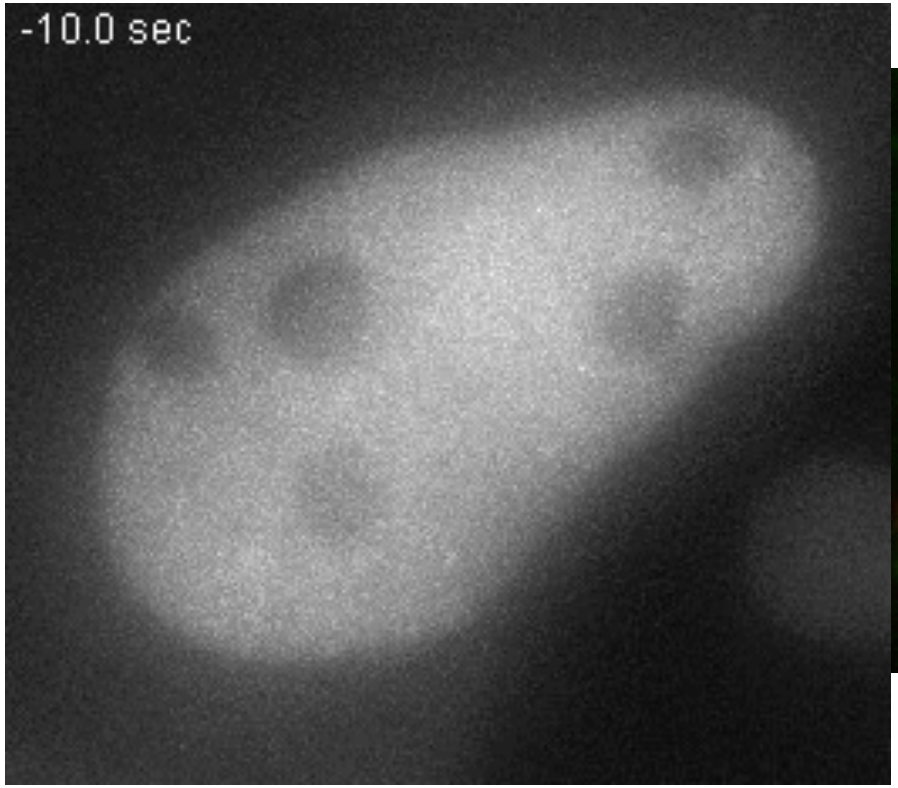


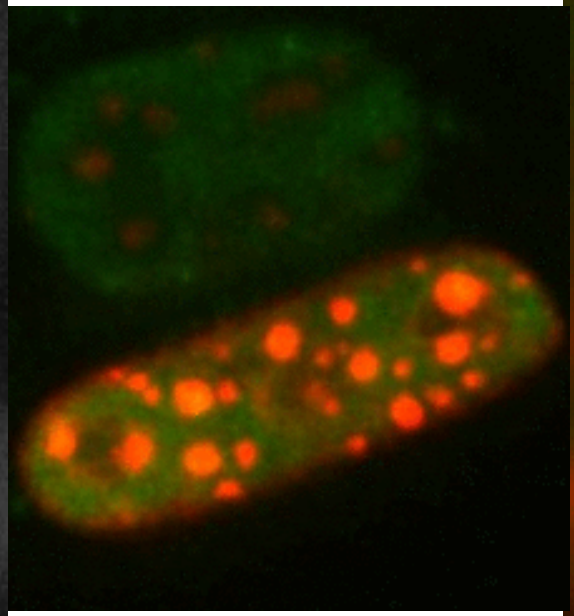
Potential advantages

- 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

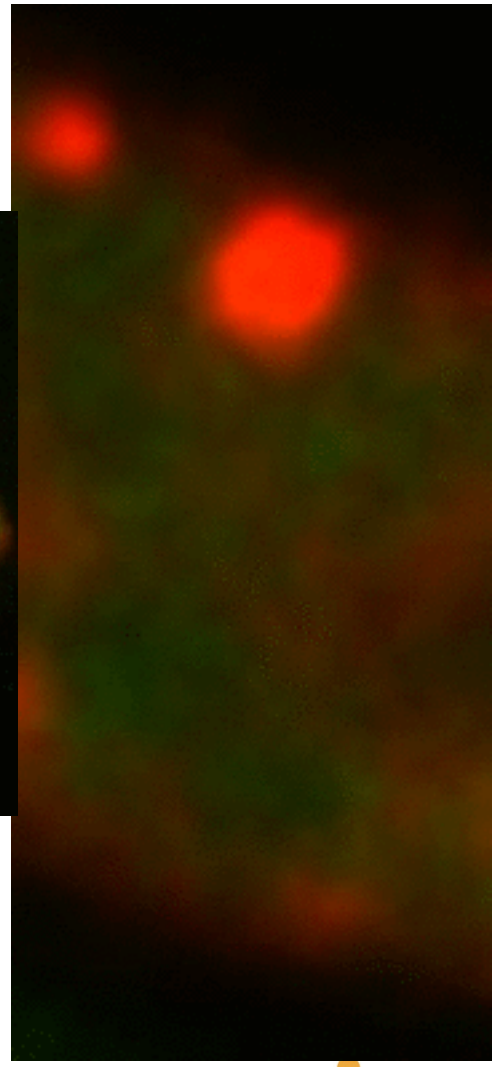
Live cell imaging of heavy ion traversals in euchromatin and heterochromatin

GFP-NSBS1



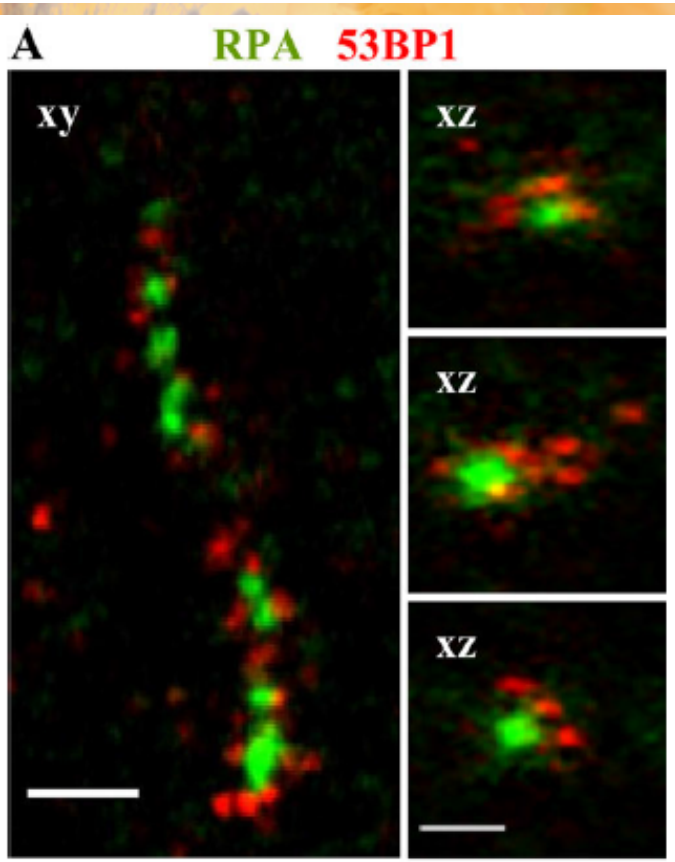


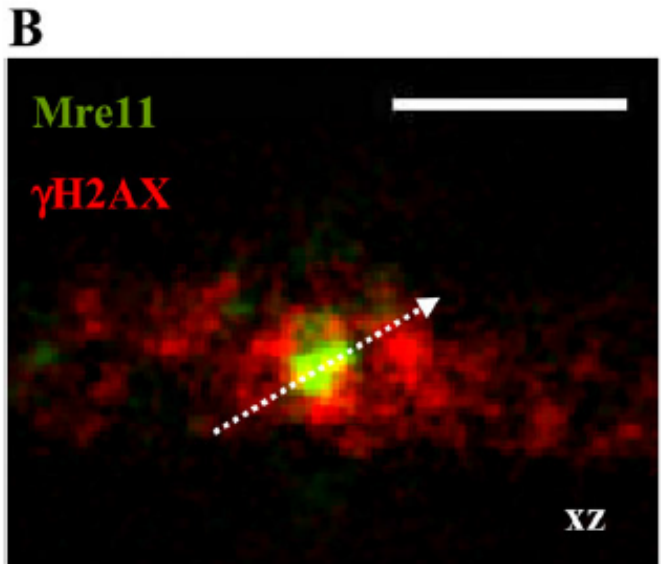
GFP-XRCC1

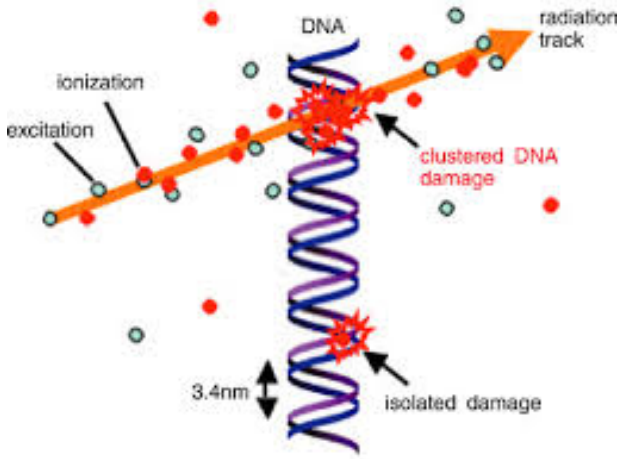


Jakob *et al., Proc. Natl. Acad. Sci. USA* 2009*; Nucl. Acids Res*. 2011

Clustered DNA breaks induced by charged particles







Biological dose estimation of UVA laser microirradiation utilizing charged particle-induced protein foci

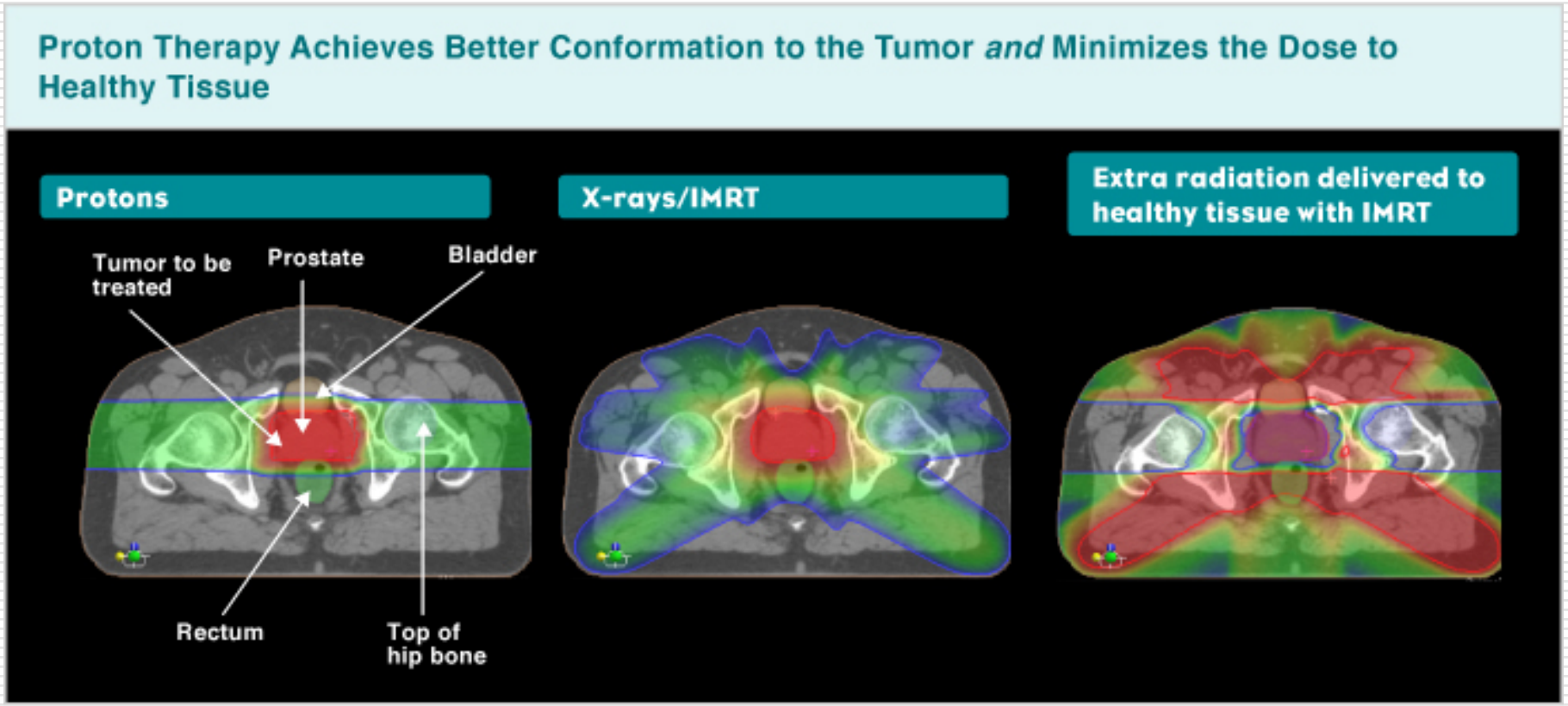
J. Splinter[1], B. Jakob[1,*], M. Lang[2], K. Yano[3], J. Engelhardt[2], S. W. Hell[2], D. J. Chen[3], M. Durante[1,4] and G. Taucher-Scholz[1]

[1]Department of Biophysics, GSI Helmholtz Center for Heavy Ion Research, Planckstrasse 1, D-64291 Darmstadt, Germany, [2]Department of High Resolution Optical Microscopy, German Cancer Research Center, D-69120 Heidelberg, Germany, [3]Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA and [4]Institute for Condensed Matter Physics, Technical University Darmstadt, D-64289 Darmstadt, Germany.

