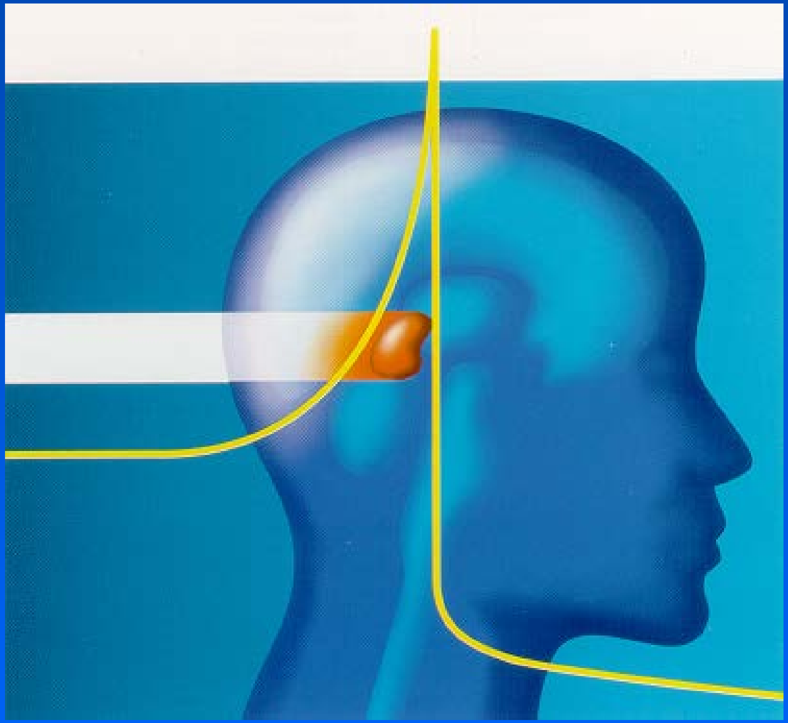
Cancer Therapy Using Ion Accelerators



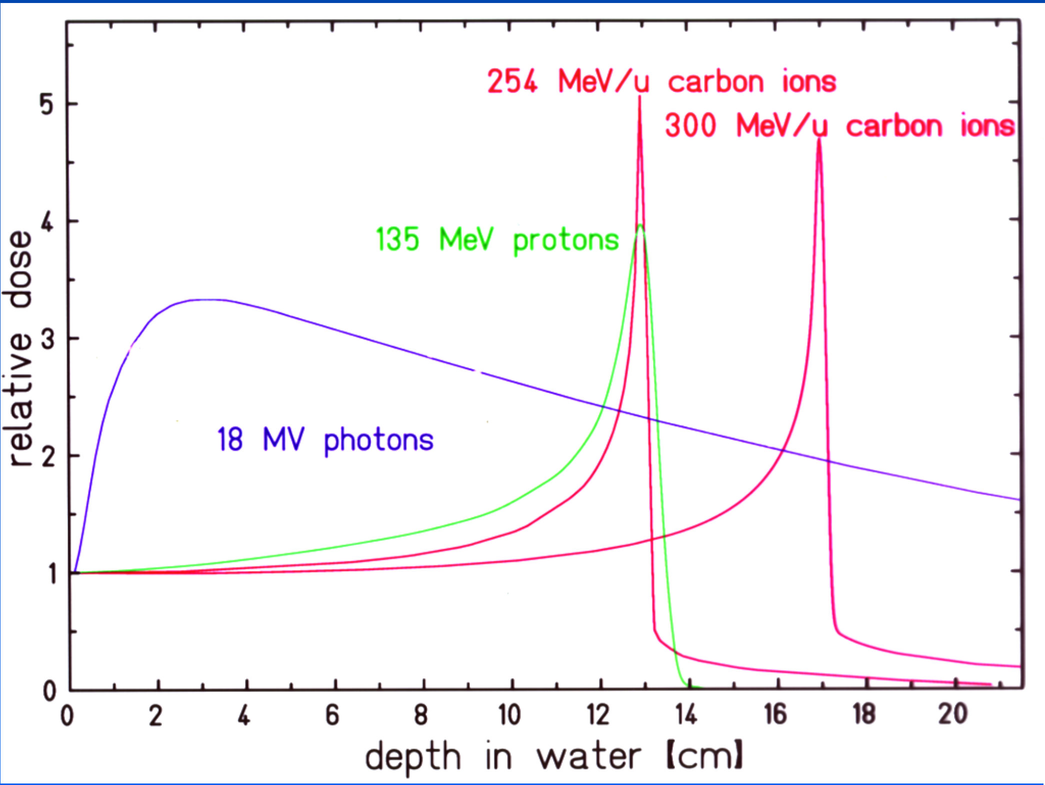
Prof. Dr. Thomas Haberer

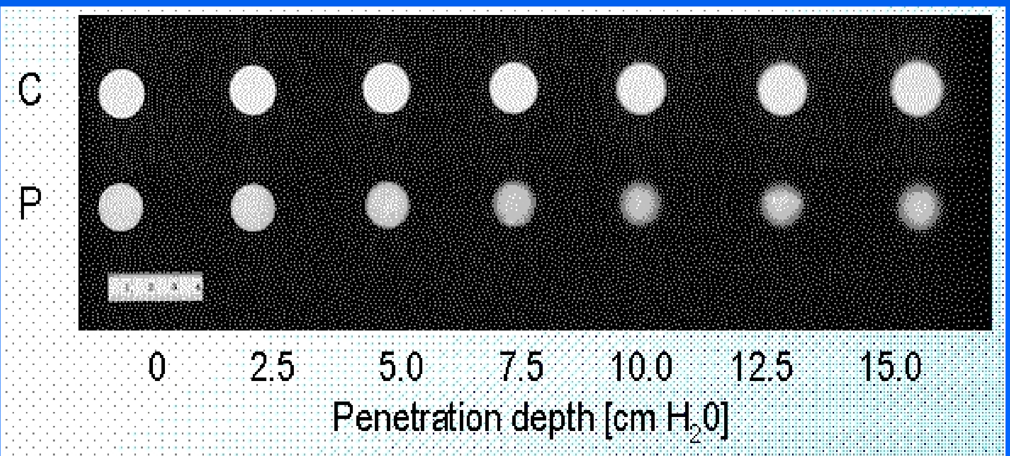
Heidelberg Ion Beam Therapy Center

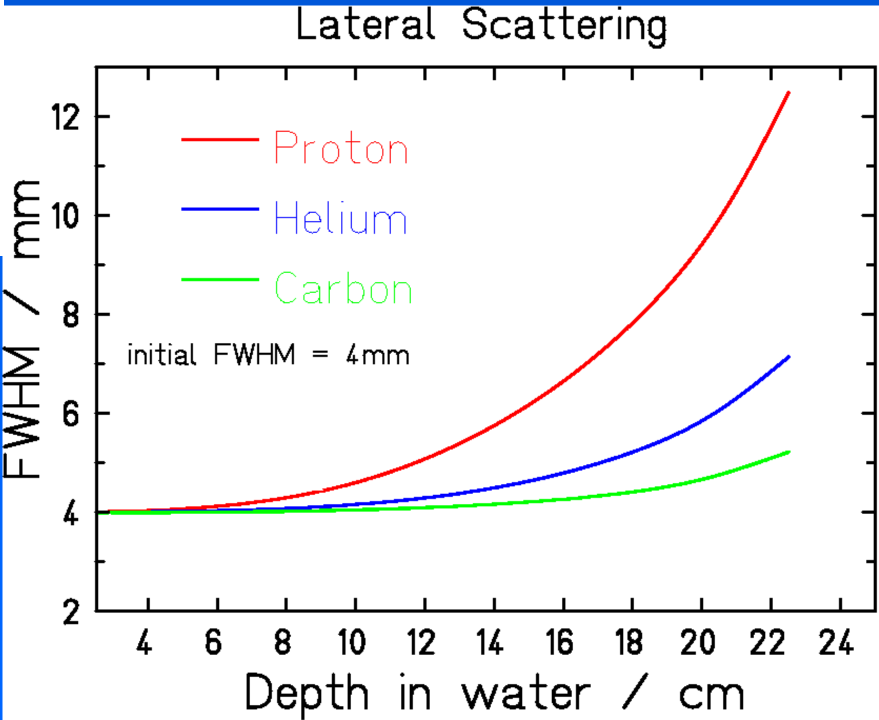
Cern Accelerator School Senec 2012

Rationale / Physics

- inverted depth-dose distribution
- mild lateral scattering







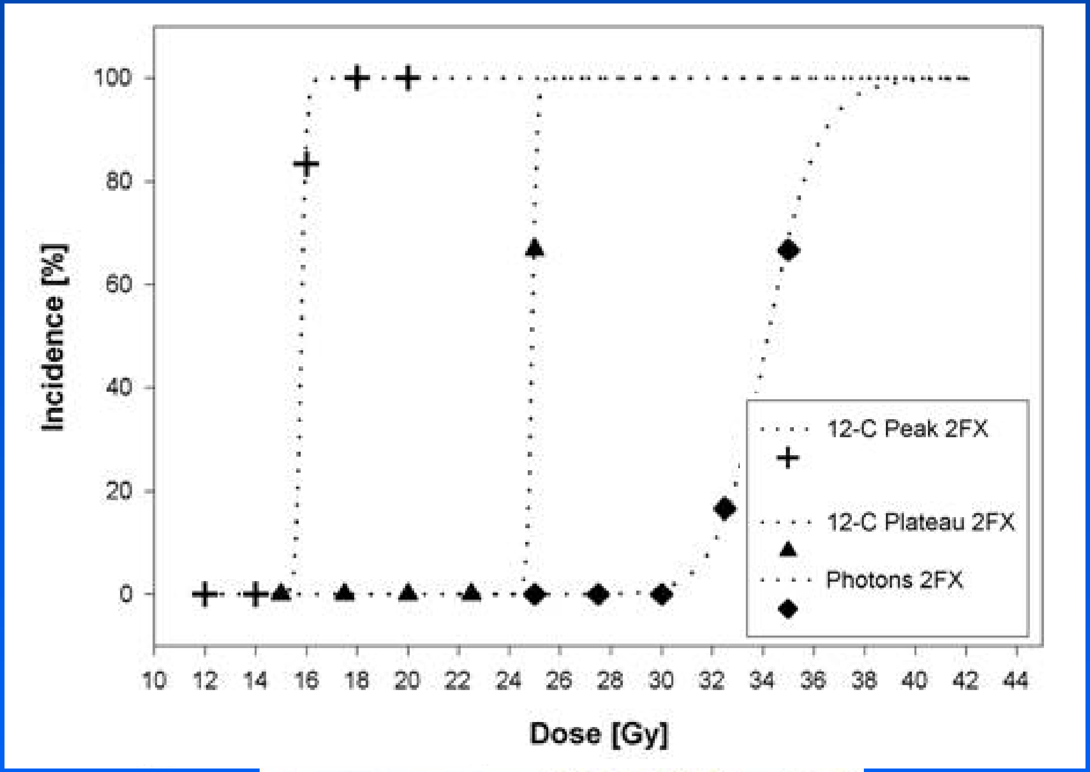
Increased Relative Biological Effectiveness

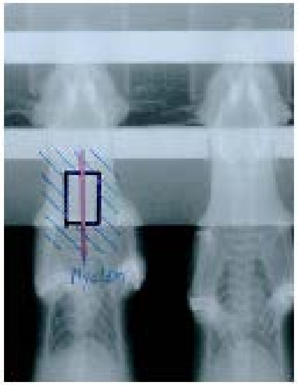
radiation induced myelopathy in rats after 2 carbon fractions

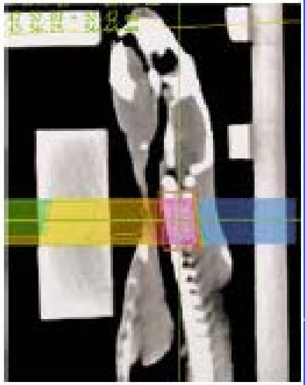
RBEs:

Plateau: ~1.4

Peak: ~ 2.3



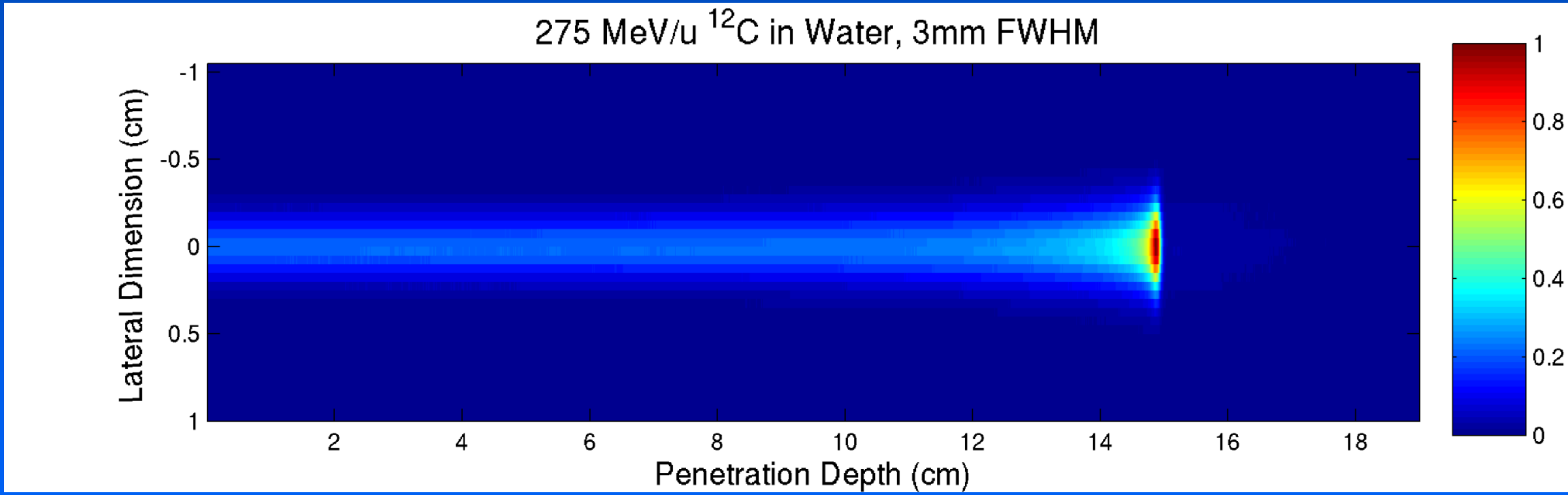




Debus, Karger, Peschke, Scholz, …
Rad. Res. 2003

Goal

The key element to improve the clinical outcome is **local control!**

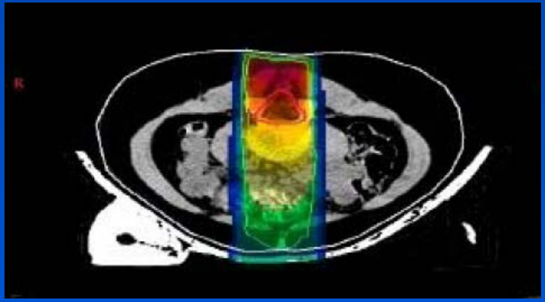


entrance channel:
- low physical dose
- low rel. biol. effiency

tumour:
- high physical dose
- high rel. biol. effiency

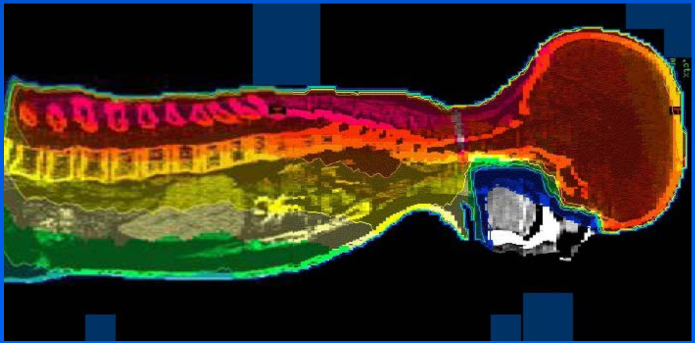
Medulloblastoma

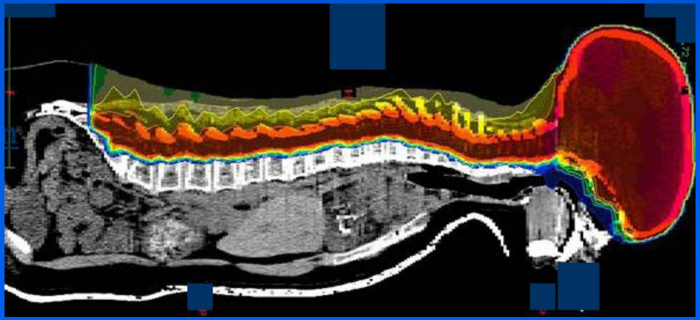
conventional



charged particles

Target dose 32 Gy/GyE



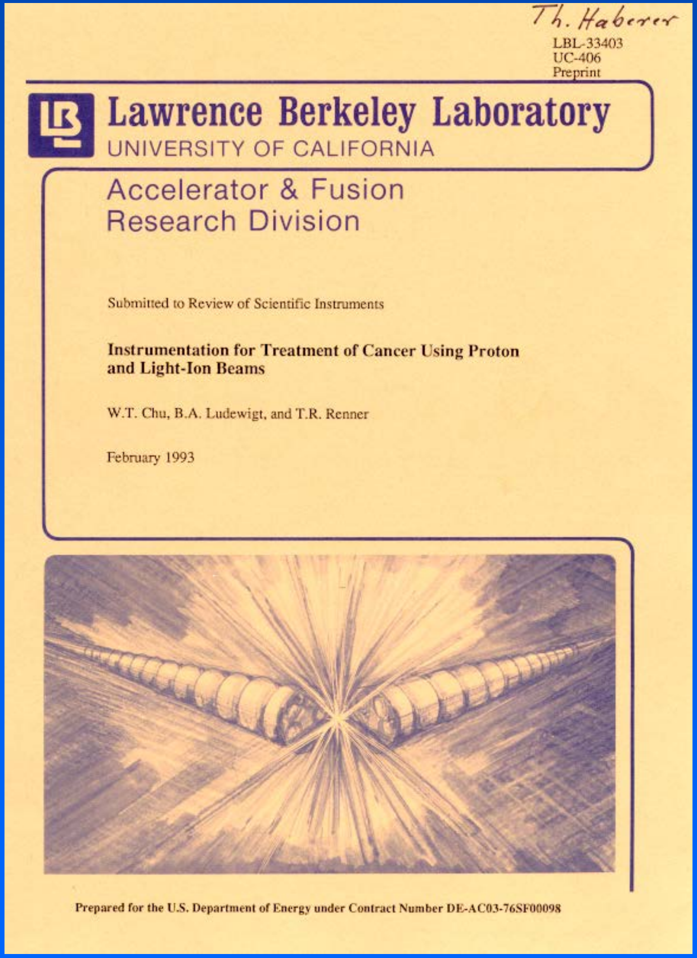


Dose comparison

22 Gy	bone marrow	< 1 GyE
18 Gy	heart	<.5 GyE
20 Gy	intestinal	<.5 GyE

Standard Approach

- Facilities being built at existing research accelerators
- Fixed energy machines with moderate flexibility (if at all)
- Dose delivery not exactly tumor-conform


Th. Haberer
LBL-33403
UC-406
Preprint

Lawrence Berkeley Laboratory
UNIVERSITY OF CALIFORNIA

Accelerator & Fusion
Research Division

Submitted to Review of Scientific Instruments

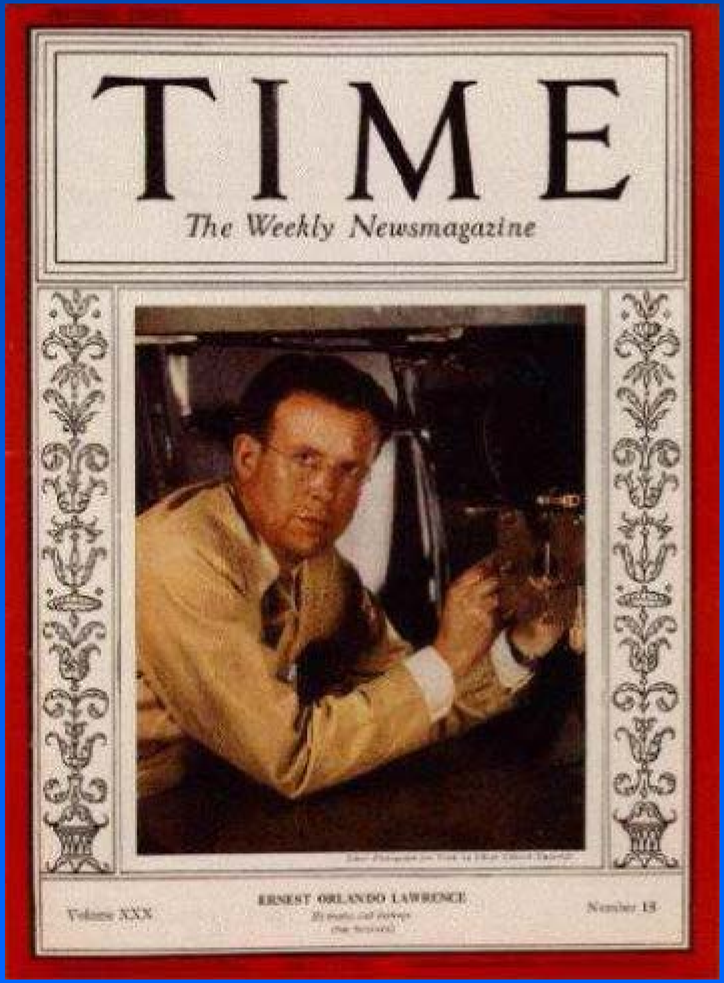
Instrumentation for Treatment of Cancer Using Proton and Light-Ion Beams

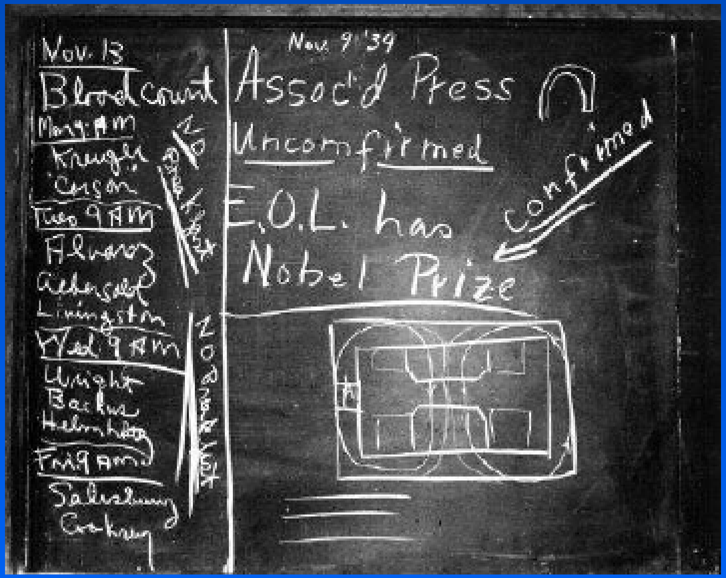
W.T. Chu, B.A. Ludewigt, and T.R. Renner

