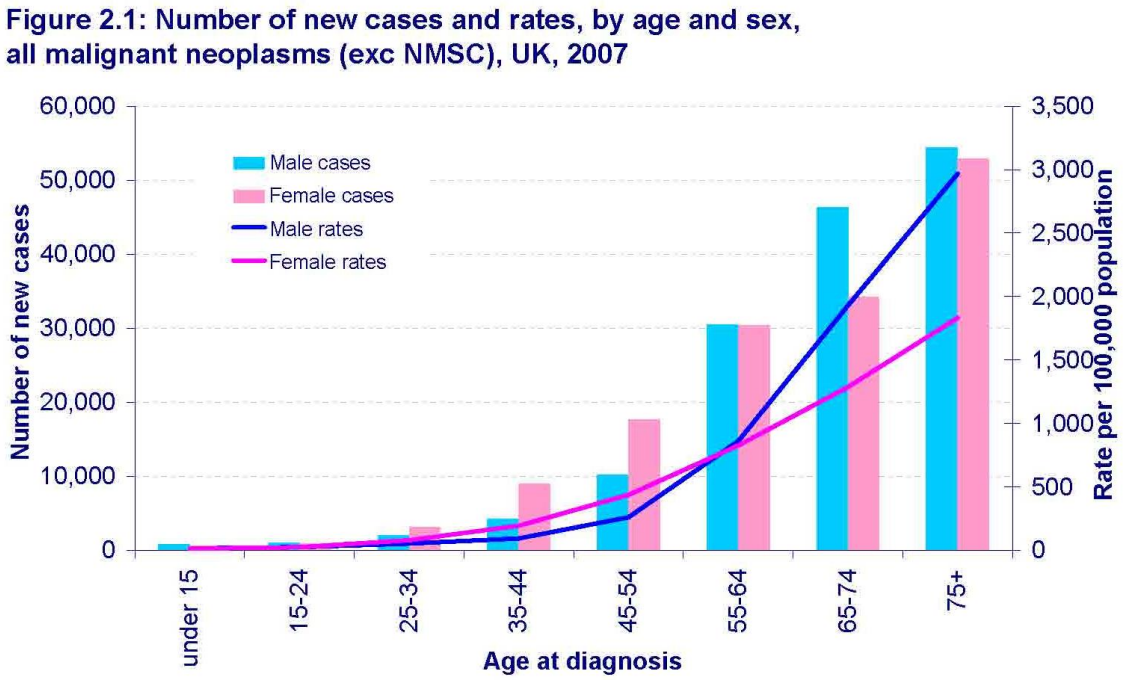
Particle therapy

proton-CT – a novel diagnostic tool

Dieter Roehrich
UiB

- **Particle therapy – a treatment of cancer**
- **Bragg peak position – the critical parameter in dose planning**
- **Proton-CT – a novel diagnostic tool for quasi-online dose plan verification**

Cancer statistics and therapies

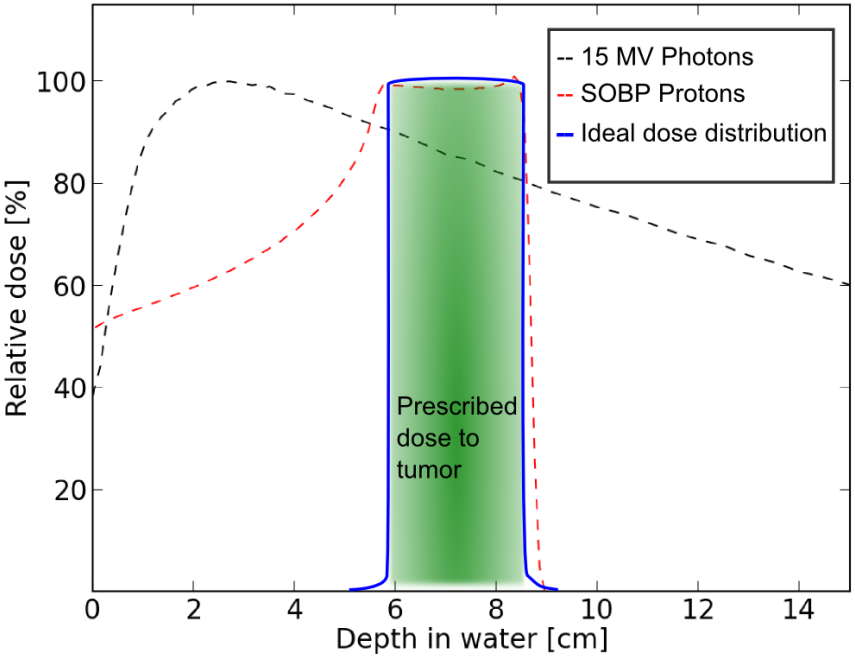


- **Radiotherapy is an important weapon in the battle against cancer**
  - **Contributions to successful treatment of cancer**
    - **45-50% surgery**
    - **40-50% radiotherapy**
    - **10-15% chemotherapy**

K. Peach, Heavy Ions in Science and Health workshop, Bergen, 2012

Radiotherapy with photons and hadrons

- **The goal of radiation therapy is to irradiate the tumor with the prescribed dose and minimize the dose to healthy tissue**

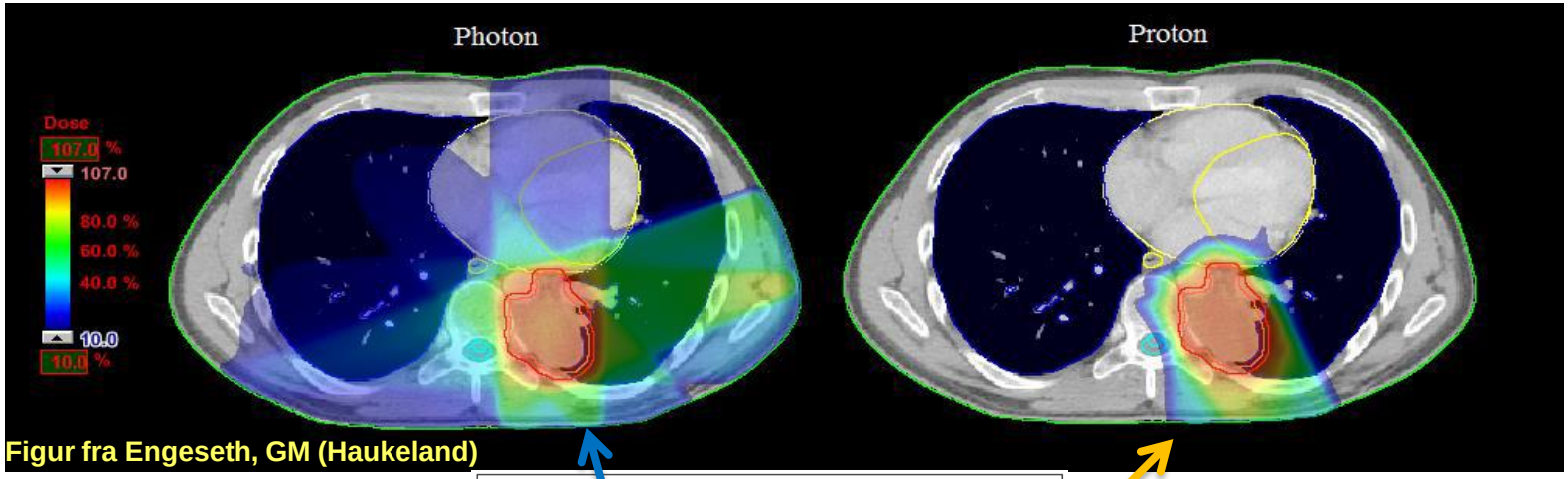


- **photons**
  electromagnetic radiation

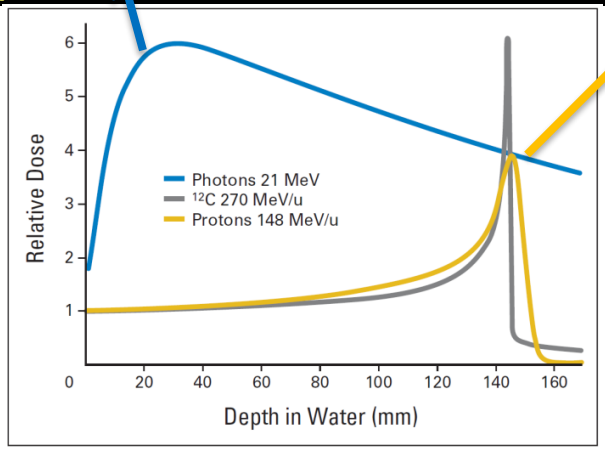
- **hadrons**
  protons and heavier nuclei,
  e.g. carbon nuclei

Radiotherapy – photons vs hadrons (I)

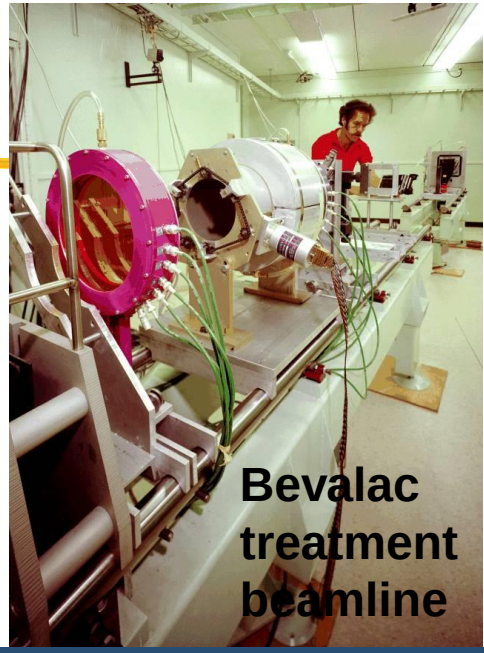
- **Treatment goal**
  - **Effective eradication of all tumor cells <-> avoid injury to healthy tissue**
- **Do we achieve the goal in the clinical routine?**



Figur fra Engeseth, GM (Haukeland)

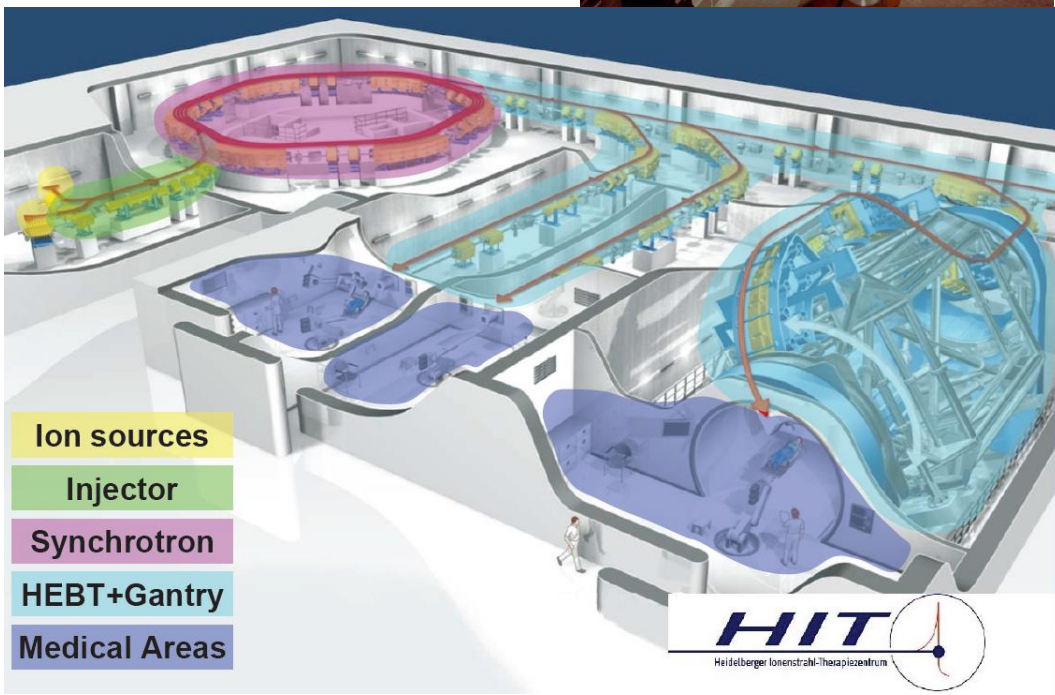


Why carbon ions? (I)



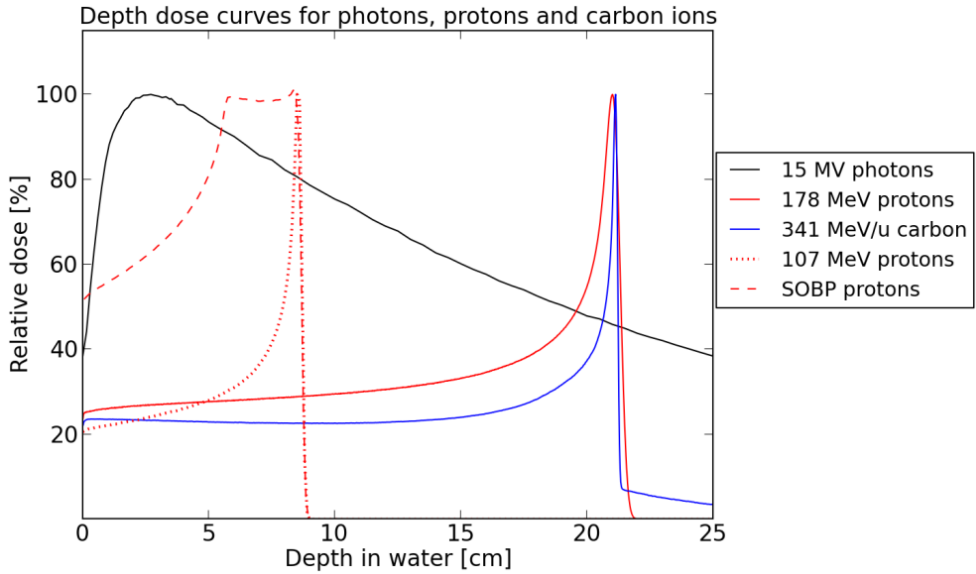
History

- **LBL (1975-1986)**
- **Japan (since 1994): NIRS, Gunma, …**
- **Germany (since 1997): GSI, HIT, …**