Mutagenesis pp. 1–9, 2010

GSI

Treatment plans with protons: prostate

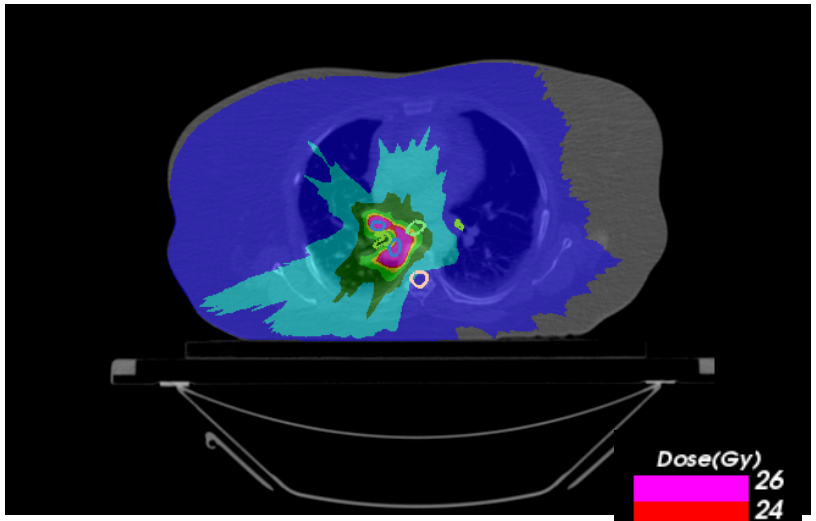


Courtesy of Reinhold Schulte, LLUMC

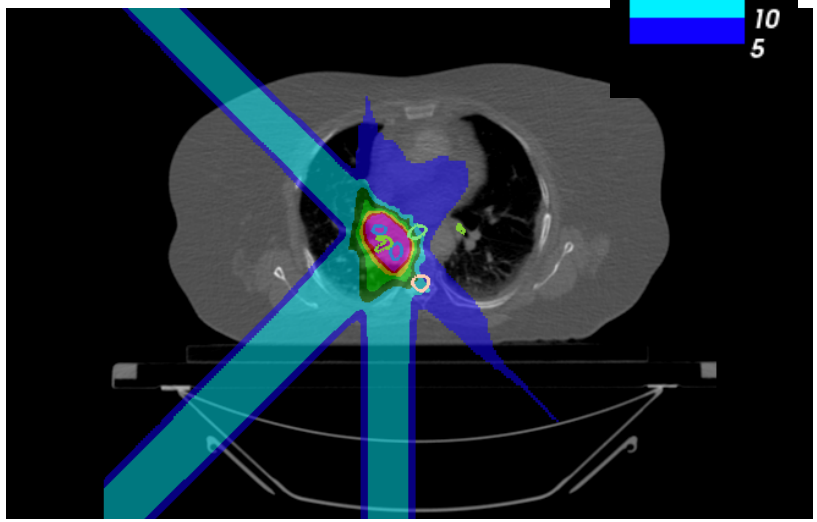
Lung tumors: SBRT vs. C-ions

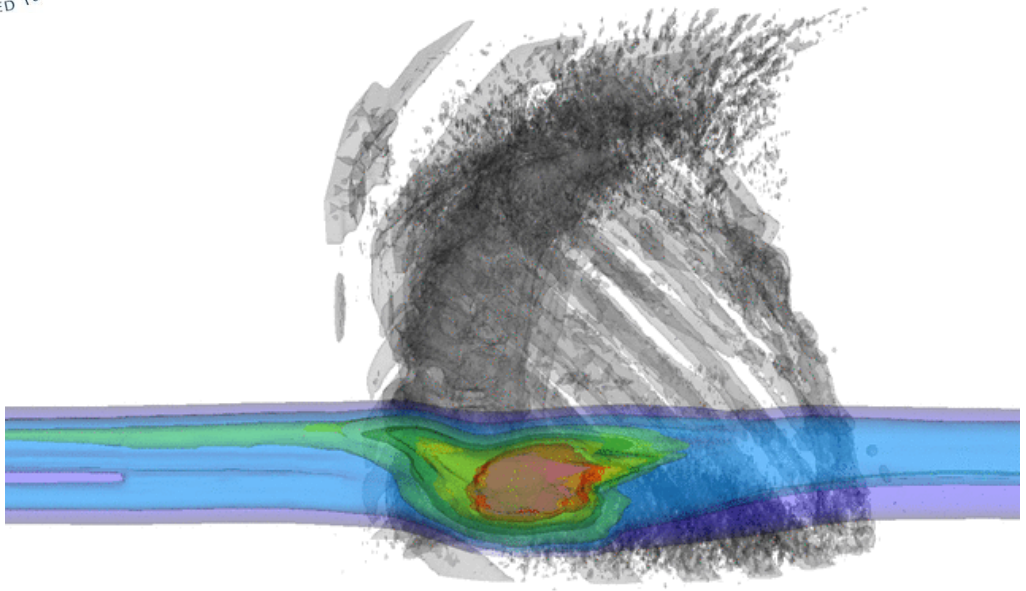
Single fraction, 25 Gy

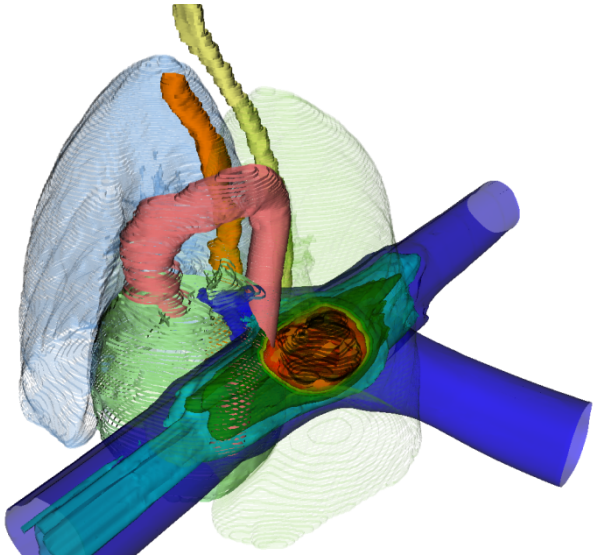
X-rays



C-ions

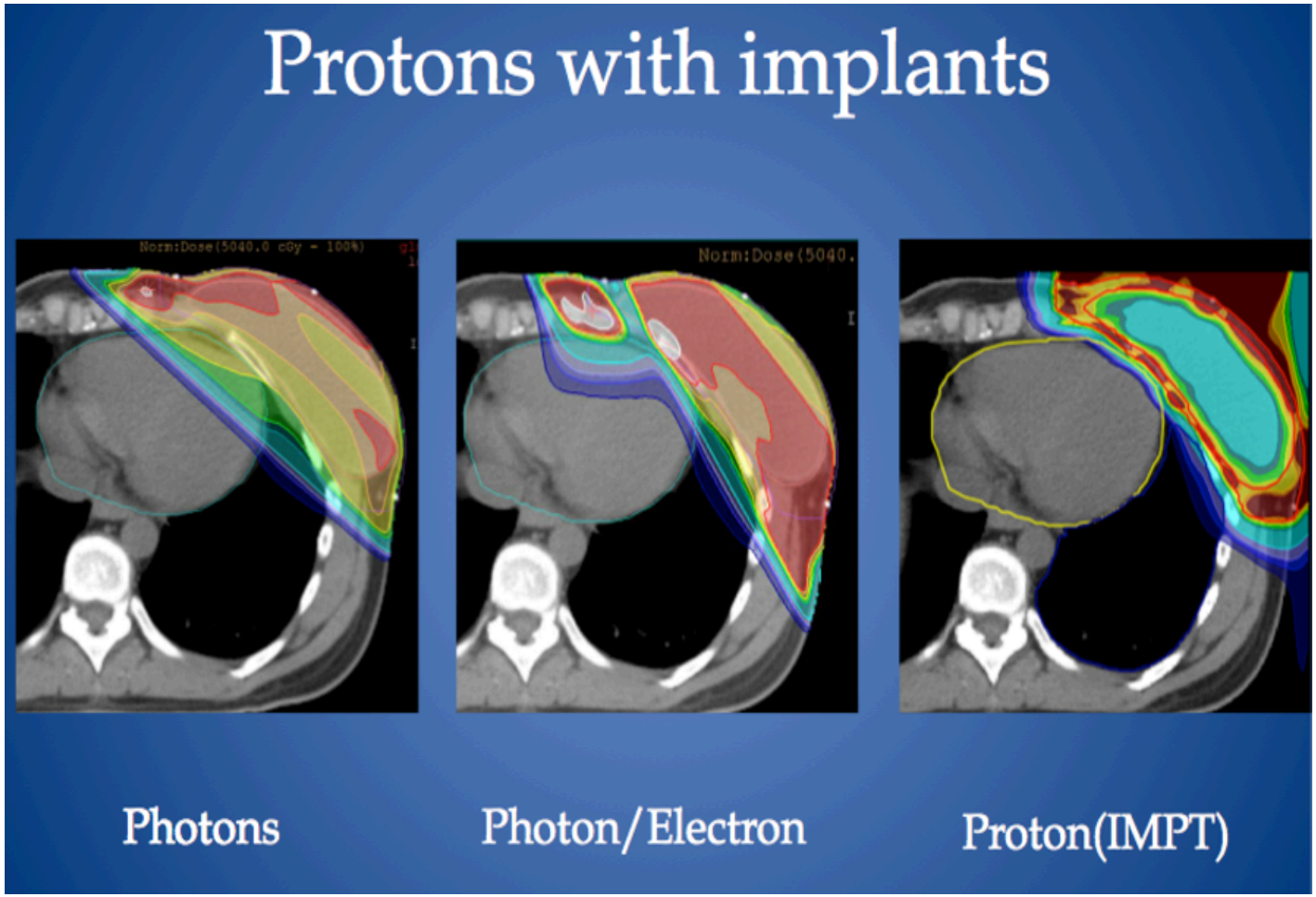






Kristjan Anderle, Ph.D. thesis, TU Darmstadt, 2014

Treatment plans with protons: breast



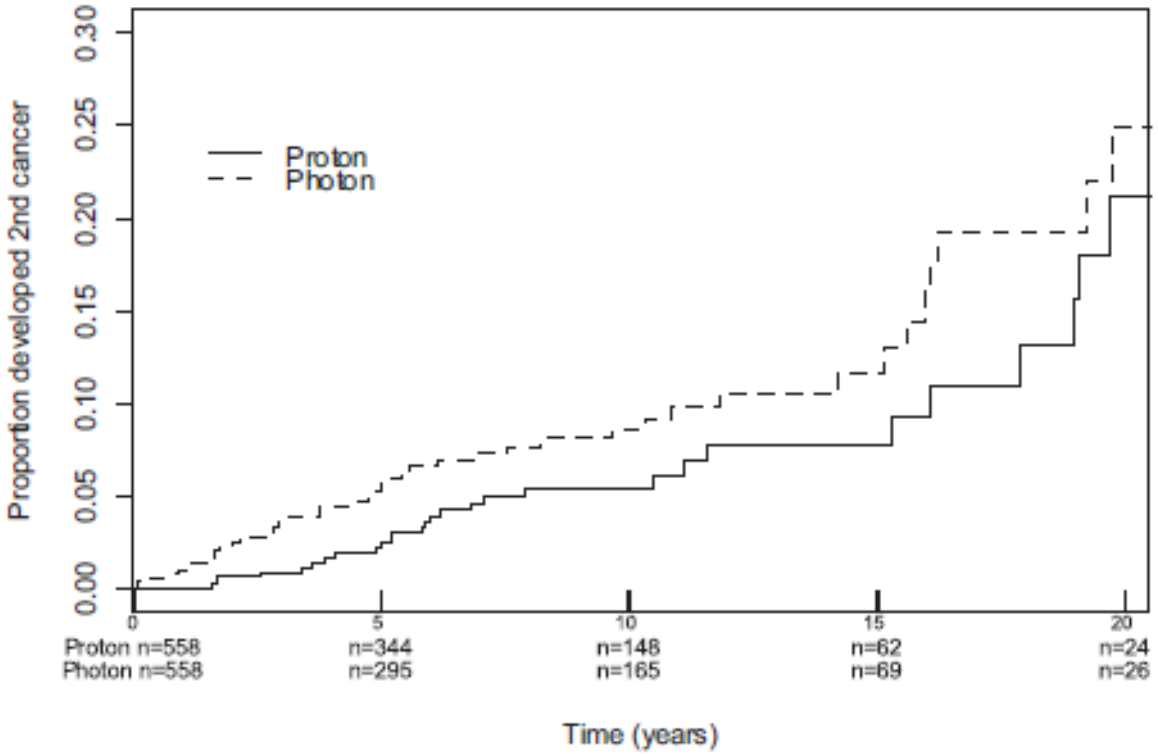
MGH 1811

MacDonald et al, Int J Radiat Oncol Biol Phys, 1-7, 2013

Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

Christine S. Chung, MD, MPH,* Torunn I. Yock, MD, MCh,† Kerrie Nelson, PhD,‡ Yang Xu, MS,§ Nancy L. Keating, MD, MPH,§,¶ and Nancy J. Tarbell, MD†,||

International Journal of Radiation Oncology biology • physics



Clinical indications for particle therapy

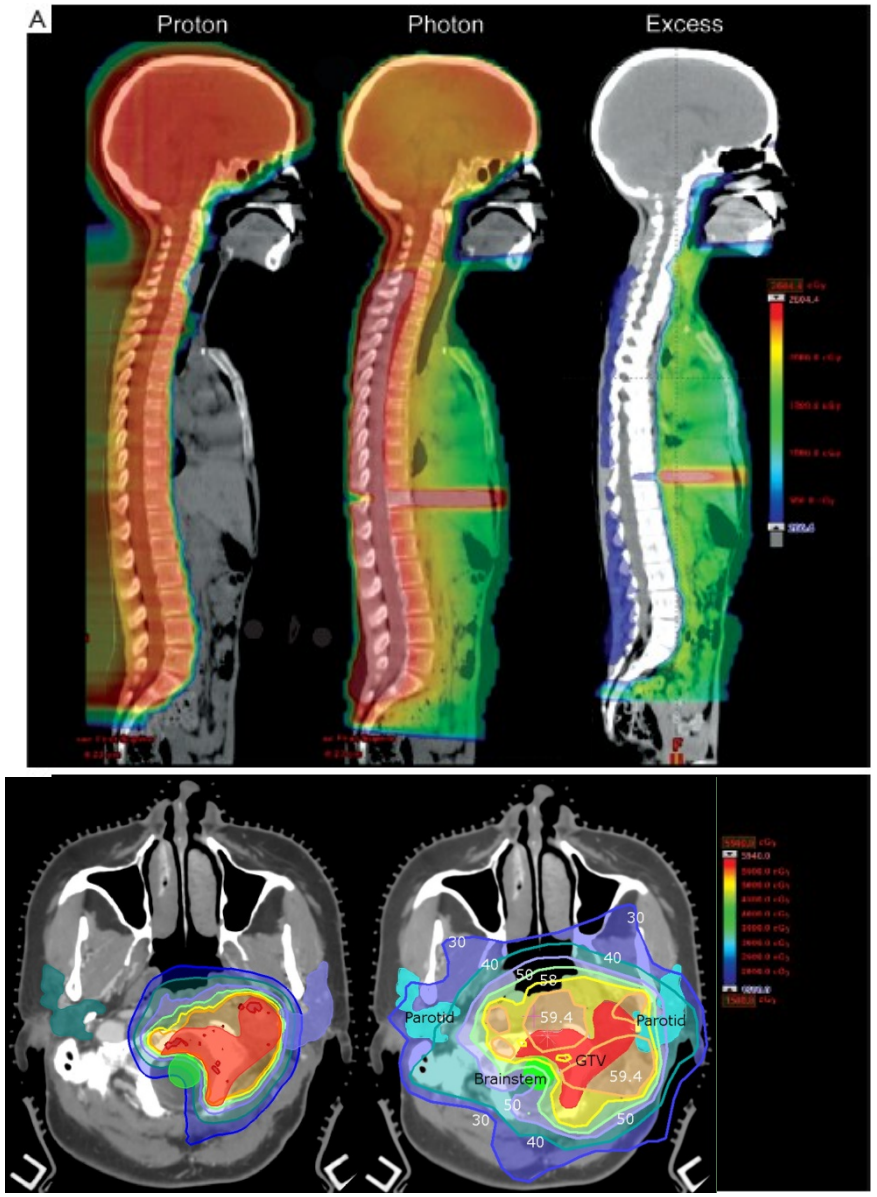
Established clinical indications

- Skull base and spine tumors
- Hepatocellular carcinoma
- Eye tumors
- Pediatric tumors

More research needed for

- Thoracic malignancies
- Head and Neck tumors
- Pelvic and abdominal sites

ASTRO Model Policy, May 2014

