Particle therapy at GSI

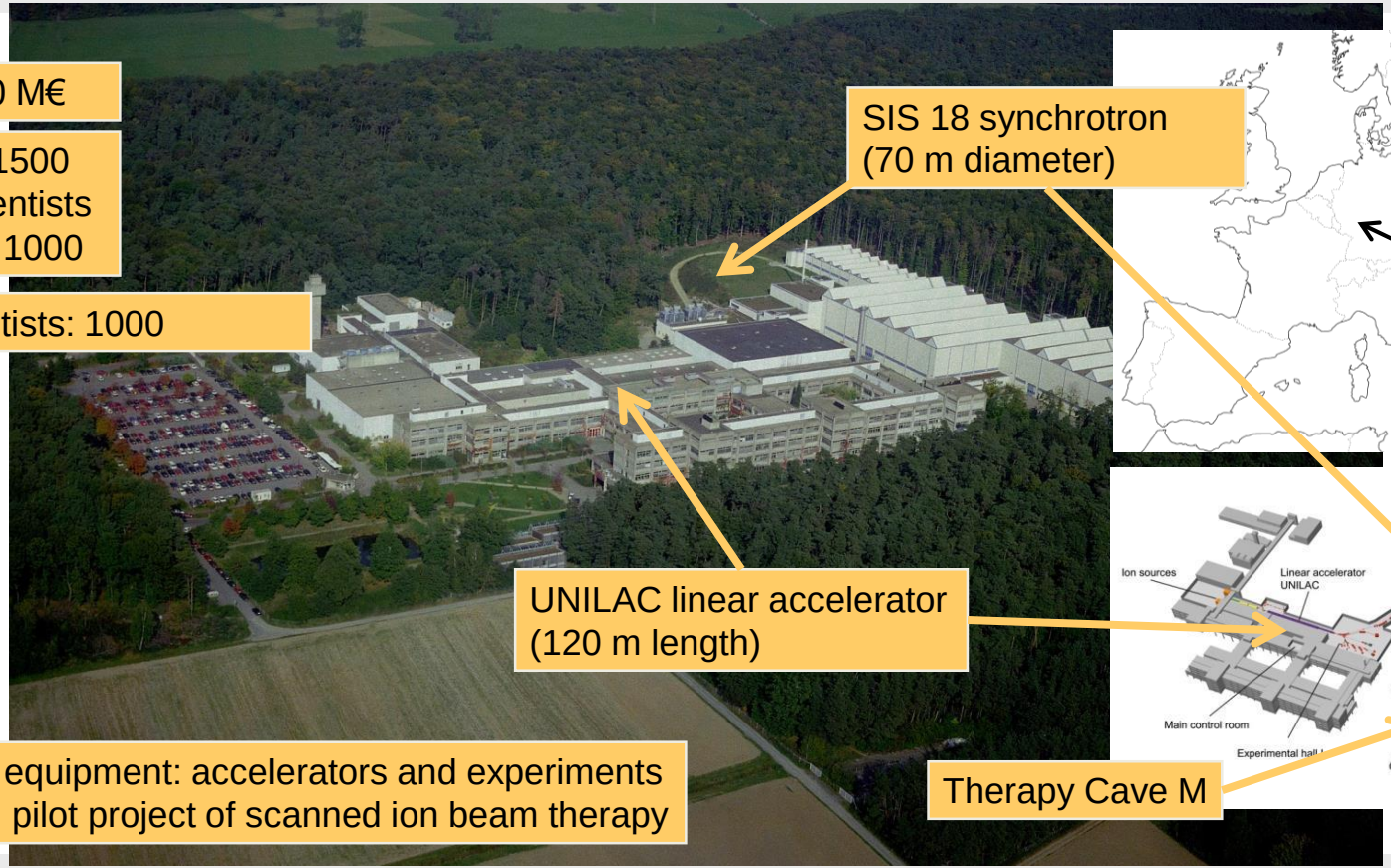
Christian Graeff

GSI Helmholtz Center for Heavy Ion Research

Budget: ~180 M€

Employees: 1500
including scientists
& engineers: 1000

Visiting scientists: 1000



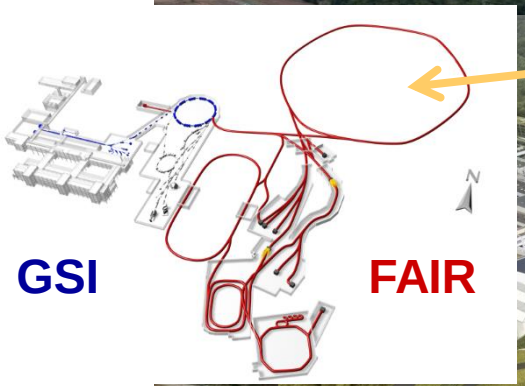
SIS 18 synchrotron
(70 m diameter)

UNILAC linear accelerator
(120 m length)

Therapy Cave M

Large facility equipment: accelerators and experiments
1997 – 2008: pilot project of scanned ion beam therapy

FAIR construction & Phase 0 research



Realized today – FAIR Phase 0

Future Beams:
Intensity: primary HI 100-fold
secondary RIB 10000-fold
Species: Z = -1 – 92
(anti-protons to uranium)
Energies: ions up to 35 - 45 GeV/u
antiprotons 0 -15 GeV
Precision: full beam cooling

The Biophysics Department

Interaction of ion irradiation with biology: therapy & space

Director: Marco Durante
Deputy: Christian Graeff
Administrative Director: Corinna Kausch

Particle therapy

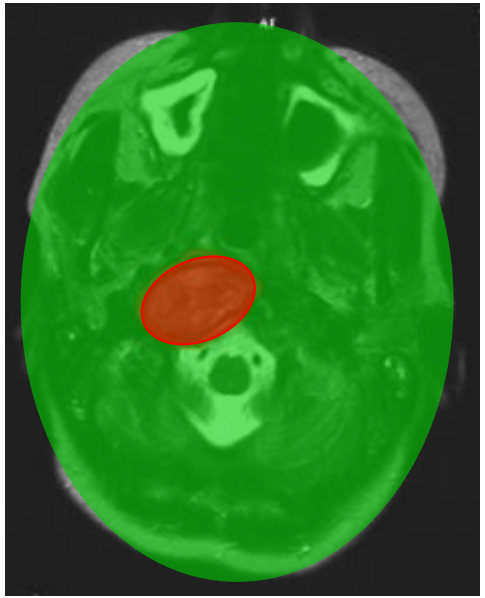
- … is a form of radiotherapy to cure cancer and other diseases
- **protons** or light ions (mainly **carbon**) at up to **70% of the speed of light**, from large particle accelerators (synchrotrons or cyclotrons) are directed at the target

Task of radiotherapy:

Destroy the tumor

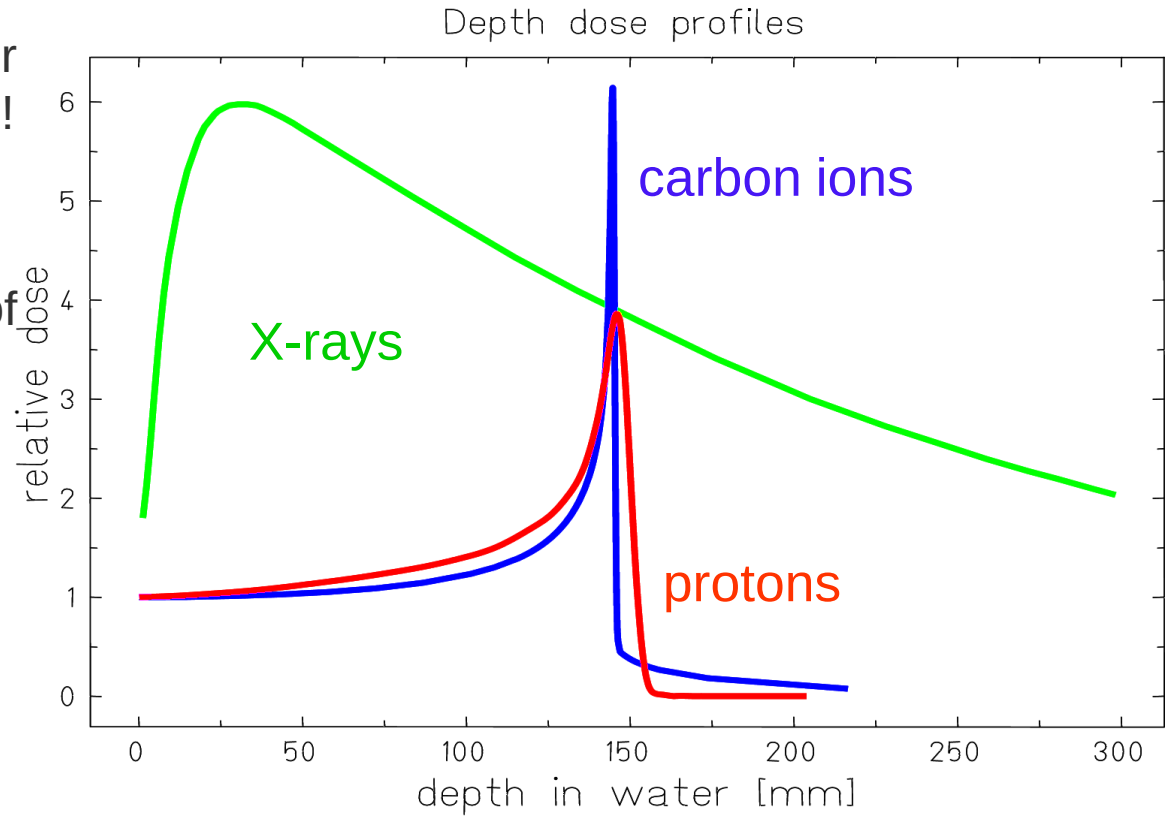
but at the same time

spare the healthy tissue



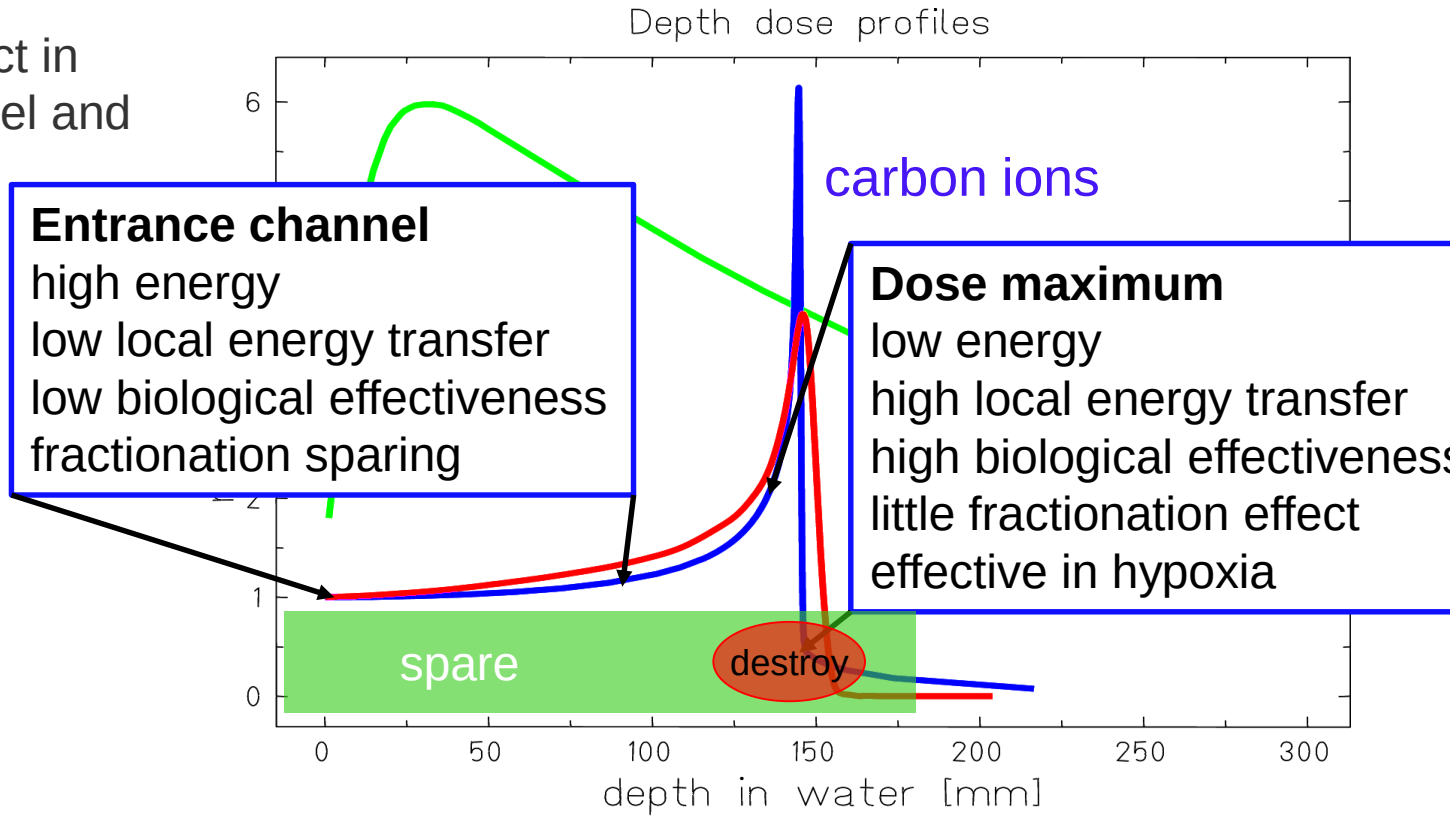
Why particle therapy?

- Particles are much better at sparing healthy tissue!
- Particles slow down in tissue
- Dose maximum at end of range

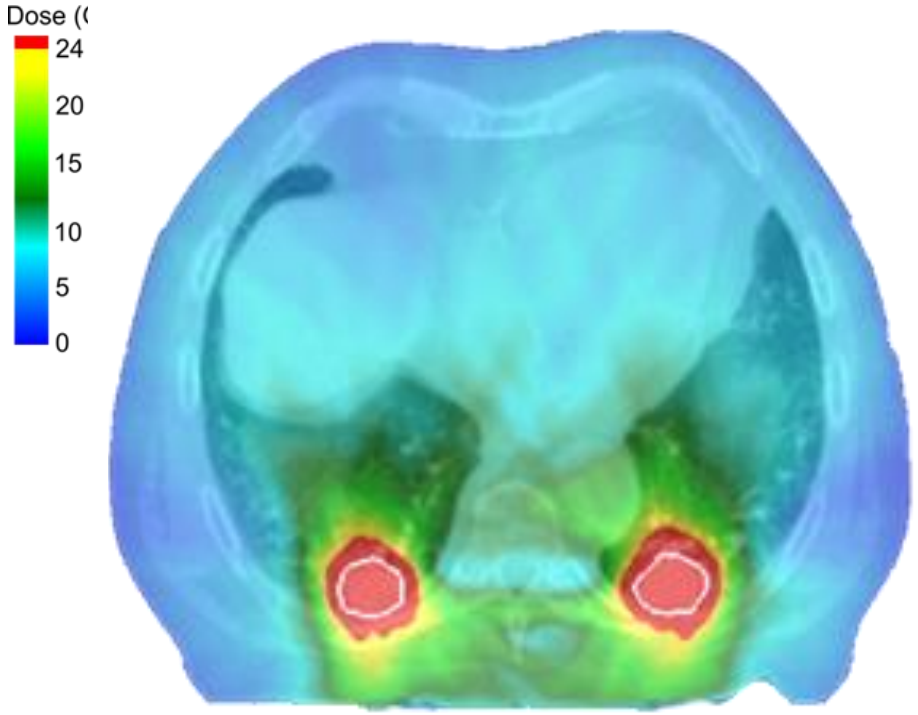


Why carbon ion therapy? Dose quality!