February 1993

Prepared for the U.S. Department of Energy under Contract Number DE-AC03-76SF00098

Ernest Orlando Lawrence
Nobel Prize 1939





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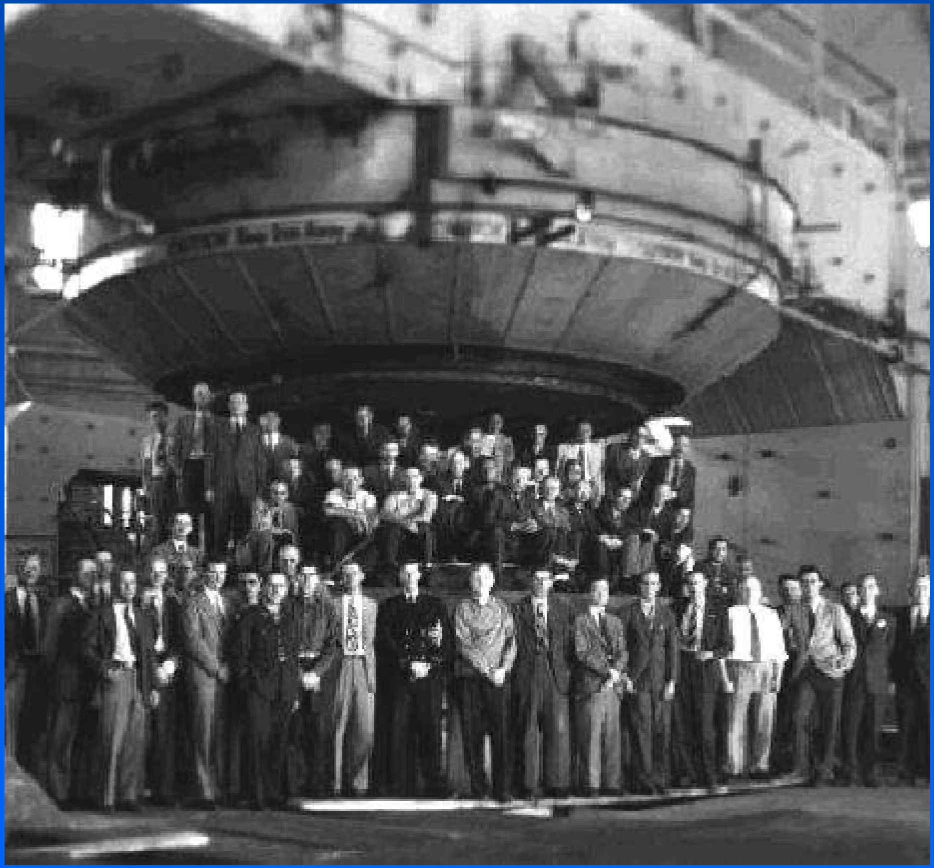
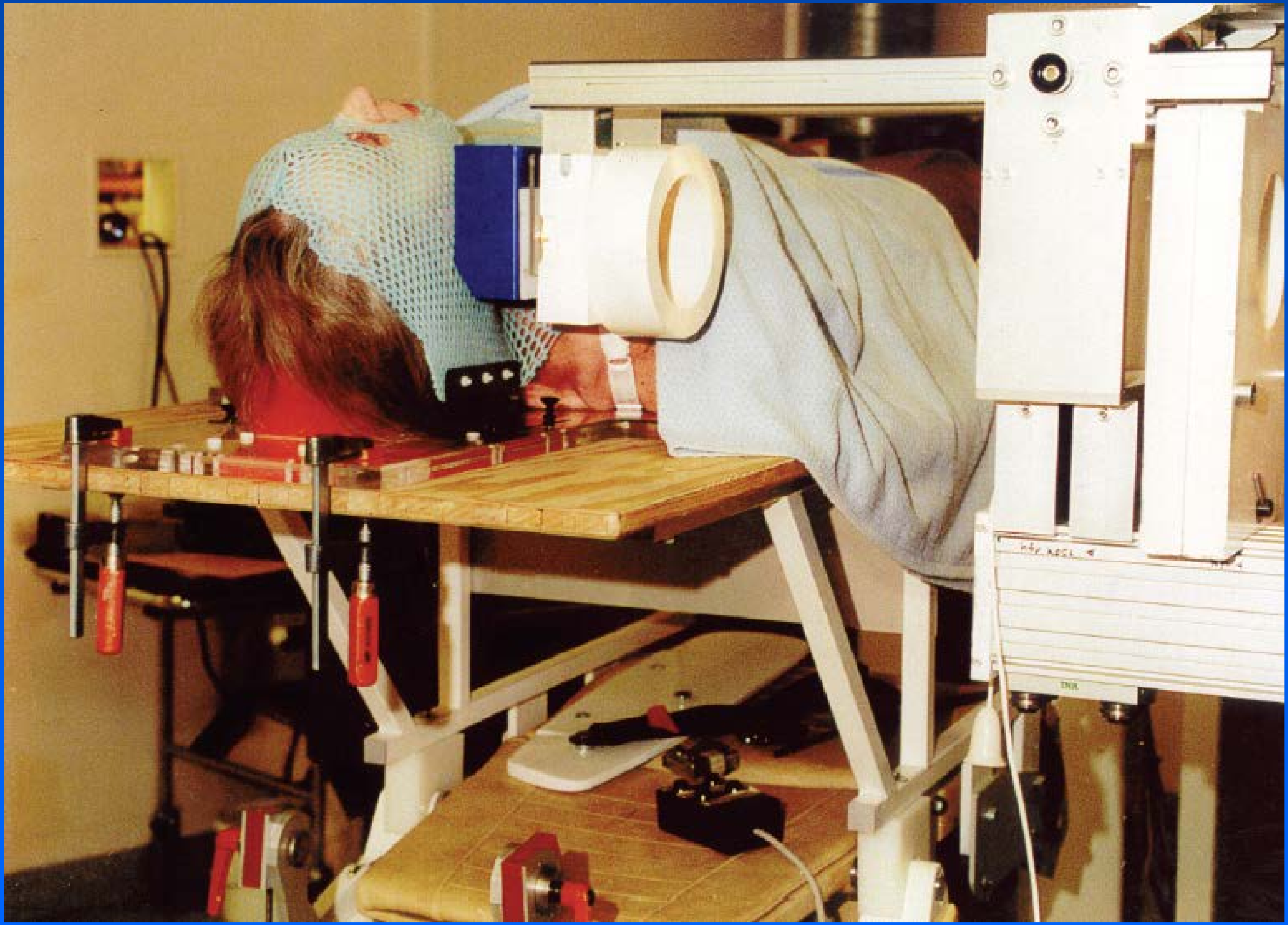
184 inch Cyclotron @ LBL 1947 / 1986



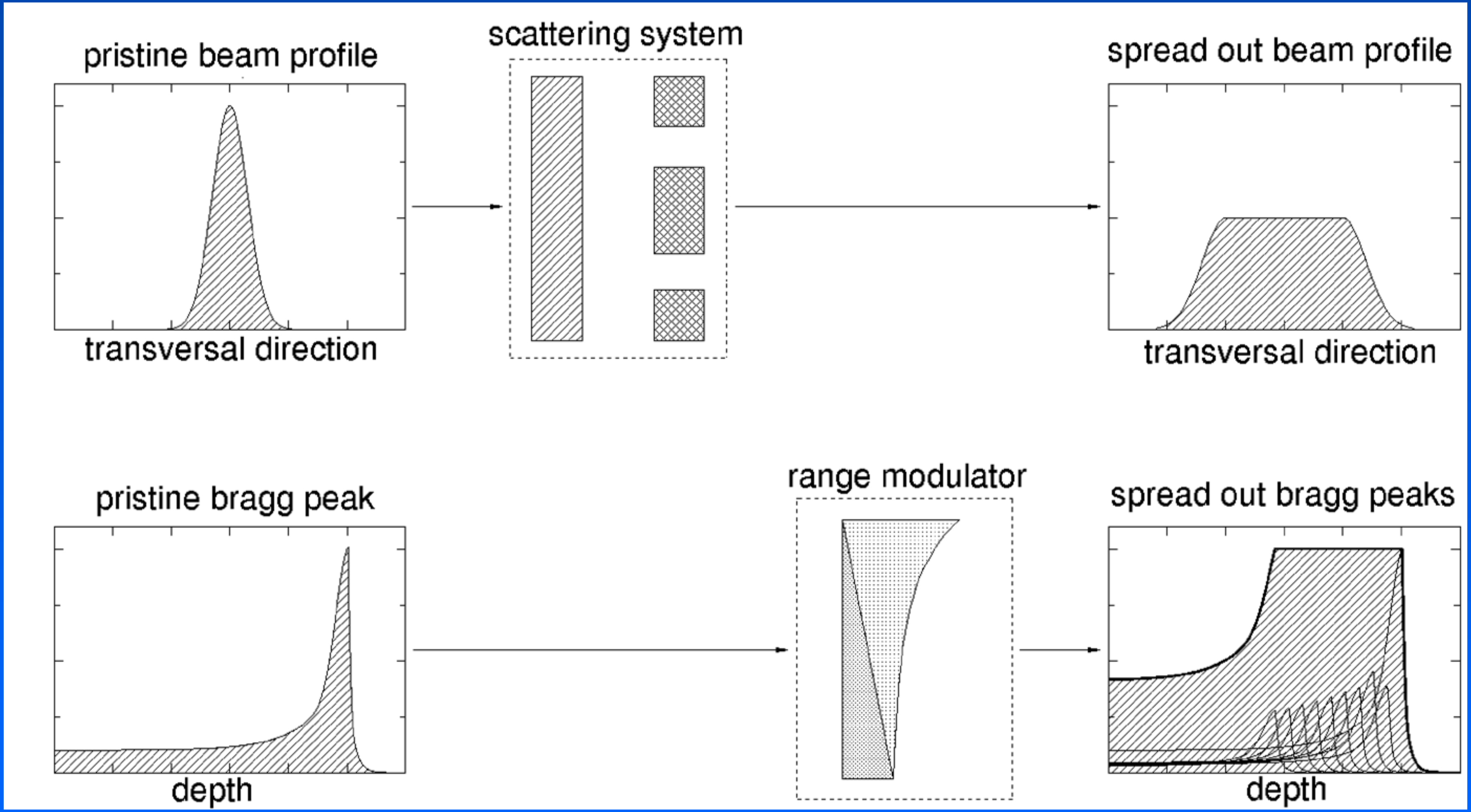
Patient Treatment in Labs



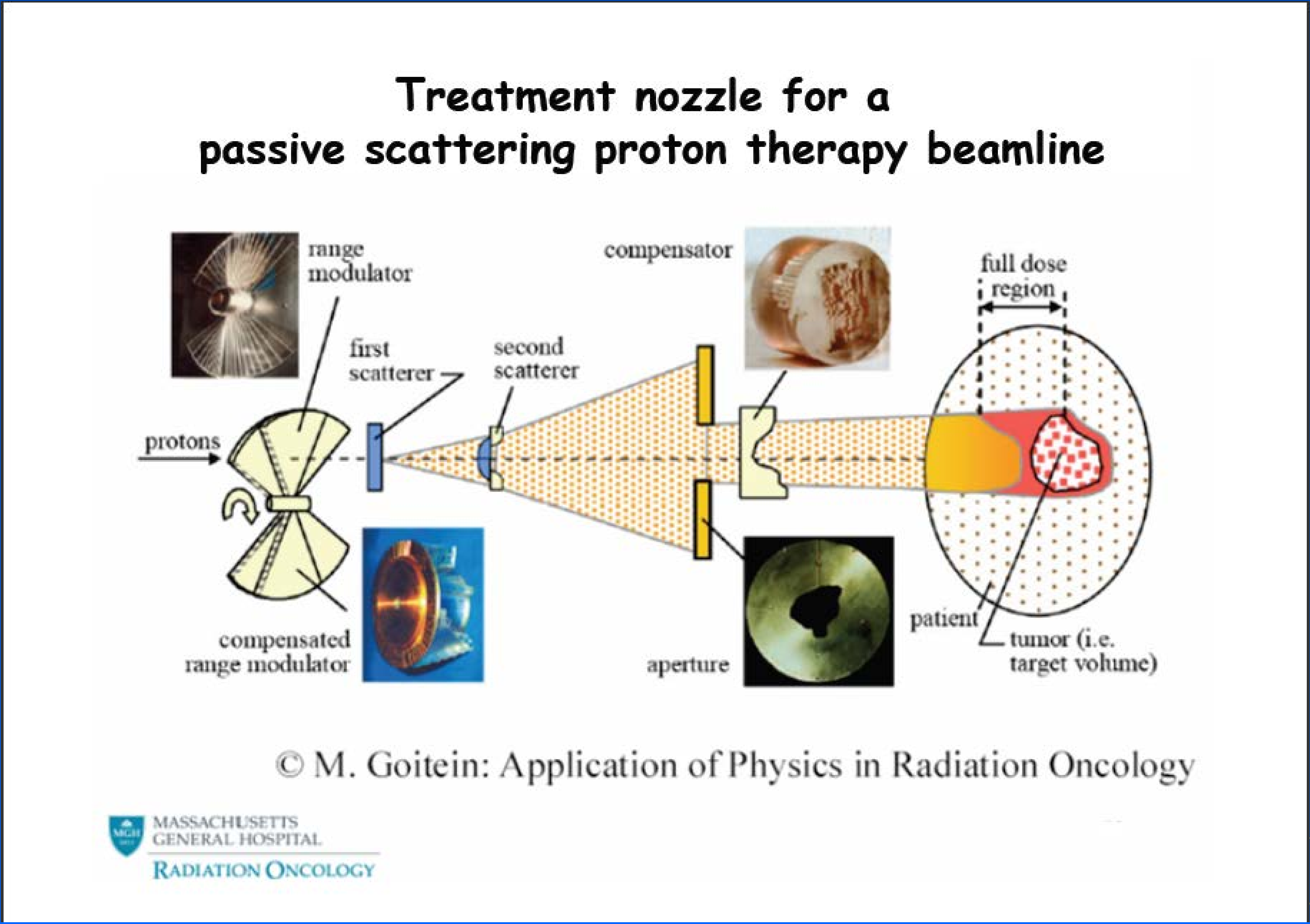
Courtesy E. Blomquist, Svedborg Lab, Uppsala

Heidelberg Ionenstrahl-Therapie Centrum

Passive Dose Delivery



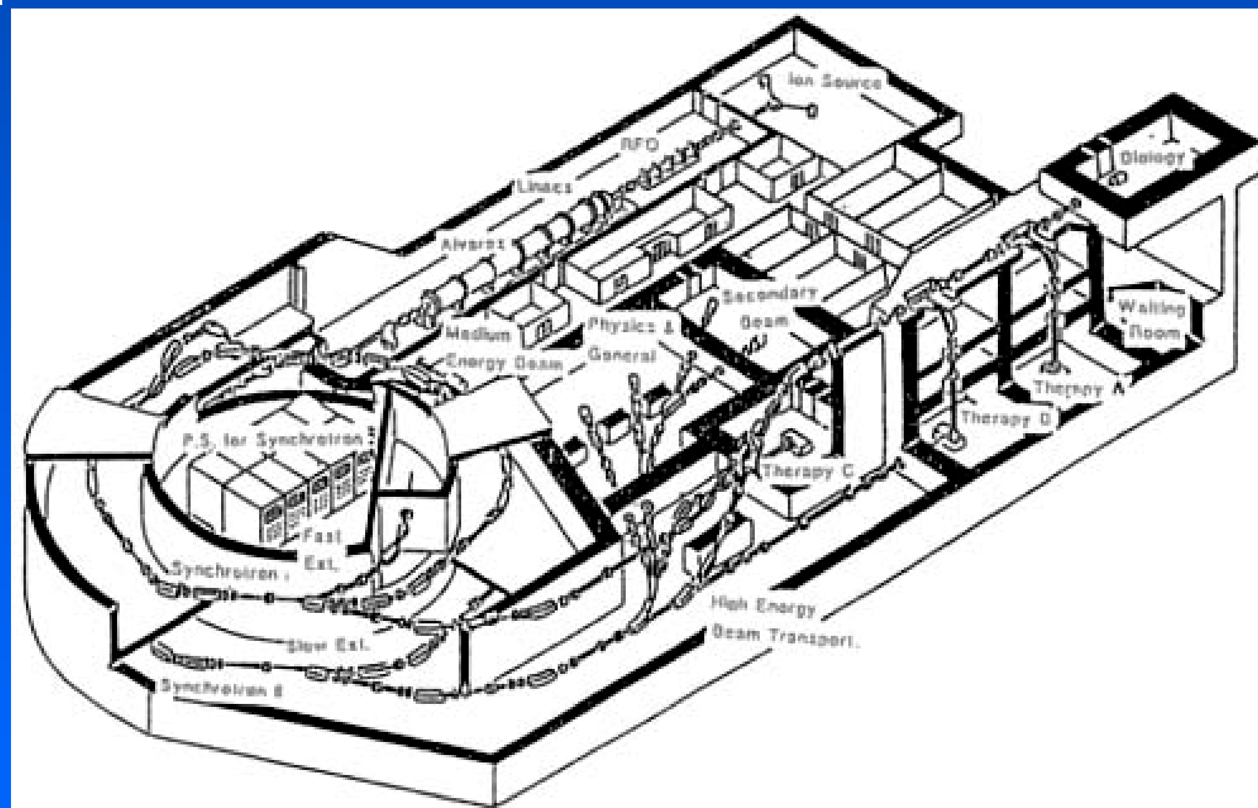
Passive Dose Delivery



Situation / Clinical Centers

- In 1994 the first dedicated clinic-based facilities, LLMUC (protons) and HIMAC (carbon), started
- Nowadays more than 50 proton treatment protocols are approved and reimbursed in the US
- LLUMC treats up to 180 patients per day

Heavy Ion Medical Accelerator, Chiba, Japan



"The major secondary dose contributors are neutrons from the proton treatment nozzle. These external neutrons account for a much higher secondary dose (by about two orders of magnitude) than the internal neutrons."

Jiang, Wang, Xu, Suit and Paganetti (2005)

Having spent about $125 million on a proton facility to reduce dose to normal tissues, does it make sense to spray the patient with a total body dose of neutrons, the RBE of which is poorly known, and end up with a second cancer risk similar to IMRT ?

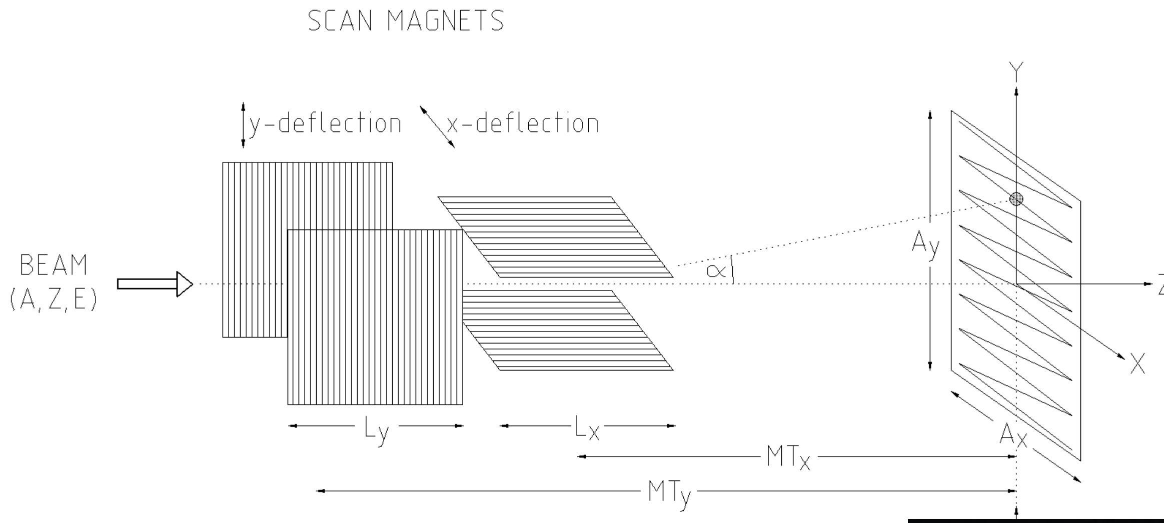
E.J. Hall, Int J Radiat Oncol Biol Phys 2006;65:1-7

Dose Delivery Concept @ GSI/HIT

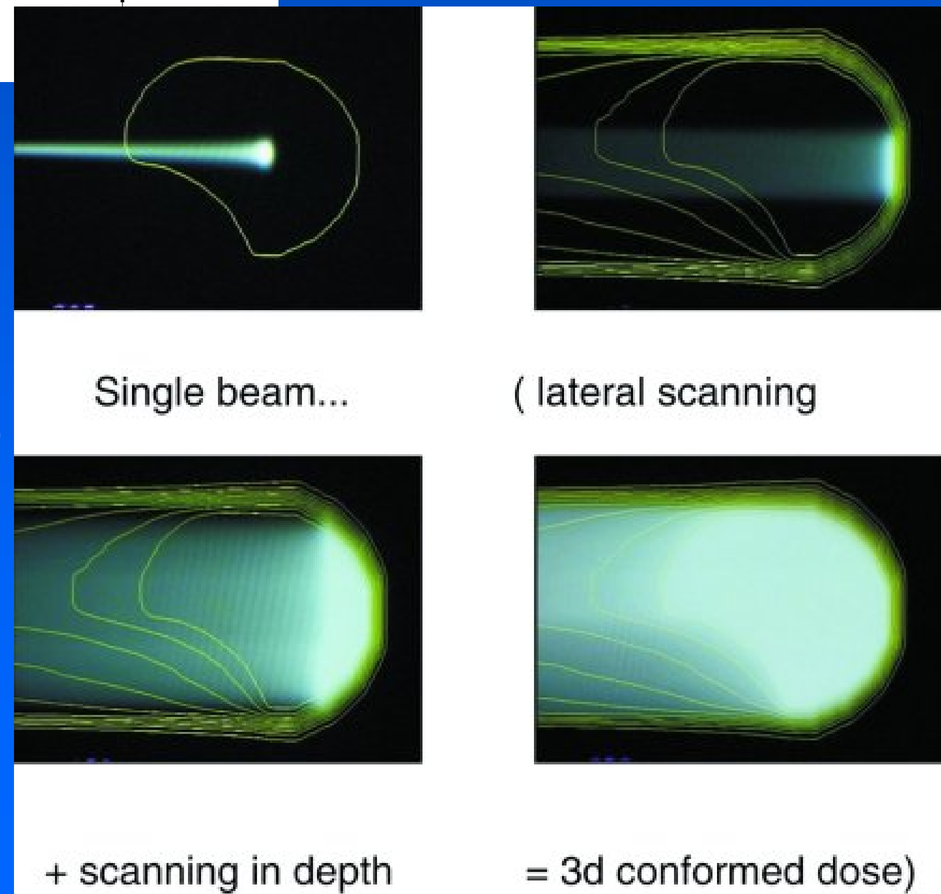
Idea:
Dose distributions of utmost tumor conformity can be produced by superimposing many thousands Bragg-peaks in 3D.
Sophisticated requirements concerning the beam delivery system, the accelerator, the treatment planning, QA, ... result from this approach.