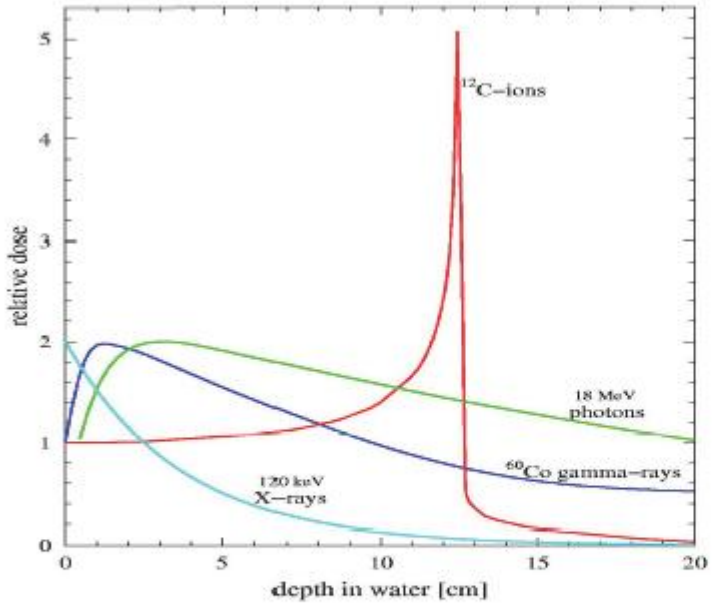


Medulloblastoma treatment, MD Anderson Cancer Center, USA

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ VOLUME 327 20–27 DECEMBER 2003



Charged particles stop – but we don‘t know exactly where they stop.....

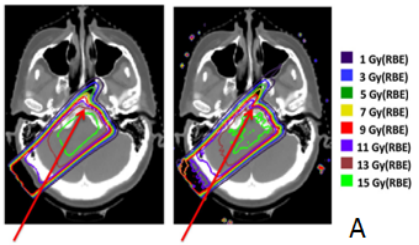
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Range uncertainty

Range verification

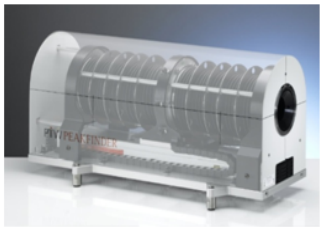
Source of range uncertainty in the patient	Range uncertainty
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	± 0.3 mm
Compensator design	± 0.2 mm
Beam reproducibility	± 0.2 mm
Patient setup	± 0.7 mm
Dose calculation:	
Biology (always positive)	+ 0.8 %
CT imaging and calibration	± 0.5 %
CT conversion to tissue (excluding I-values)	± 0.5 %
CT grid size	± 0.3 %
Mean excitation energies (I-values) in tissue	± 1.5 %
Range degradation; complex inhomogeneities	- 0.7 %
Range degradation; local lateral inhomogeneities *	± 2.5 %
Total (excluding *)	**2.7% + 1.2 mm**
Total	**4.6% + 1.2 mm**

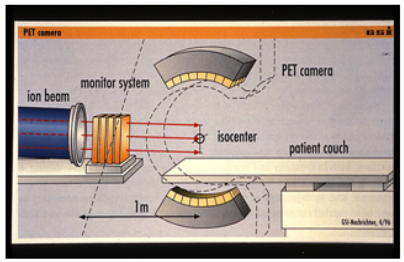
NuPECC report „Nuclear Physics in Medicine“, 2014



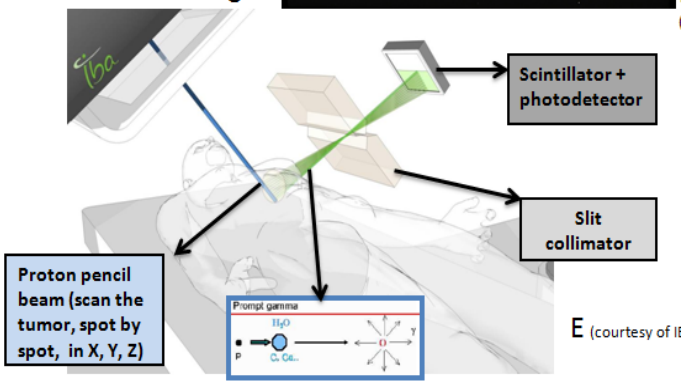
A

B

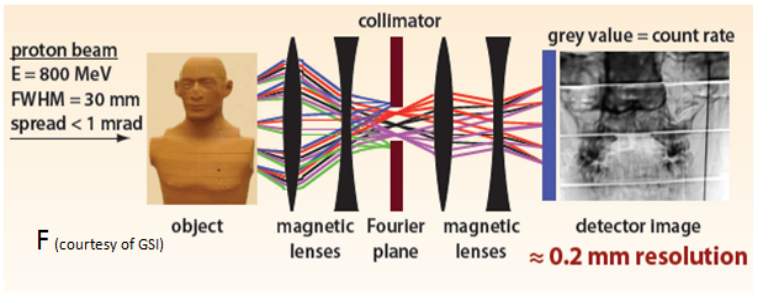

C



D (courtesy of GSI)