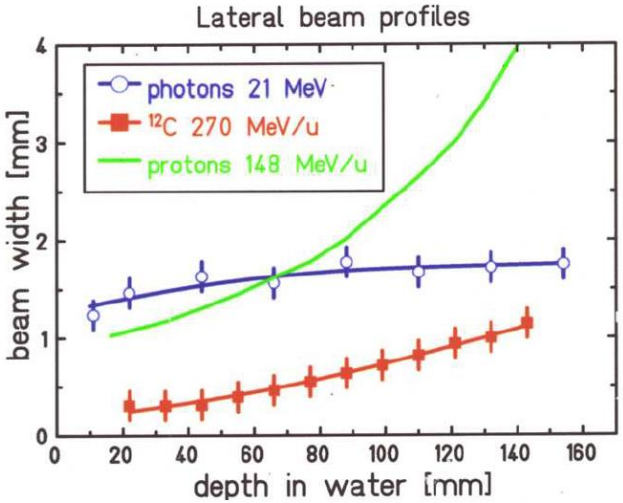


Why carbon ions? (II)

- **Energy loss (Bethe-Bloch) and Bragg peak**



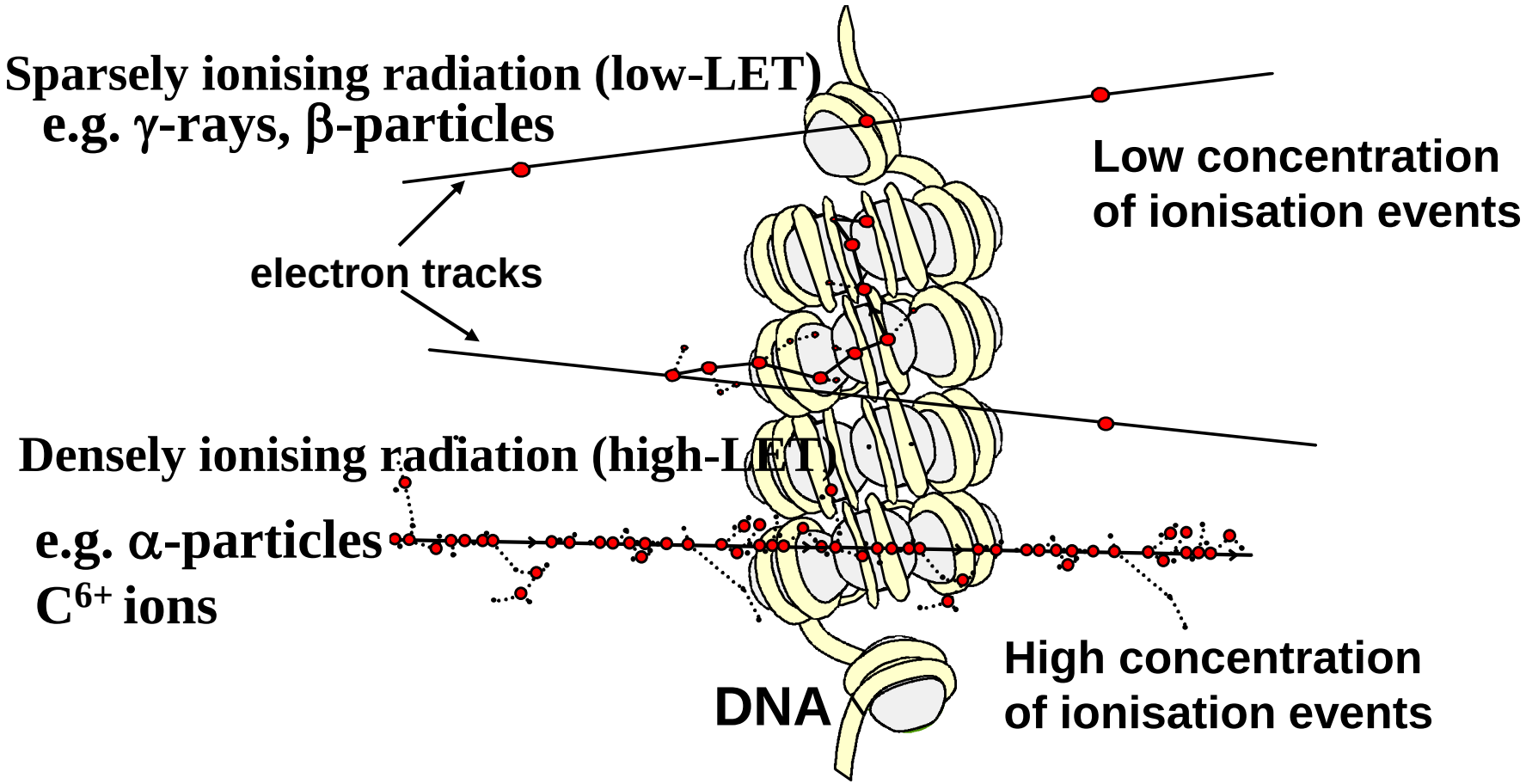
- **Lateral beam profile**



Why carbon ions? (III)

- **Radiation-induced DNA damage**

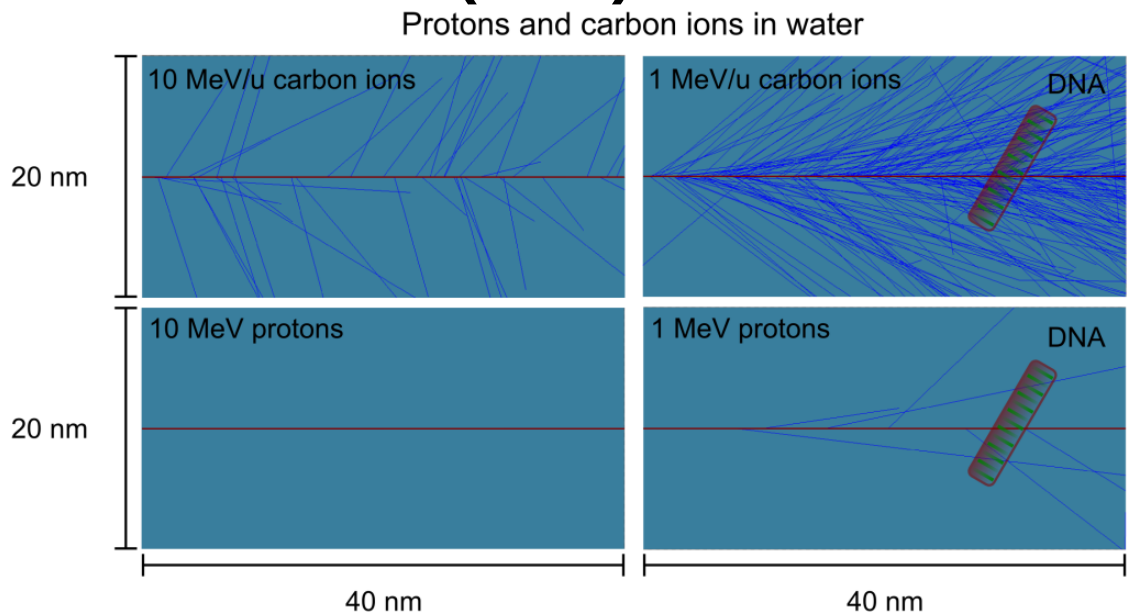
C-ions are very effective – high Relative Biological Effectiveness RBE



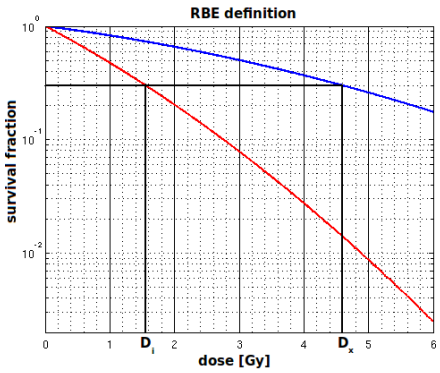
Why carbon ions? (IV)

- **Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE)**

$$LET = \frac{dE_{transferred}}{dx}$$

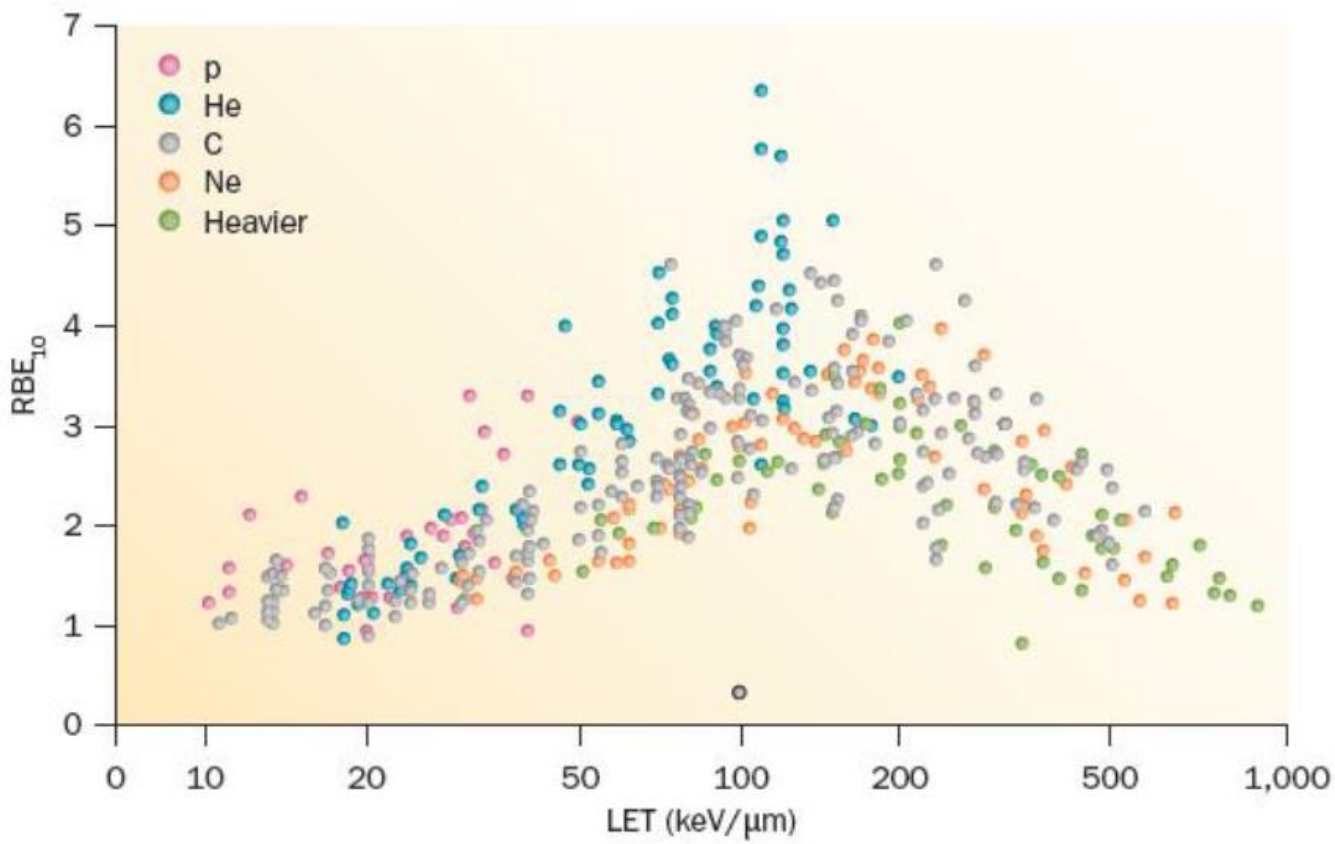


$$RBE = \frac{DOSE_{x-ray}}{DOSE_{test}}$$



Why carbon ions? (V)

- **LET and RBE**
  -> RBE (^{12}C, in Bragg peak): 3-4



NuPECC, Nuclear Physics in medicine - Chapter 1 - Hadrontherapy, 2013

Why carbon ions? (VI)

- **Bragg peak and RBE**
  - Comparison photons, protons, carbon ions

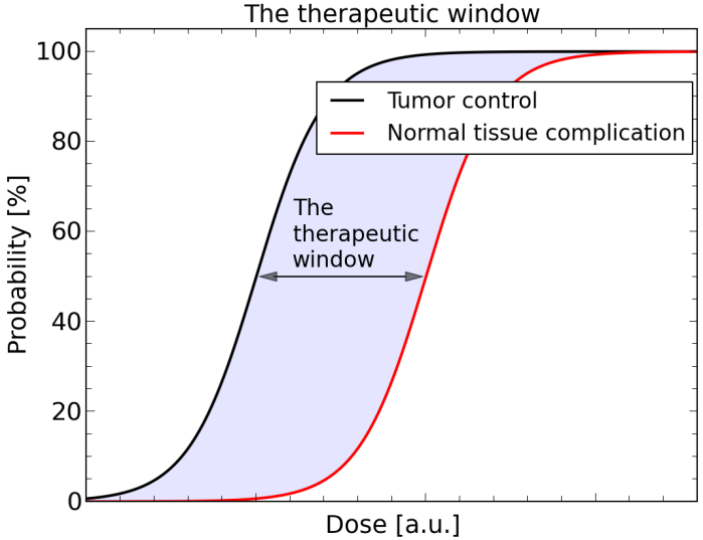
	Photons	Protons	Carbon ions
Integral out-of-field dose	1	0.3-0.5	<0.3
RBE	1	1.1	>3 (in Bragg peak)

Qualitative difference between photons and carbon-ions:
potential improvement by 10

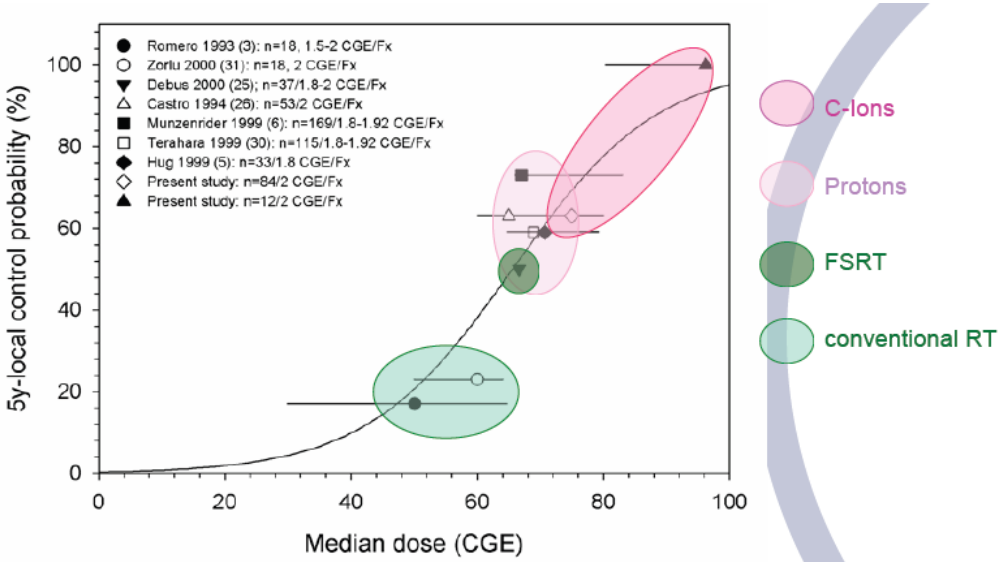
Integral out-of-field dose: the smaller the better (ideally 0)
RBE: the higher the better