Realization:
Dissect the treatment volume into thousands of voxels. Use small pencil beams with a spatial resolution of a few mm to fill each voxel with a pre-calculated amount of stopping particles taking into account the underlying physical and biological interactions.

$\Rightarrow$ **Extreme intensity modulation via rasterscanning**



Protons (Pedroni et al., PSI):
spot scanning gantry
1D magnetic pencil beam scanning
plus
passive range stacking (digital range shifter)



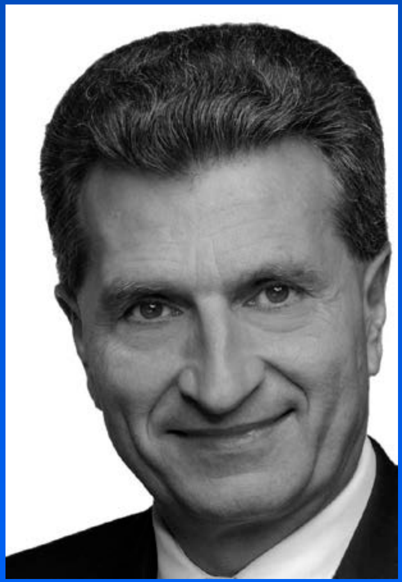
Ions (Haberer et al., GSI):
raster scanning, 3D active,
2D magnetic pencil beam scanning
plus
active range stacking (spot size, intensity) in the accelerator

Beam Scanning

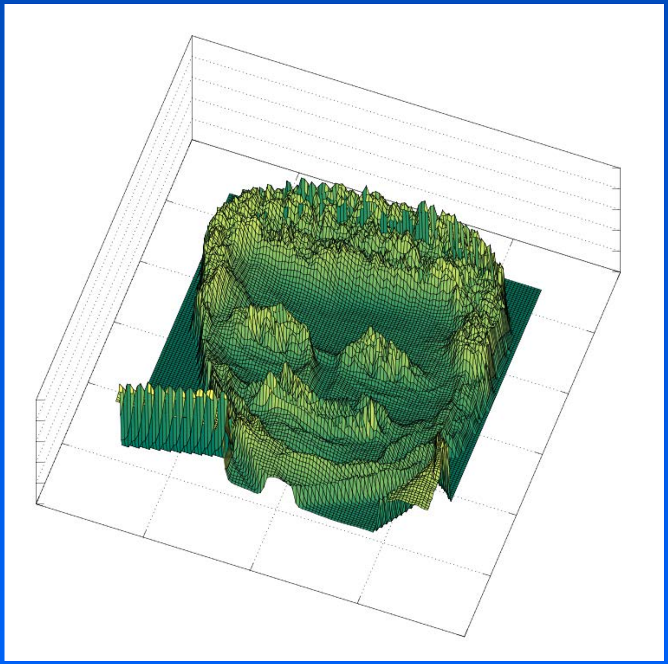
Th. Haberer, Heidelberg Iontherapy Center

Beam Scanning!

2D-example for dose modulation



original photograph



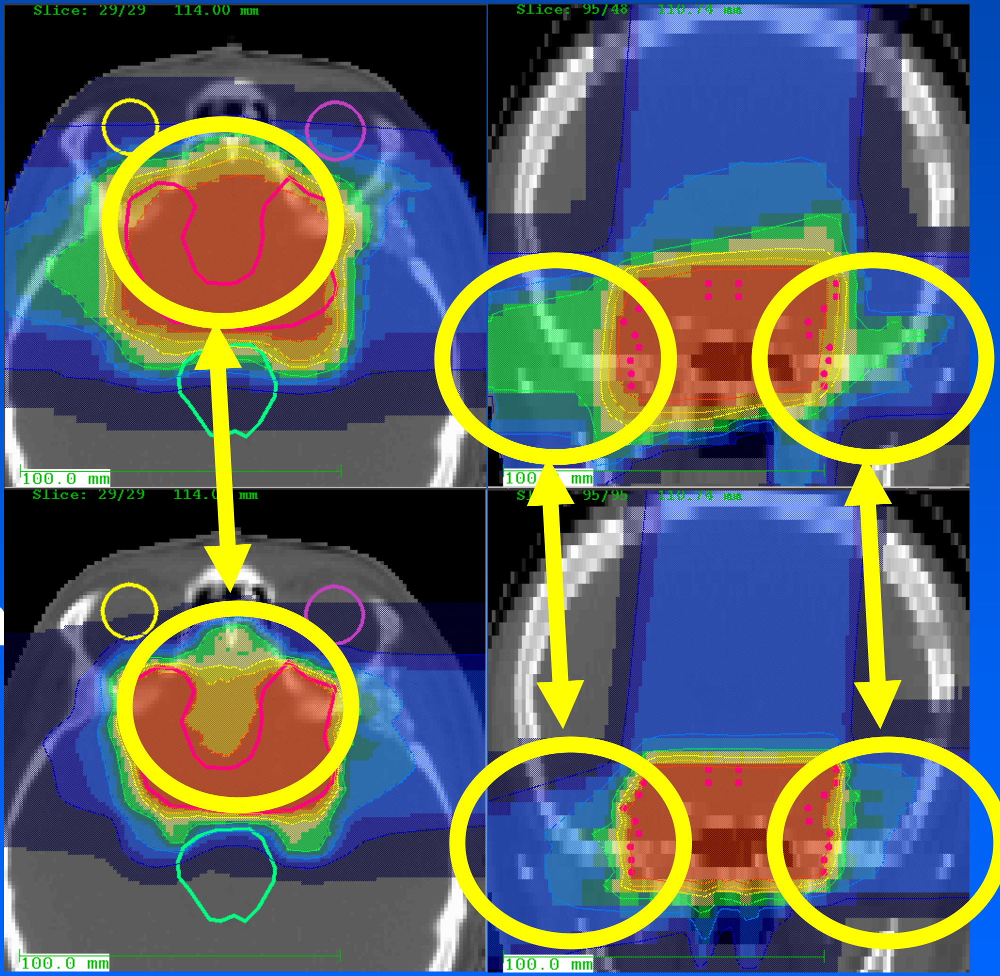
fluence map

irradiated radiographic film
rasterscan @ HIT

Courtesy Jakob Naumann (HIT), Martin Bräuer (SIEMENS)

Scanning vs. Passive

protons, passive
ithemba, 2 fields



rasterscanned carbon
GSI, 2 fields

From: O. Jäkel,
„Bestrahlungsplanung
für die Schwerionentherapie“,
2002

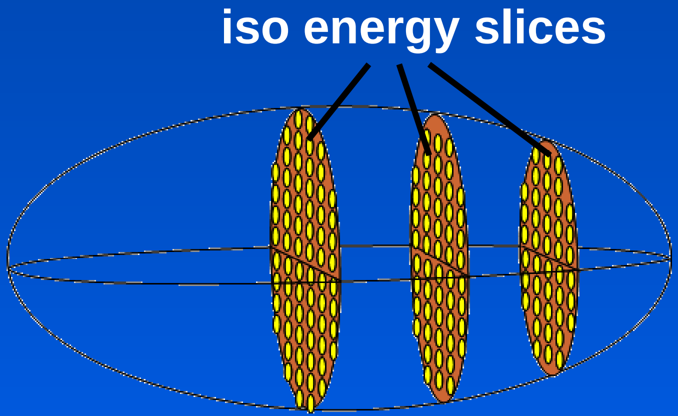
Longitudinal Scan Direction

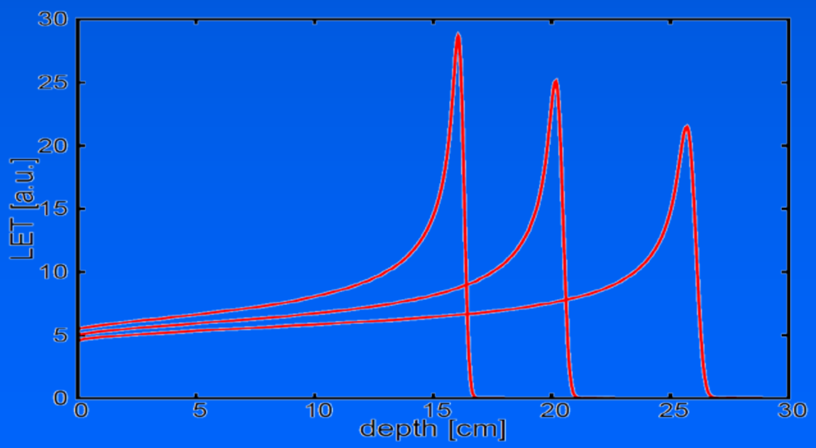
Selection of layers (iso energy slices) is achieved by varying the beam energy:

Actively (synchrotron!)

or

Passively (energy degrader plus energy selection system (filter))





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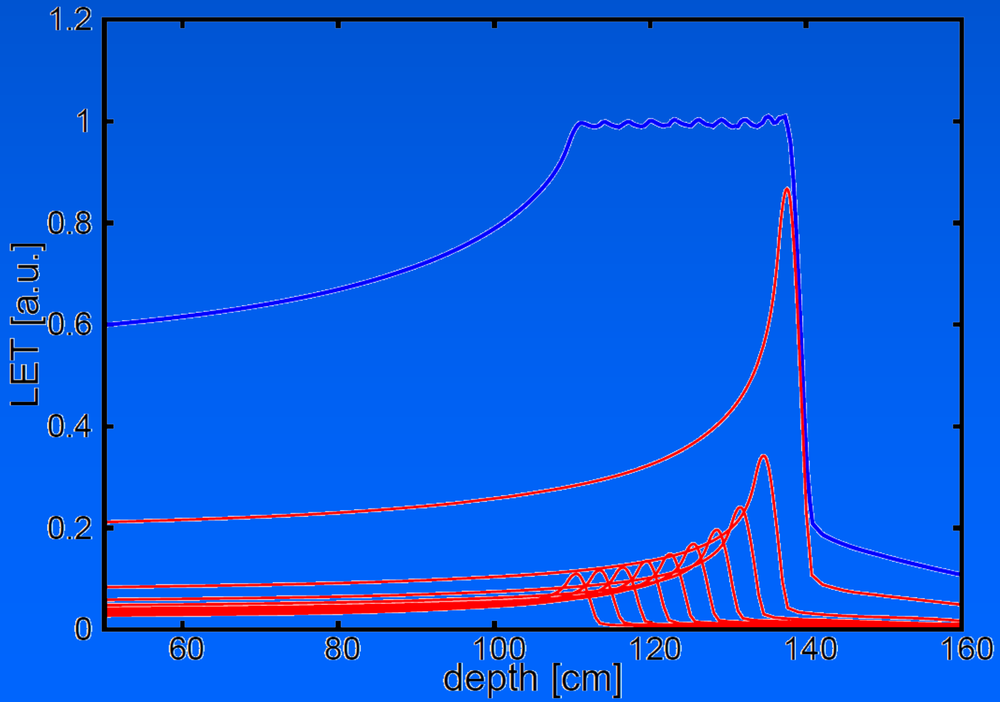
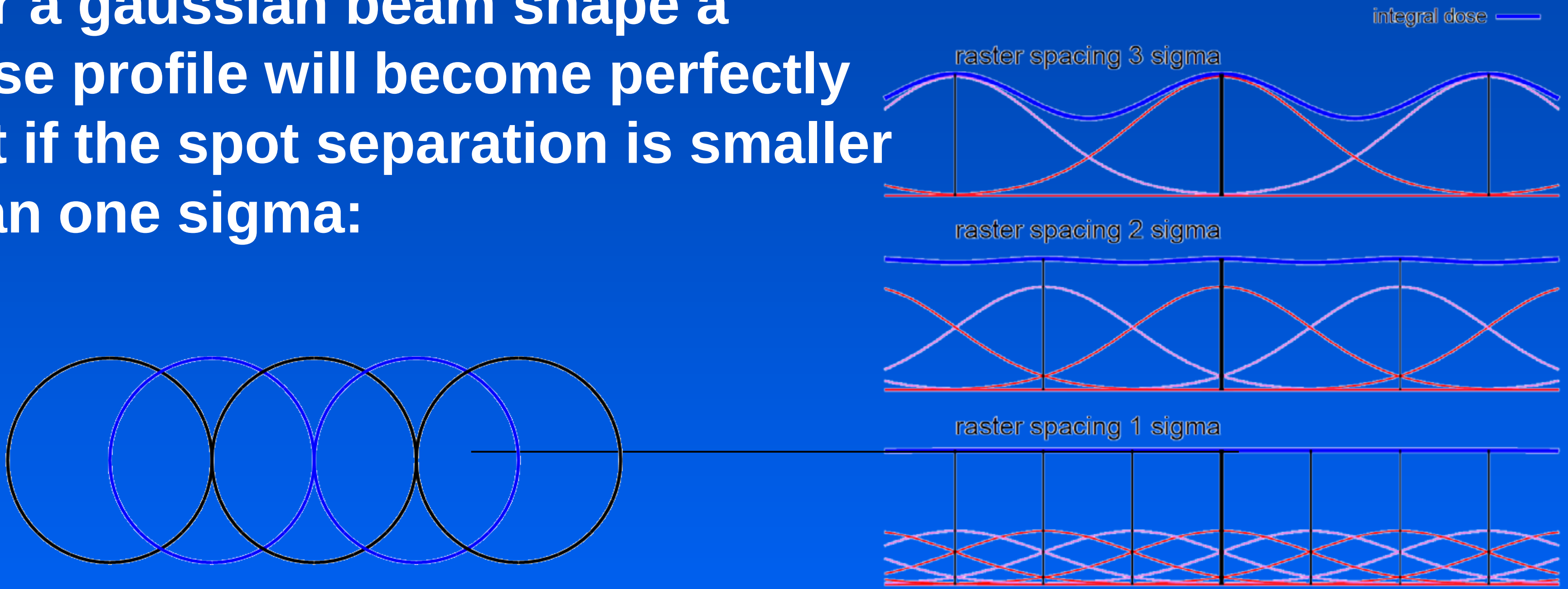
Longitudinal Scan Direction

Due to the shape of the bragg peak not only the region where the particle stops is irradiated, but also the region before the peak ("plateau region"). This has to be taken into account during treatment planning.



Scanning Grid

For a gaussian beam shape a dose profile will become perfectly flat if the spot separation is smaller than one sigma:

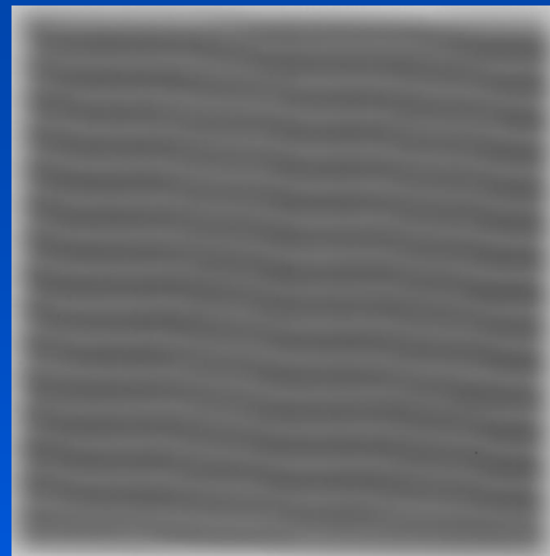


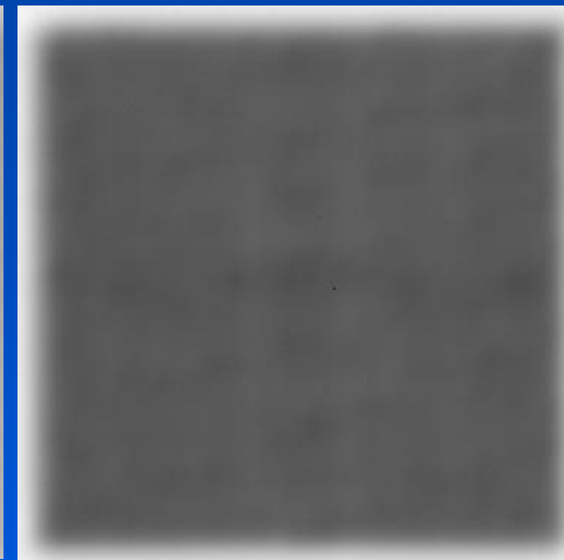
Dose profiles are clinically acceptable at a spacing of ~2σ;

For treatment planning at HIT a spacing of 0.8σ or less is used as a rule of thumb to allow for some error in spot size.

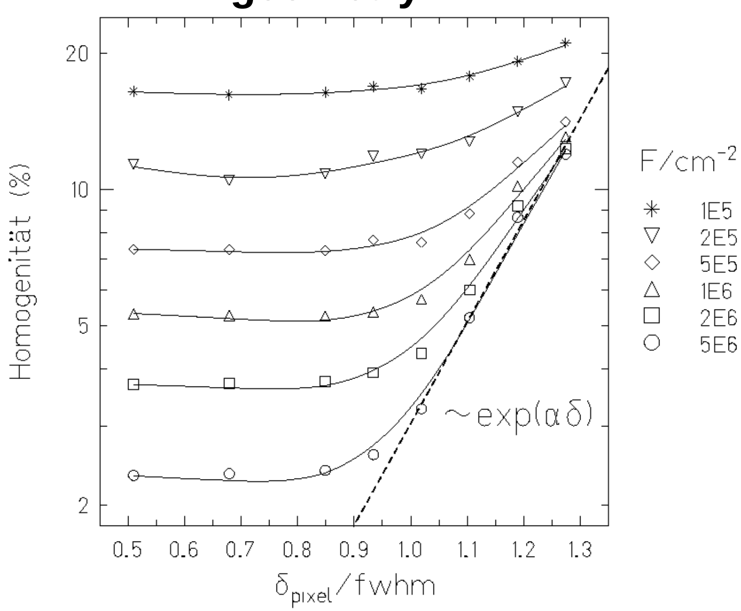
Active / Lateral

- homogeneity of fluence distributions

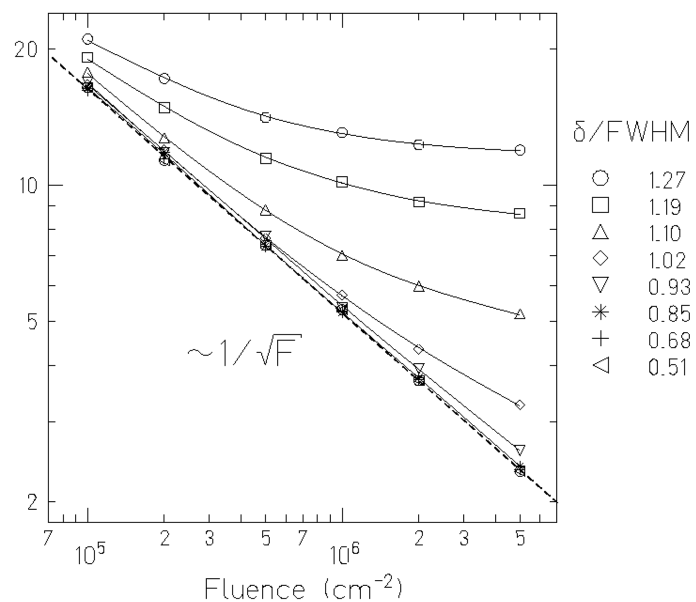




geometry



statistics



Flavours of Scanning
Raster Scanning vs Spot Scanning

Spot scanning (FBPTC/IBA, PSI, MDA/Hitachi, RPTC/Varian)

After irradiation of a point the beam is turned off. The beam is then moved to the next point. Once the scanner magnets have reached the new designated values, the beam is turned on again. Requires a fast beam shut-off system that can be operated at high frequencies.

Raster scanning (GSI/HIT/Siemens)

The beam is not turned off between two points, provided that the points are close enough. Requires fast scanning magnets to keep the dose applied between two points at an acceptable level.