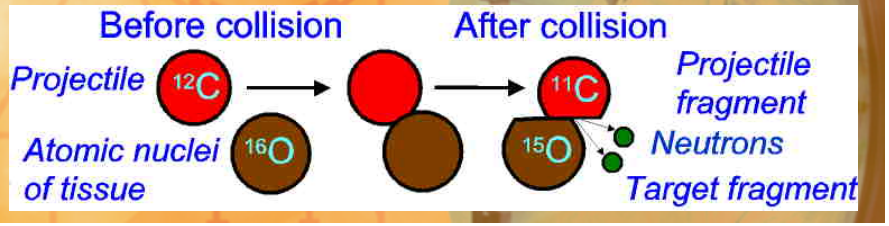


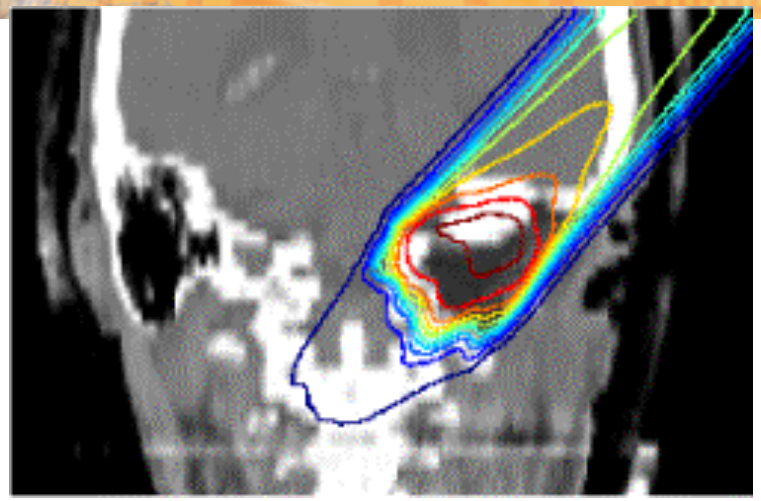
E (courtesy of IBA)



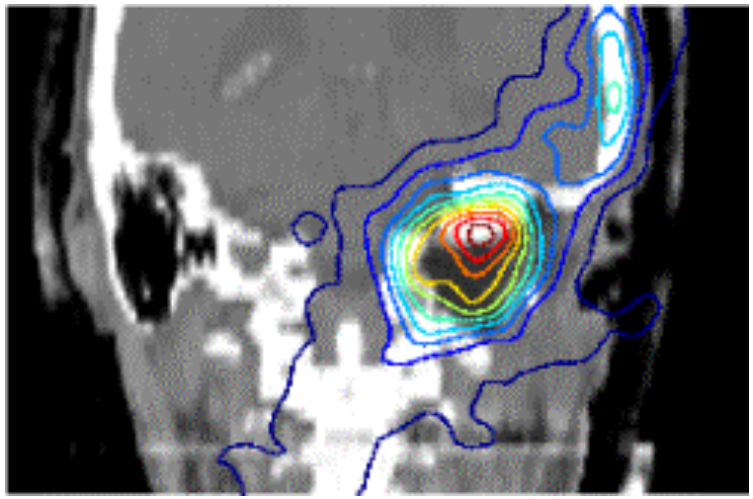
F (courtesy of GSI)

In situ control with PET

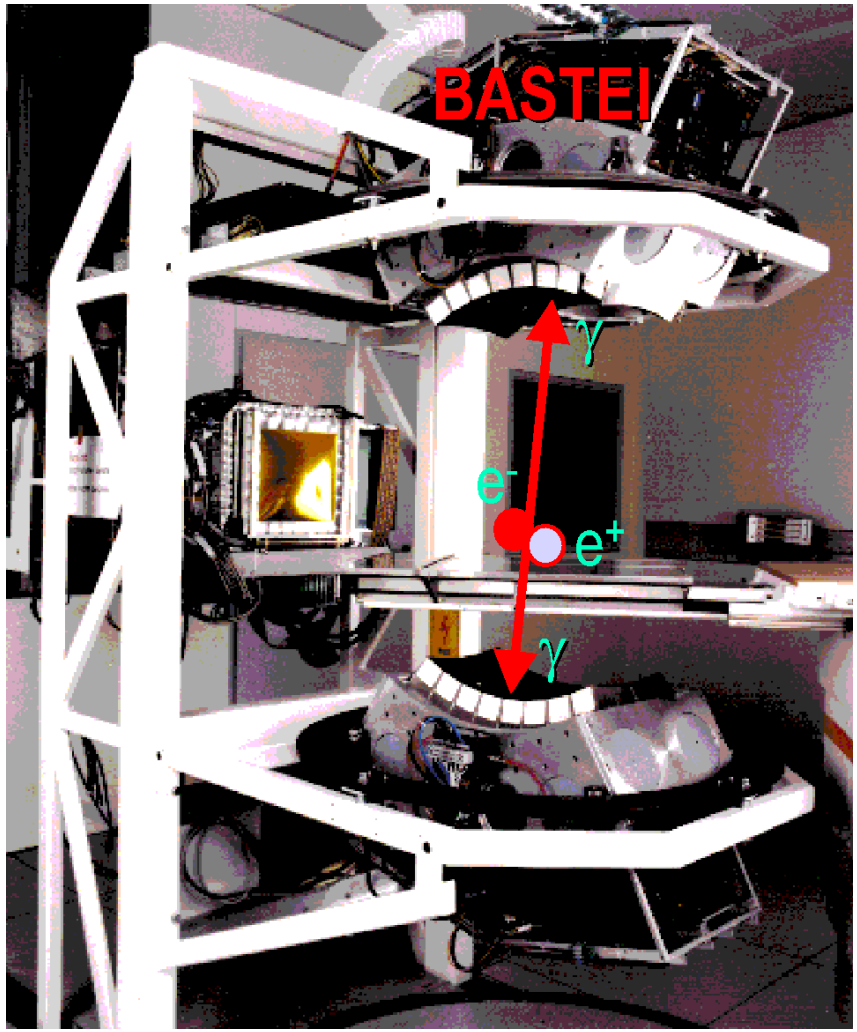




dose plan

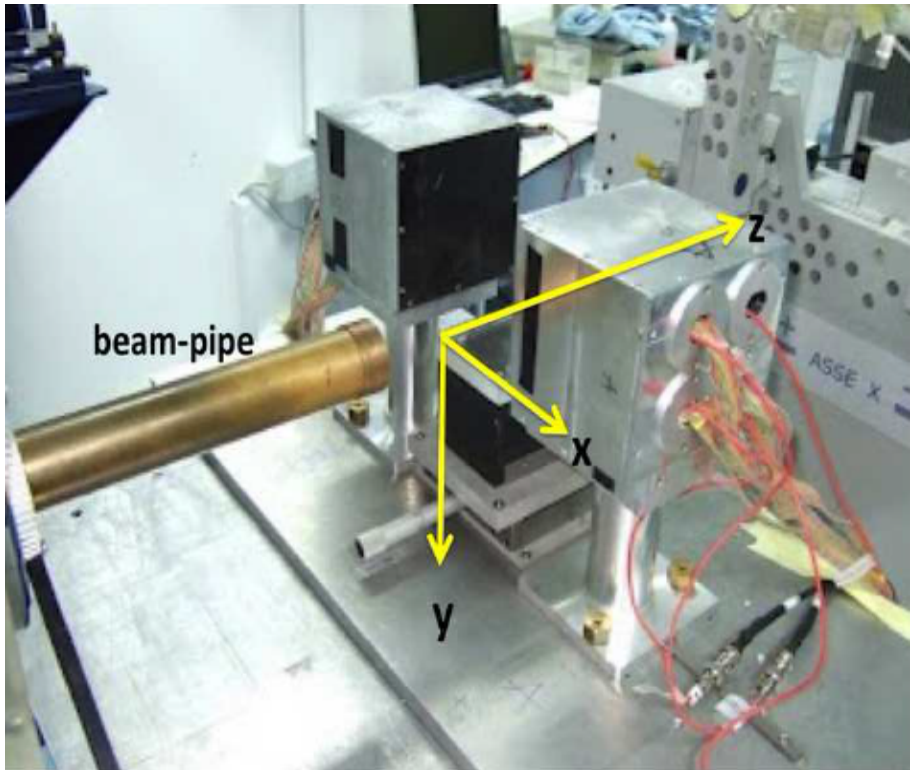


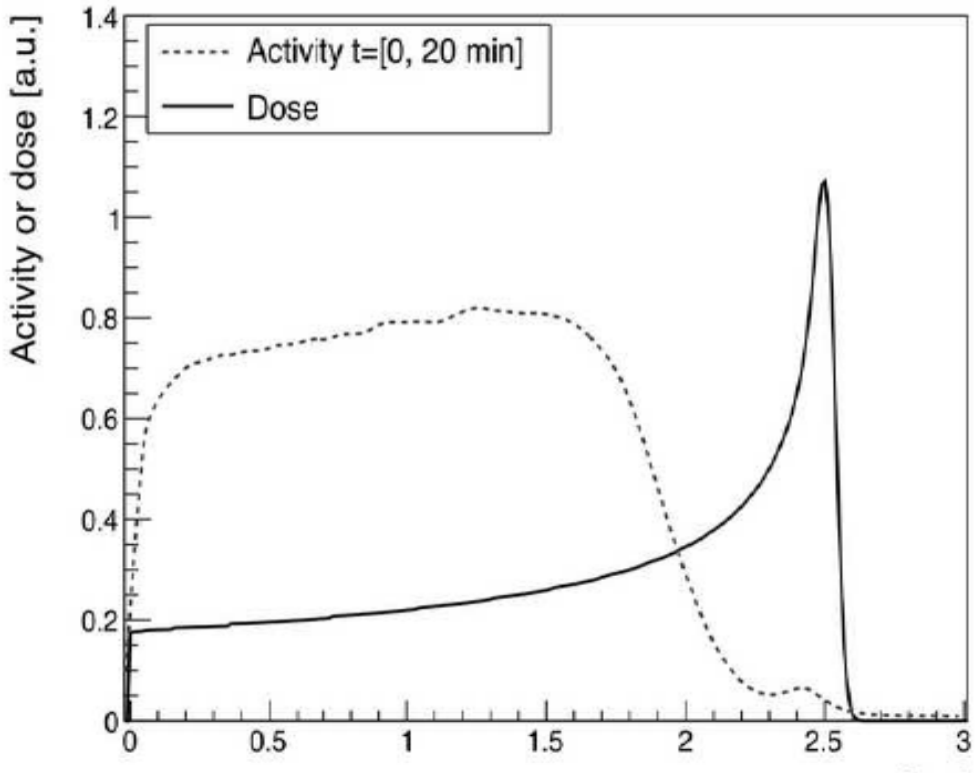
measured



Courtesy of Wolfgang Enghardt, HZDR, Dresden

Proton range monitoring with in-beam PET: Monte Carlo activity predictions and comparison with cyclotron data



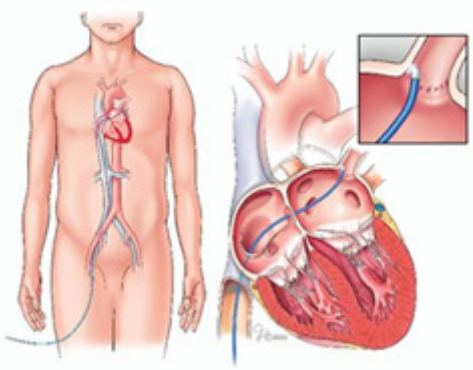


Kraan *et al., Phys. Med.* 2014

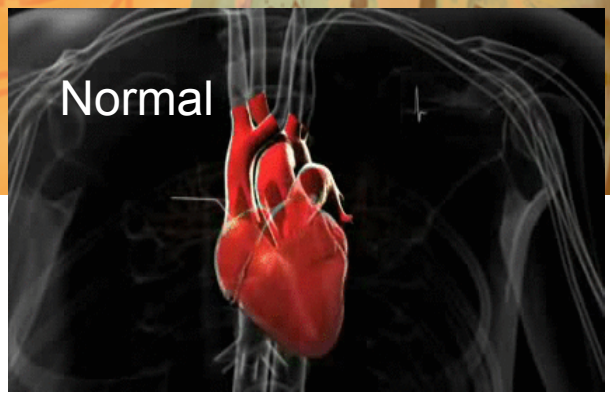
INFN Istituto Nazionale di Fisica Nucleare

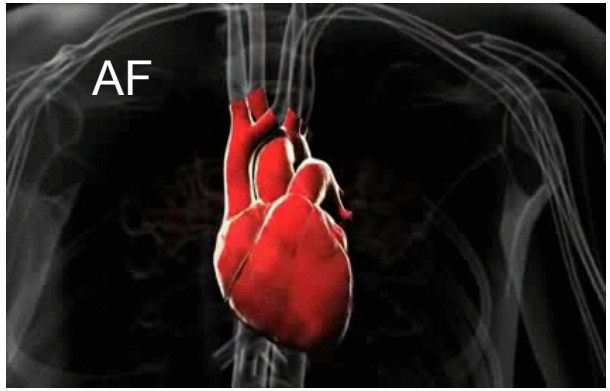
IN SUPREMÆ DIGNITATIS 1343 UNIVERSITÀ DI PISA