From principal arguments to clinical studies

- **Carbon ions provide a wide therapeutic window**

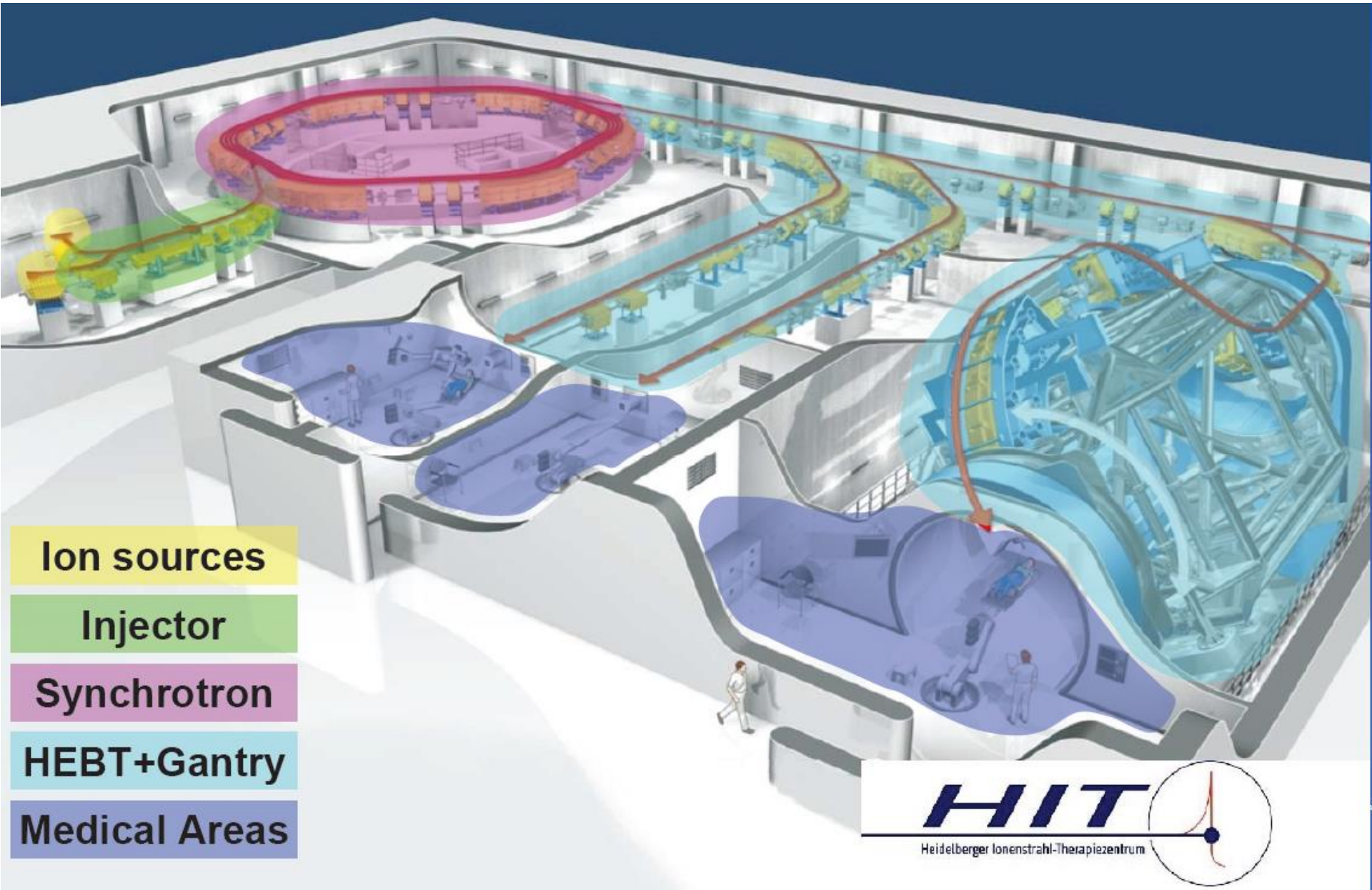


- **Confirmed by clinical results**

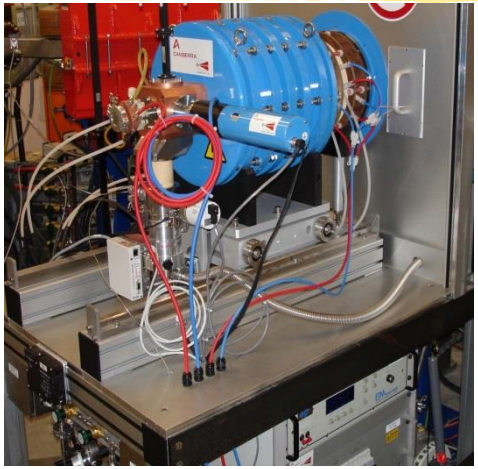


[Schulz-Ertner, IJROBP 2007]

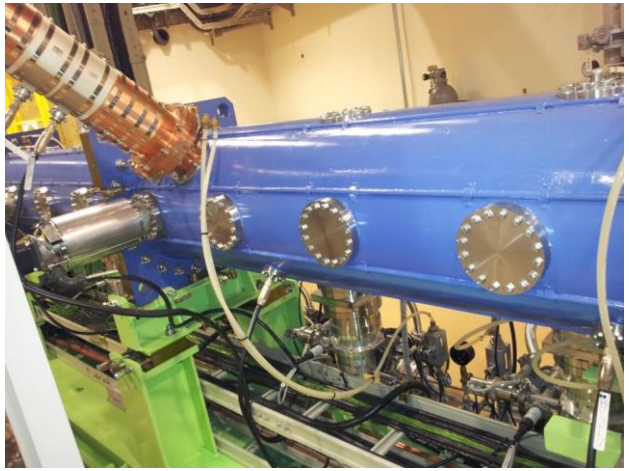
The particle beam treatment facility - e.g. HIT



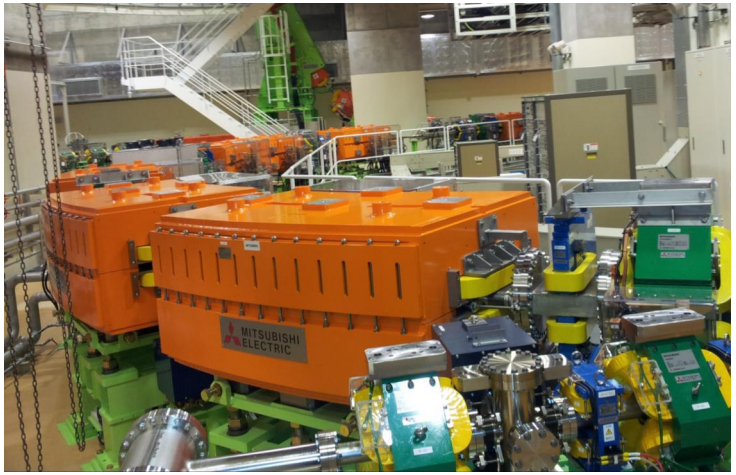
The particle beam treatment facility



ECR ion source (p, He, C)

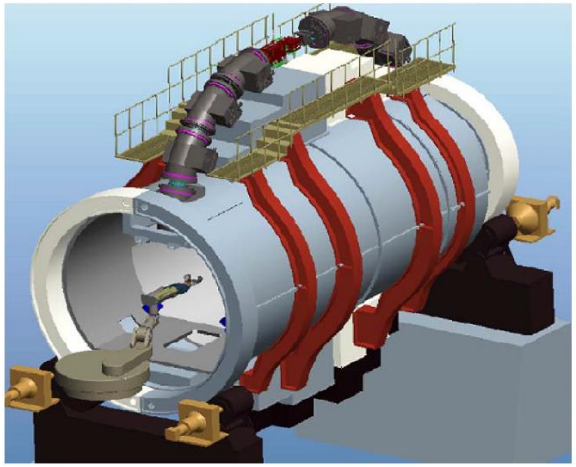


LINAC



Synchrotron

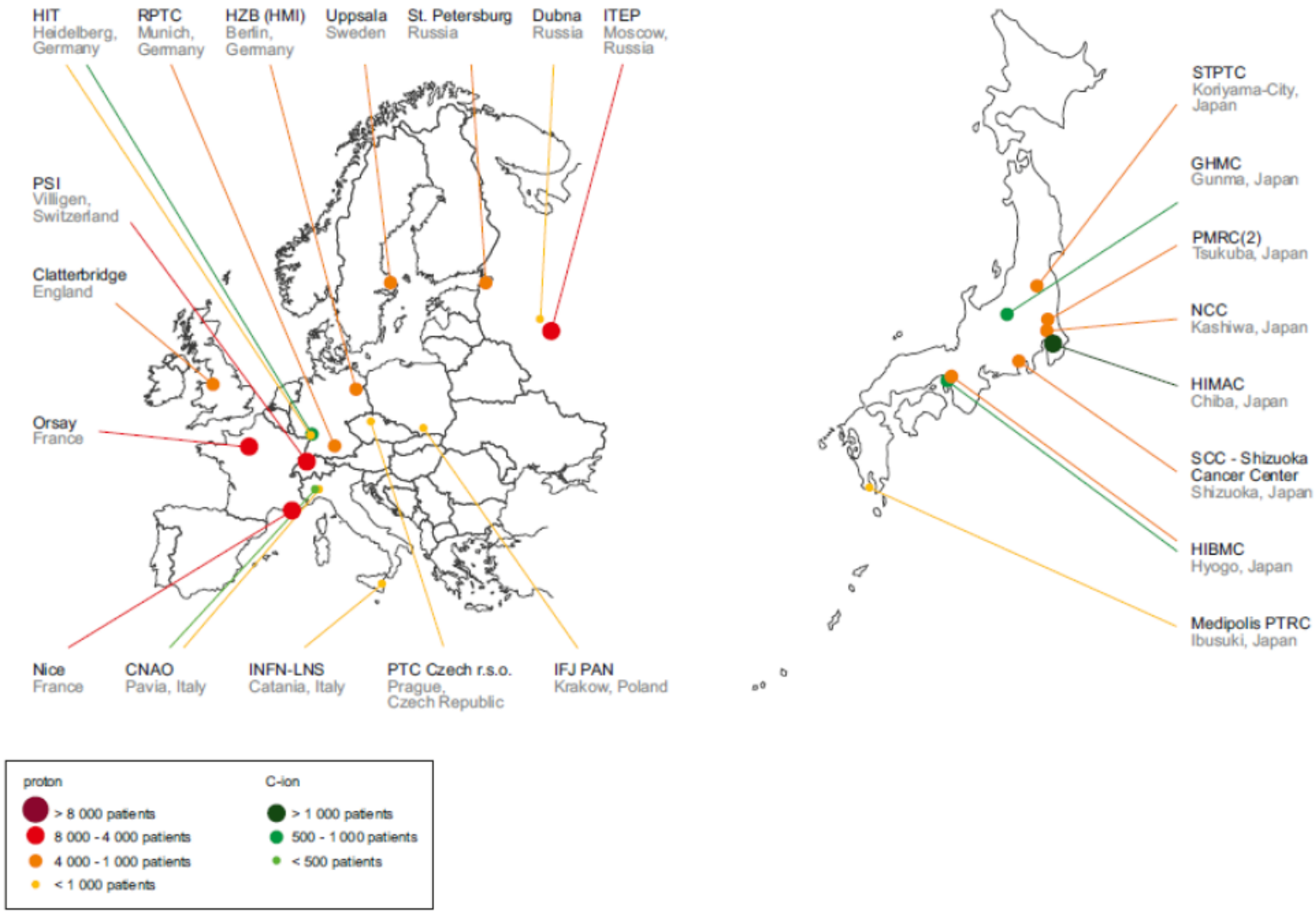
Treatment room



Superconducting gantry

Extraction and beam transport

Hadron facilities in operation

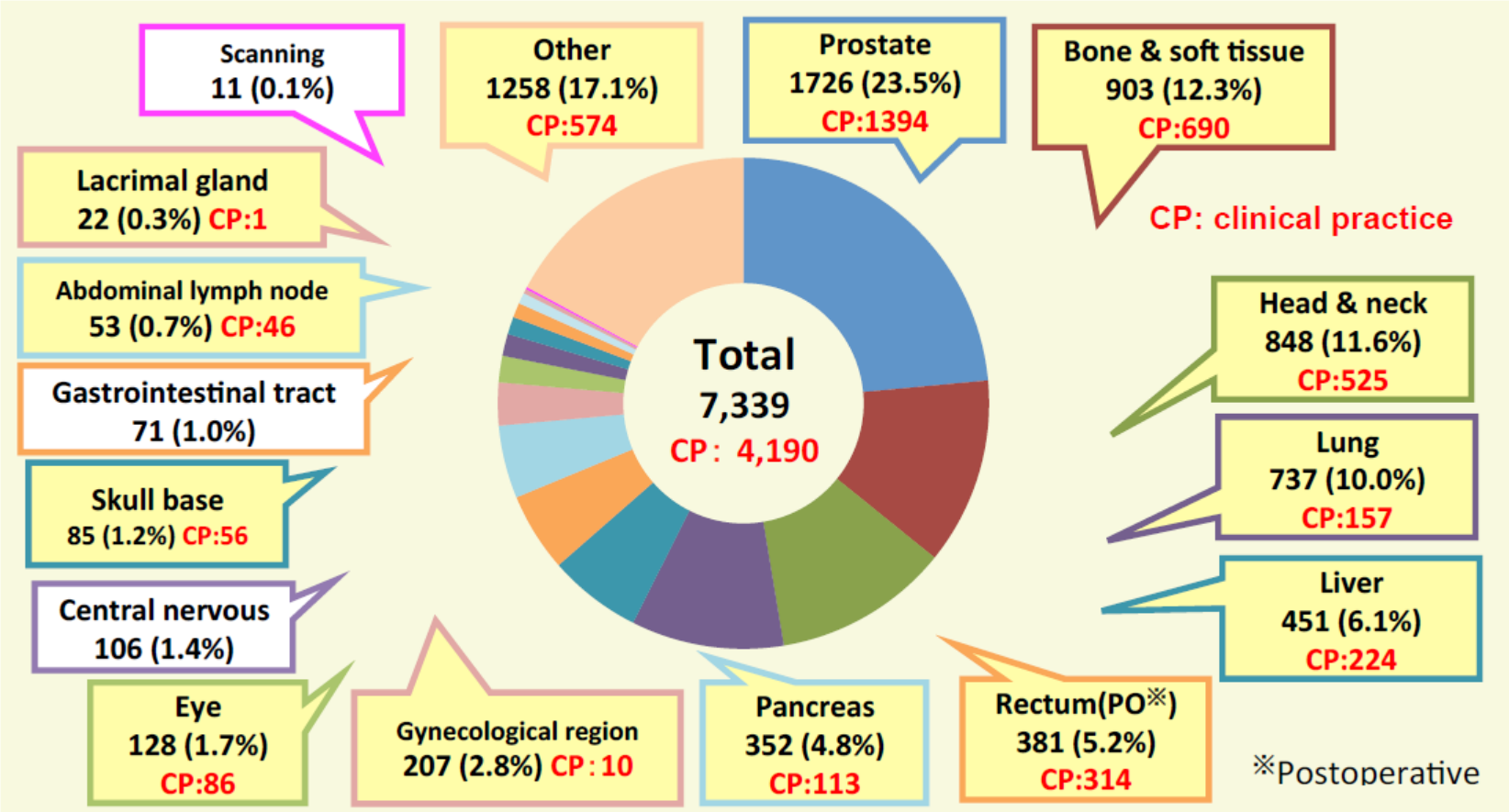


NuPECC, Nuclear Physics in medicine - Chapter 1 - Hadrontherapy, 2013

Clinical results

Carbon ion clinical research at NIRS (Japan)