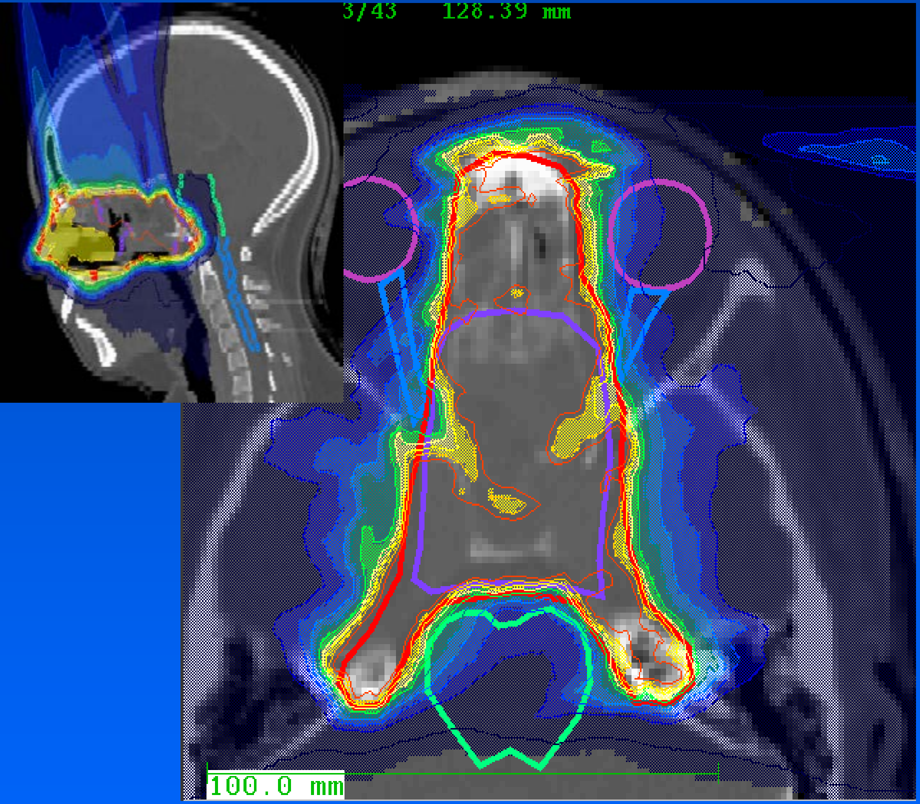
Flavours of Scanning
Dose Controlled vs Intensity Controlled

The decision when a raster point has received the designated dose can be based on two different criteria:

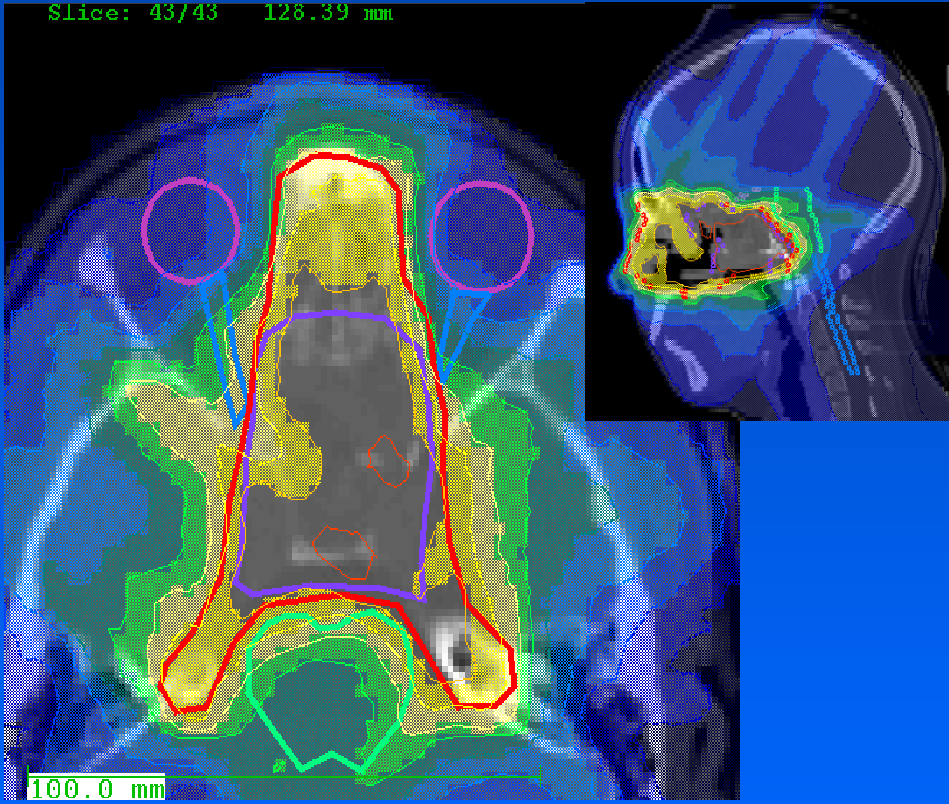
- **dose: the delivered dose is measured and integrated continuously. As soon as the desired dose is reached, irradiation is switched to the next point. This requires a fast and accurate dose measurement and generates a small dose overshoot (most facilities use this method).**
- **intensity: irradiation is switched to the next point after a previously calculated (or fixed) time. This requires a very precisely controlled beam intensity (e.g. a system with intensity feedback). This mode is currently being implemented on an experimental basis at some facilities.**

Scanned Carbon vs. Intensity Modulated Photons

scanned carbon 3 fields



IMRT 9 fields



reduced integral dose
steeper dose gradients
less fields
increased biological effectiveness

courtesy O. Jäkel, HIT

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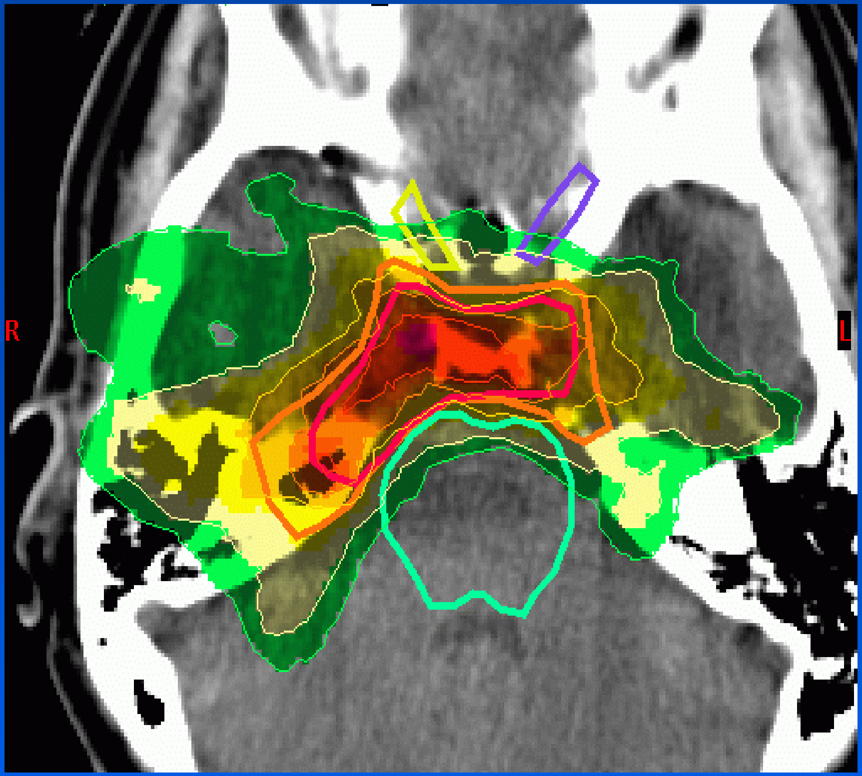
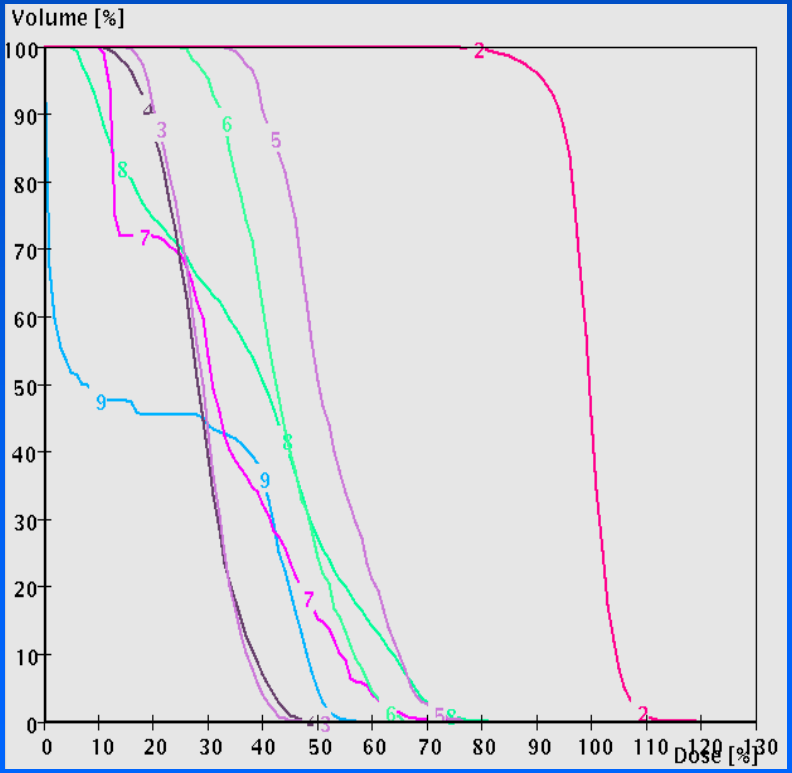
Adenoid cystic carcinoma

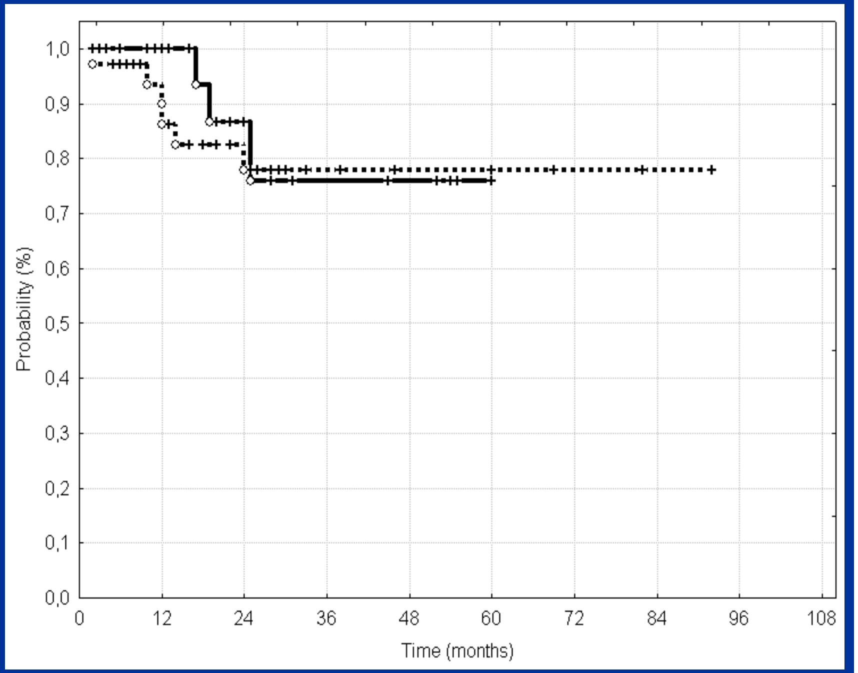


combined photon IMRT
+
carbon ion boost

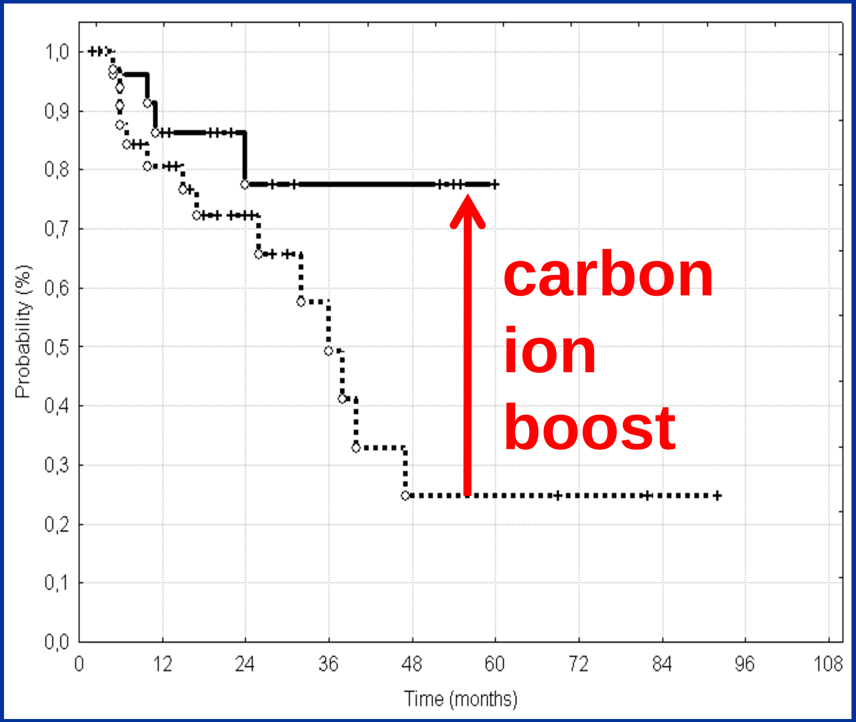


CTV: 54 GyE
GTV: 72 GyE
OAR <54 GyE

IMRT (photons) vs IMRT (photons) +C12 : locally advanced adenoid-cystic carcinoma



survival



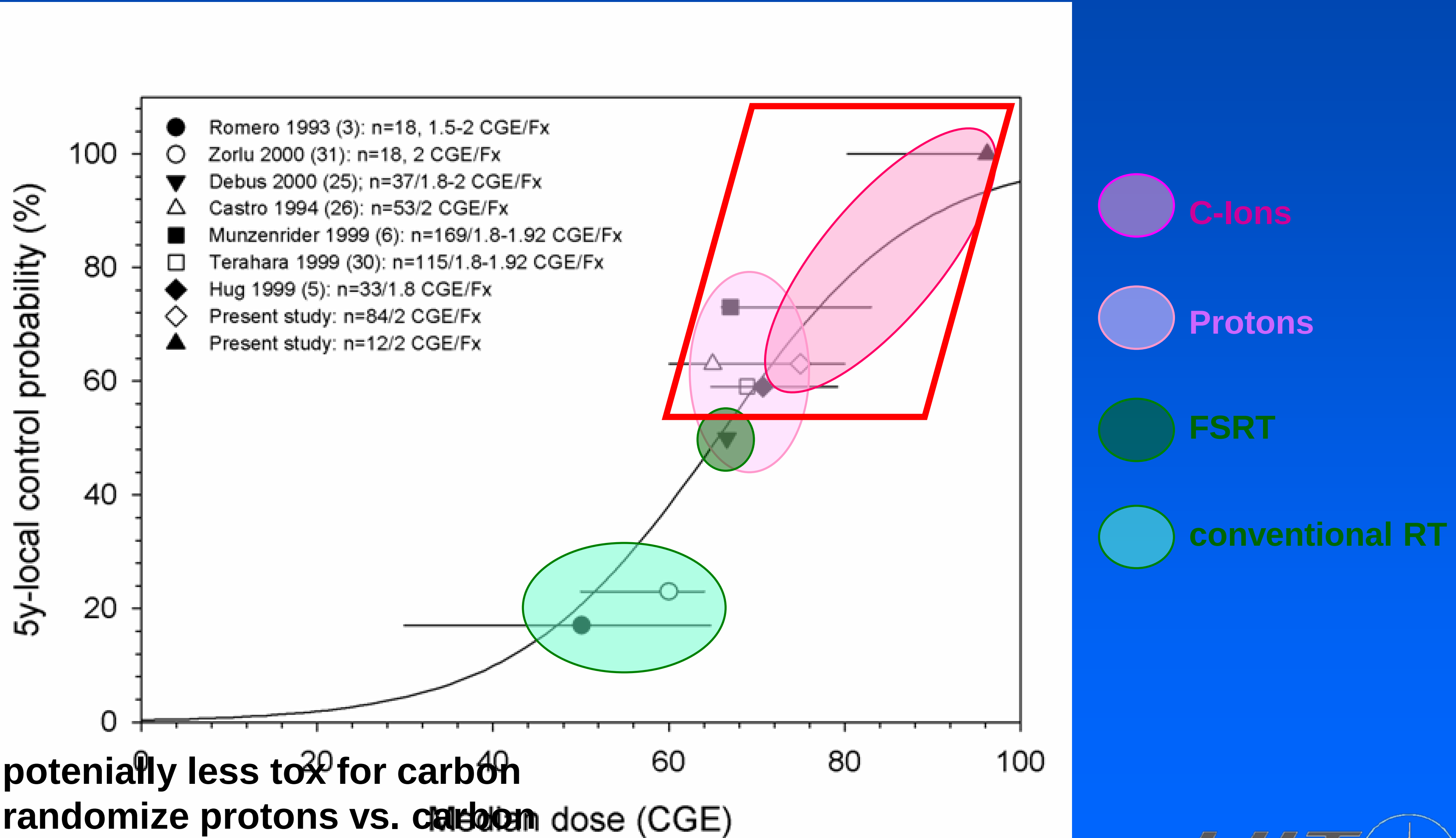
local control

- acute toxicity acceptable
- late toxicity > CTC Grad 2 < 5%

Schulz-Ertner, Cancer 2005

Th. Haberer

Motivation: Dose Response Relationship Radiotherapy of Skull Base Chordomas



potenially less tox for carbon
randomize protons vs. carbon

[Schulz-Ertner, IJROBP 2007]

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History of Beam Scanning

Date of first patient treatment using a scanned beam:

11/1996 Paul-Scherrer-Institute (PSI), Villigen

12/1997 Gesellschaft für Schwerionenforschung (GSI), Darmstadt

05/2008 MD Anderson, Houston

12/2008 Francis H. Burr PTC, Boston

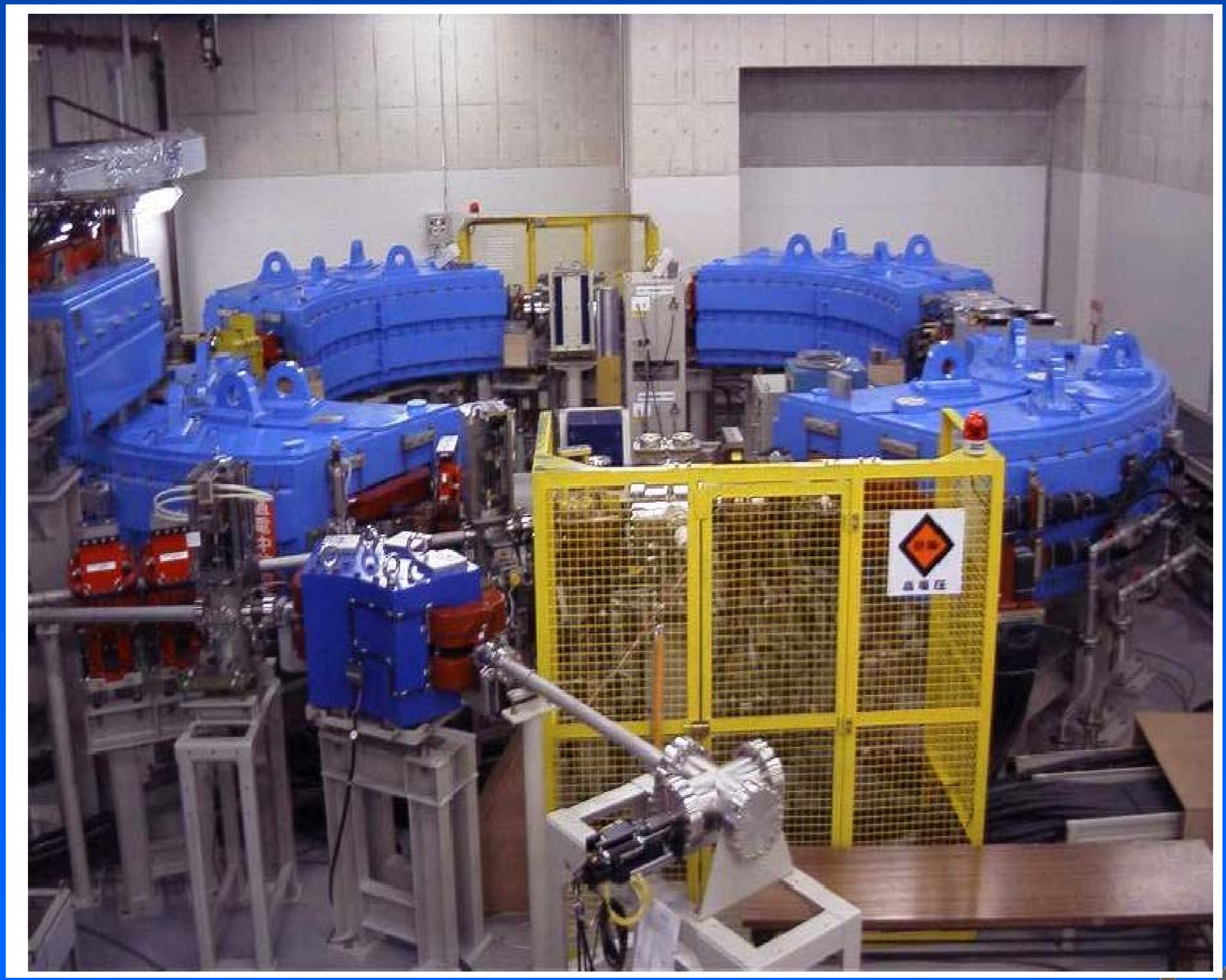
03/2009 Rinecker PTC, Munich

11/2009 Heidelberg Ion Therapy Centre (HIT)

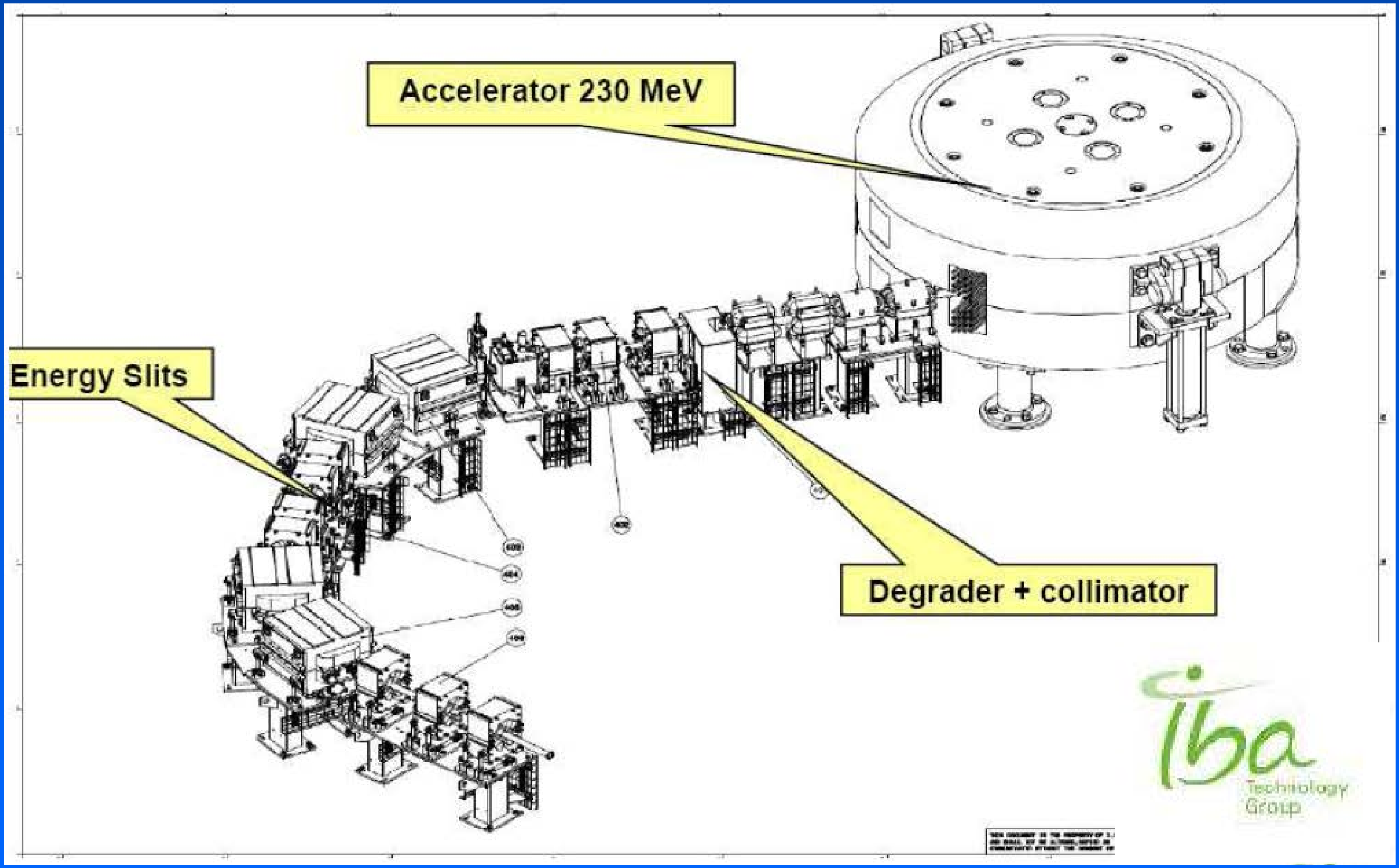
Work on scanning systems is currently in progress at many facilities, like NIRS Chiba, MPRI Bloomington, LLUMC Loma Linda, …