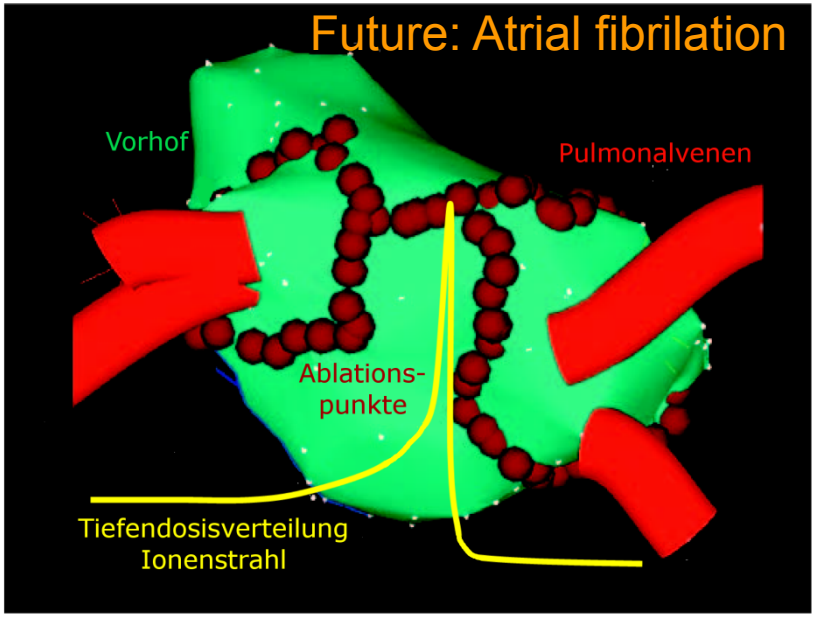
Particle therapy for heart arrhythmia

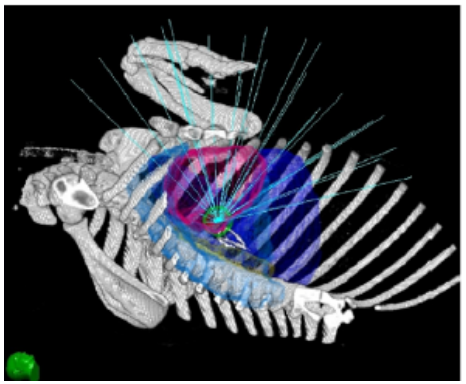


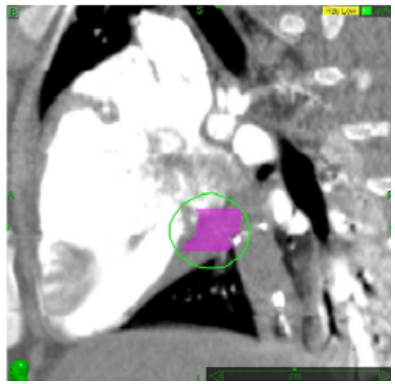
- Atrial fibrillation affects about 5% of middle-aged population and is associated with high risk of stroke and death
- Catheter ablation of pulmunary vein is the current non-pharmacological solution







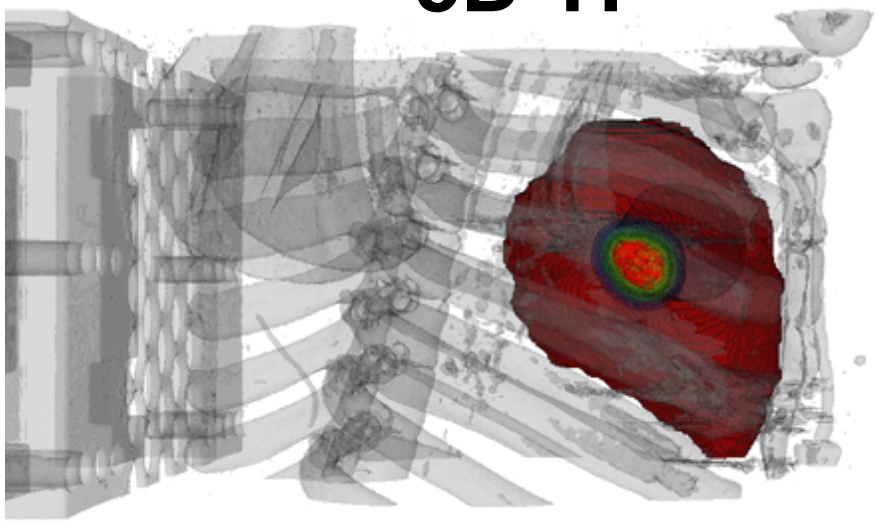


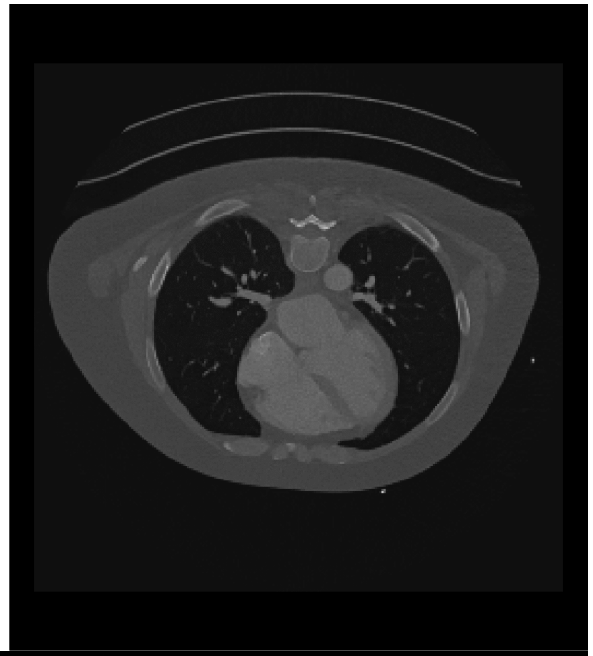


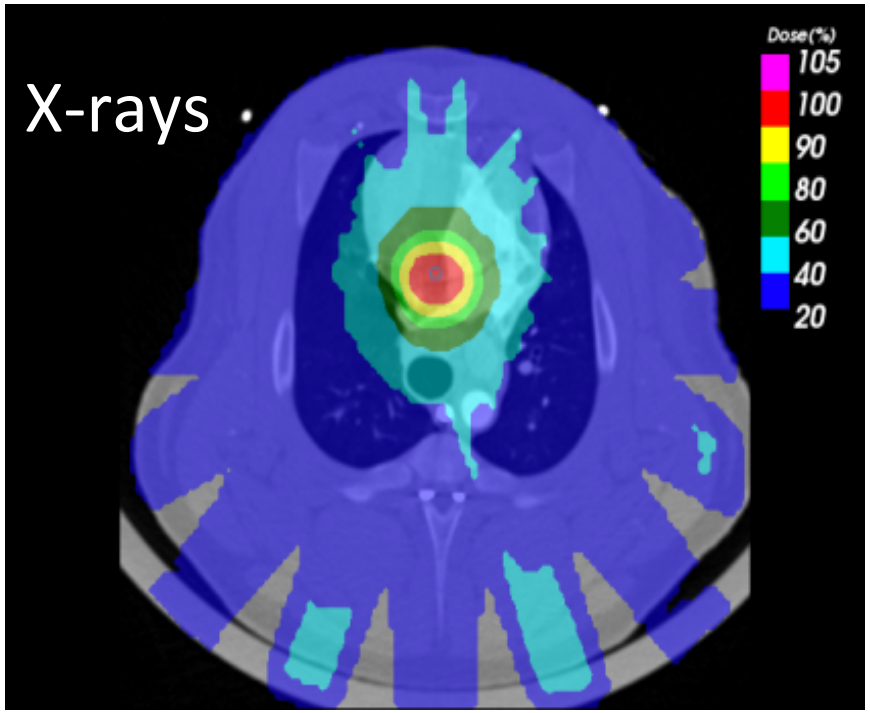
- CyberHeart: cardiac lesion induced by a Cyberknife (*Heart Rhythm*., June 2010)