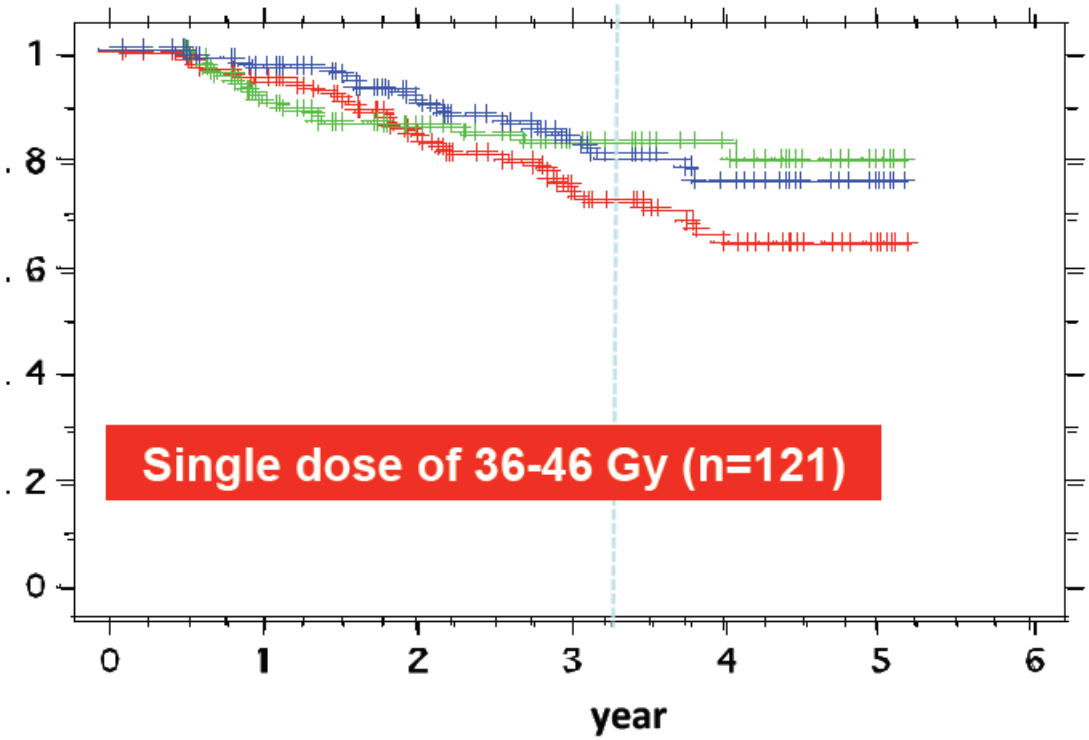
- **57 phase I and phase II protocols since June 1994**
- **Number of patients enrolled for carbon ion radiotherapy at NIRS:**



T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013

Clinical results (NIRS) – lung cancer

Single fraction carbon ion therapy for peripheral stage 1 non-small cell lung cancer

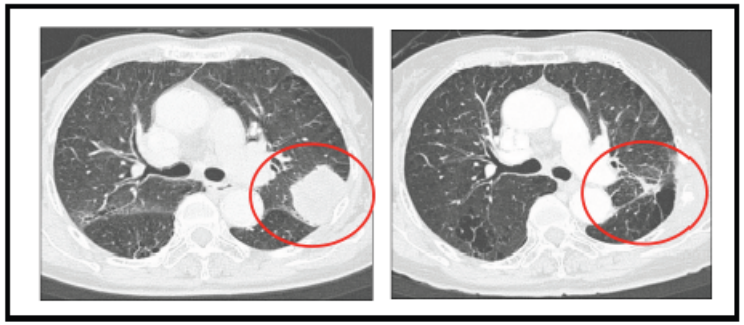


Local control rate(5 y):79%

Cause-spec. survival rate(5y):75%

Overall survival rate(5y):64%

T2N0M0 Sq.CC 71 F

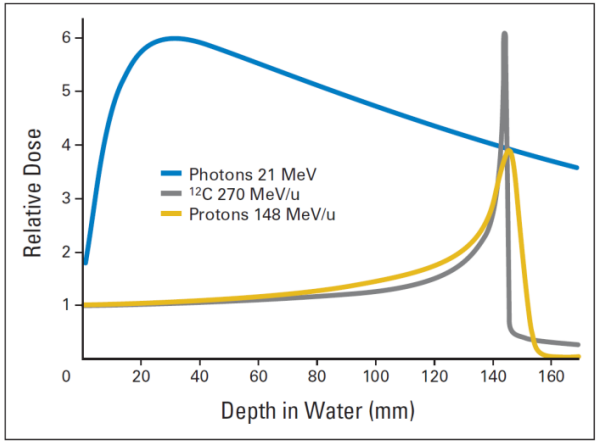


Before After

NO Grade 3 Reactions in this series

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013

The Bragg peak position



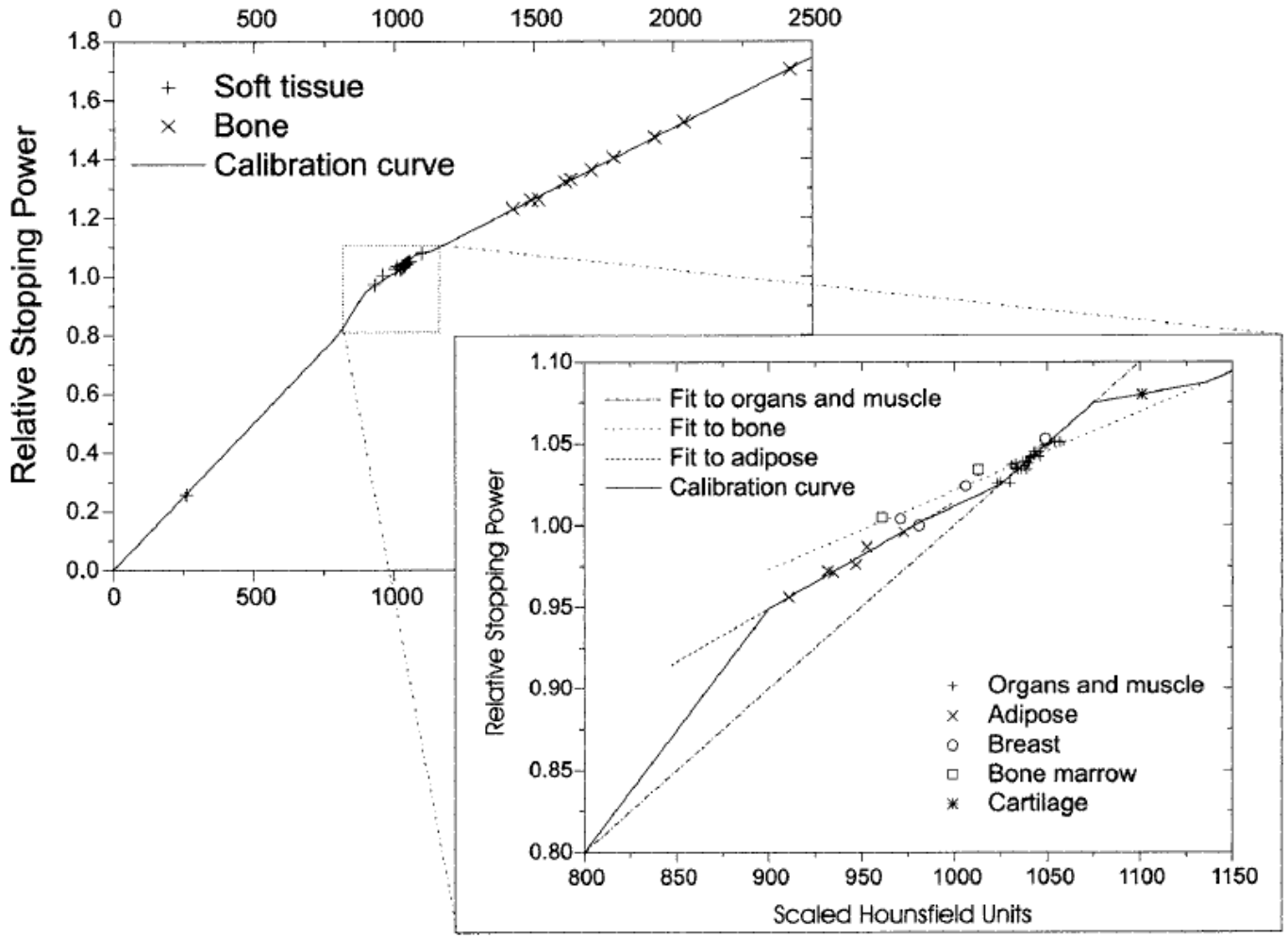
- **Key advantage of ions: Bragg peak**
  - **Relatively low dose in the entrance channel**
  - **Sharp distal fall-off of dose deposition (<mm)!**

- **Challenge**
  - **Stopping power of tissue in front of the tumor has to be known – crucial input into the dose plan for the treatment**
  - **Stopping power is described by Bethe-Bloch formula:**

    - dE/dx ~ (electron density) x ln((max. energy transfer in single collision)/(effective ionization potential)^2)

- **Current practice**
  - **Derive stopping power from X-ray CT**
  - **Problem:**
    X-ray attenuation in tissue depends not only on the density, but also strongly on Z (Z^5 for photoelectric effect)

Stopping power calculation from X-ray CT



Schaffner, B. and E. Pedroni, *The precision of proton range calculations in proton radiotherapy treatment planning: experimental verification of the relation between CT-HU and proton stopping power.* Phys Med Biol, 1998. 43(6): p. 1579-92.

Range uncertainties

Clinical practice:

- **Single energy CT: up to 7.4 % uncertainty**

How to deal with range uncertainties in the clinical routine?

- **Increase the target volume by up to 1 cm in the beam direction**
- **Avoid beam directions with a critical organ behind the tumor**

Unnecessary limitiations -> reduce range uncertainties

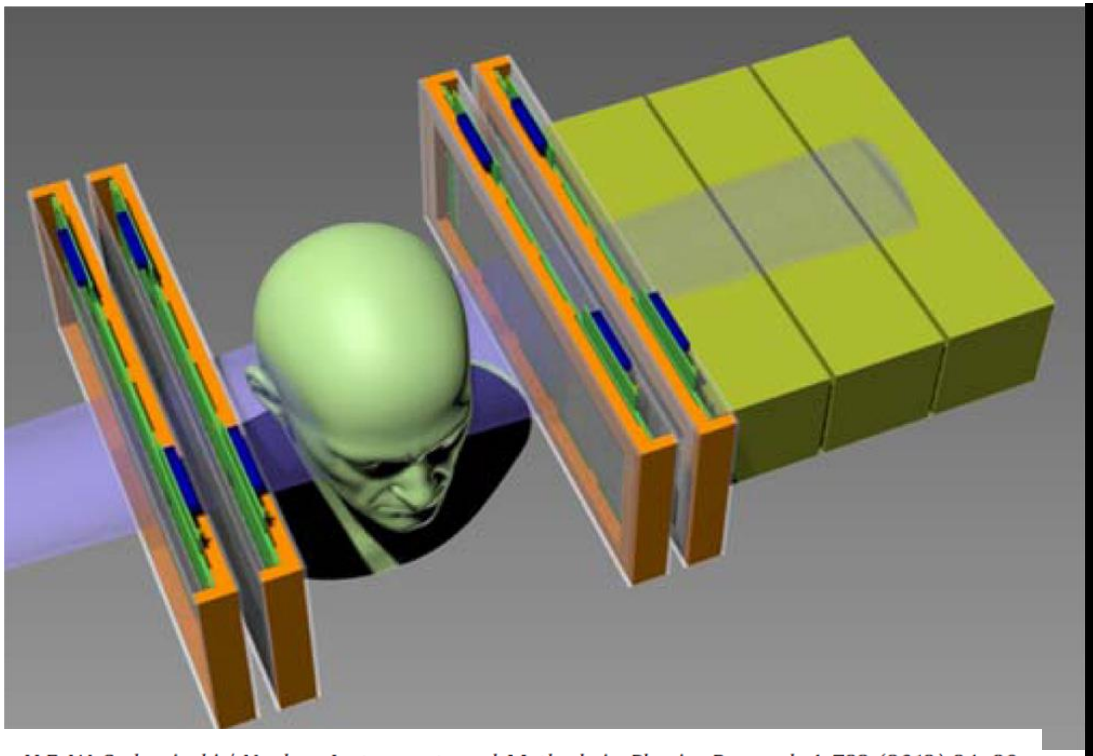
Estimates for advanced dose planning:

- **Dual energy CT: up to 1.7 % uncertainty**
- **Proton CT: up to 0.3 % uncertainty**

A comparison of dual energy CT and proton CT for stopping power estimation

David C. Hansen,[1, a)] Joao Seco,[2] Thomas Sangild Sørensenn,[3] Jørgen Breede Baltzer Petersen,[4] Joachim E. Wildberger,[5] Frank Verhaegen,[6] and Guillaume Landry[7]
[1)] *Department of Experimental Clinical Oncology, Aarhus University*

Proton CT



H.F.-W. Sadrozinski / Nuclear Instruments and Methods in Physics Research A 732 (2013) 34–39