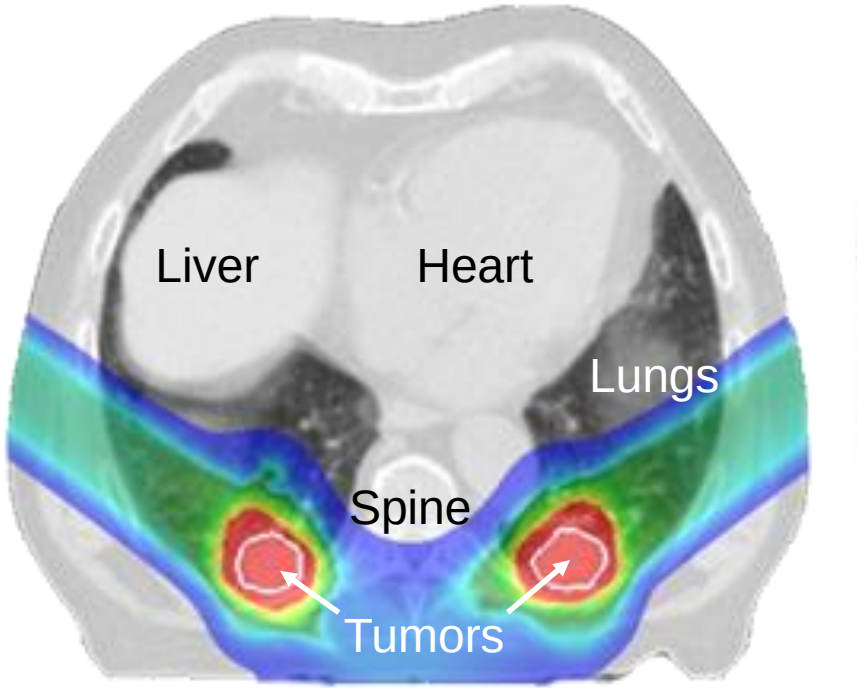
- Differential effect in entrance channel and maximum



Particle therapy: dose advantage in a patient

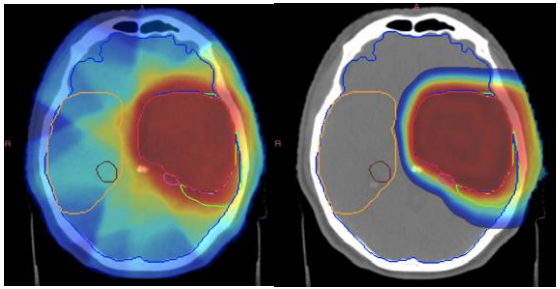


photons

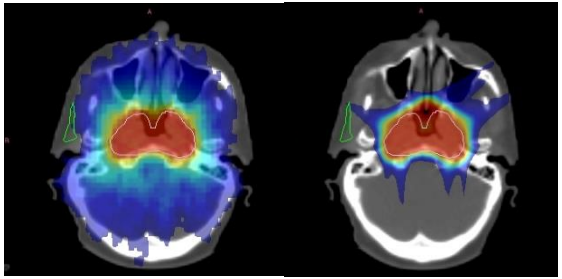


carbon

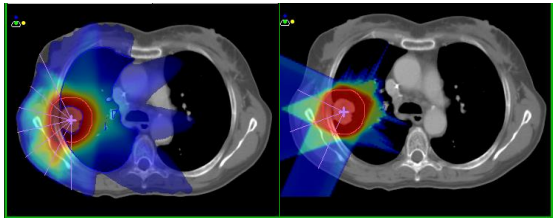
Particle therapy: dose advantage in more patients