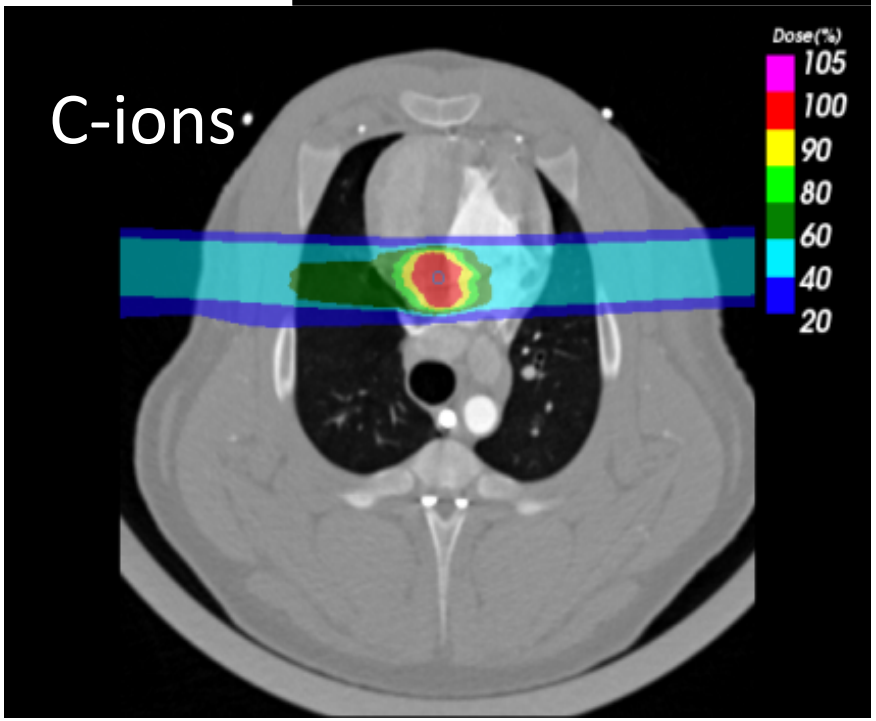
Bert *et al., Med. Phys*. 2012

5D TP

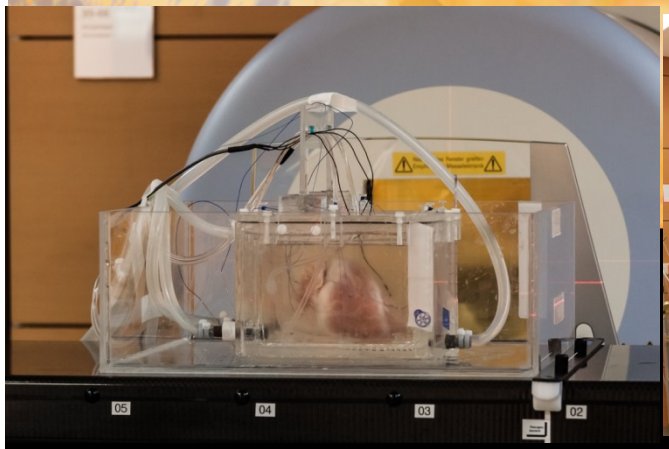








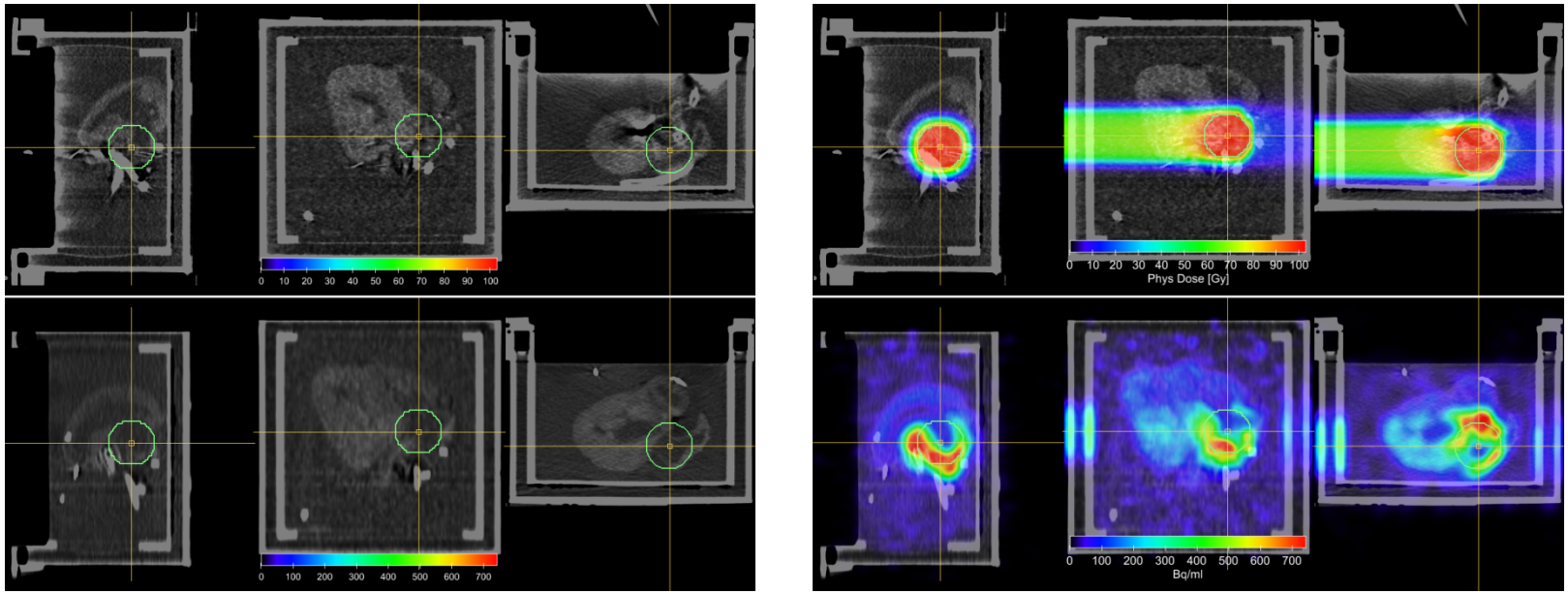
Anna Constantinesu, Ph.D. thesis, TU Darmstadt 2014



HIT
Heidelberger Ionenstrahl-Therapiezentrum

Langendorff pig heart

Results
PET Scan after Experiment



- PET was performed about 20 min after last fraction
- Heart size significantly increased towards end of lifetime
  - → Initial position of AV node has moved
- **Hot spot of activity in myocardium around AV node**
  - → **Proof: AV node has received the prescribed dose**

$T_{1/2}$ (^{12}C)	=	20.38 min
$T_{1/2}$ (^{15}O)	=	2.03 min
$T_{1/2}$ (^{13}N)	=	9.96 min
$T_{1/2}$ (^{38}K)	=	7.6 min
$T_{1/2}$ (^{30}P)	=	2.5 min
$T_{1/2}$ (^{34}Cl)	=	32.0 min

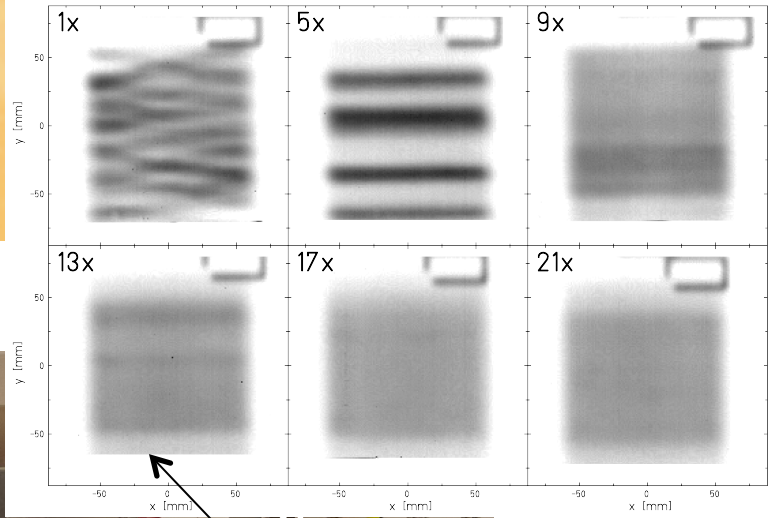
Lehmann *et al., Circulation* 2014

Animal experiment: GSI Cave M, July 2014

Groups	Dose	Pigs
AVN	0 Gy	3
	25 Gy	3
	40 Gy	3
	55 Gy	3
PV	40 Gy	3
LV	40 Gy	4

LV: only internal target volume (ITV)

AVN and PV: isotropic margins of 5 mm and ITV



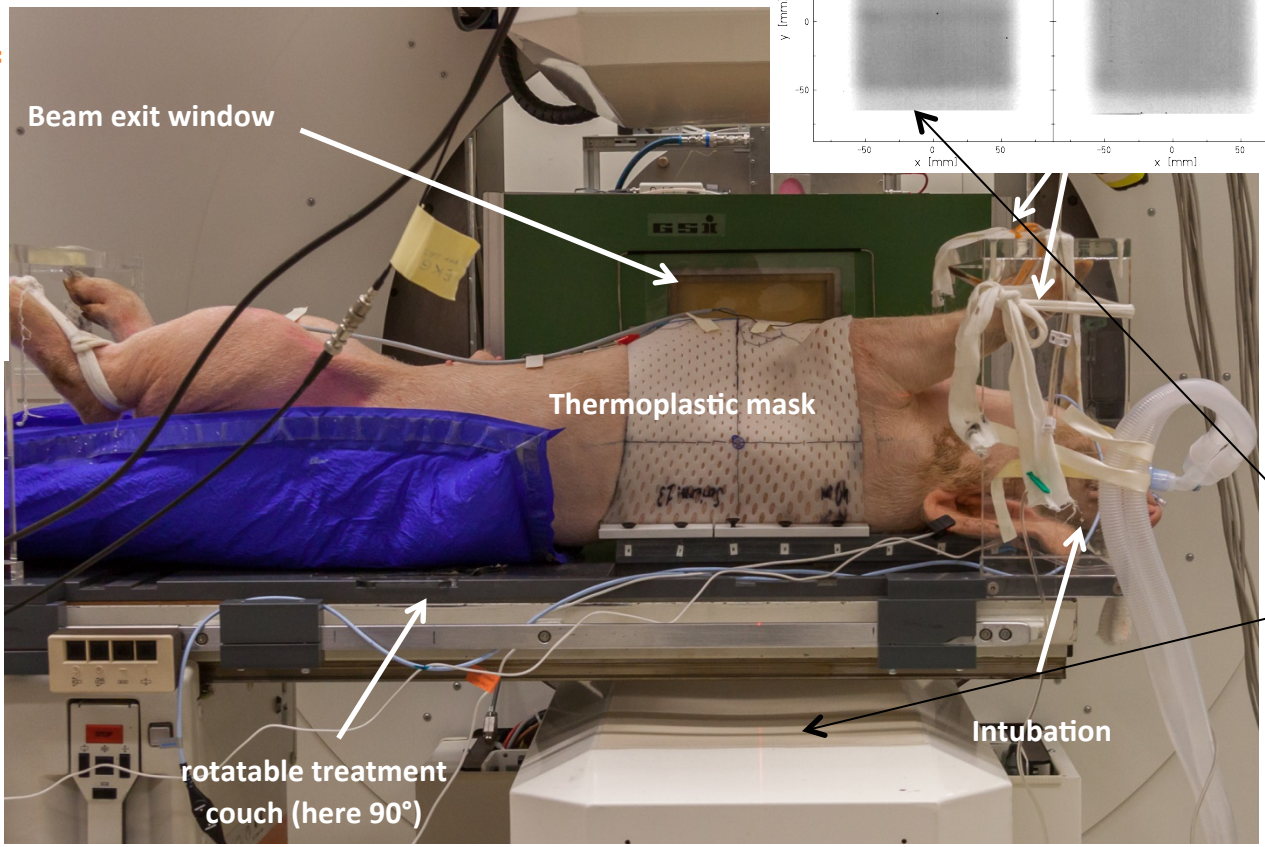
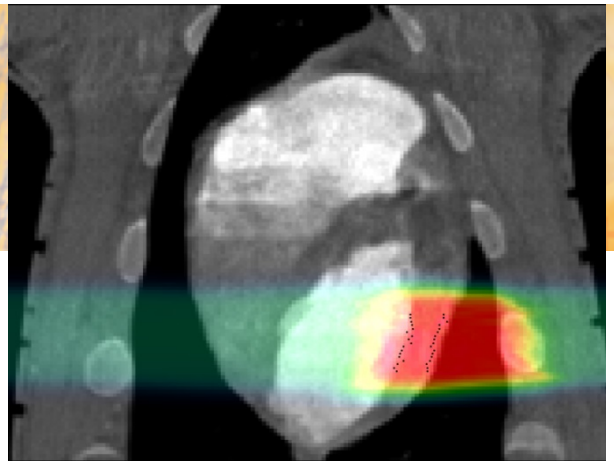
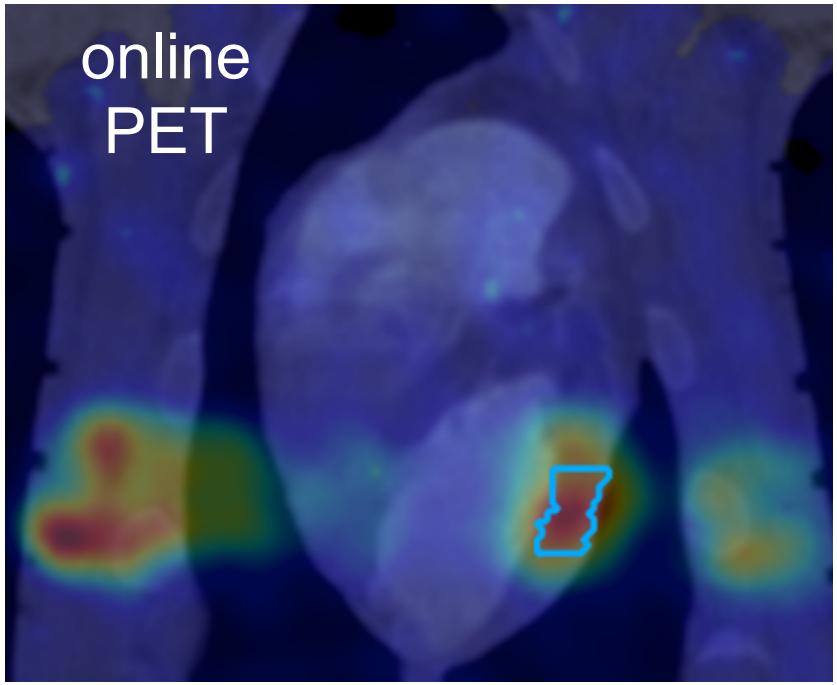
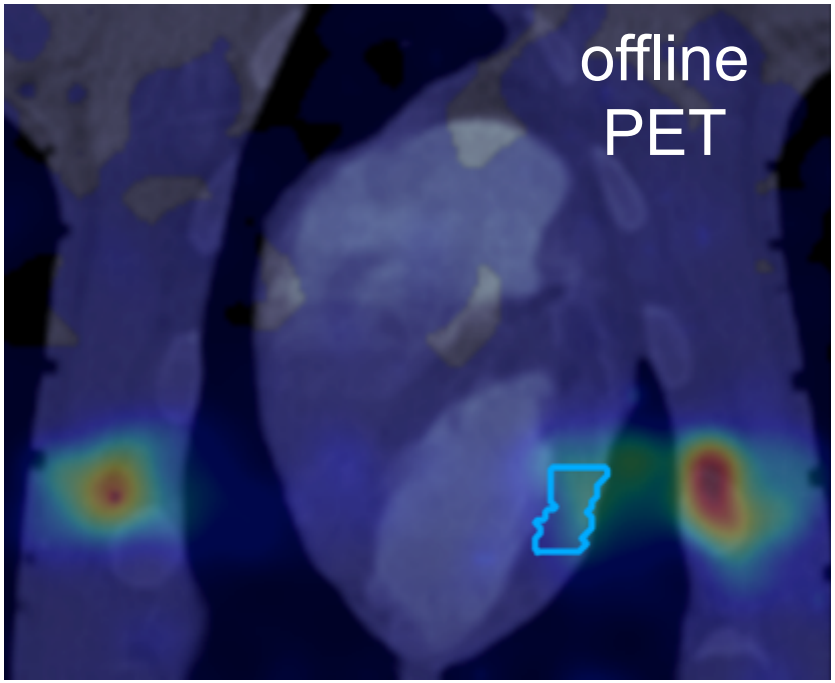