You are here

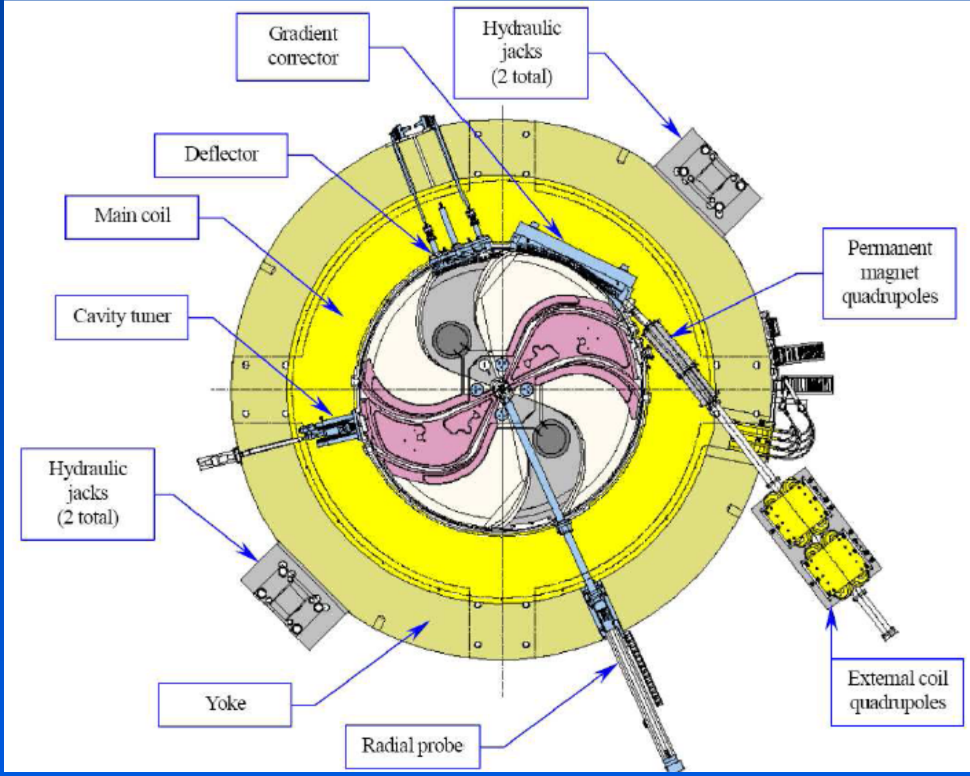
Proton-Synchrotron, Shizuoka, Japan



Cyclotron-based



Cyclotron-based



Economic requirements

- change of particle type < 60 s (dead time)
- change of treatment room < 30 s (dead time)
- number of treatment rooms ← utilization of accelerator
- 300 days per year, 16 hours per day
- ~1-2 min per treatment field (~1l, ~1-2 Gy)
  (target fraction duration: 15 min incl. 4 min beam)

- initial cost
- operational & maintenance cost

Requirement engineering

Application
- treatment of tumors with ion beams (conform, precise)

1st level requirements
- dose deposition in patient → dose delivery at isocenter

2nd level requirements
- beam application system

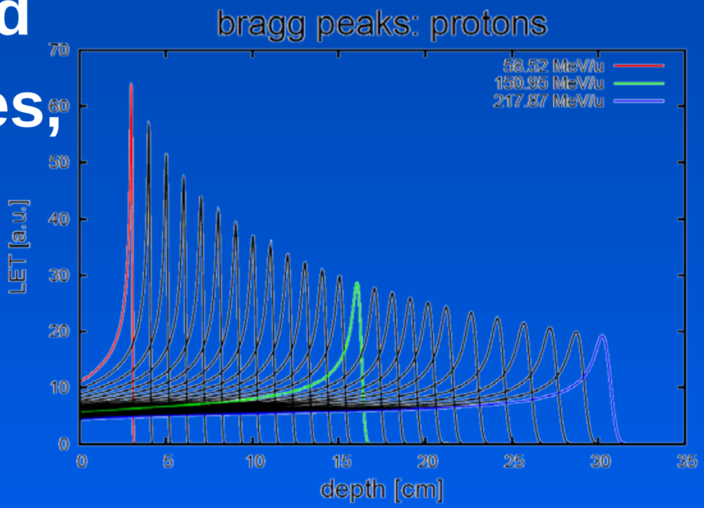
3rd level requirements
- accelerator specifications
  ← beam application system

→ accelerator requirements: interface to scanning system

Accelerator Requirements for Scanning

For scanning the accelerator should

- **allow to request different energies, beam spot sizes (“focus levels”) and intensities**
- **deliver a different combination of all of these beam parameters within a few seconds**



- **deliver all of these combinations with a high beam quality sufficient for medical use**
- **preferably provide a spill pause functionality**

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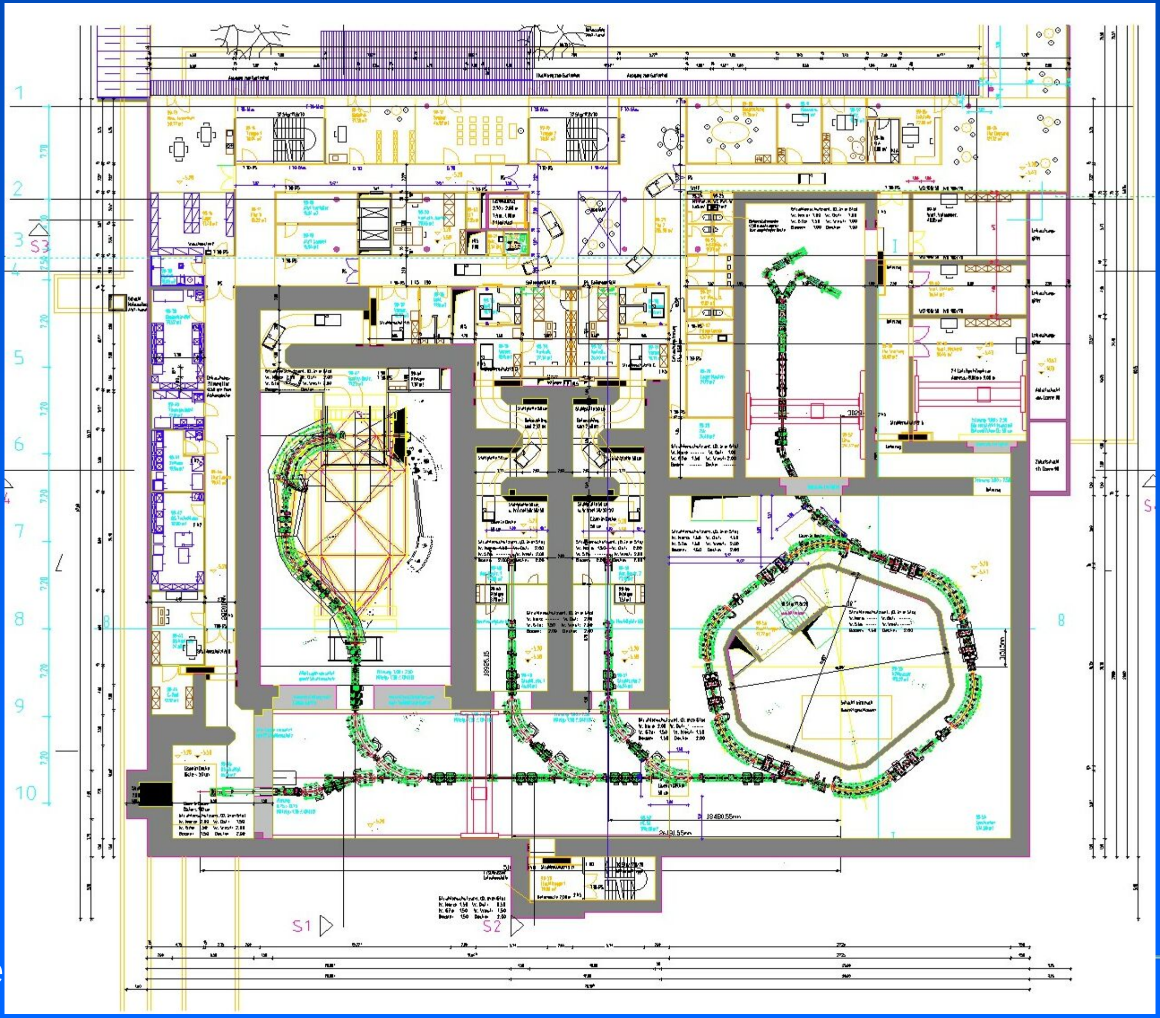
Heidelberg Ion Therapy Center (HIT)

Clinical Integration

Children‘s Hospital

National Center for Tumour Diseases

Women‘s Hospital

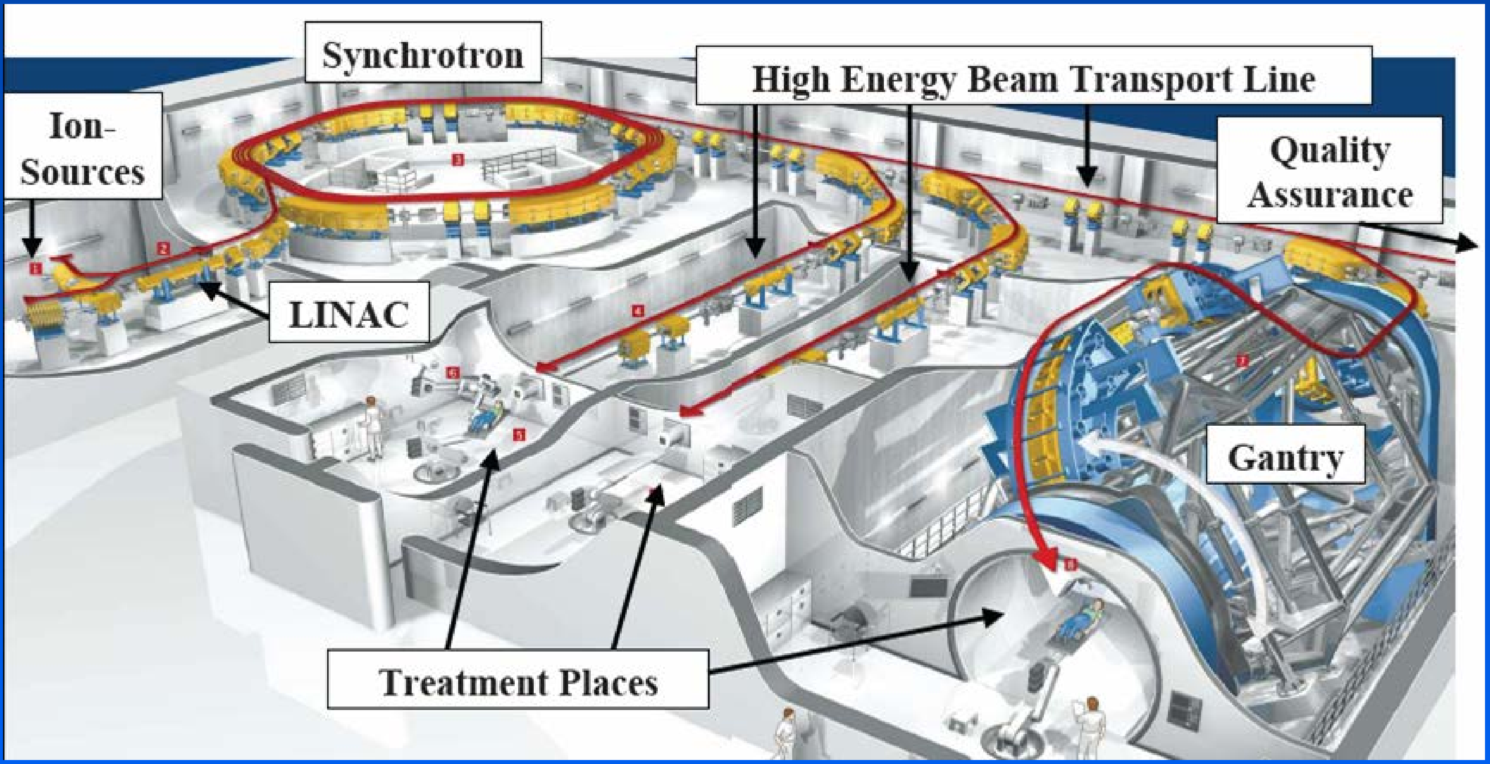


Radio-Oncology

Neuro-surgery

Heidelberg Ion Therapy Center

„Flexibility and Precision“



- compact design 60m x 70m
- full clinical integration
- rasterscanning only
- world-wide first ion gantry
- > 1000 patients and
  > 15.000 fractions/yr

- low-LET modality:
  Protons (Helium)
- high-LET modality:
  Carbon (Oxygen)
- ion selection within minutes
- R+D in a broad range

Some Facts

- Effective area 5.027 m²
- Concrete 30.000 tons
- Constructional steel 7.500 tons
- Capital Investment 120 M€

Start of construction: November 2003
Completion of building and acc.: June 2006
First patient treated: Nov. 15th, 2009

Project Partners:

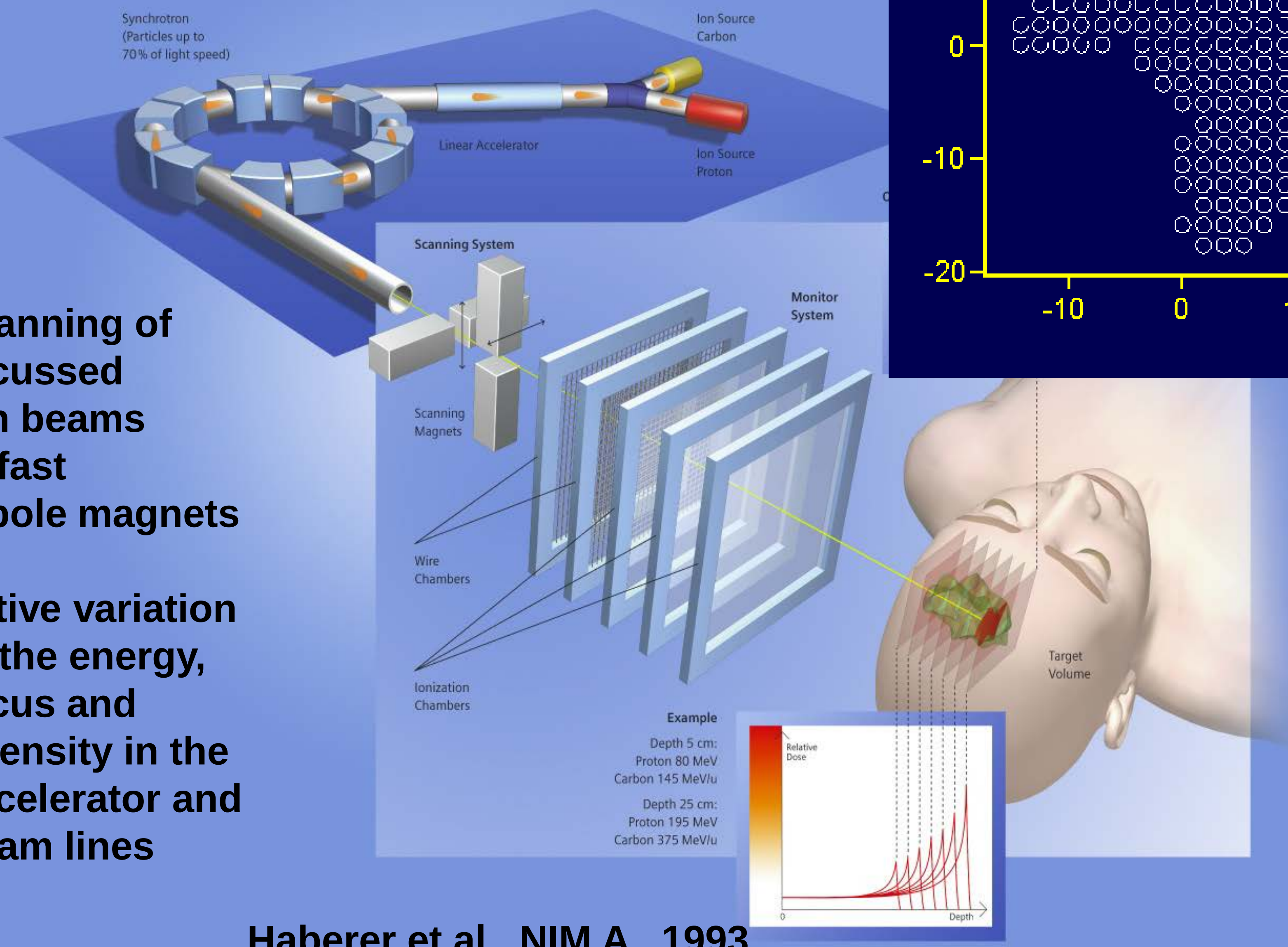
- **University** pays, owns and operates the facility
- **GSI:** feasibility study, facility design, technical proposal, tendering documents, built the accelerator
- **Siemens** supplies all components related to patient environment
- **GSI, DKFZ, Siemens …** are research partners

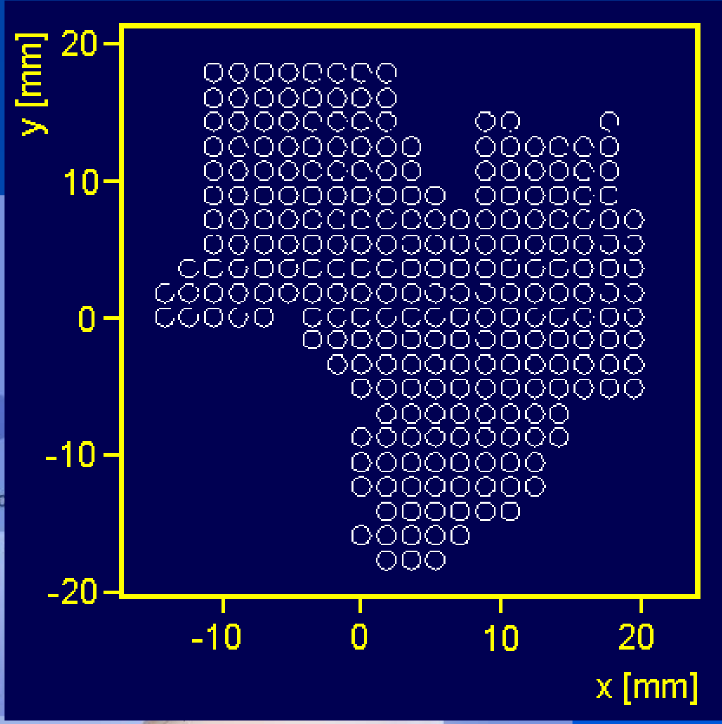
Accelerator requirements

- **scanning ready pencil beam library:**
  - energy: up to 30 cm WE, ~1 mm steps, $\Delta E/E$ ~1%
    p: 48 – 200 MeV, C: 88 – 430 MeV/u
  - spot sizes: 4 – 10 mm (3-4 steps), 2D Gaussian
  - intensity: ~10^{10} (p), ~10^{8} (C) per spill
  - ~ 100.000 combinations
- beam purity
- several quasi parallel particle types
  - – change of particle type < 60 s
- availability ~95%
- low operational & maintenance cost