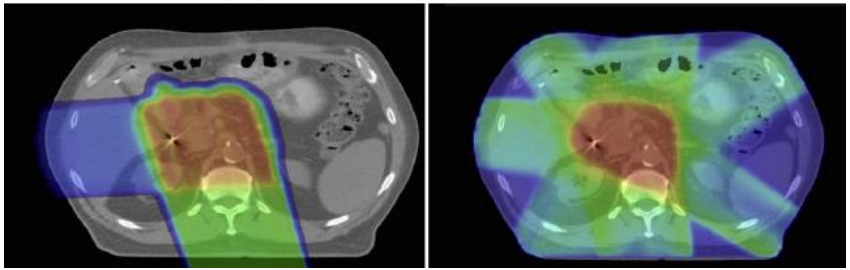
CNS



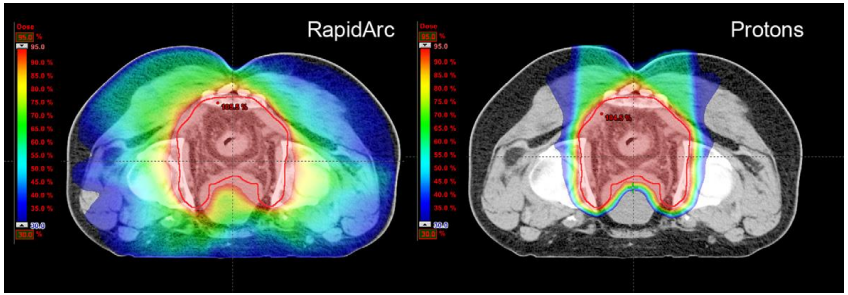
H&N



LUNG



ABDOMEN

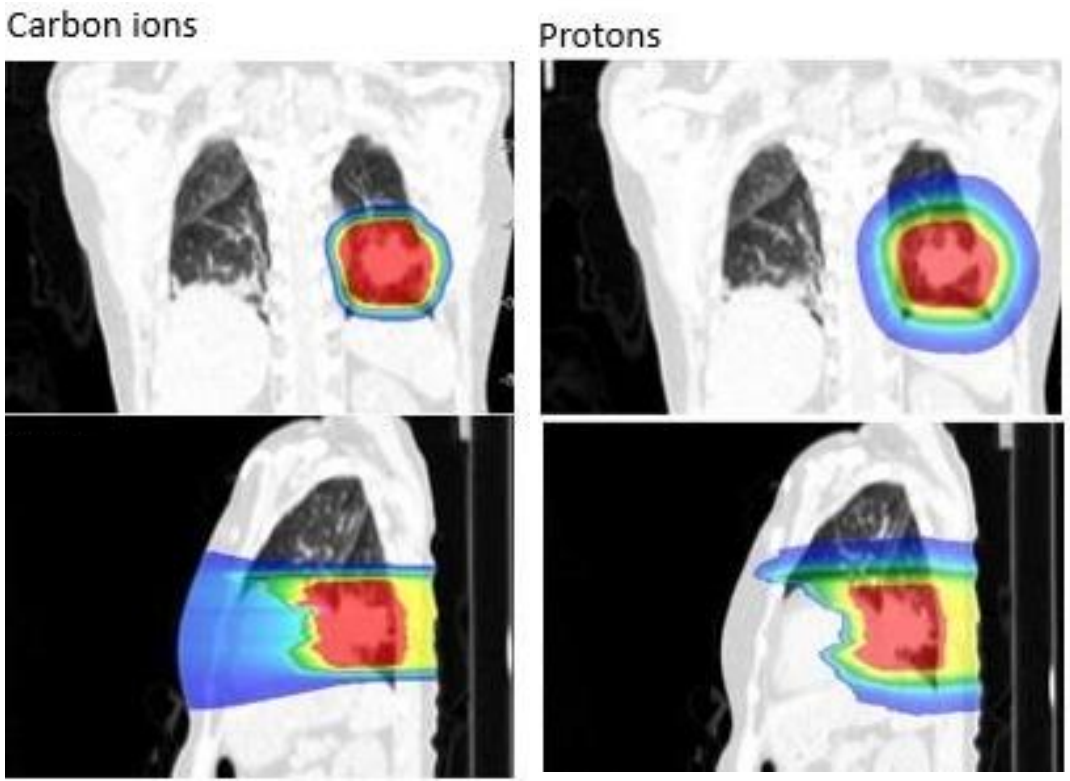


PELVIS

Courtesy of Marco Schwarz, TIFPA, Trento

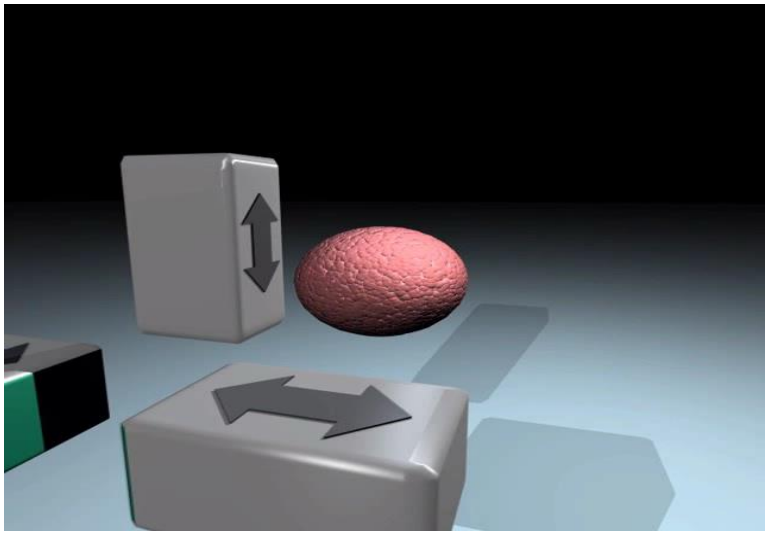
Carbon vs. Protons

- Protons:
  - smaller accelerators
  - no exit channel
  - less uncertainty in biological effect
- Carbon ions:
  - more precise beams / less scatter
  - higher biological effect in tumor
  - more effective against hypoxia, radio-resistant tumors



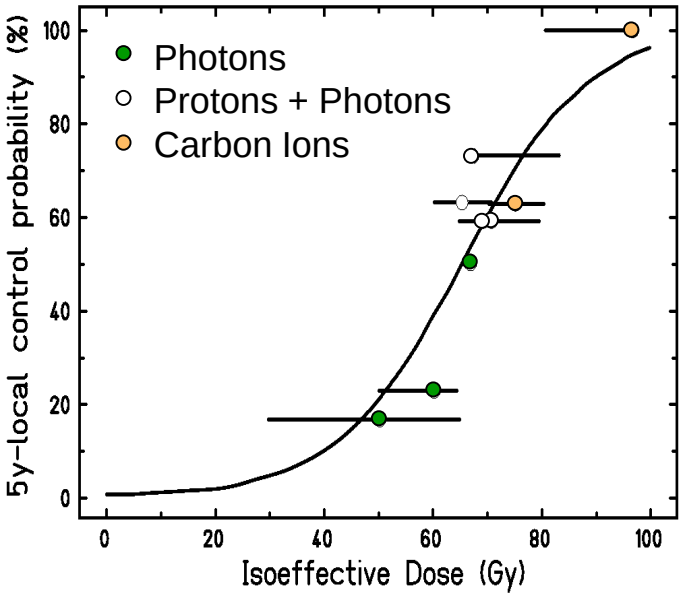
The GSI pilot project: First carbon patients in Europe

- Constructed for a clinical pilot study within a basic physics research facility
- Successful collaboration of University Clinic and Research Laboratories
- Major technical advances that are still used in today's clinics:
  raster scanning, PET imaging, fast energy switch, RBE model,…
- 440 patients treated from 1997 to 2008



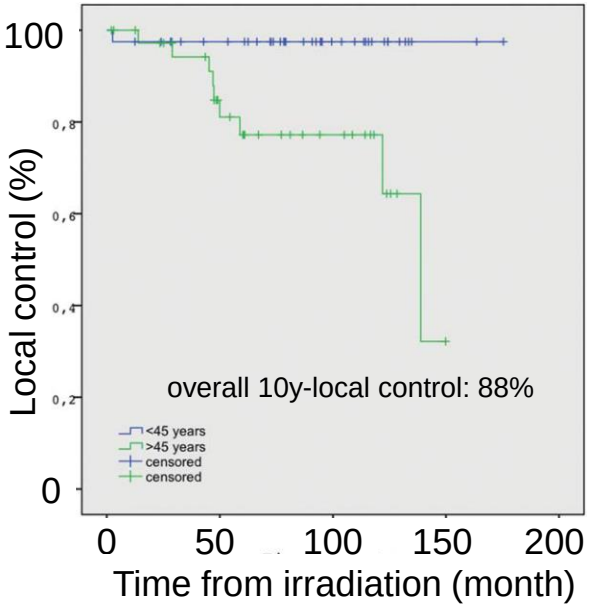
HZDR
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF
UniversitätsKlinikum Heidelberg

Clinical outcome of the pilot project



Chondrosarcoma

Schulz-Ertner et al., IJROBP 2007



Chordoma

Uhl et al., Cancer 2014

Pascal, treated in the carbon ion pilot project

- Chondrosarcoma discovered and surgically removed in 2003
- Recurring tumor in 2007 at age 8
- Treated in GSI Cave M with carbon ions

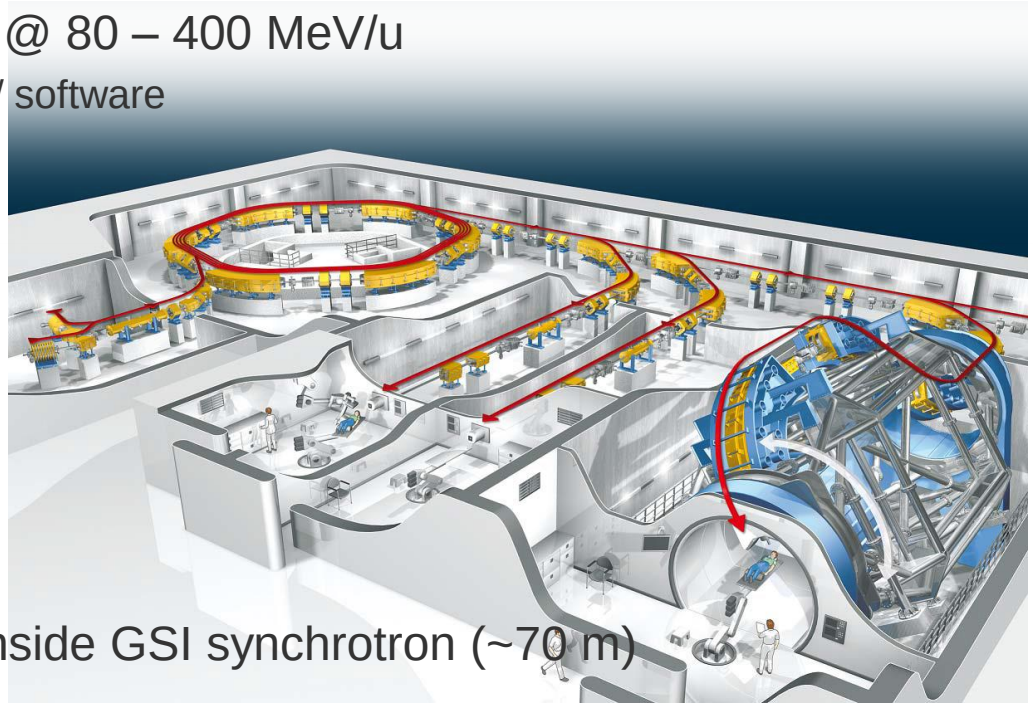
- Local control of tumor for 10 years and counting
- Under regular supervision in Heidelberg
- 2017 - preparing to enroll in informatics