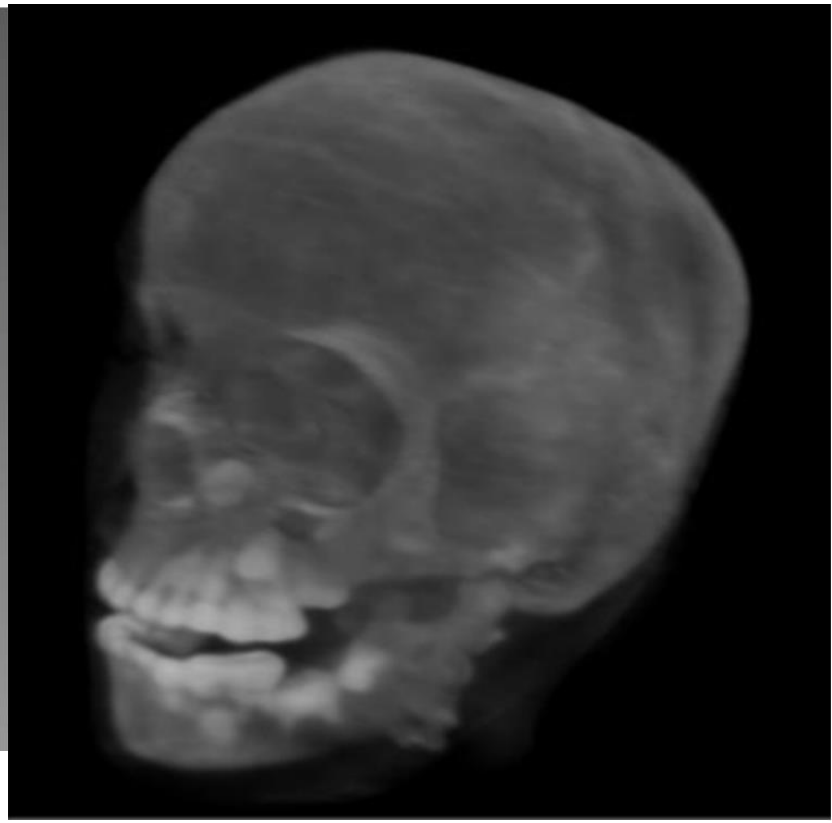
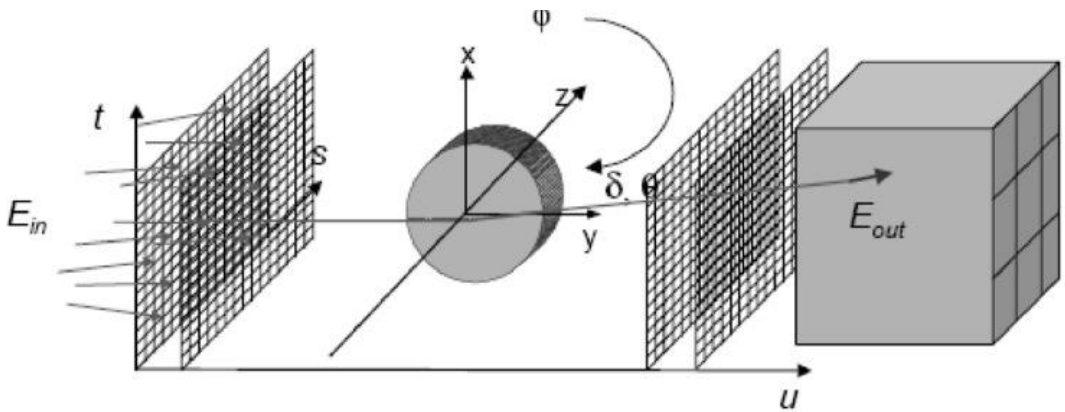


Fig. 14. 3D rendering of the pCT-reconstructed RSP map of a pediatric anthropomorphic head phantom.

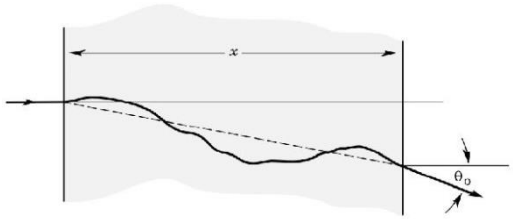
V.A. Bashkirov et al. / Nuclear Instruments and Methods in Physics Research A 809 (2016) 120–129

Proton-CT
- quasi-online dose plan verification

- high energetic proton beam quasi-simultaneously with therapeutic beam
- measurement of scattered protons
  - position, trajectory
  - energy/range



- reconstruction of trajectories in 3D and range in external absorber
  - trajectory, path-length and range depend on
    - nuclear interactions (inelastic collisions)
    - multiple Coulomb scattering (elastic collisions)
    - energy loss dE/dx (inelastic collisions with atom



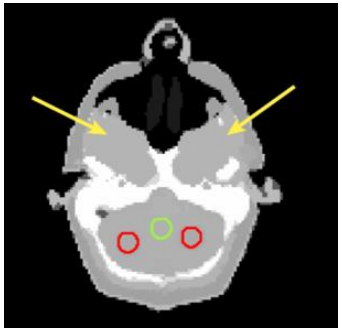
- MS theory and Bethe-Bloch formula of average energy loss in turn depend on electron density in the target (and ionization potentials)

  -> 3D map of electron density in target

  -> online verification of dose plan

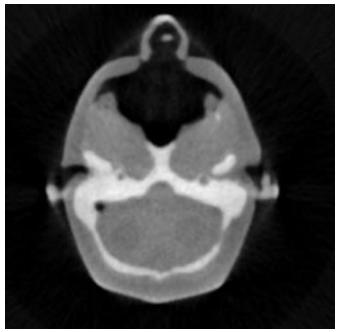
Proton-CT - images

- **Traversing proton beam creates three different 2D maps**
  → three imaging modalities

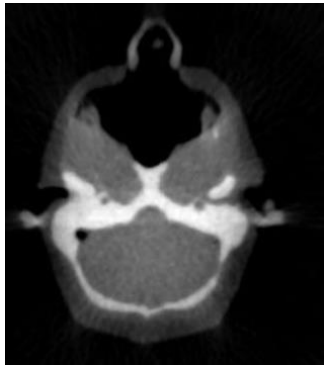


Phantom

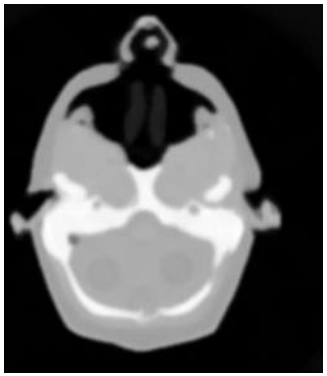
- **Transmission map**
  – records loss of protons due to nuclear reactions



- **Scattering map**
  – records scattering of protons off Coulomb potential



- **Energy loss map**
  – records energy loss of protons (Bethe-Bloch)

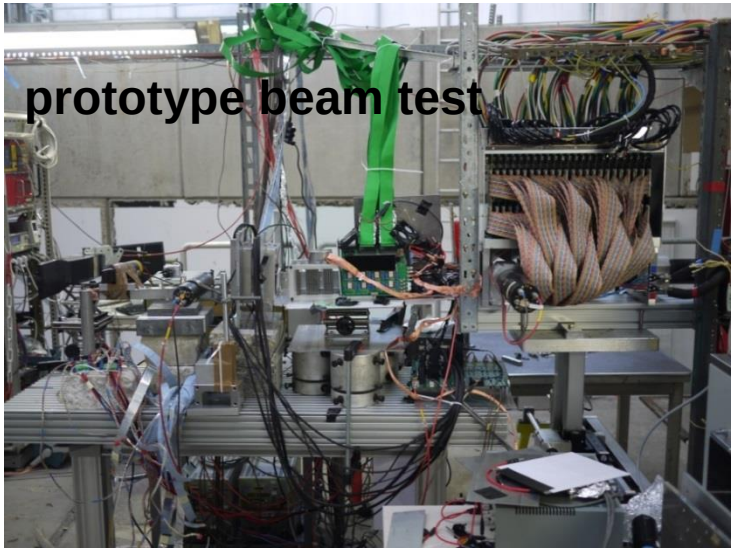


Cecile Bopp. PhD thesis, Strassbourg, 2013

Proton-CT

High energetic proton beam traversing the target – intensity ~10^9 protons/sec

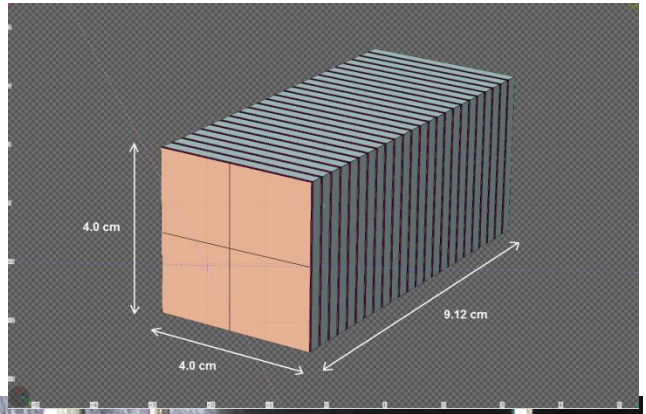
- **Detector requirements**
  - **High position resolution (tens of μm)**
  - **Simultaneous tracking of large particle multiplicities**
  - **Fast readout**
  - **Radiation hardness**
  - **Front detector: low mass, thin sensors (50 μm)**
  - **Back detector: range resolution <1% of path-length**
- **Conceptual design**
  - **Extremely high-granularity digital tracking calorimeter**
- **Technical design**
  - **Monolithic Active Pixel Sensors (MAPS)**
  - **Planes of CMOS sensors for tracking and as active layers in a sampling calorimeter**

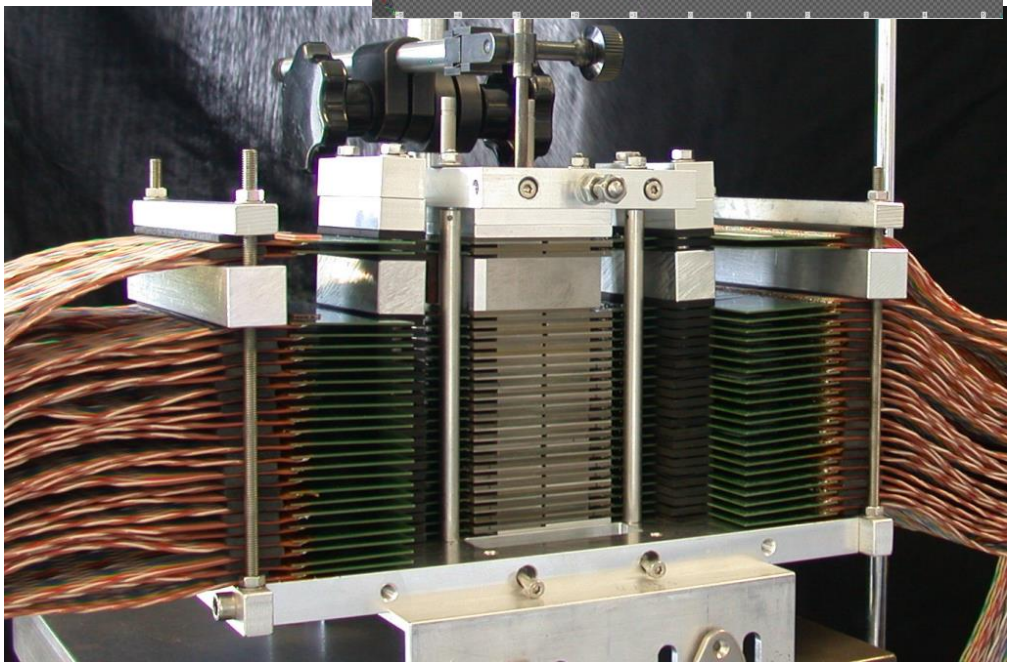


Digital tracking calorimeter prototype (I)

Silicon-tungsten sampling calorimeter

- optimised for electromagnetic showers
- compact design 4x4x11,6 cm^3
- 24 layers
  - absorbers:
    3.5 mm of W (≈ 1 X_0)
    Molière radius: 11 mm
  - active layers:
    MAPS – MIMOSA 23*
    4 chips per layer
    -> 96 chips in total



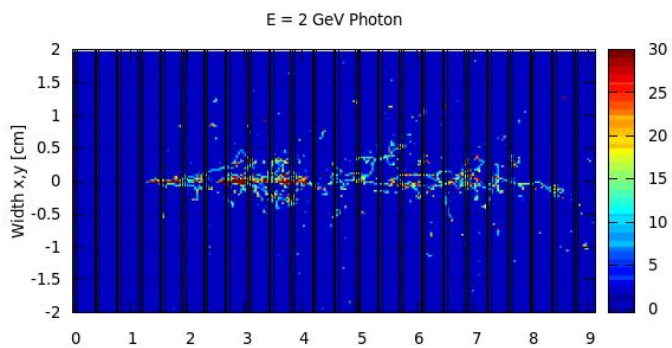


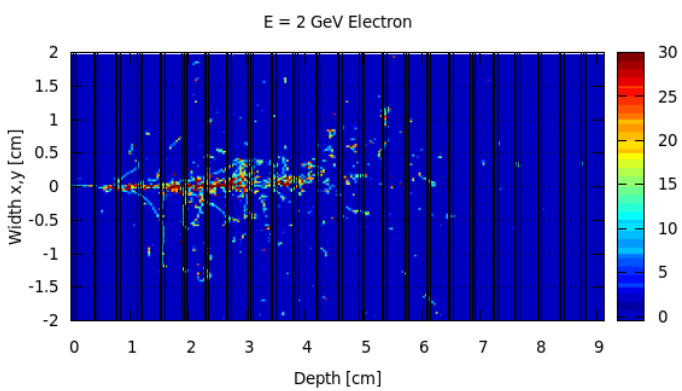
* IPHC Strasbourg

Simulation results

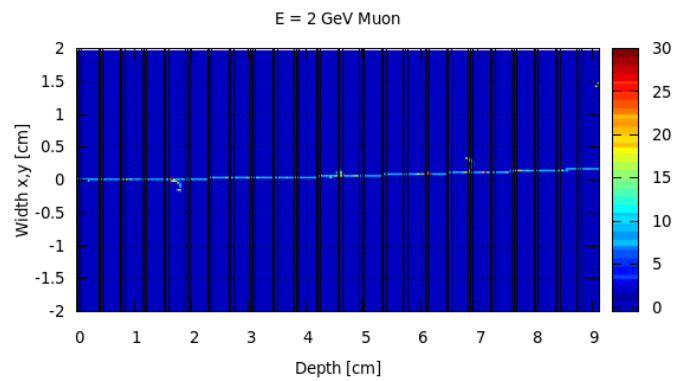
Detector response

Photons and electrons (e.m. shower)