HIT Heidelberg Ionenstrahl-Therapie Centrum

Rasterscan Method



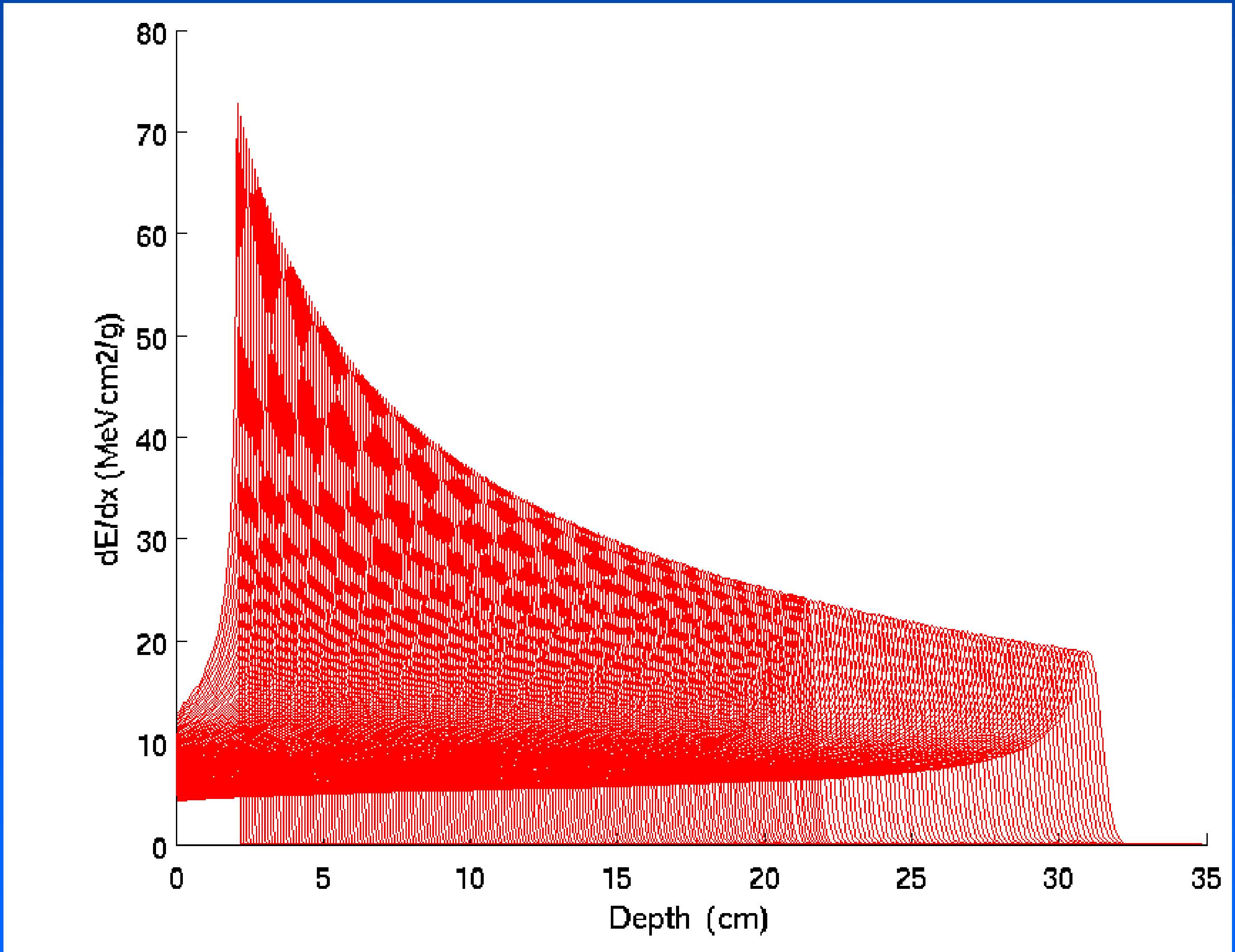


scanning of focussed ion beams in fast dipole magnets

active variation of the energy, focus and intensity in the accelerator and beam lines

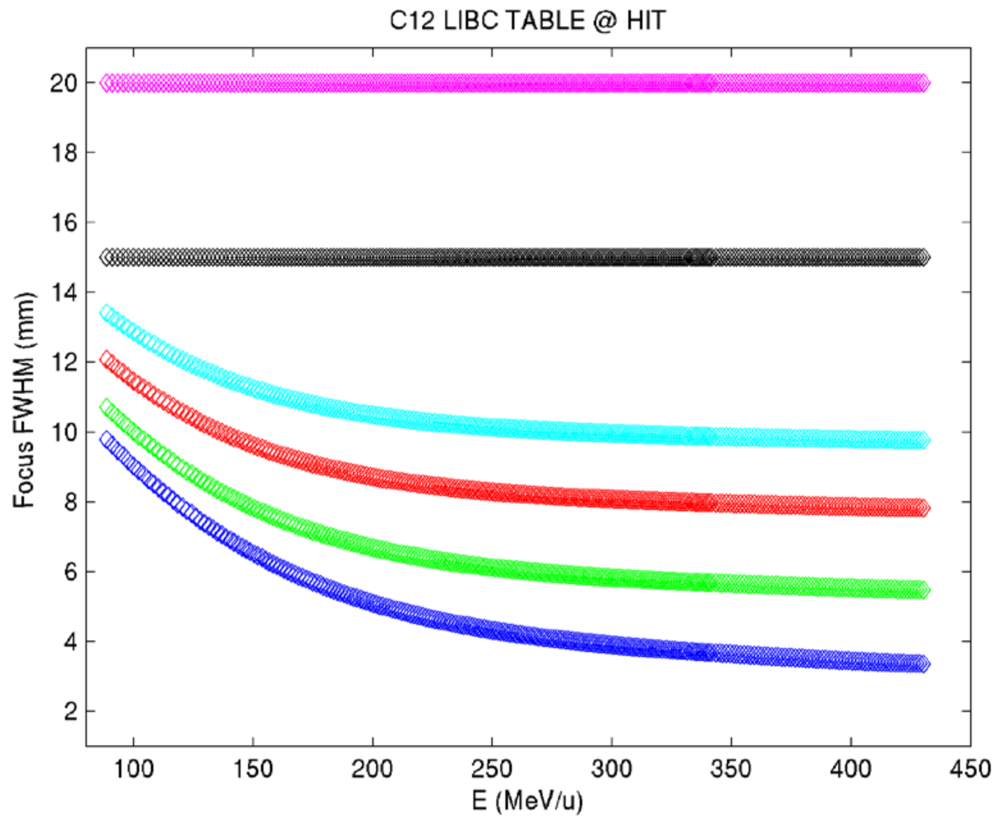
Haberer et al., NIM A , 1993

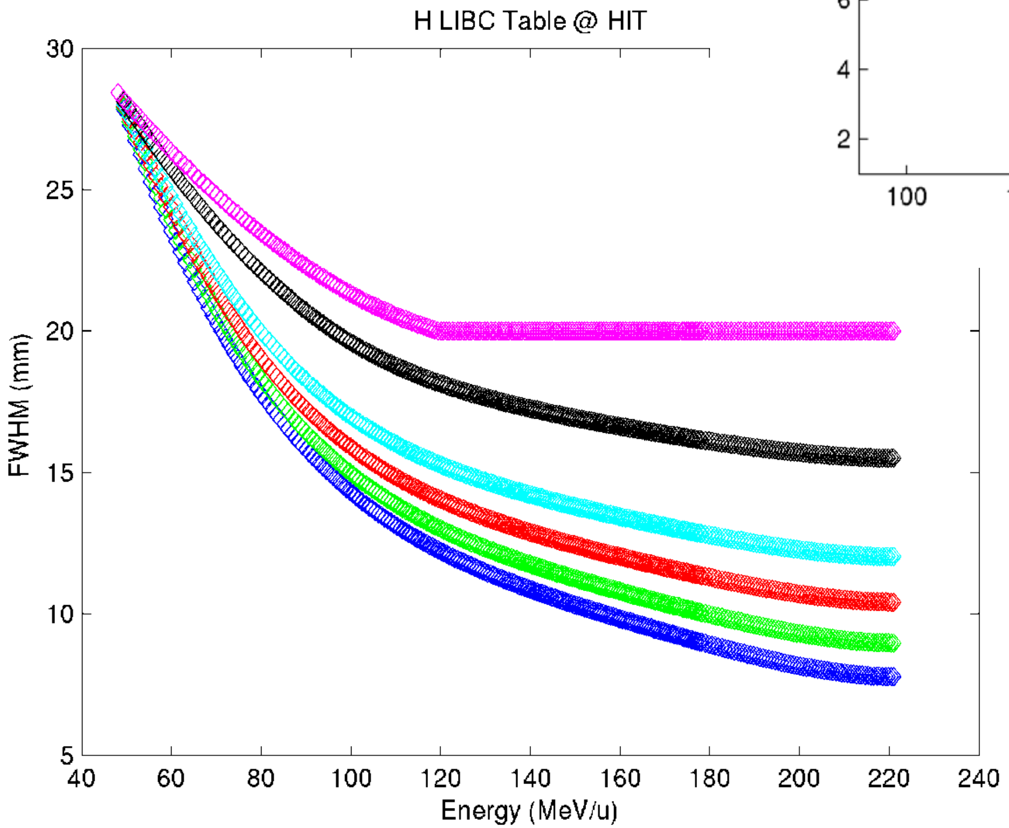
The Proton Data Base for HIT



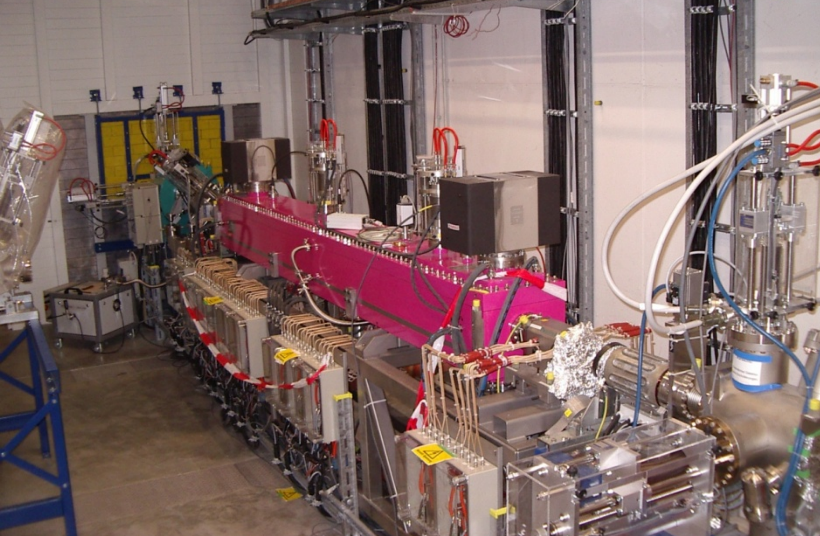
K. Parodi and A. Mairani, (HIT and FLUKA Collaboration)

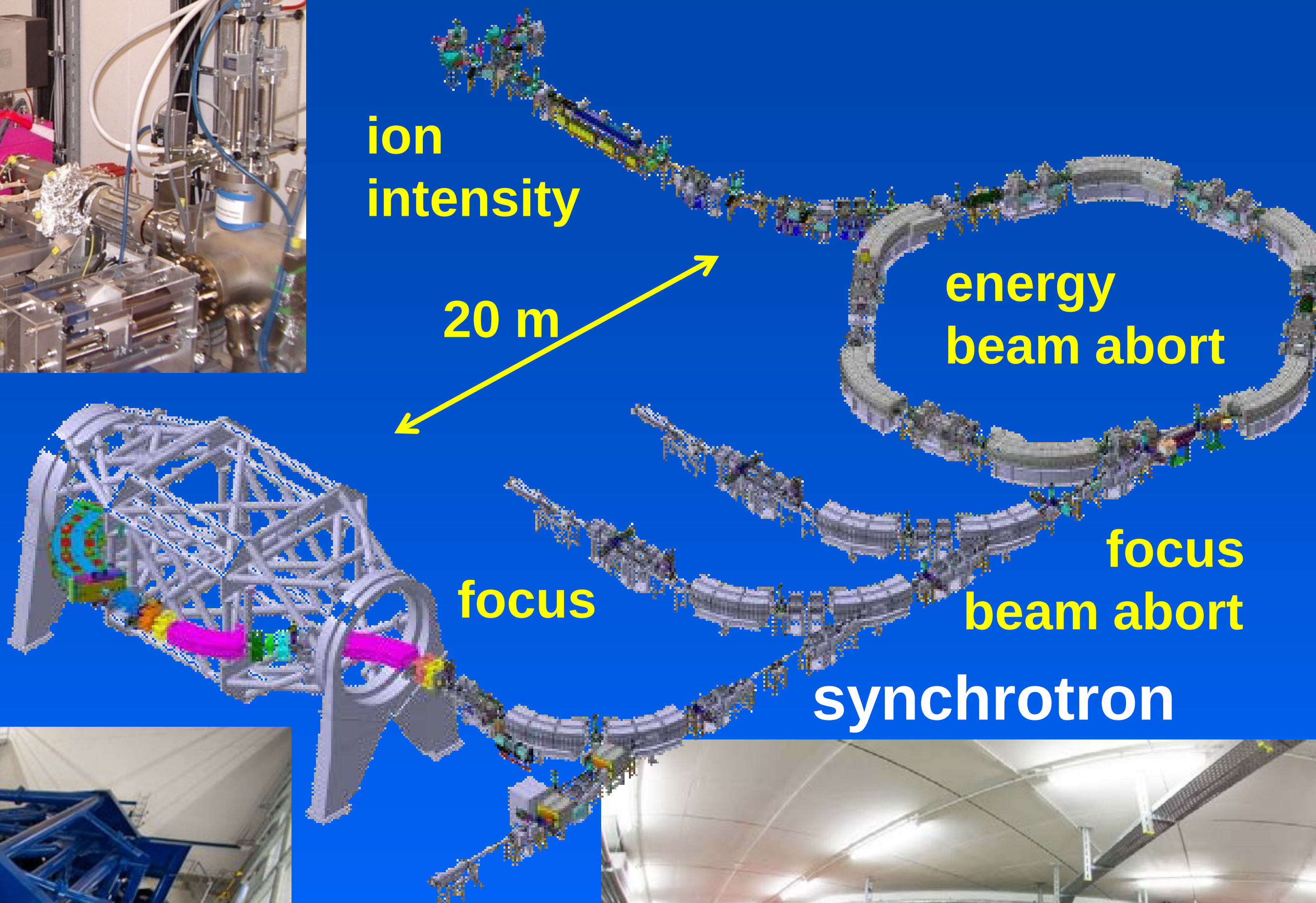
Spot Size Libs for Carbon and Protons





GSI
Gesellschaft für Schwerionenforschung Darmstadt

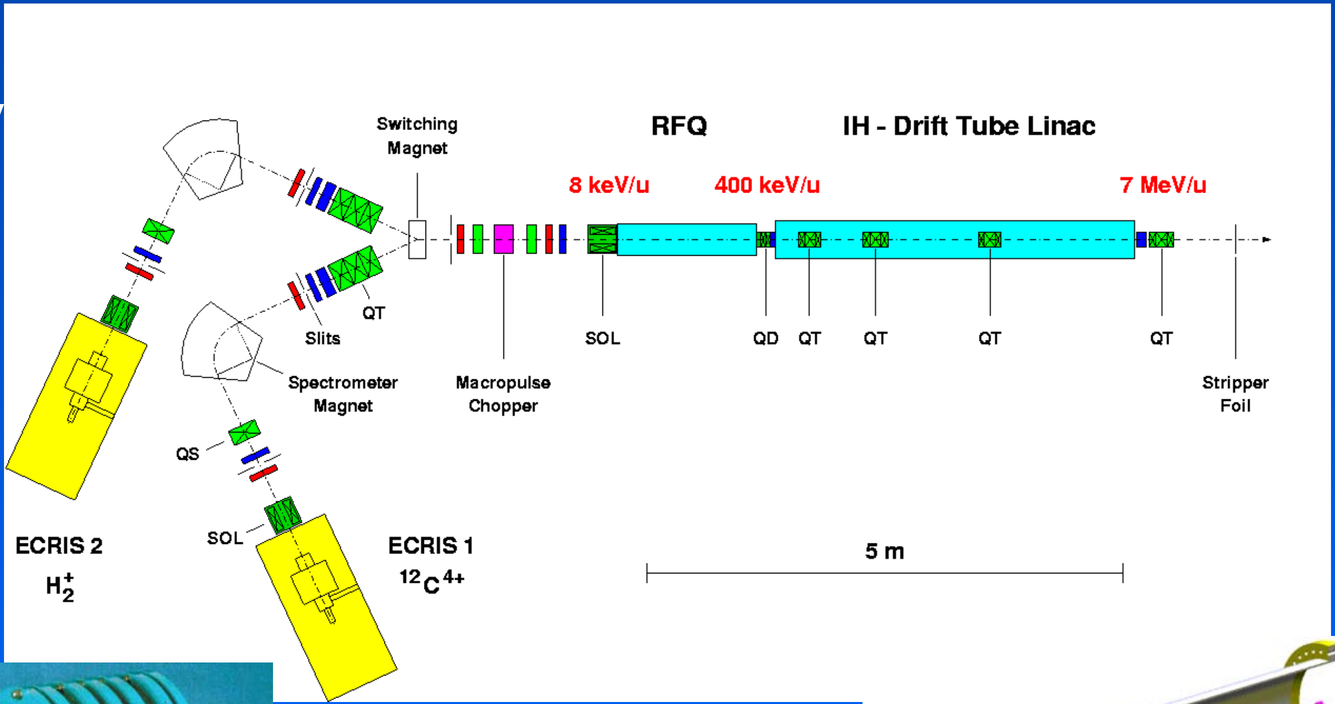




HIT / Linac

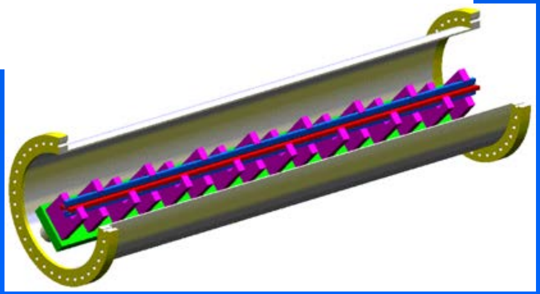
Cooperation: GSI + IAP@ Univ. Frankfurt/M.

- **compact design**
- **proven technology**
- **fast change of the ion species**
- **fast intensity variation (1000-times)**
- **constant beam parameter**