- No longterm side effects

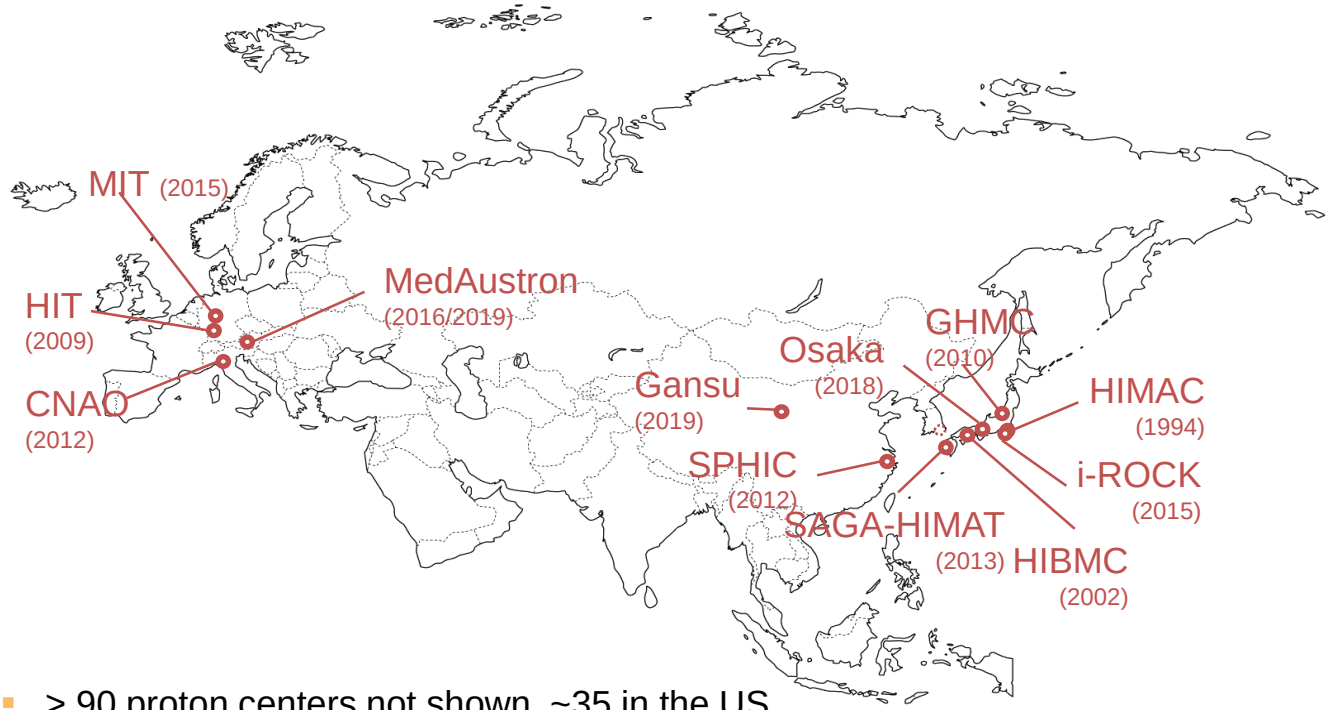
http://www.deutsche-uniklinika.de/themen-die-bewegen/hinter-den-kulissen-patienten-erzaehlen/chondrosarkom/

Heidelberg Ion Beam Therapy (HIT)

- Proposal 1998 – start 2003 – first patient 2009
- Proton, Carbon, (Helium, Oxygen) @ 80 – 400 MeV/u
  - GSI: accelerator, Siemens: hardware / software
  - owned by University Clinic Heidelberg
- >5000 patients treated
  - 3000 carbon, 2000 proton
  - Annual target is 600-700 patients
  - up to 16h per day, 6 days per week
  - >300 days / year
  - many active clinical studies
- More details in talk of Dr. Hoene
- Fun fact: entire facility (60 m) fits inside GSI synchrotron (~70 m)



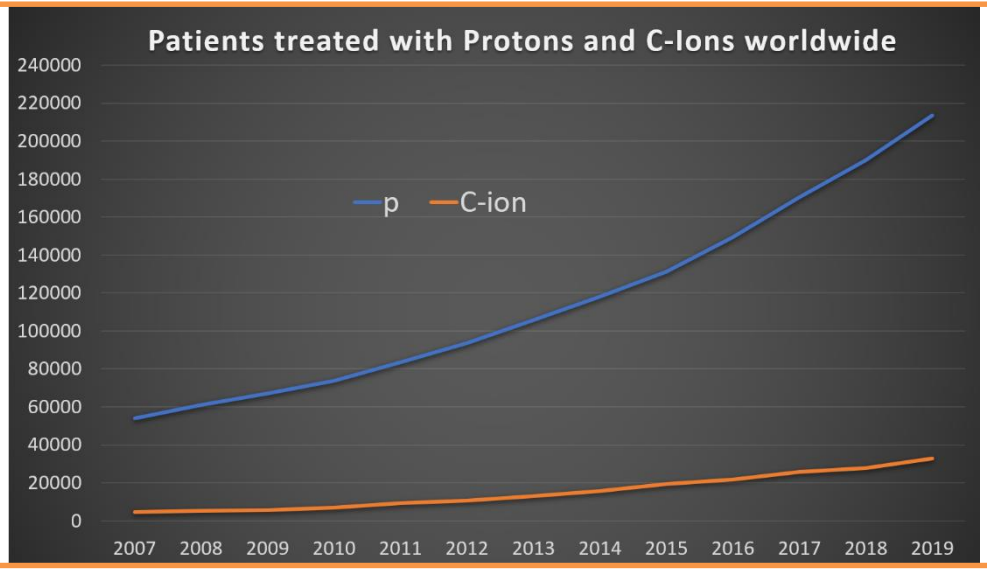
Carbon ion beam centers worldwide



- > 90 proton centers not shown, ~35 in the US
- 1 carbon center in the US in planning stage

Patient statistics

250,000 patients treated with particles –
a giant success story for **clinical transition of basic science**



For comparison – about the same number of patients is treated with conventional radiotherapy in **Germany alone each year**

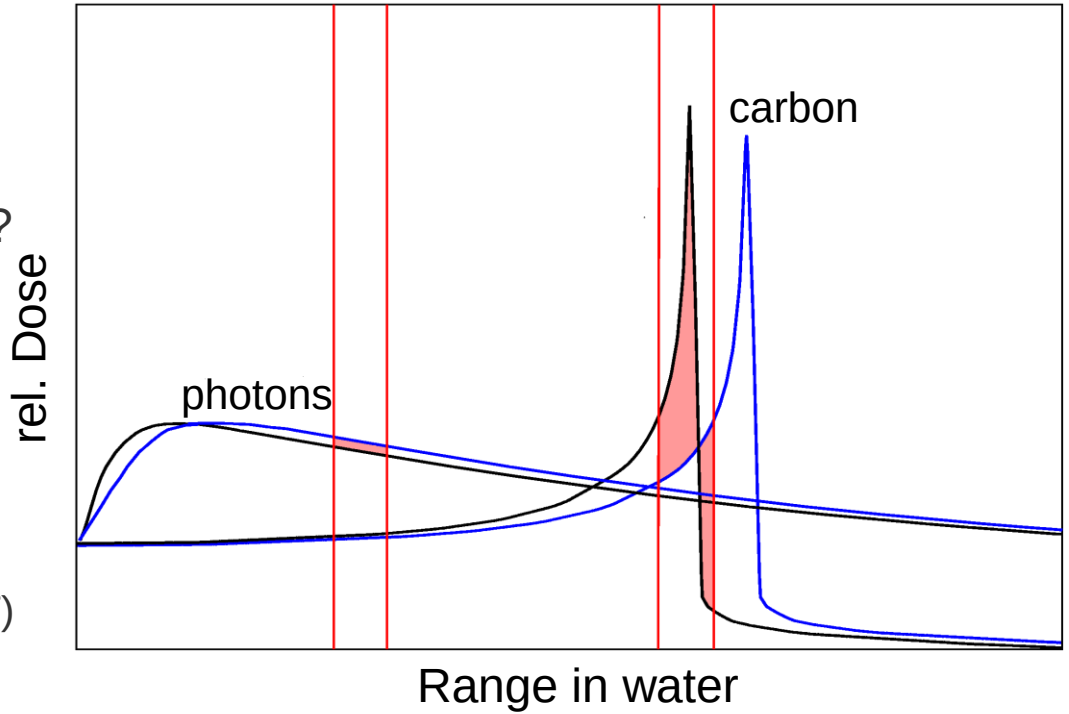
Still an emerging technology: Research topics