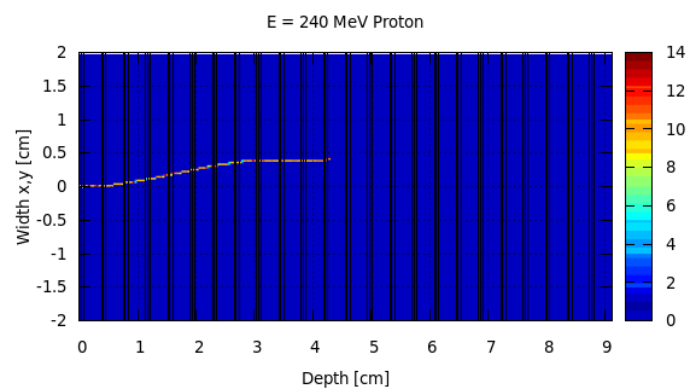




muons (MIP)



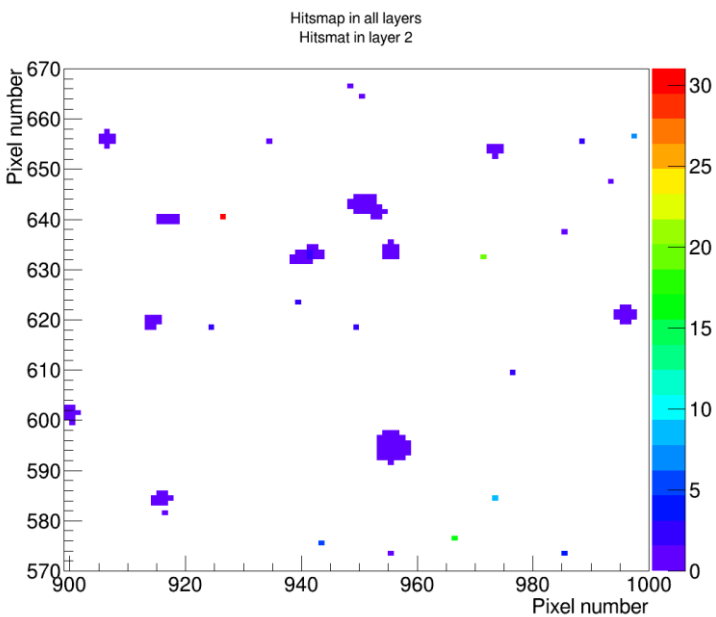
protons

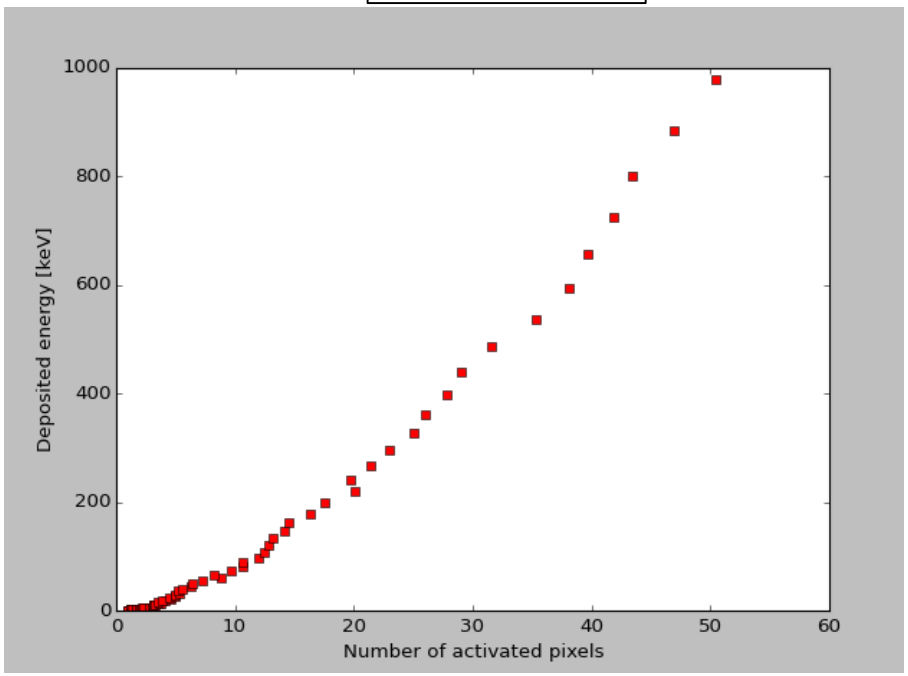


Digital tracking calorimeter – rangemeter (II)

Range measuring resolution

H. Pettersen



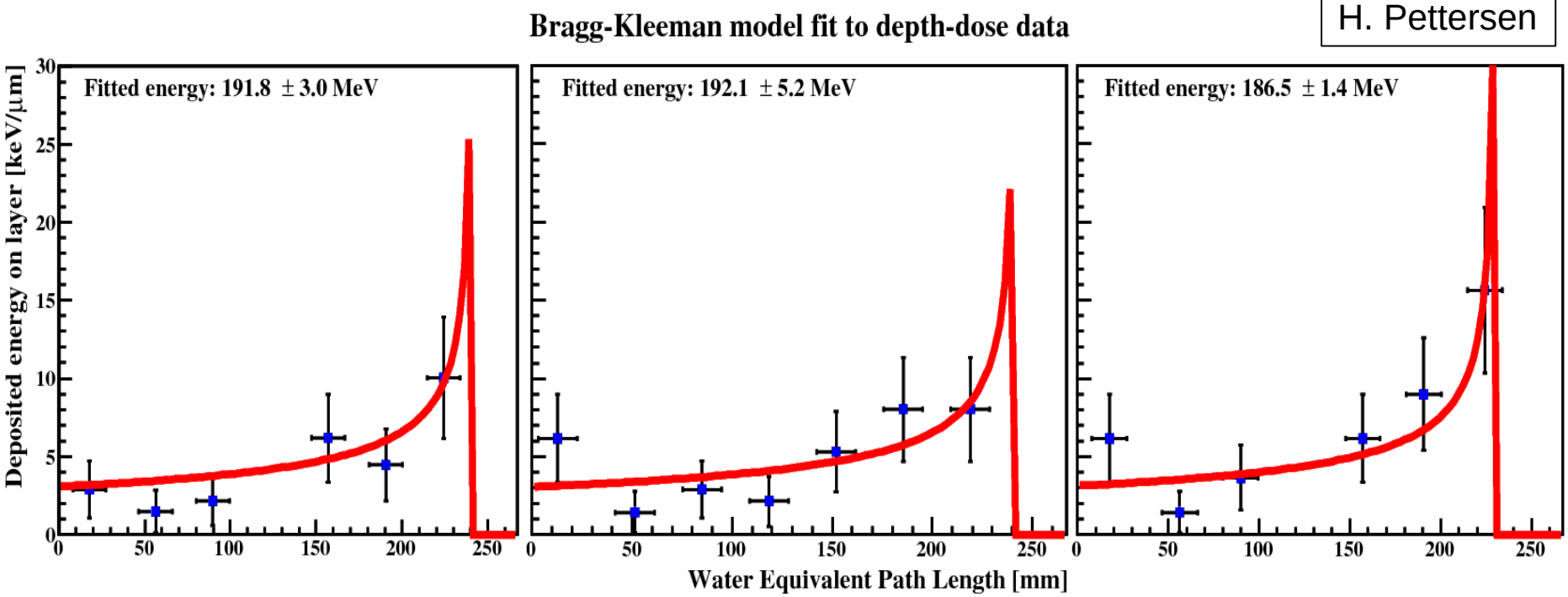


- **Energy loss measurement**
  - **hadron tracks:**
    number of hits in a sensitive layer along the particle trajectory (”cluster size”) depends (weakly) on the energy loss

Digital tracking calorimeter – rangemeter (IV)

- **Tracking of a single proton, collecting clusters along the trajectory and fitting a Bragg curve***

H. Pettersen

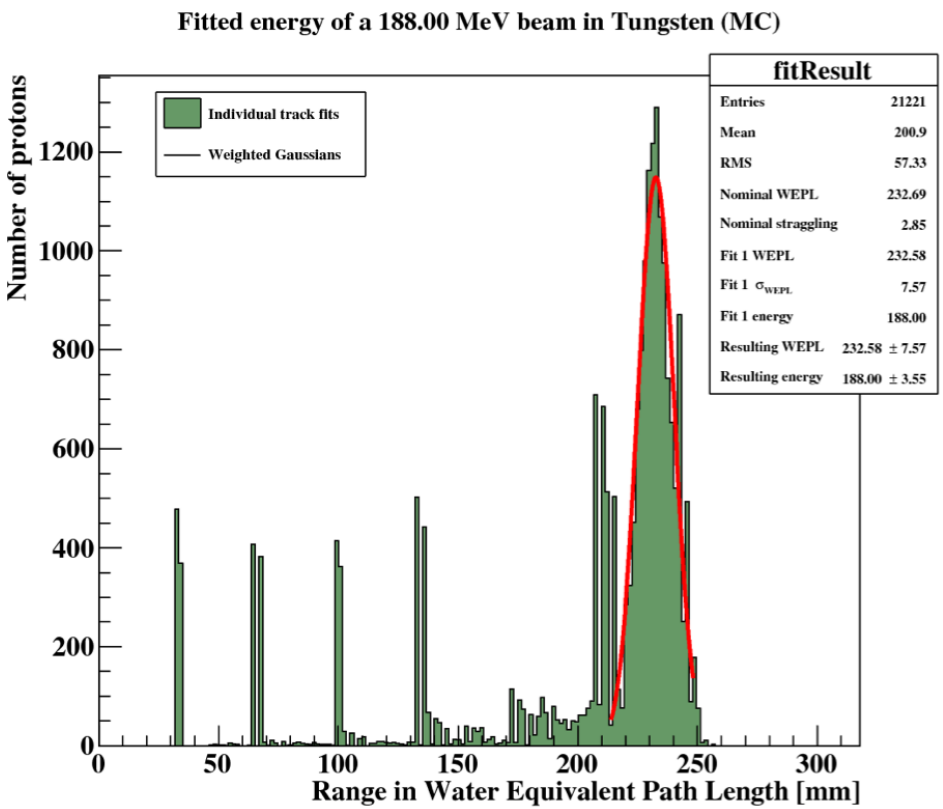


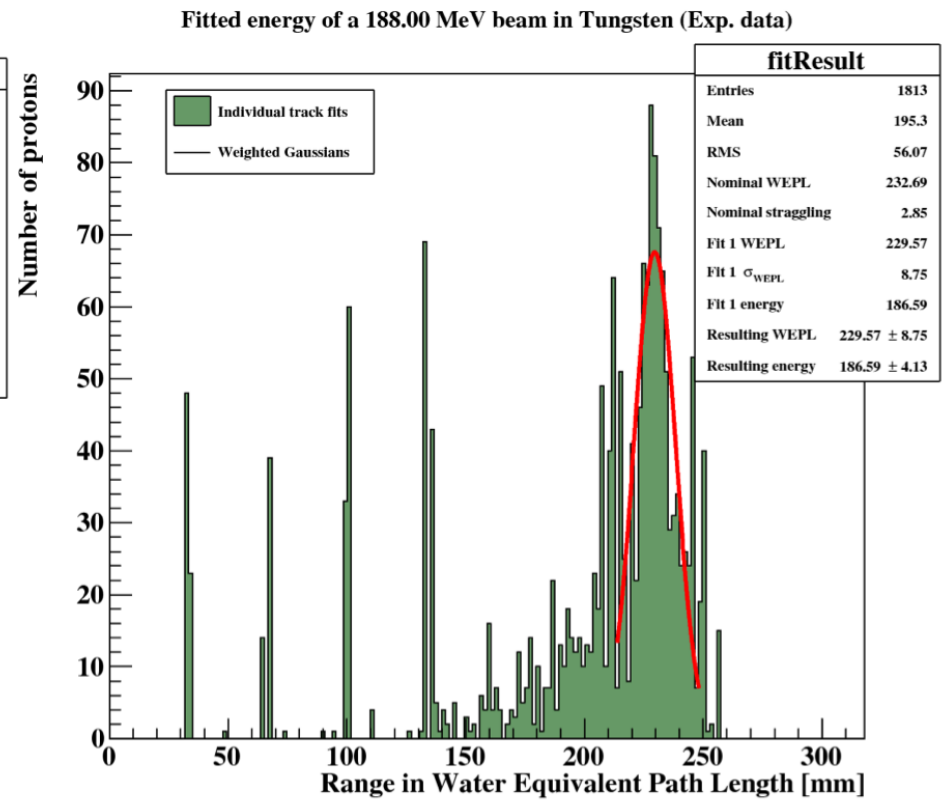
* Bortfeld, T. *An Analytical approximation to the Bragg curve for therapeutic proton beams.* Med. Phys 24 2024-33 (1997)

Digital tracking calorimeter – rangemeter (V)

- **Energy/range resolution for 188 MeV protons**

H. Pettersen





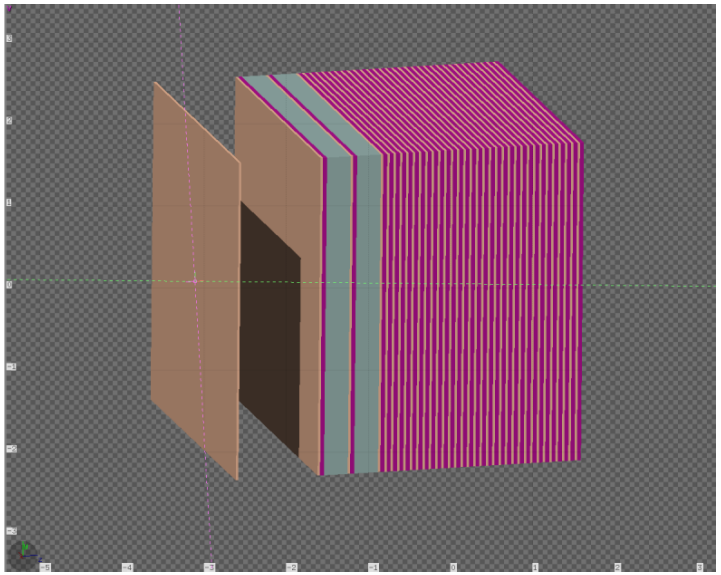
Towards a clinical prototype – Bergen pCT Collaboration