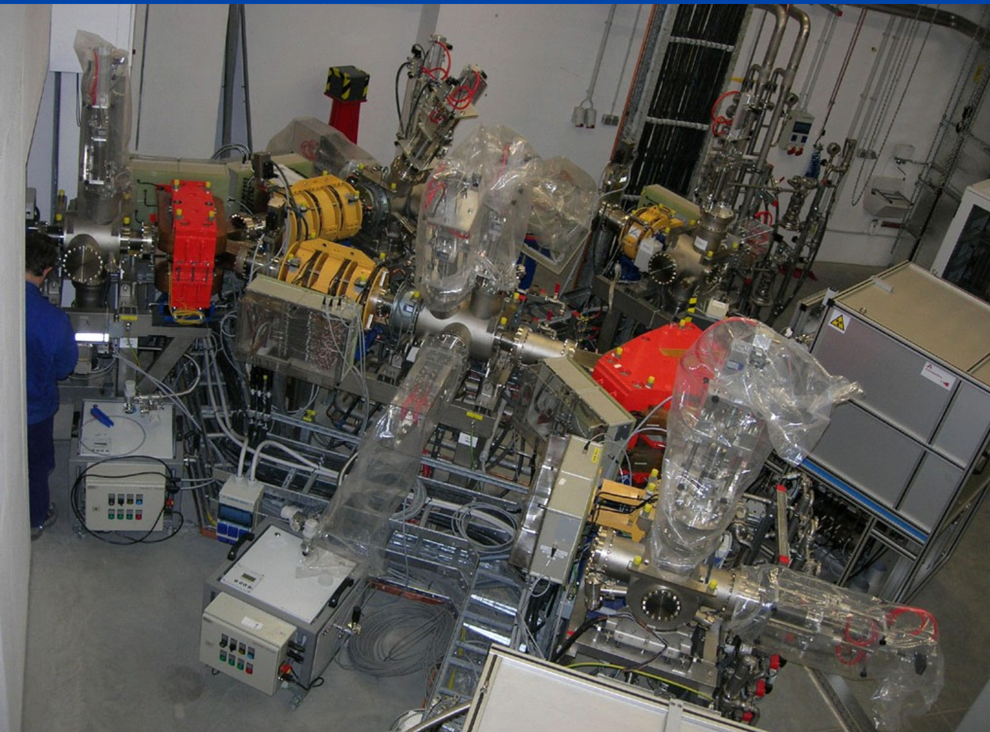


Ion source

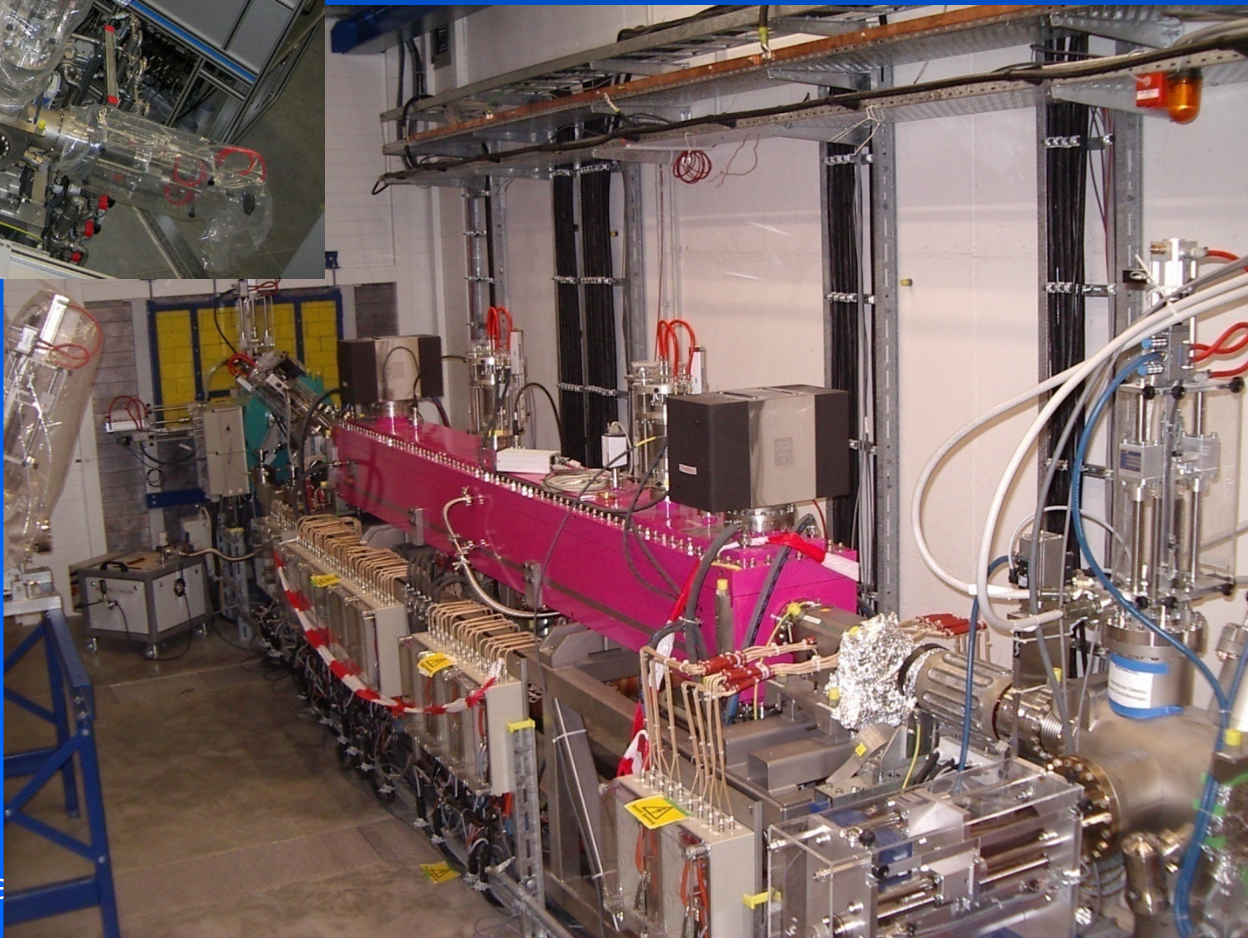
RFQ



Injector

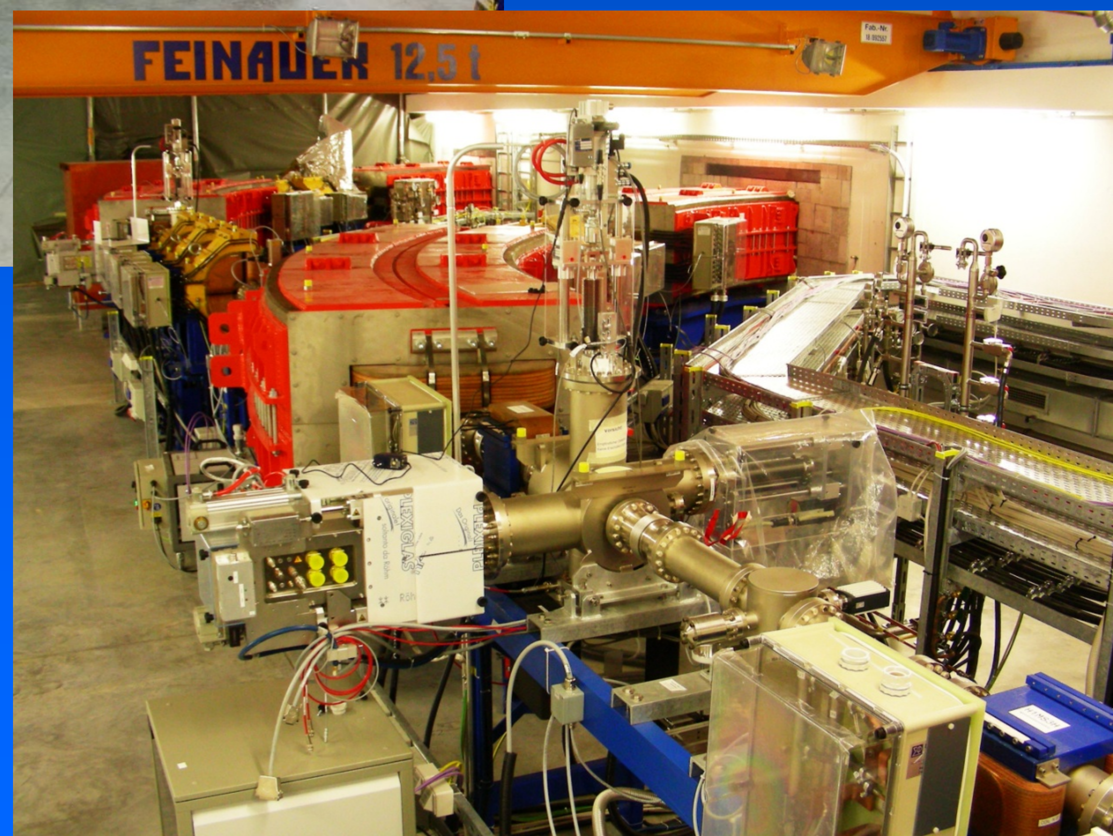


RFQ + IH-DTL



Ion sources

high energy
beam transport



synchrotron

Th. Haberer, Heidelberg Ion Therapy Center

Approval

- HIT is a medical product
- HIT is an inhouse product
- Siemens delivers medical products in a compatible way
- HIT has to fulfill the basic requirements of the MDD (medical device directive)
- A full-blown risk analysis (ALARA!) has been performed by HIT, Hospital and GSI staff
- More than 1000 measures to avoid or minimize risks for patients, users and third parties have been defined, are validated and will be monitored during the facility lifetime
- > 10 manyears

HIT Heidelberg Ionenstrahl-Therapie Centrum

HIT / Approval + CE-Label …

Baden-Württemberg
REGIERUNGSPRÄSIDIUM KARLSRUHE
ABTEILUNG 5 - UMWELT

Universitätsklinikum Heidelberg
- Kaufmännische Direktorin -
Im Neuenheimer Feld 672
69120 Heidelberg

Heidelberg 31.10.2009
Name Christiane Griesbach
Durchwahl 06221 1375-221
Aktenzeichen 54.4b1-467/Uniklinik HD, Rad. Klinik (INF 450), 5. HIT
(Bitte bei Antwort angeben)

Kassenzeichen: 8911240005569
Bitte bei Zahlung angeben!
Betrag: 3306,00 EUR

Durchführung der Strahlenschutzverordnung (StrlSchV)
Genehmigung zum Betrieb einer Anlage zur Erzeugung ionisierender Strahlen gemäß § 11 Abs. 2 StrlSchV
Ihr Antrag vom 01.09.2009 und Ihre Schreiben vom 15. und 30.10.2009

Anlagen
1 Sachverständigenverzeichnis
1 Messstellenverzeichnis
1 Überweisungsträger

Genehmigung Nr. A/12/099/09

4. Verwendungszwecke:
- Bestrahlung von Menschen in Ausübung der Heilkunde im Horizontal-bestrahlungsplatz H1
- Bestrahlung von Messaufbauten mit Phantomen und Strahlungsdetektoren im Rahmen der Grundlagenforschung
- Bestrahlung von Materialien zur Veränderung von Materialeigenschaften im Rahmen von Forschungsprojekten
- Bestrahlung belebter Objekte (biologische Zellen / Zellkulturen, Gewebe / Gewebebestandteile, Pflanzen und Versuchstiere)
- Qualitätssicherung und Dosimetrie
- Wartungsbetrieb

UniversitätsKlinikum Heidelberg
HIT
Heidelberger Ionenstrahl-Therapie

Erklärung zu Produkten für besondere Zwecke gemäß Anhang VIII der Richtlinie 93/42/EWG vom 14. Juni 1993 über Medizinprodukte

Hersteller:	Universitätsklinikum Heidelberg Im Neuenheimer Feld 672 69120 Heidelberg
Medizinprodukt:	**Heidelberger Ionenstrahl-Therapie (HIT) Anlage Bestrahlungsplatz H1**
Klassifizierung:	**Klasse IIb** gemäß Anhang IX der Richtlinie 93/42/EWG
Konformitätsbewertungsverfahren:	**Anhang VIII 2.1**

Die o.g. Eigenherstellung entspricht den unter Berücksichtigung ihrer Zweckbestimmung auf sie anwendbaren, in Anhang I der Richtlinie 93/42/EWG genannten grundlegenden Anforderungen. Eine Auflistung der nicht bzw. nicht vollständig eingehaltenen grundlegenden Anforderungen ist in Anlage I zu dieser Erklärung enthalten.

Heidelberg, den 14.11.2009

Dipl.-Volkswirtin Irmtraut Gürkan
(Kaufmännische Direktorin des Universitätsklinikums Heidelberg)

Der Unterzeichner erklärt, dass er verantwortlich zeichnet für die Ausstellung dieser Hersteller-erklärung, die ihre Gültigkeit bei einer wesentlichen Änderung an dem o.g. Medizinprodukt verliert.

Autor: A.Höss/H.Rösch	Erstellung: 26.10.2009	Revisions-Nr.: V01-000	Seite 1 von 1
Titel: HIT-Herstellererklärung		Pfad/Dateiname: HIT-Herstellererklärung V01-000.doc	

SIEMENS

EC DECLARATION OF CONFORMITY

according to Annex II.3 of Council Directive 93/42/EEC of June 14, 1993

Manufacturer	Siemens AG Wittelsbacherplatz 2 DE-80333 Muenchen Germany
Facility	Siemens AG, Medical Solutions Business Unit Particle Therapy System Hofmannstrasse 26, DE-91052 Erlangen, Germany
Medical device	IONTRIS Treatment room H2
Product identification	10013850
Classification	Class IIb (according to Annex IX to Council Directive 93/42/EEC)

We declare the compliance of the above medical device with the requirements of the Council Directive 93/42/EEC of June 14, 1993.
The conformity of the full quality assurance system is certified by:
TÜV SÜD Product Service GmbH
Ridlerstrasse 65
80339 Muenchen
Germany

The identification number of the notified body for implementation of the procedure set out in Annex II to the above Directive is 0123.
This declaration of conformity is issued under the sole responsibility of Siemens AG.
This declaration supersedes any declaration issued previously for the same treatment room.

Place and date	Erlangen, September 14, 2010	
Name	Holger Schmidt (Head of Business Unit)	Jürgen Buckow (Head of Quality Management)
Signature		

For conditions of guarantee and liability please refer to our General Conditions of Sale.

Document number 10013802-VA1X QCE ION 04 — Page 1 of 1

EC DECLARATION OF CONFORMITY

Approval radiation protection law

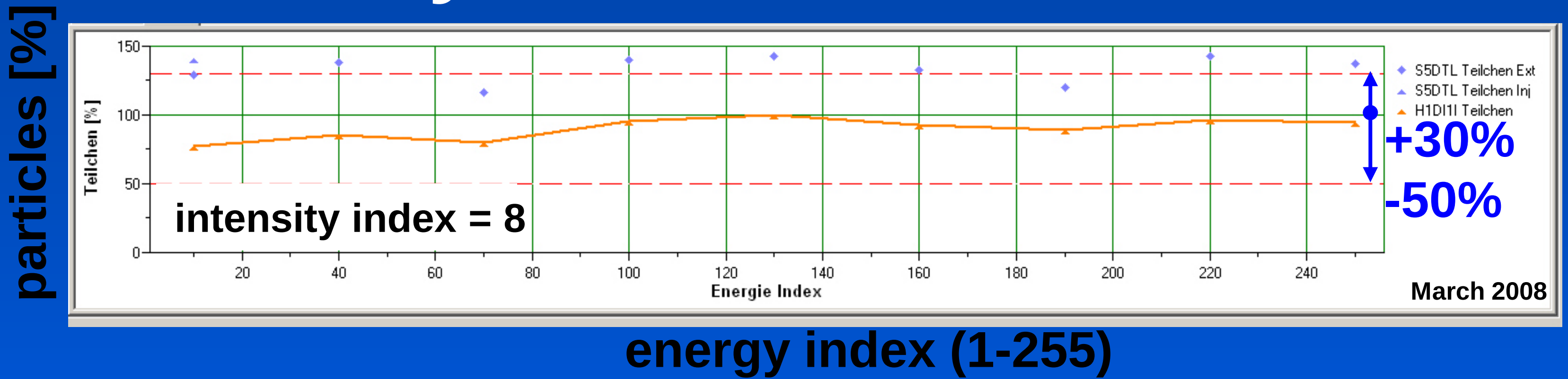
Medical device directive „In-house-product declaration“

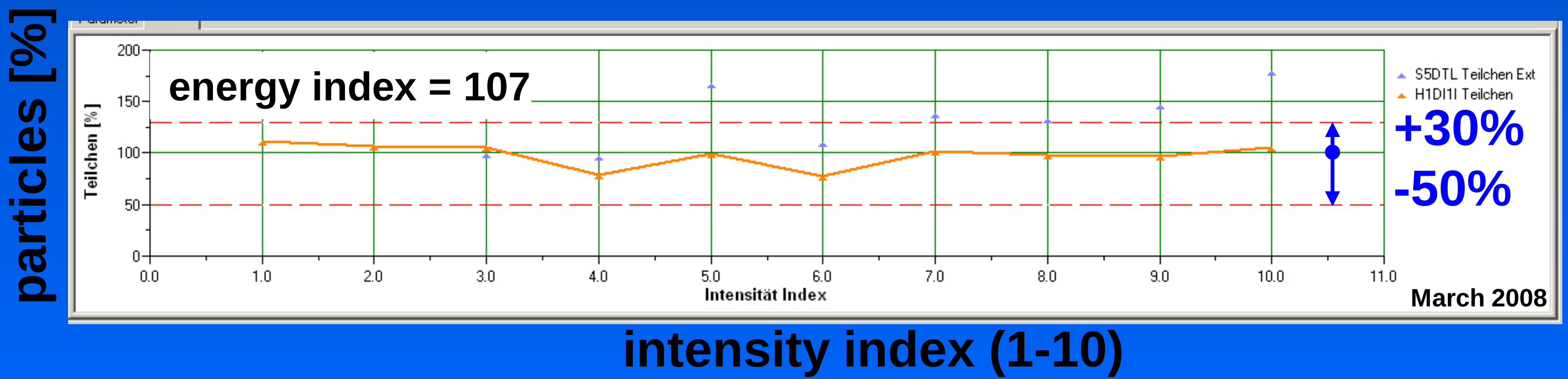
CE-label by Siemens Health Care

November 2009

HIT Heidelberg Ionenstrahl-Therapie Centrum

Intensity Protocol for Carbon



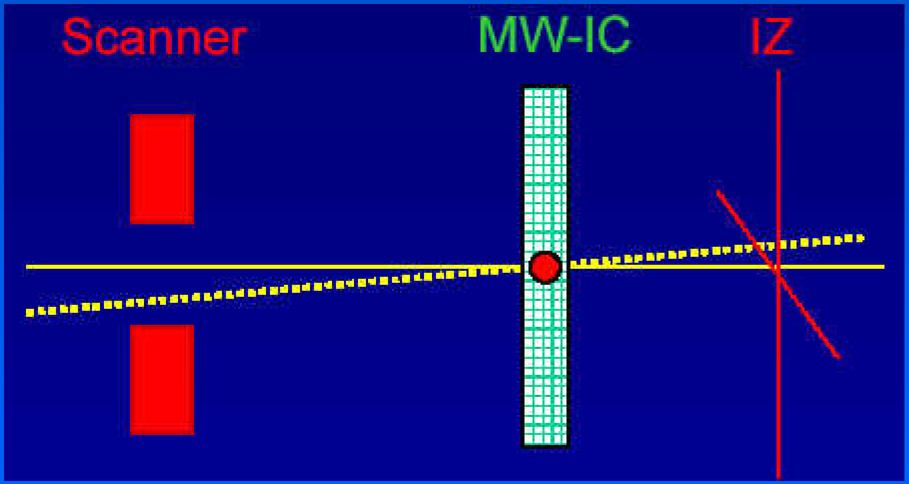


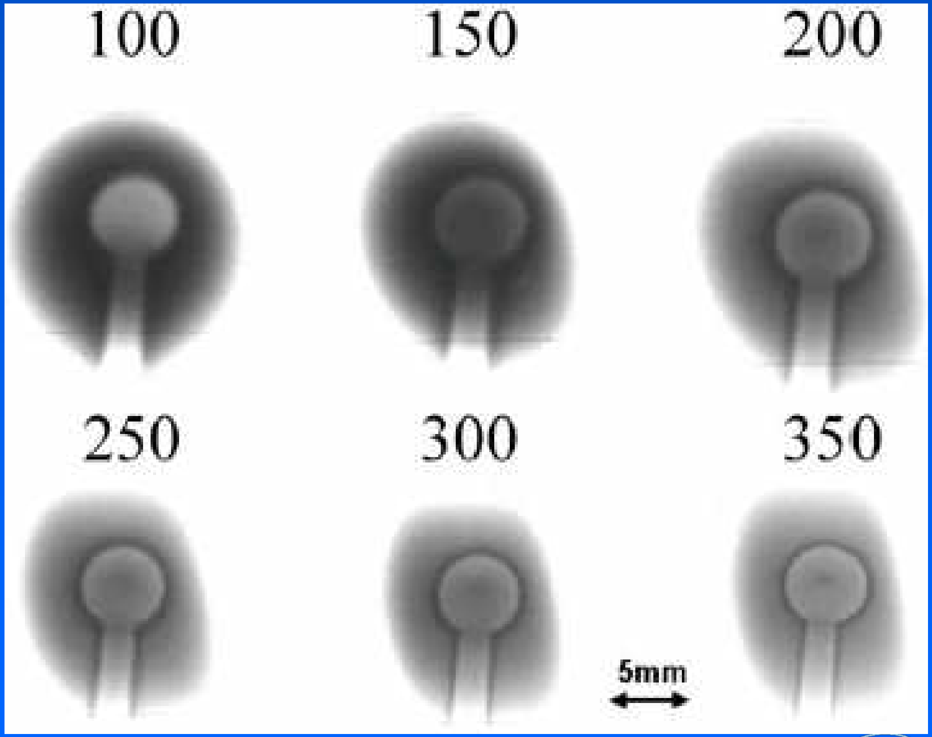
I-index	1	2	3	4	5	6	7	8	9	10
ions / s*	2.0E06	3.0E06	5.0E06	8.0E06	1.0E07	1.5E07	2.0E07	3.0E07	5.0E07	8.0E07

***: according to LIBC (library of ion beam characteristics)**

Pencil Beam Position

- position of the pencil beam depends on the beam energy and the beam spot size
- check the position and width at the iso-center using a tungsten sphere in front of a X-ray film





Medical Equipment

Identical patient positioning systems

- fixed beam
- gantry

Workflow optimization

- automated QA procedures
- automated patient hand over from shuttle

Inroom position verification

- 2D
- 3D Cone beam CT

Open for future applications and workflows

Workflow

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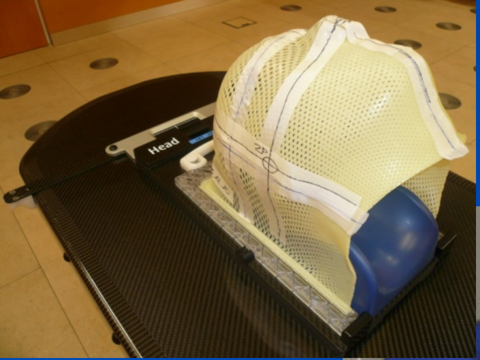
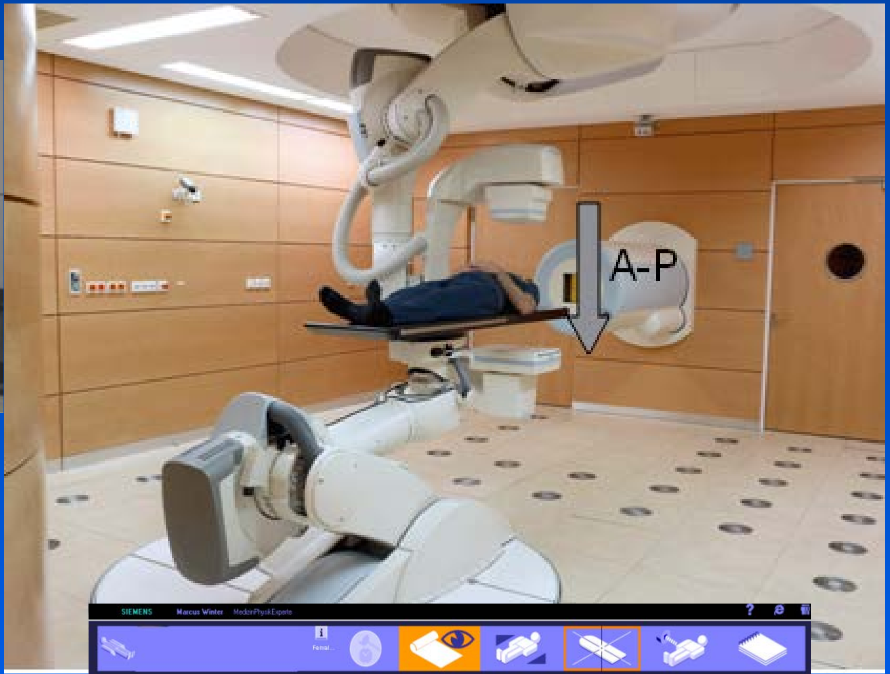
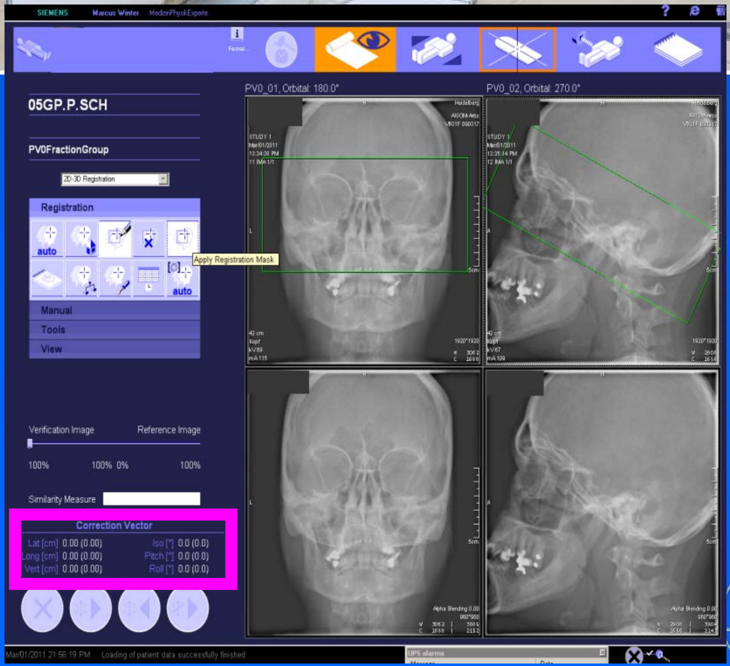
Process

- patient immobilization
- 3D-imaging (CT, MRI, PET, ...)
- definition of target volume + organs at risk
- definition of treatment modality
- dose calculation + treatmentplan evaluation
- patient positioning
- treatment
- follow-up

IGRT / 2D – 3D Matching







- **2D orthogonal X-ray projections**

- **Calculation of a DRR (Digital X-Ray Reconstruction) based on the planning-CT**

- **Matching of X-ray and DRR**

- **Calculation of a correction vector in 6 dimensions:**
  3 translations (lat/vert/long)
  3 rotations (iso/pitch/roll)