- **Treatment planning**: robust optimization, beam mixing, ‘kill painting’, optimization of LET, better RBE models, Monte Carlo vs. beam models, …
- **Imaging**: Online (particle) imaging, Dual Energy CT, MR-based treatment planning, 3D/4D setup imaging, MRI-particle therapy, better 4DCT, MRI-generated 4D-CT, …
- **Range uncertainty**: prompt emissions, PET, particle imaging, robust setup, IGRT / SGRT, …
- **Delivery**: Faster scanning, FLASH, Motion-compensation, Mini-beams, Arc, …
- **Accelerator designs**: cheaper, smaller, more flexible (>Maurizio’s talk)
- **Radiobiology**: Repair mechanisms, combined & targeted therapy, immune therapy, OER, high LET effects, …
- **Clinical**: Evidence, efficacy, patient selection, workflow, new applications, …

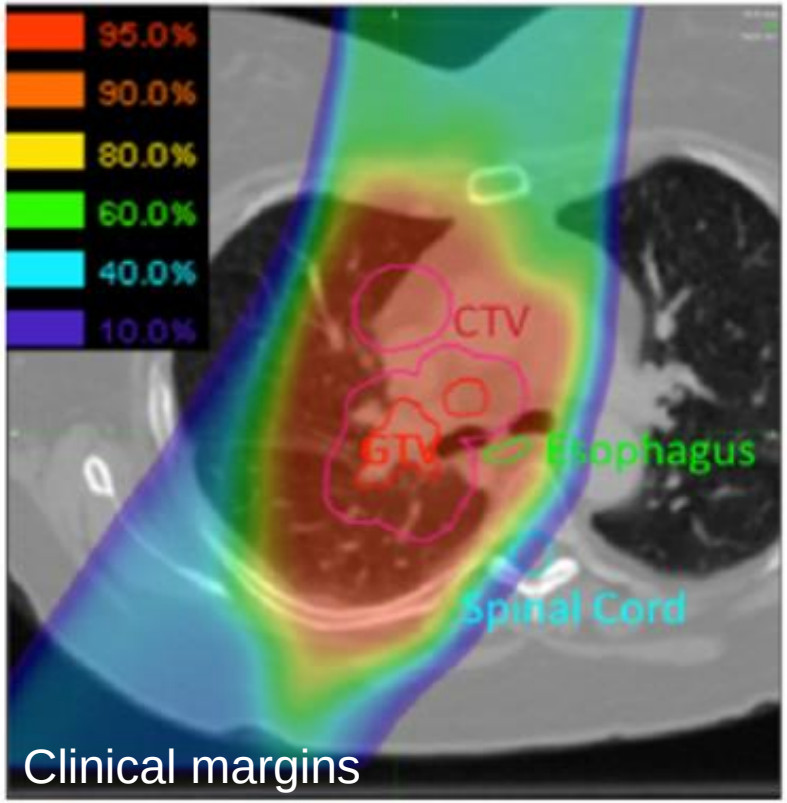
Range uncertainty

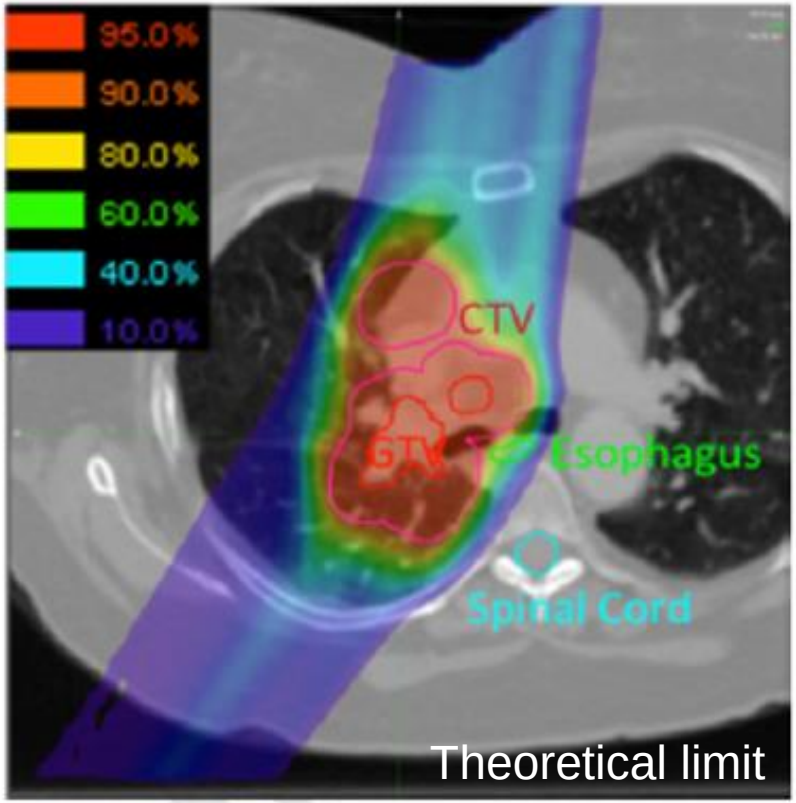
- Dose maximum at end of range is also a danger
- What if the beam does not stop at the planned position?

- Measures to reduce this uncertainty
  - larger treatment volume
  - better planning images (DECT)
  - 3D setup imaging
  - beam monitoring techniques

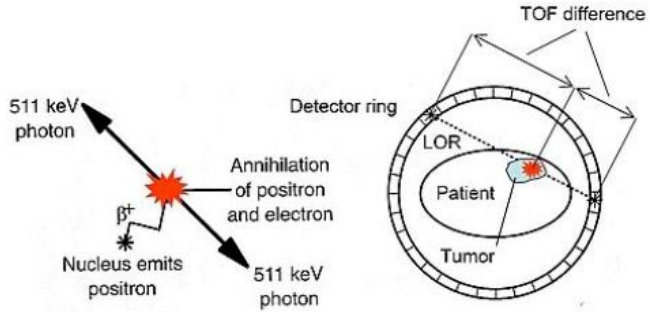


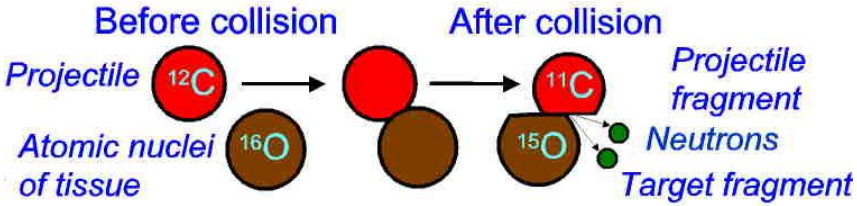
Clinical vs. theoretical accuracy

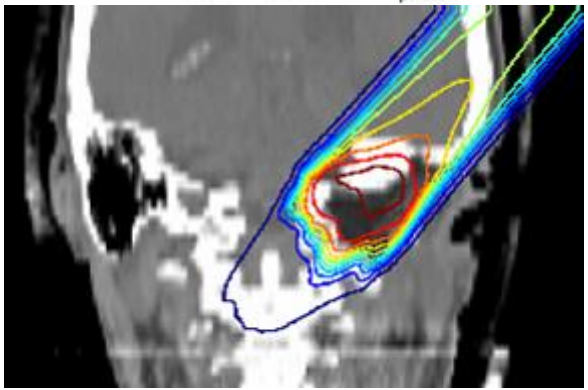




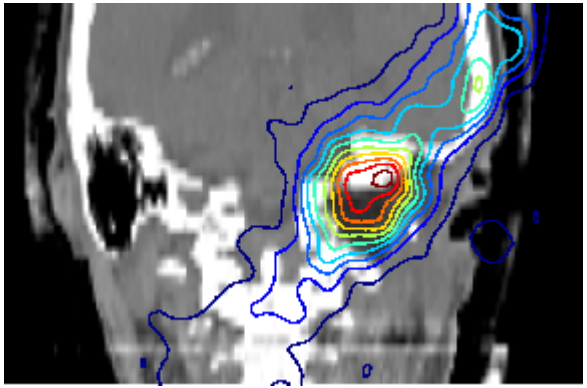
PET imaging to assess beam range



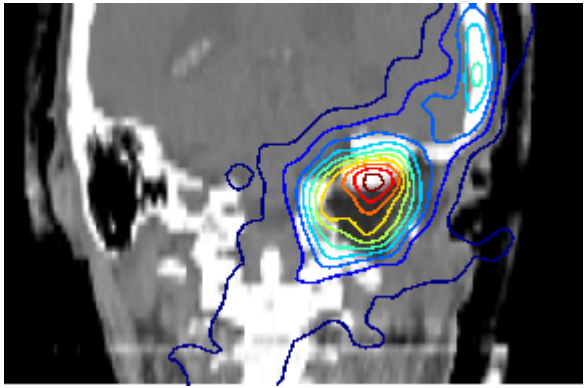




Treatment plan



Predicted β^+-activity



Measured β^+-activity

[Enghardt et al. HZDR]