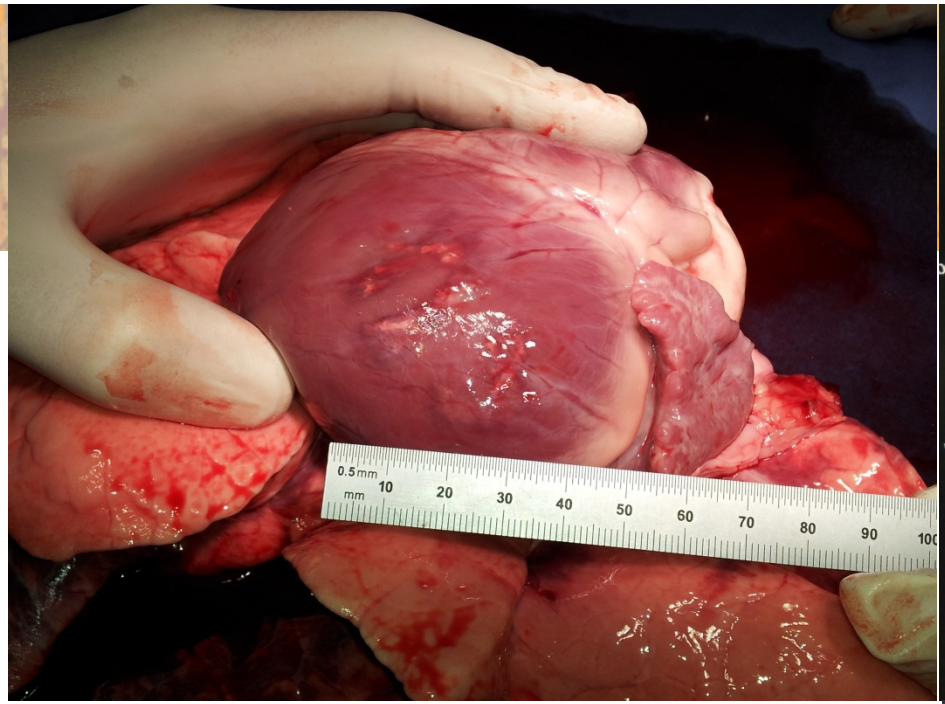
Photo: Matthias Prall, GSI

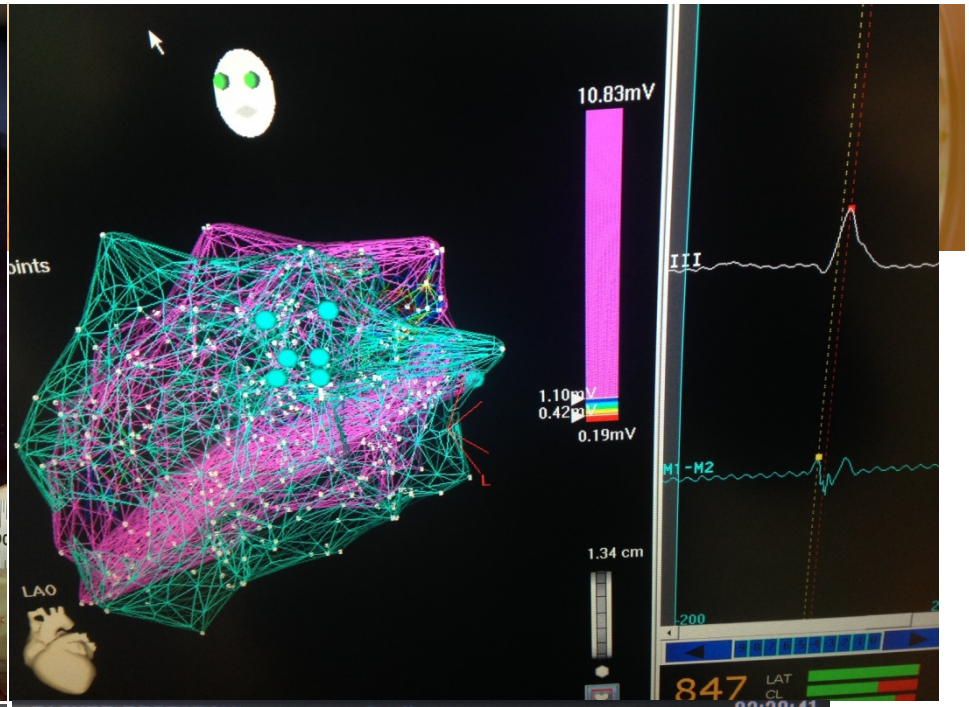
Treatment plan – TRiP984D

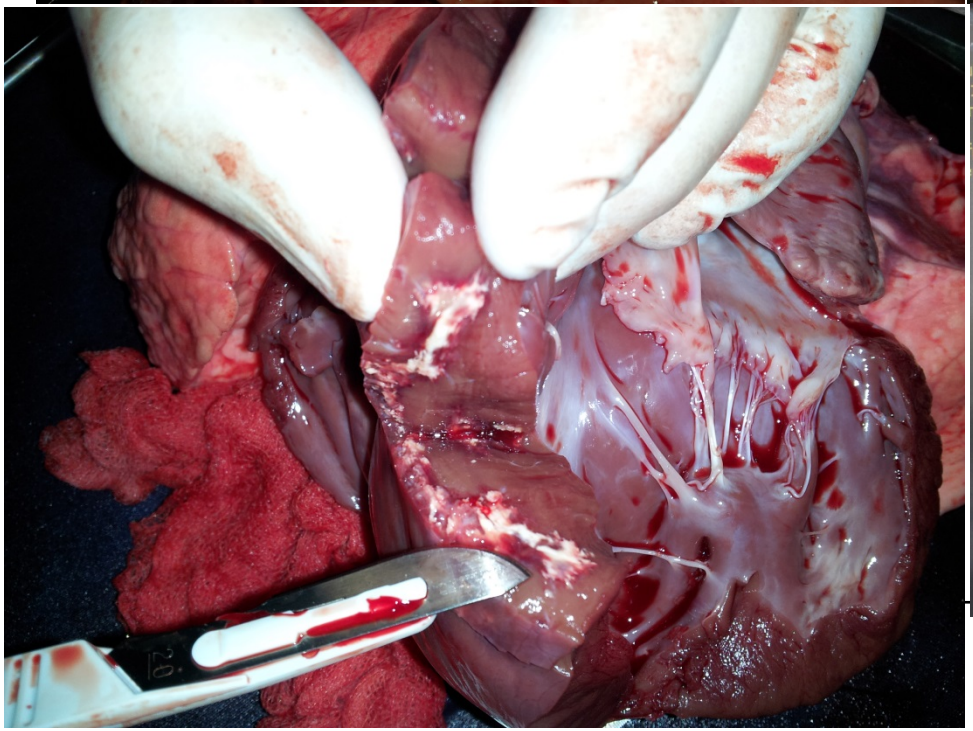


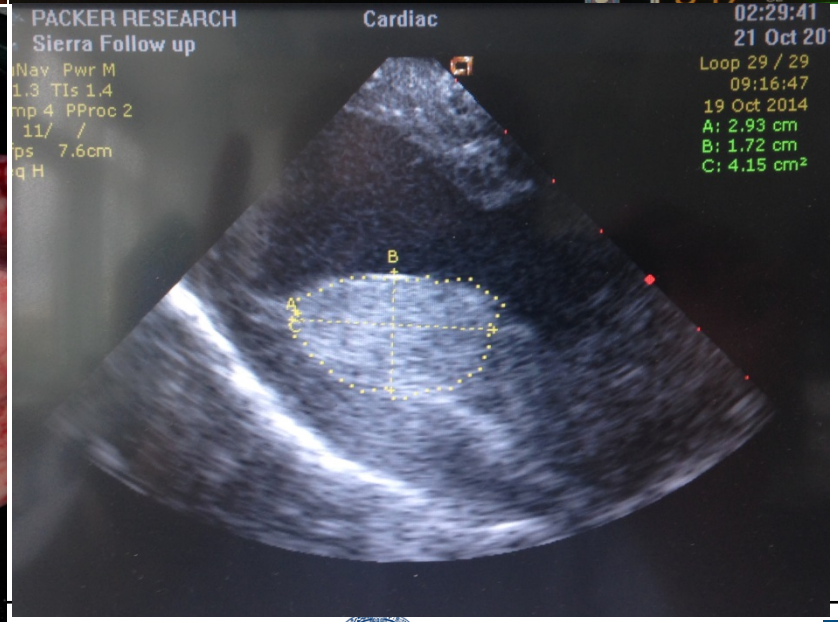












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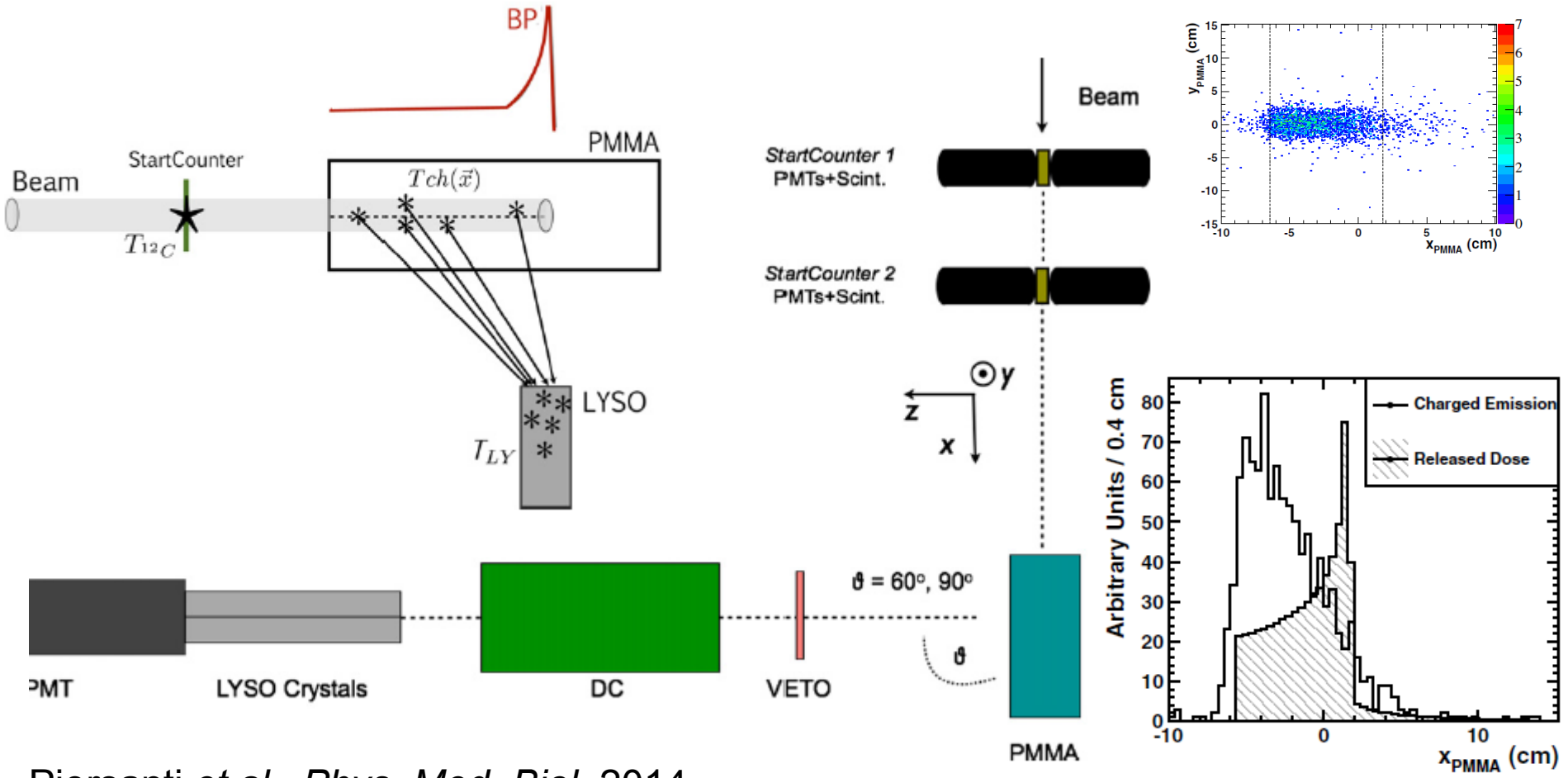
MAYO CLINIC