1st Patient @ HIT-H1

Shuttlesystem

- oncolog dignity carrier
- connection between
  PET-CT and
  treatment rooms

Combs SE et al., Der Nuklearmediziner, 2011

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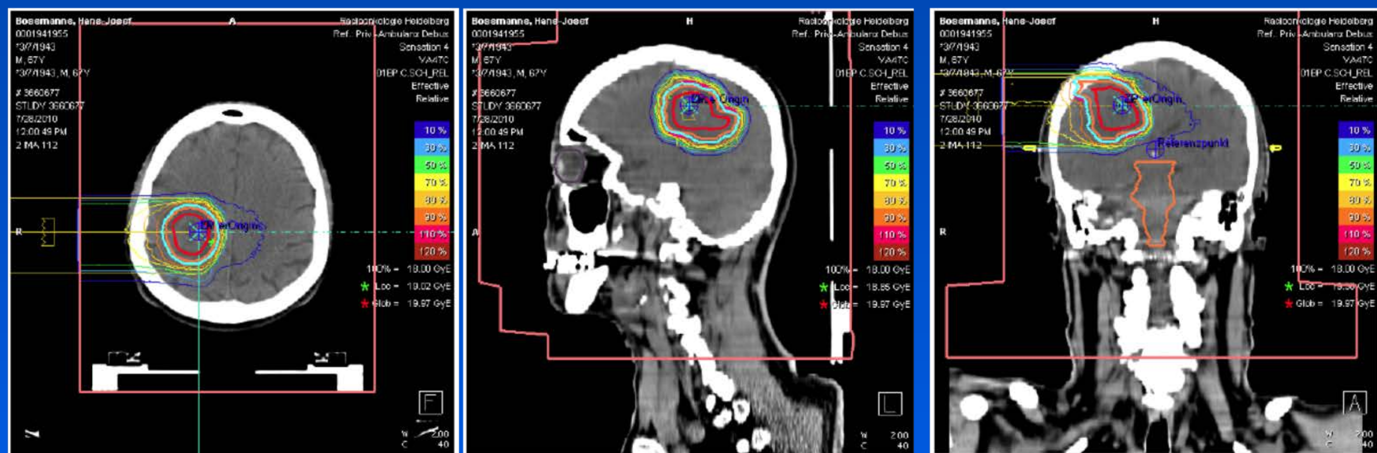
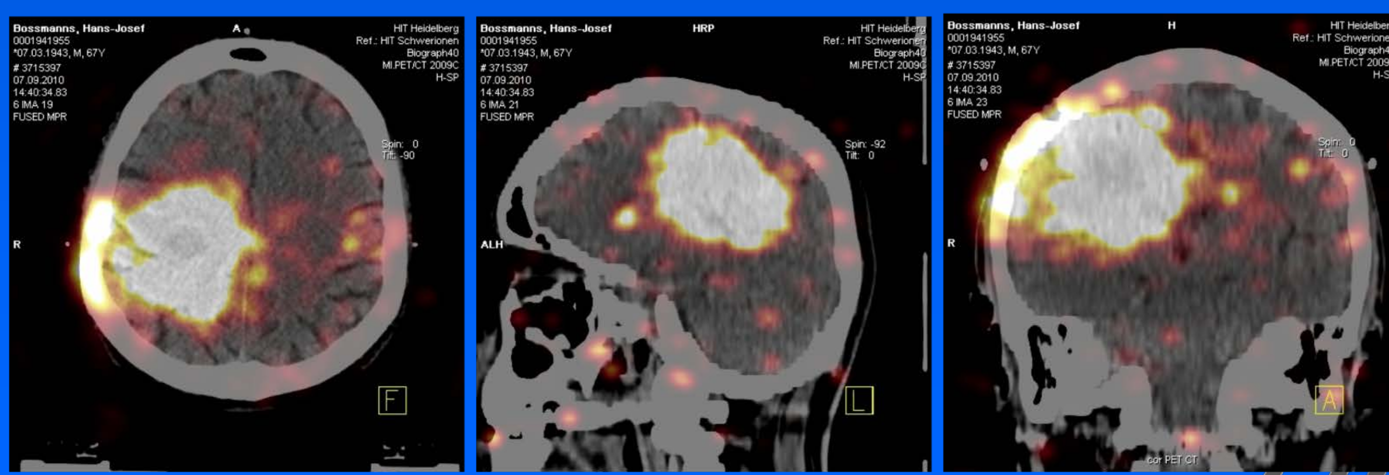
PET For Dose Verification offline after 2 min

Planned dose (on planning CT)



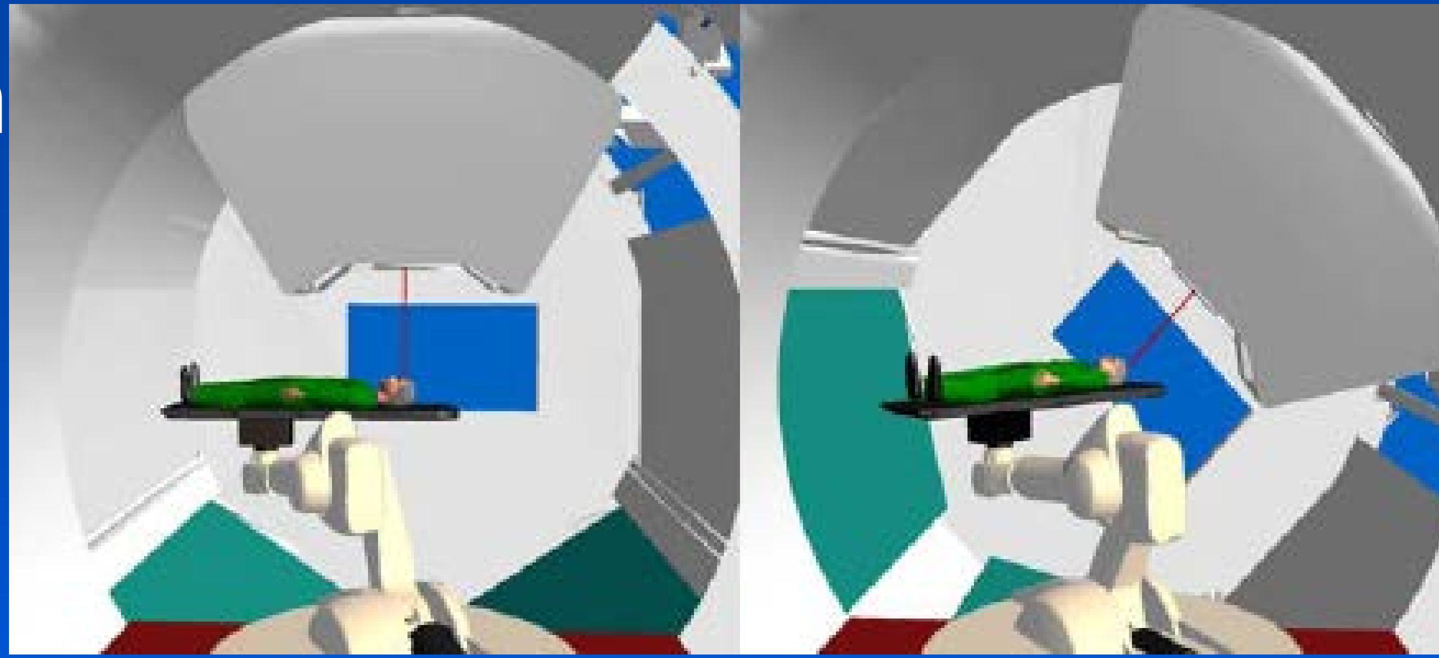
Measured PET/CT



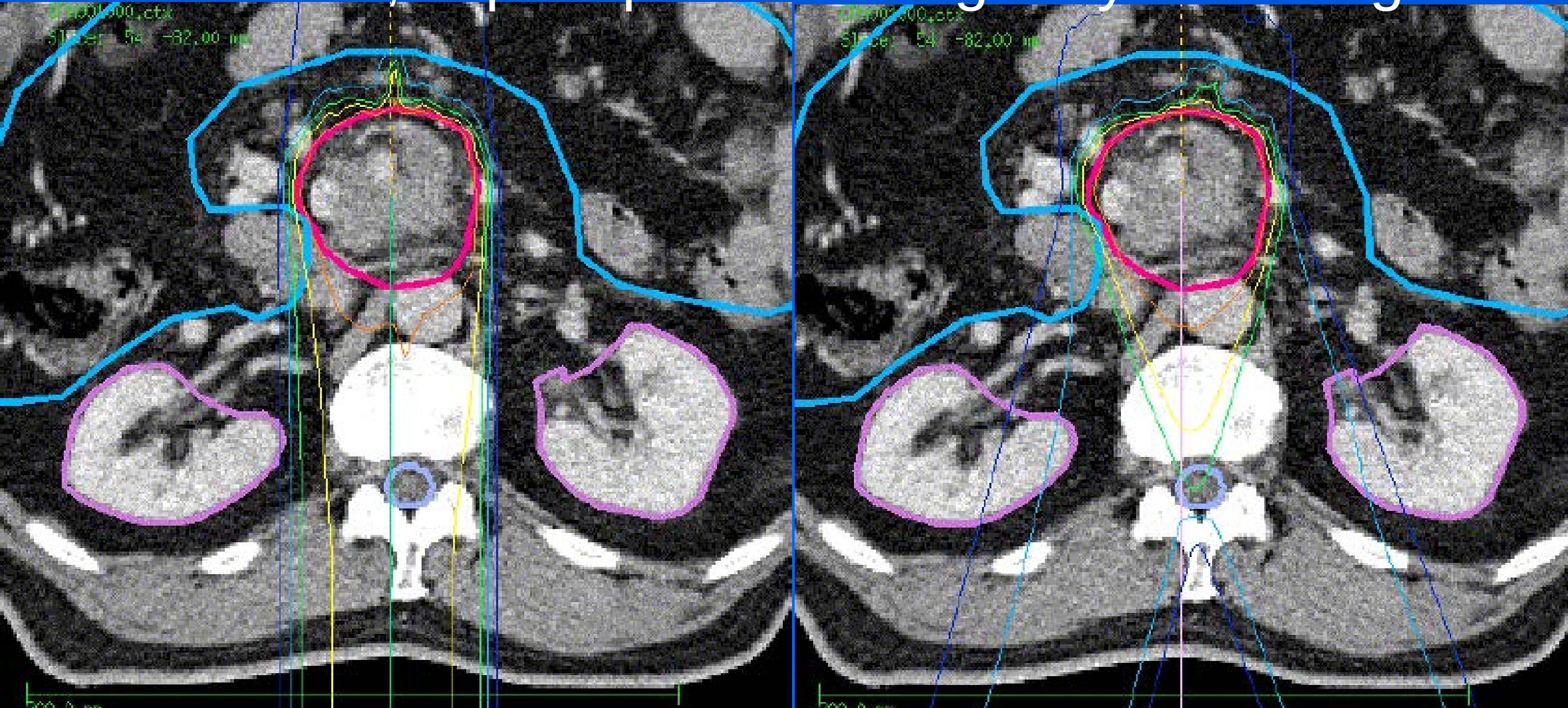
Parodi et al 2010

Motivation Gantry

Advantage of a rotating beamline



Pancreas, supine position via gantry advantageous



Scanning Ion Gantry / Requirements

Clinical:

- Iso-centric set-up and a fixed floor
- Identical field size in all beamlines of 20 cm x 20 cm
- Integration of fluoroscopy systems in two planes (IGRT, organ movement)

Technical / financial:

- 2D-parallel scanning mode via edge focussing (large SAD ~ 50m)
- Full 360° rotation (clinical workflow, minor investment saving)
- Normal conducting elements (field quality ~10^{-4} in 90-degree bending magnet, price, 330 days 24/7 op.)
- Barrell-type (less bending than cork-screw)
- Scanning upstream to the last bending (radius vs. weight)
- Truss-based structure

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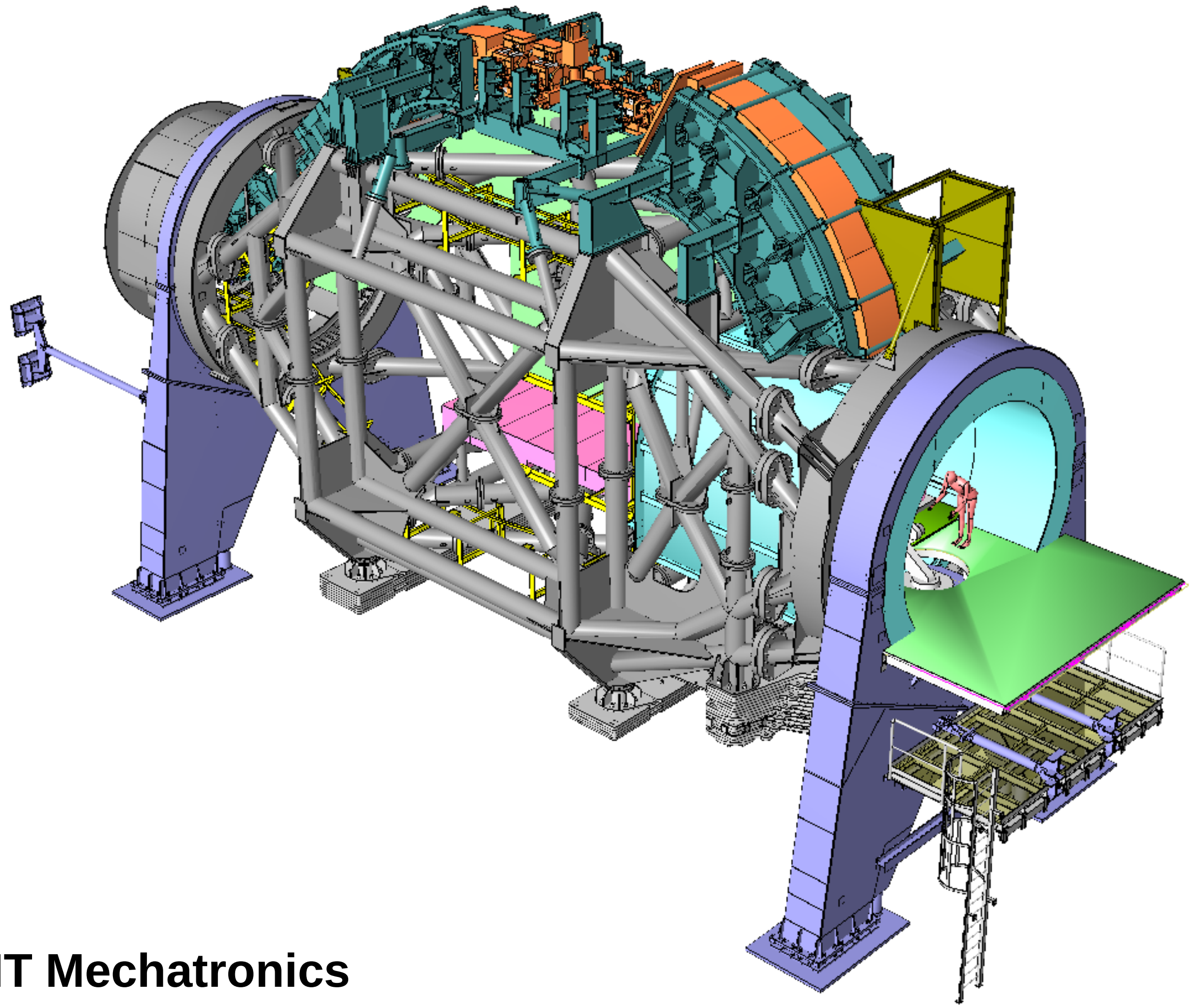
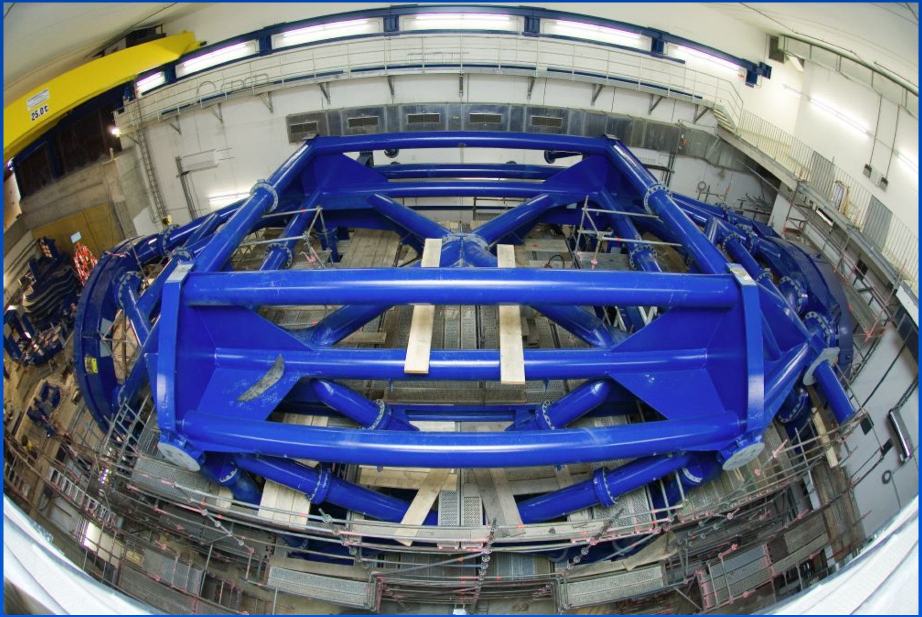
Design for HIT

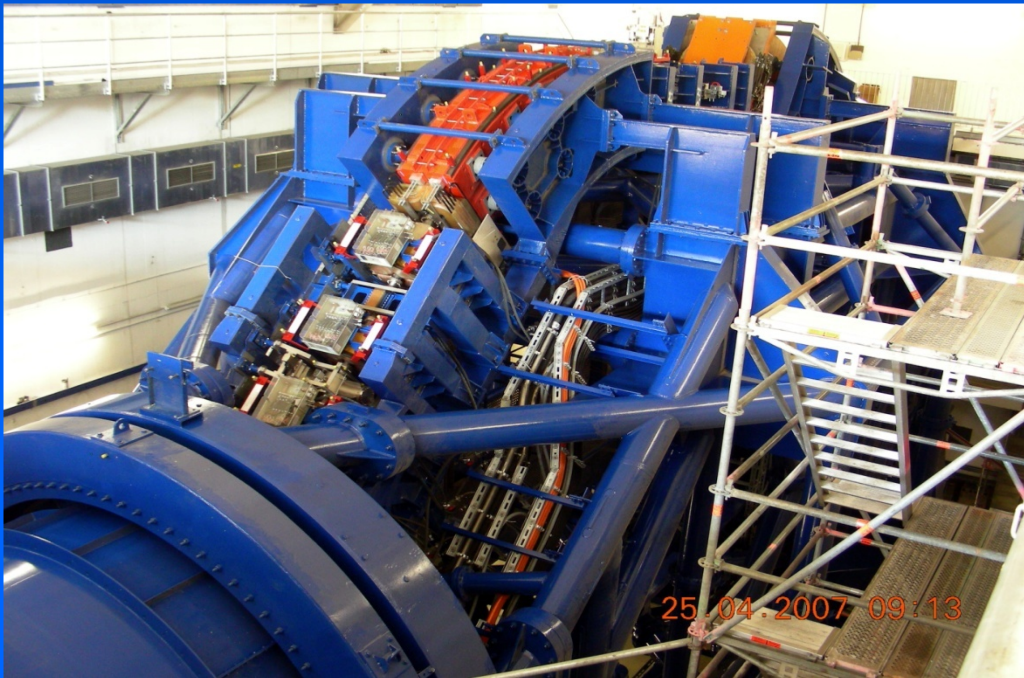
- isocentric barrel-type
- world-wide first
  ion gantry
- 2D beam scanning
  upstream to final
  bending, almost
  parallel due to edge
  focussing
- ± 180° rotation
  3° / second
- 13m diameter
  25m length
  600 to rotating
  (145 to magnets)



MT Mechatronics

Mounting





Patient Environment / Nozzle

Patient Gantry Room November 2007

Tilt floor, pending on Gantry position

Nozzle

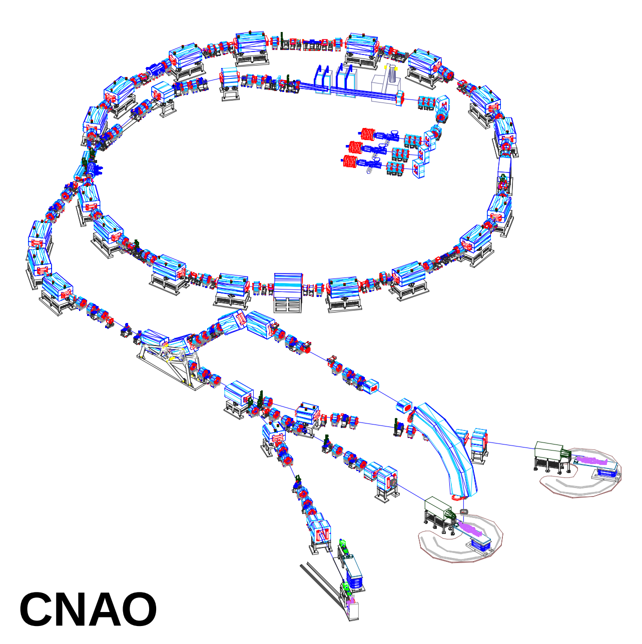
Bumber mats

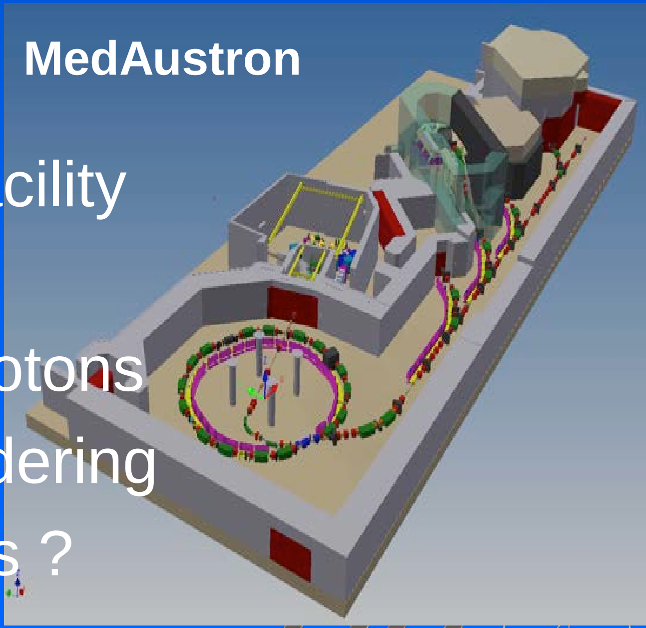
Patienttable, Roboter

The HIT Gantry Rotates

European Projects

- Uppsala: protons, IBA
- Prague: protons, IBA
- Dresden: protons, IBA, R+D-oriented
- Krakow: protons, IBA, fixed-beam, R+D
- Essen: protons, IBA
- Trento: protons, IBA
- Halle, Berlin, …
- Marburg: carbon/protons, Siemens test facility
- CNAO, Pavia, carbon/protons
- MedAustron, Wiener Neustadt, carbon/protons
- Lyon/ETOILE: carbon/protons, active tendering
- Caen/ARCHADE: carbon (protons), status ?





Thank you!

Rasterscan@HIT/H1 Carbon 430 MeV/u

Rasterscan@HIT/Gantry Carbon

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