PET with radioactive beams

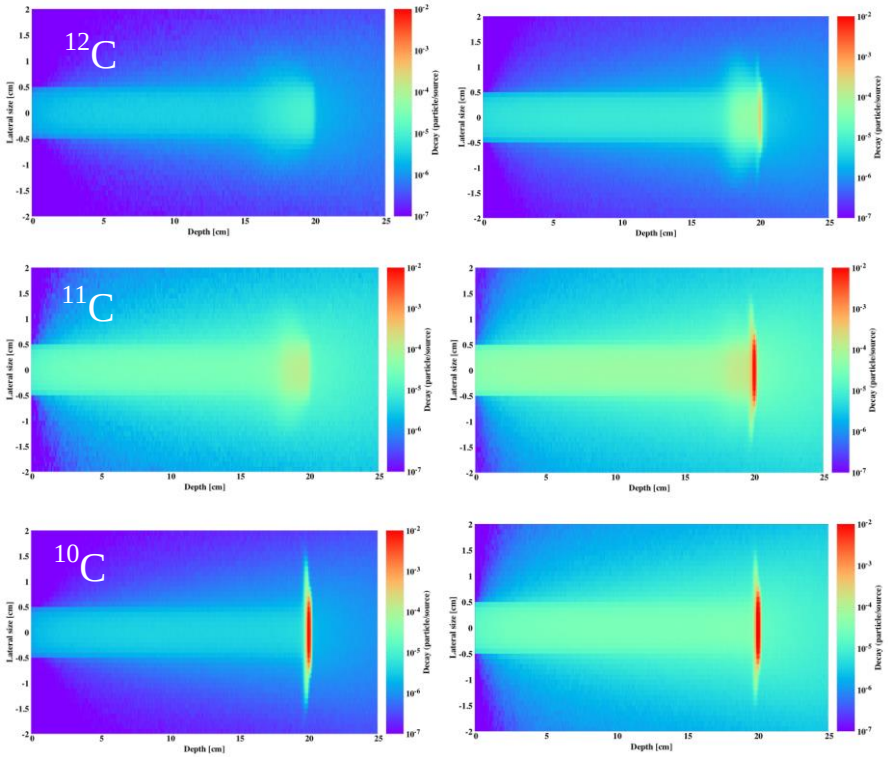
- Instead of waiting for the beam to produce a few radioisotopes – directly treat with them!
- Much higher signal or much faster measurement
- Much better correlation of measurement to beam range

➢ to be realized within
ERC grant of Marco Durante

B • A • R • B
BIOMEDICAL APPLICATIONS OF RADIOACTIVE ION BEAMS

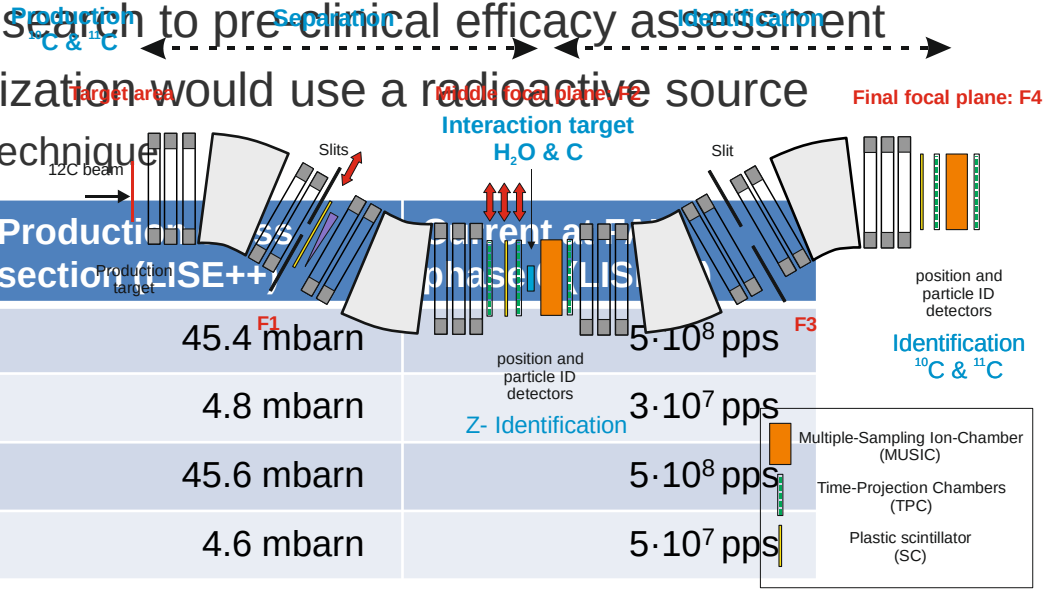
erc European Research Council

T=20 s T=20 min



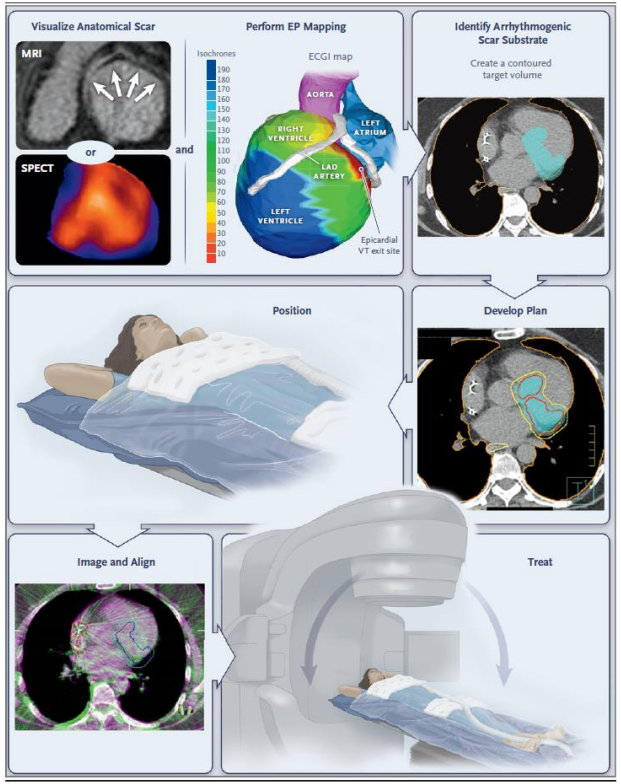
Radioactive beams – possible at FAIR

- Production of $^{10}C/^{11}C$ is very inefficient – huge intensity needed in primary beam
- In-flight separation of the high energy beam in the GSI fragment separator FRS
- BARB project from basic research to pre-clinical efficacy assessment
- A later possible clinical realization would use a radioactive source
  - low energy beam with ISOL technique