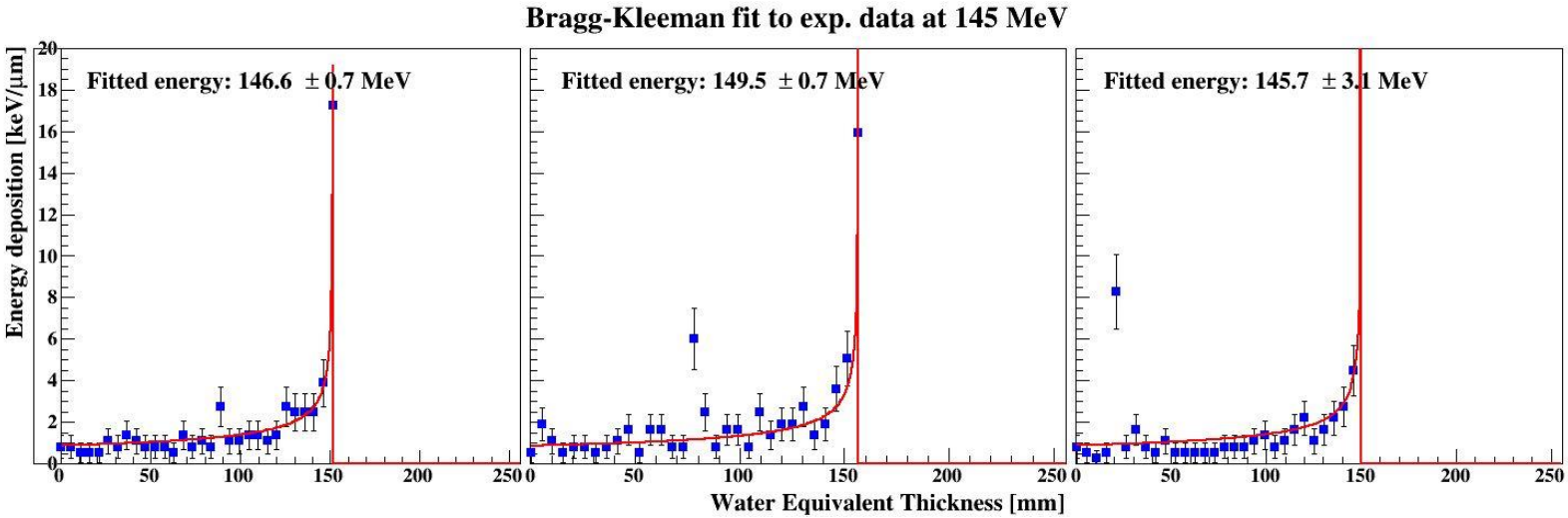
- **Organisation**
  - UiB, HiB, HUS
  - International collaboration
    - Utrecht
    - …
  - Joining forces with another pCT project (Padova - Piero Giubilato, ERC grant iMPACT - 1.8 MEUR) – under discussion
- **Financing**
  - Toppforsk (26 MNOK, 5 years)
  - BFS (18 MNOK, 4 years)
  - Helse Vest
- **Next steps**
  - Finishing the optimisation of the design
  - Production of ALPIDE chips

Towards a clinical prototype (I)

Optimisation of the design

- geometry
- longitudinal segmentation
  - number of sensitive resp. absorber layers
- absorber
  - energy degrader, mechanical carrier, cooling medium
  - material choice: Al
  - thickness (2-4 mm)

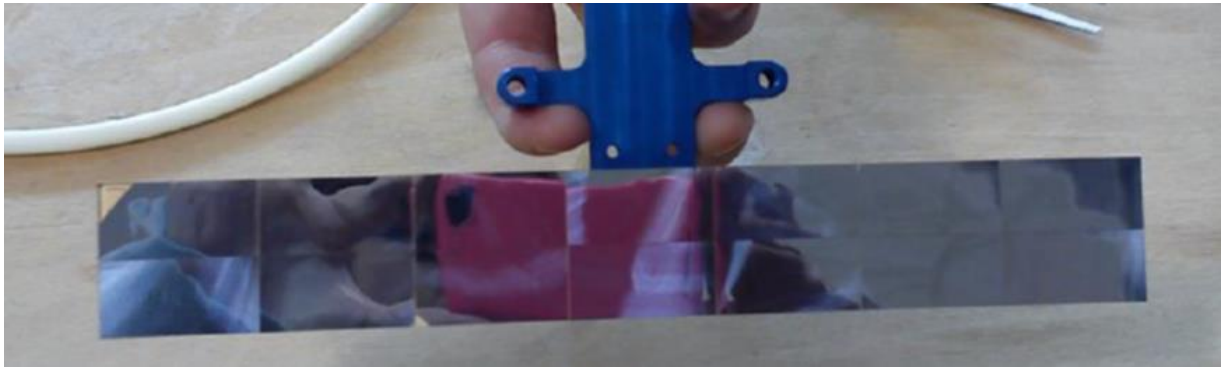




Towards a clinical prototype (II)

Optimisation of the design

- sensors – MAPS
  - ALPIDE chip
    - Design team: CCNU Wuhan, CERN Geneva, YONSEI Seoul, INFN Cagliari, INFN Torino, IPHC Strasbourg, IRFU Saclay, NIKHEF Amsterdam
    - sensor for the upgrade of the inner tracking system of the ALICE experiment at CERN
    - chip size ≈ 3x1.5 cm^2, pixel size ≈ 28 µm, integration time ≈ 4 µs
    - on-chip data reduction (priority encoding per double column)

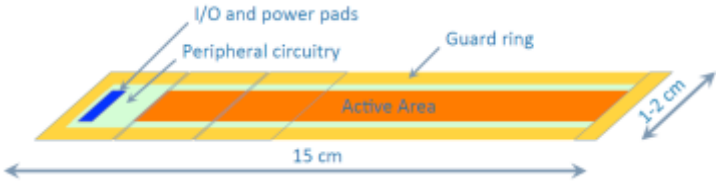


M. Magner, IFEE 2014

Towards a clinical prototype (III)

Strategy

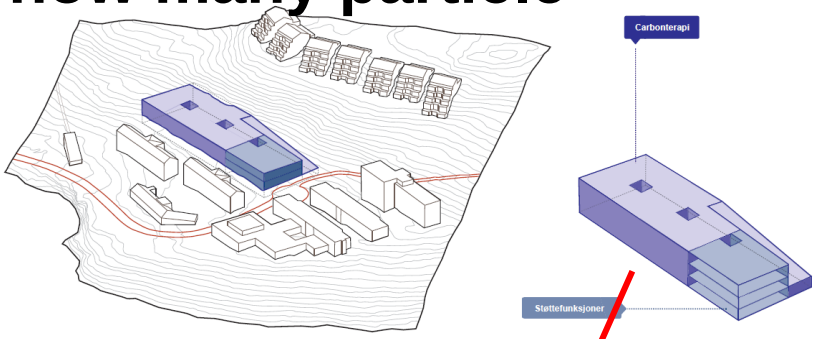
- **Modular structure – exchangeable front layers (tracking and absorber layers)**
- **Use the existing ALPIDE chips as sensitive layers**
- **R&D project to tailure ALPIDE design to medical applications**
  - **Faster charge collection and readout: 4 µs -> < 1 ns**
  - **Larger sensors - wafer-scale integration by stitching**



  - **Thinner sensors (in case of tracking station between nozzle and patient)**

Hadron therapy in Norway

Ongoing discussion in Norway on how many particle therapy facilities are to be build



What can we hope for in Bergen?

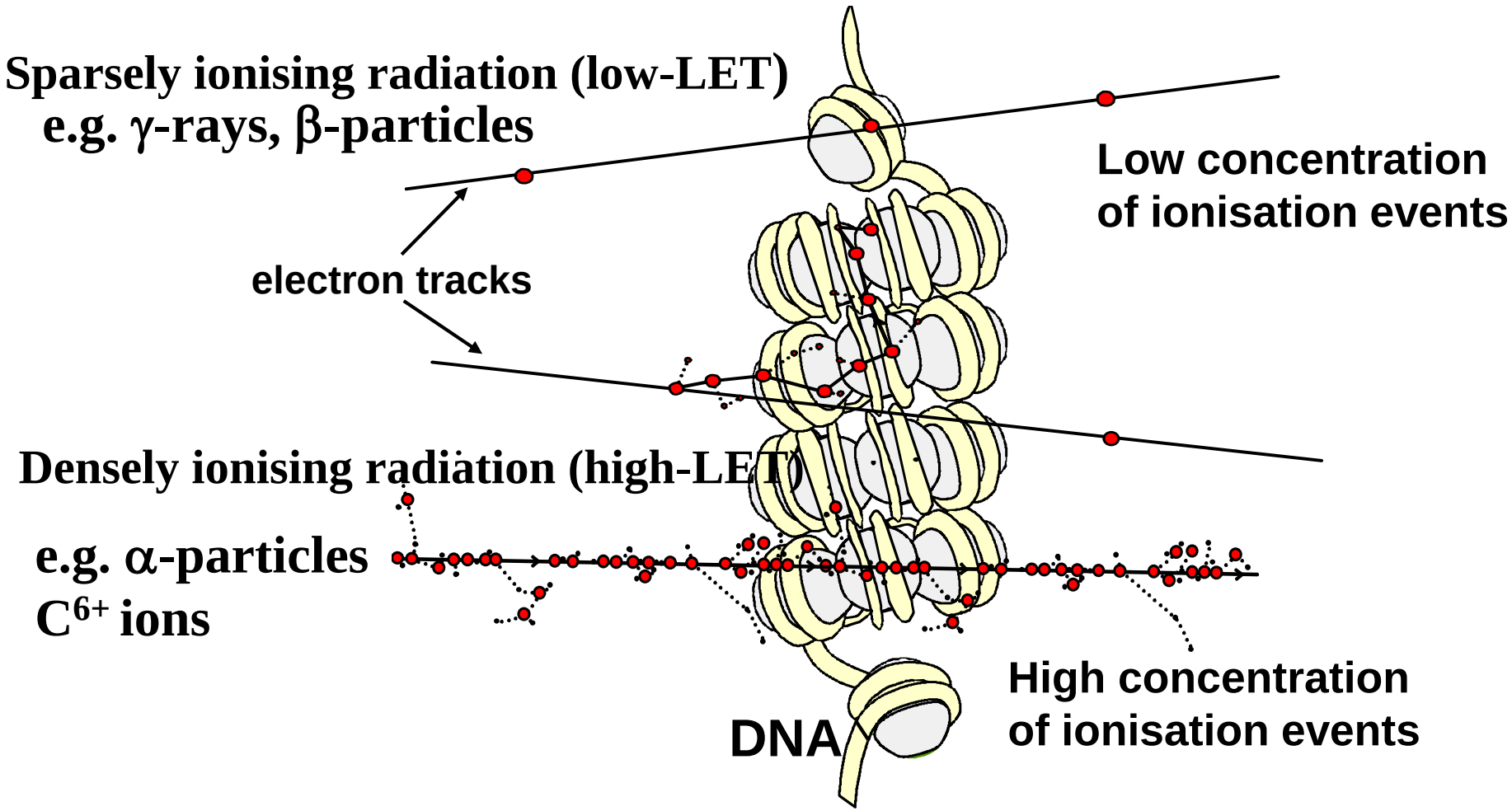
- **Combined proton and carbon facility**
- **State-of-the-art technology**
  - **fast scanning/repainting system**
  - **active energy modulation**
  - **beam gating system**
  - **several treatment rooms**
  - **superconducting gantry for carbon ions**

University Hospital

The End

Why carbon ions? (IV)

- **Radiation-induced DNA damage**

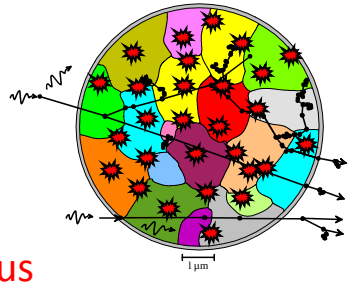


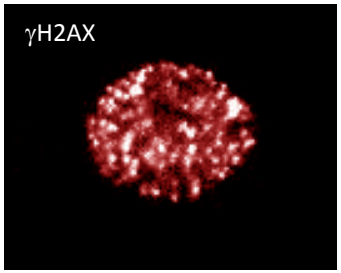
Why carbon ions? (V)

- **LET and RBE**

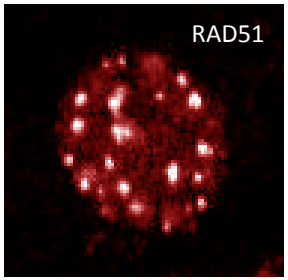
Low-LET (e.g. γ-rays)

1 Gy corresponds to:
~1000 electron tracks
~20-40 DSB
Relatively homogeneous



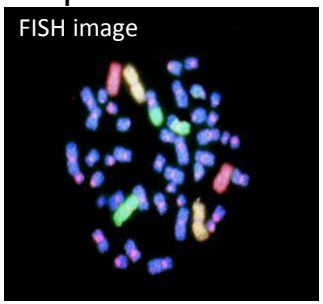


Induction of double strand breaks (DSB)



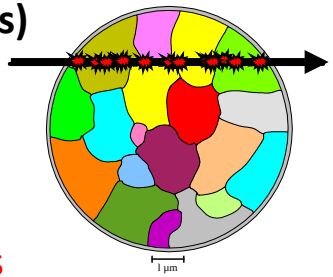
Repair

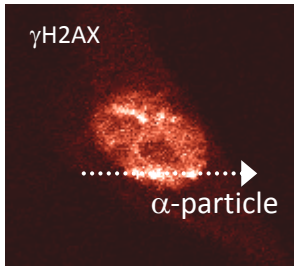
Simple aberrations

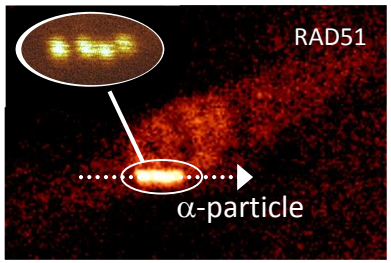


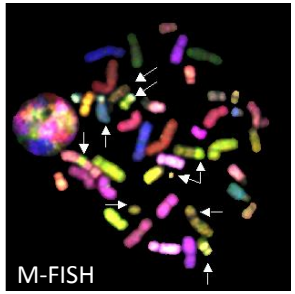
High-LET (e.g. α-particles)