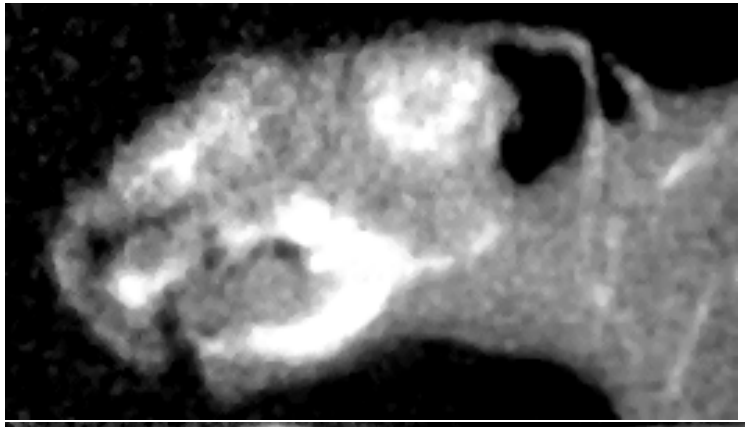
Prompt charged particles



Piersanti *et al., Phys. Med. Biol*. 2014

Mouse Proton Tomography

800 MeV proton beam at LANL



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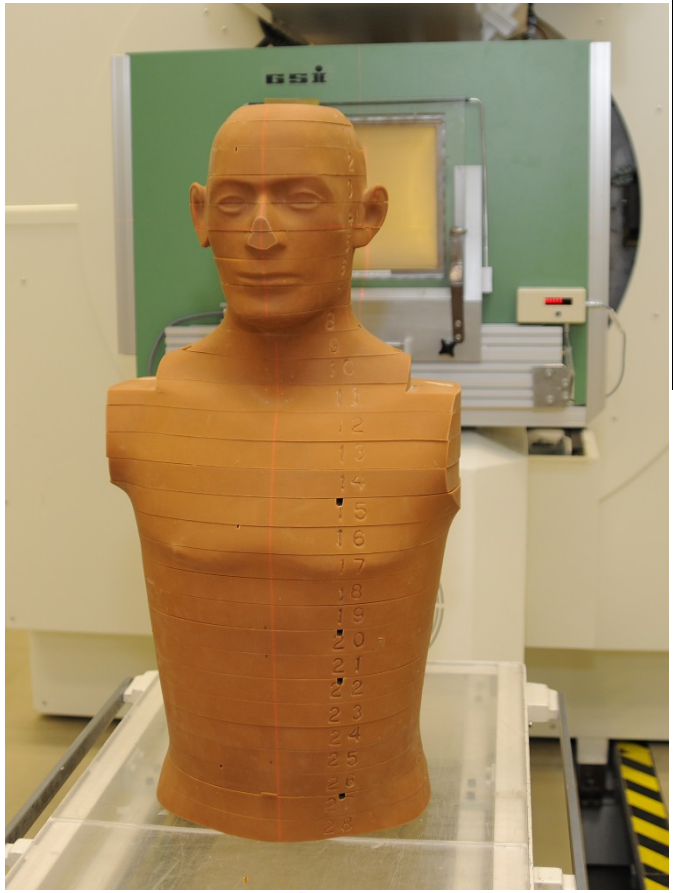
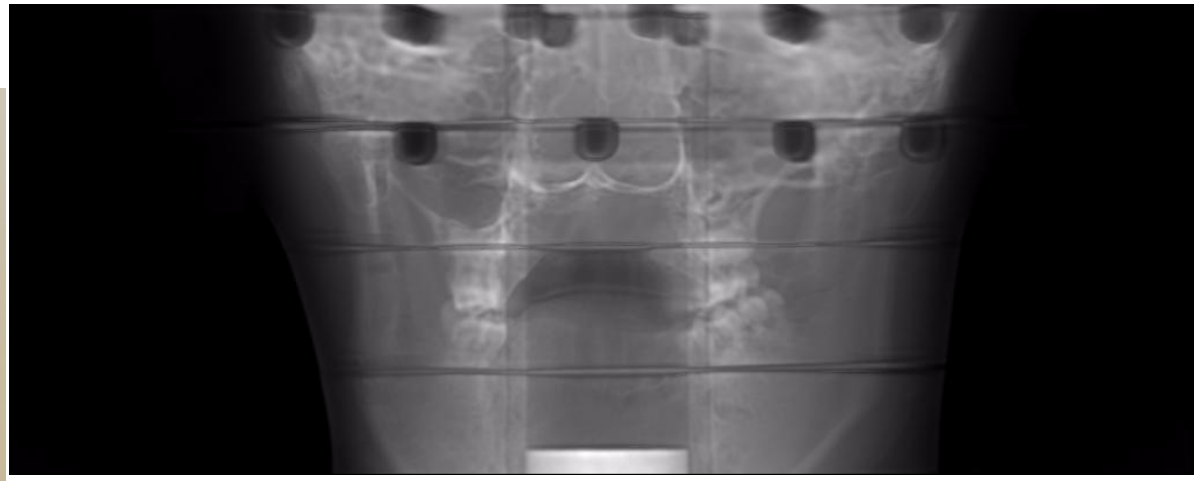
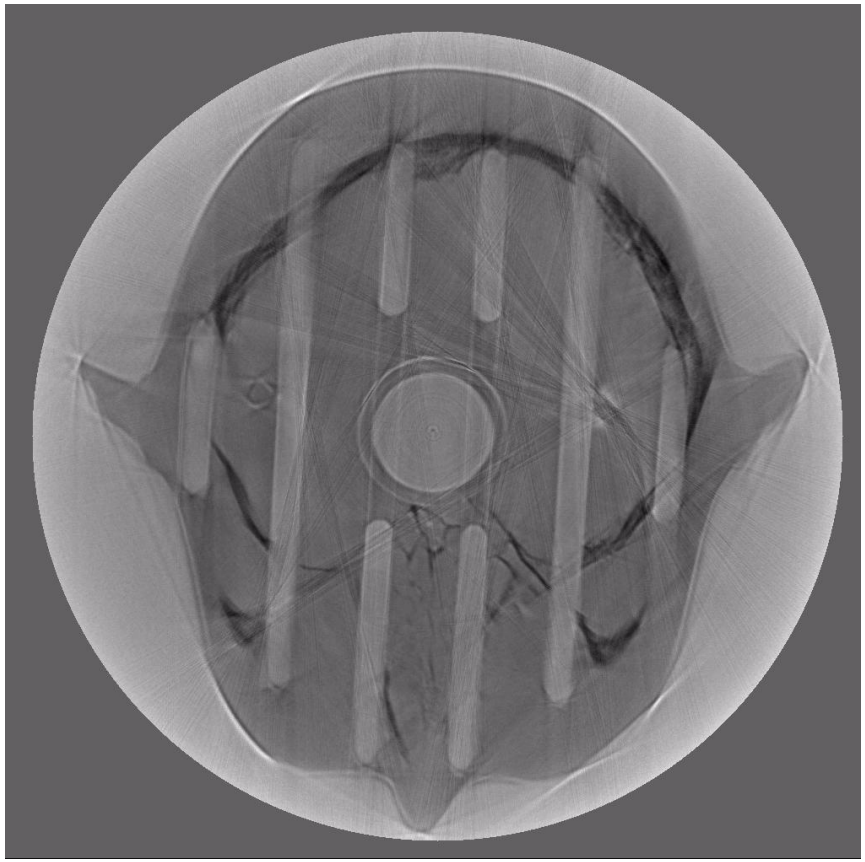
Human phantom Tomography – 800 MeV protons LANL







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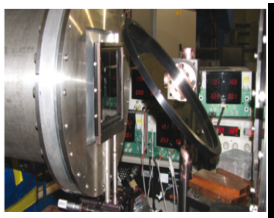
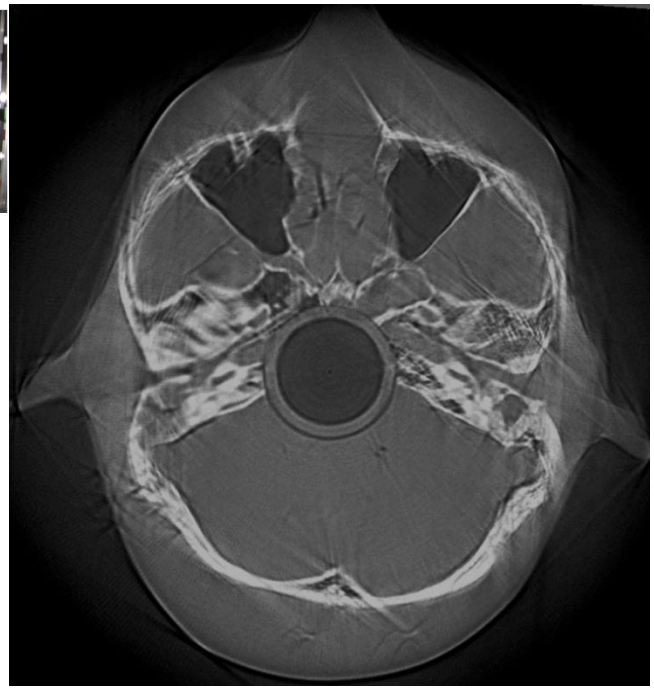
Proton Tomography
Comparison with state of the art X-ray CT

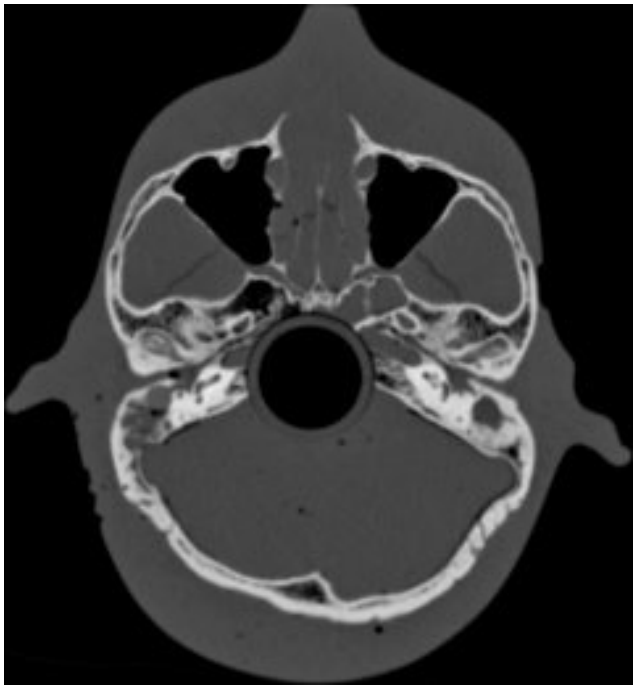
BIO*MAT Biophysics

proton CT





X-ray CT



- CT algorithm from textbook
- C codes from scratch
- intermediate result

- Siemens Biograph™ TruePoint™
- > 30 years development

FAIR

Conclusions

- The future of particle therapy strongly depends on the applications of nuclear physics research
- Range uncertainty is one of the main hindrance to a widespread use of particle therapy: only with a higher precision we can safely go into radiosurgery and treat moving targets
- What‘s next: new accelerators, online beam monitors, treatment of new diseases with 4D/5D TP, combined treatments (radioimmunotherapy with HDSF PT)
- Research in particle therapy is highly interdisciplinary: nuclear physics meets chemistry/engineer/biology/medicine - but it is a formidable tool eventually going to replace almost completely X-rays (cost....) and to save many human lives from cancer and noncancer diseases