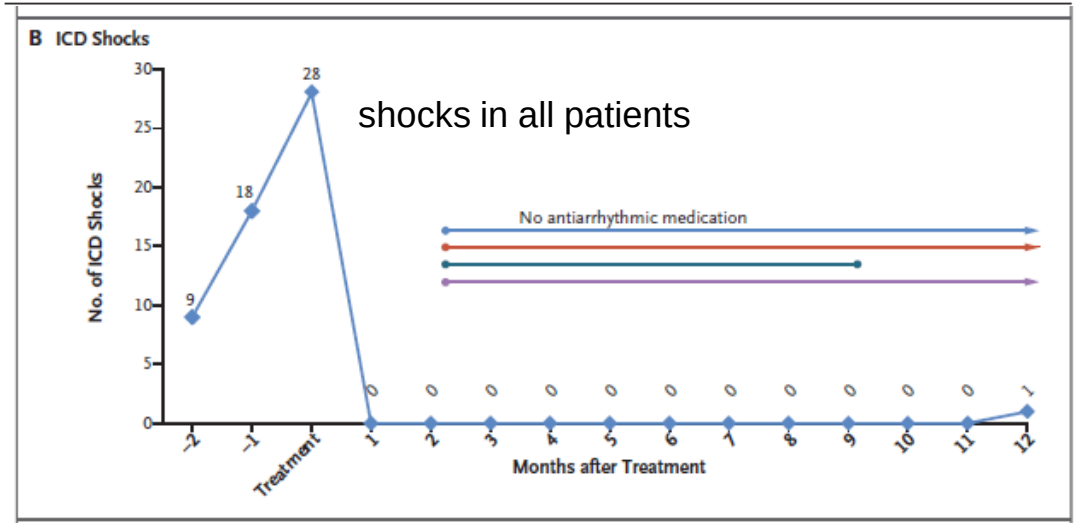


Isotope	Half life time	Production cross section (LISE++)	Current at Target (phase-0 LINAC)
^{11}C	20.33 min	45.4 mbarn	$5 \cdot 10^8$ pps
^{10}C	19.29 s	4.8 mbarn	$3 \cdot 10^7$ pps
^{15}O	122.24 s	45.6 mbarn	$5 \cdot 10^8$ pps
^{14}O	70.61 s	4.6 mbarn	$5 \cdot 10^7$ pps

Example 2: Radiosurgery ablation of cardiac arrhythmia

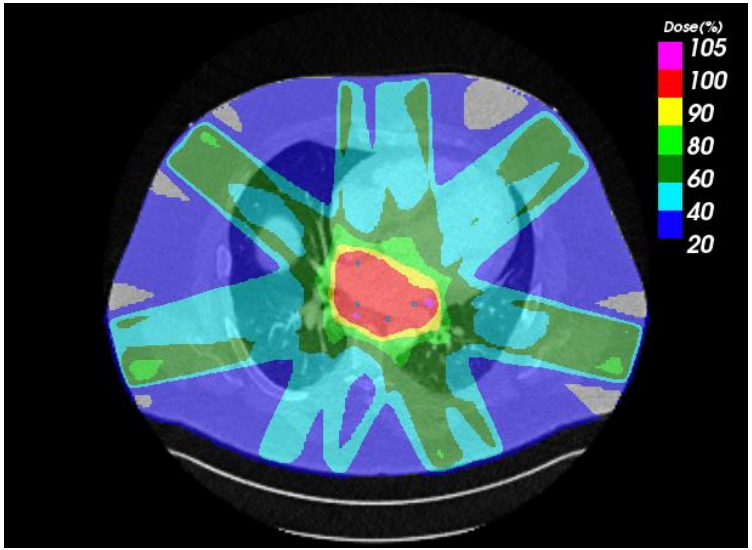


- Several animal studies with photons since 2010
- First clinical trial in 2017: 5 patients with severe arrhythmia and long prior treatment history

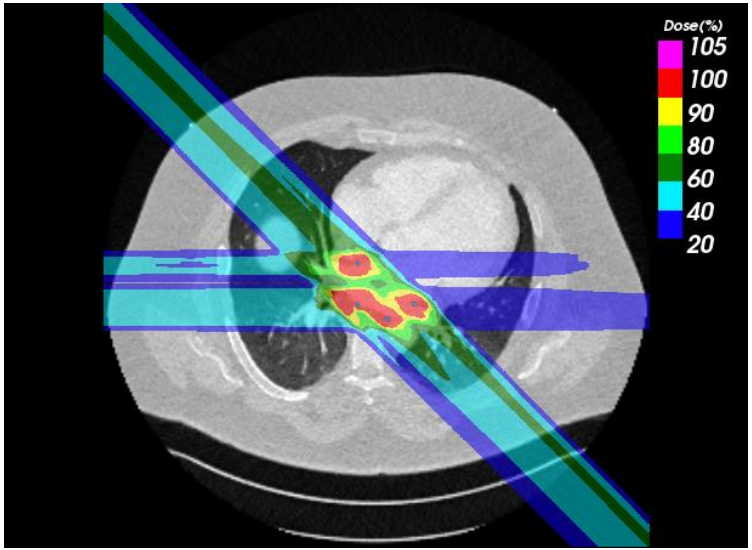


Comparison of photon to particles

- Significantly better sparing of healthy tissue



Photons

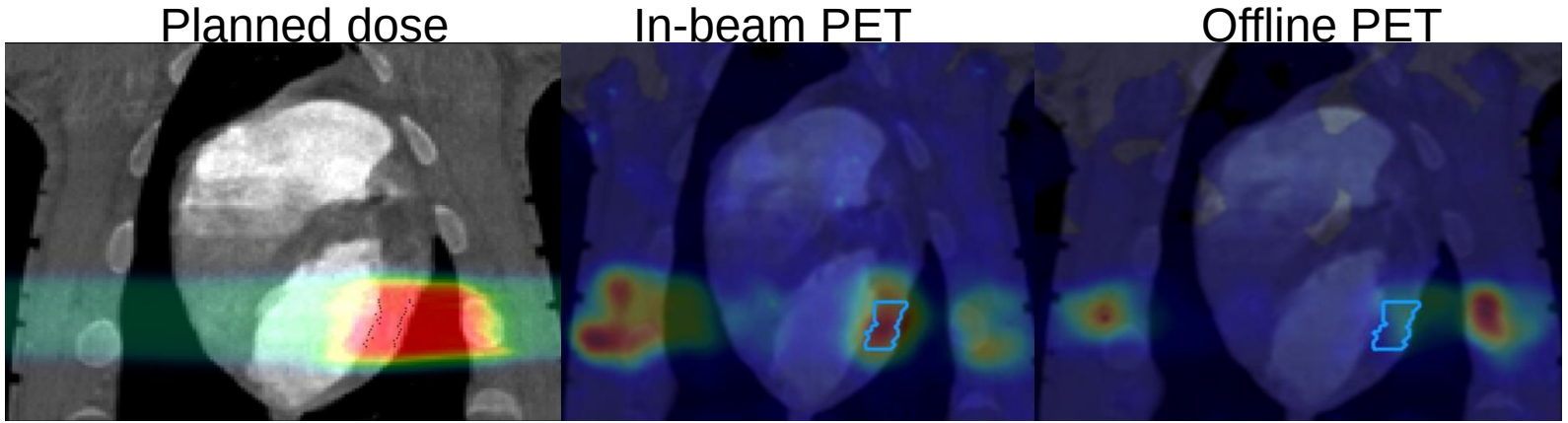


Carbon

Constantinescu et al,
J Cardiovasc Electrophysiol 2016

Feasibility study at GSI in 2014

- Single fraction irradiation, 2 opposing fields, 25 – 55 Gy
  - 14 animals (domestic pigs) treated + 3 controls
- Endpoints 6 months after irradiation
  - Electrophysiology, histology, side effects



- Onset of targeted changes in cardiac electrophysiology 4 months post-irradiation
- No irradiation-induced side effects in any animal

Lehmann, Graeff et al, Sci Rep 2016

Summary

- Particle therapy is the most advanced form of radiotherapy,
  but already a clinical reality with >100 centers worldwide
- Large dosimetric advantage due to finite range with targeted dose maximum
- Biological advantages of heavier ions vs. radioresistant tumors
- More than 250,000 patients treated –
  best clinical applications are still a research topic
  - High costs require a high patient benefit
  - well designed & executed clinical studies are necessary: better evidence needed
- Multidisciplinary research effort is necessary to optimize therapy:
  Medicine, physics, engineering & biology

Thanks for your attention!

Start of **international collaboration of biophysics** research at accelerator labs

- **Therapy**:
  High dose rate (FLASH), image guidance, radioactive beams, radionuclides
- **Space:**
  Ground-based simulation of space radiation, radiobiology, cross-sections
- New accelerator facilities & designs

250 participants from 5 continents – but only 1 Greek Lady

Your contributions & collaboration are highly welcome!

=> www.gsi.de/bio-coll