1 Gy corresponds to:
~2 alpha tracks
~20-40 DSB
Very non-homogeneous





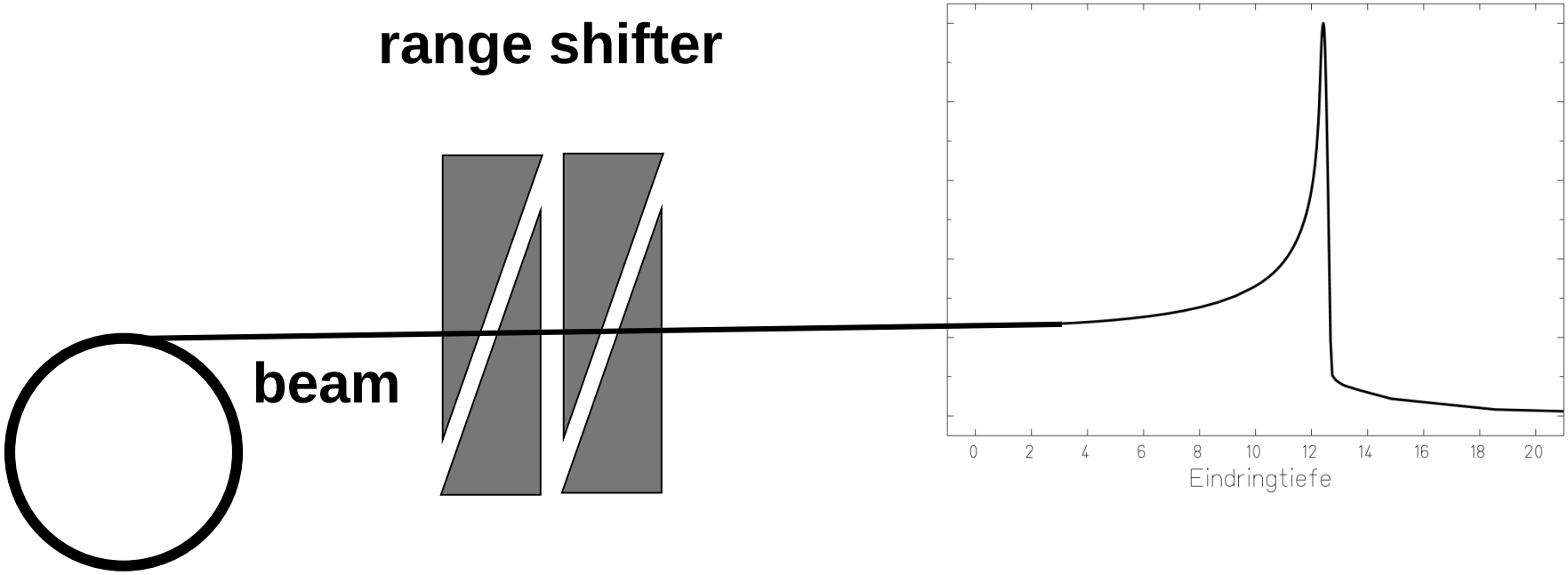




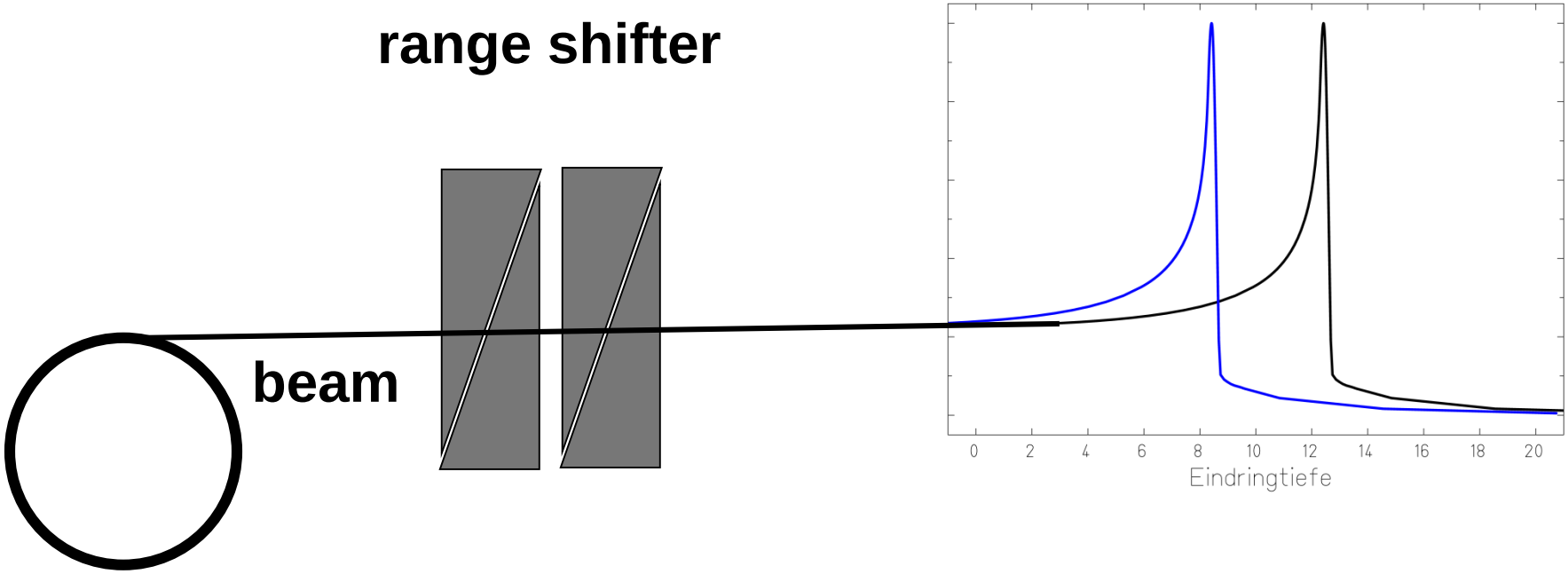
Complex aberrations

K. Peach, Heavy Ions in Science and Health workshop, Bergen, 2012

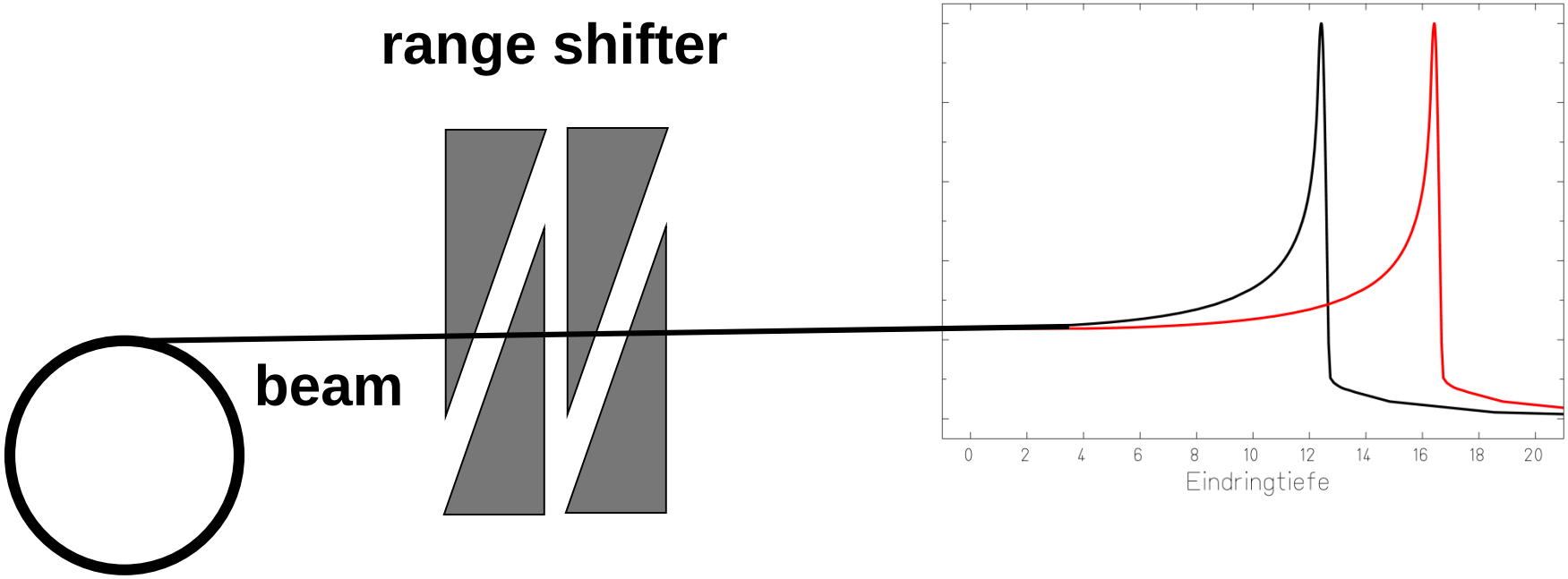
Range adaptation



Range adaptation



Range adaptation



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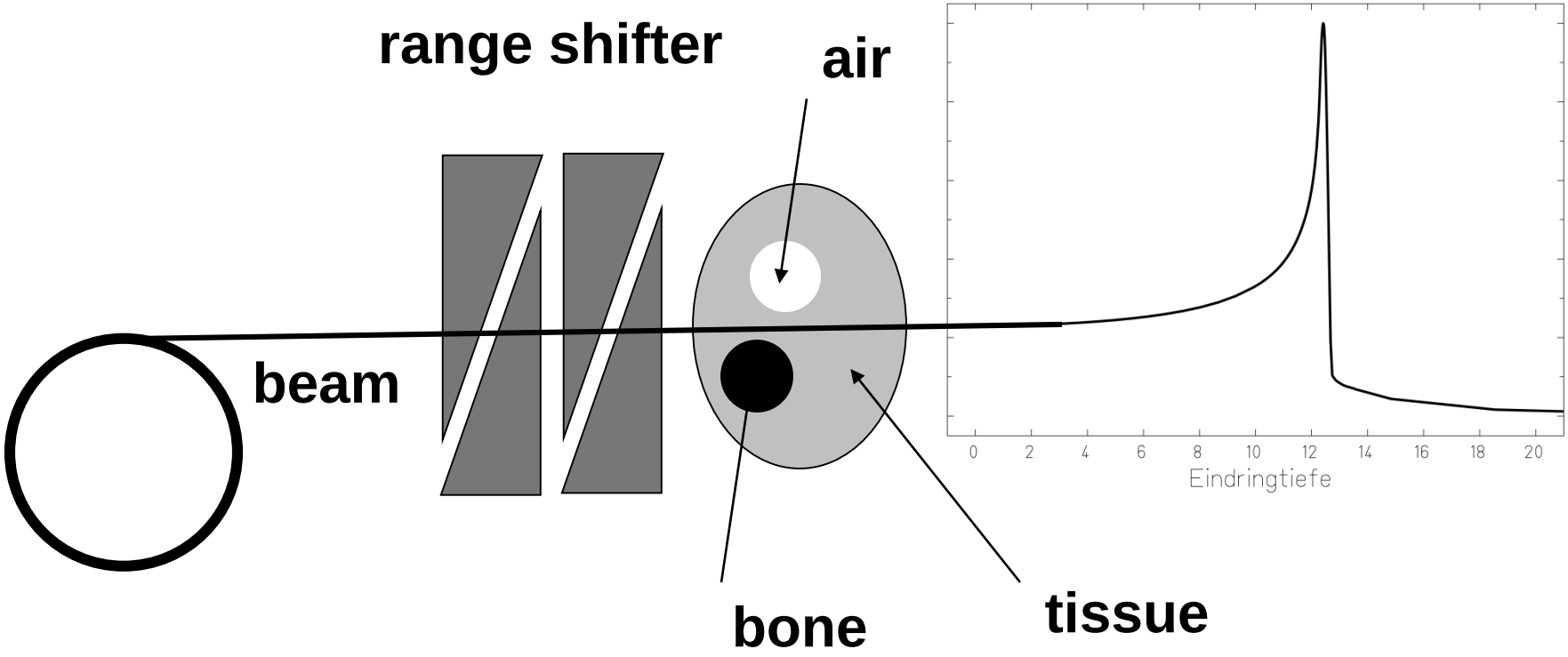

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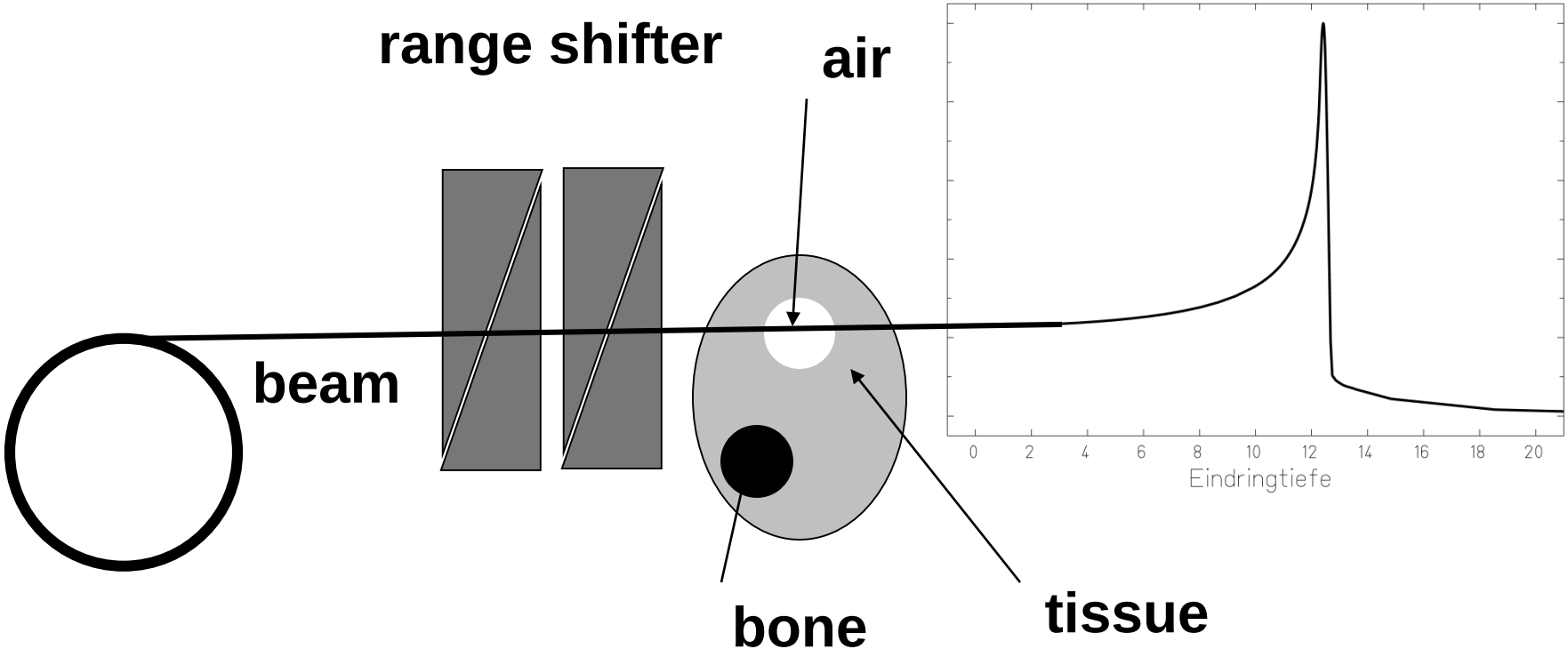
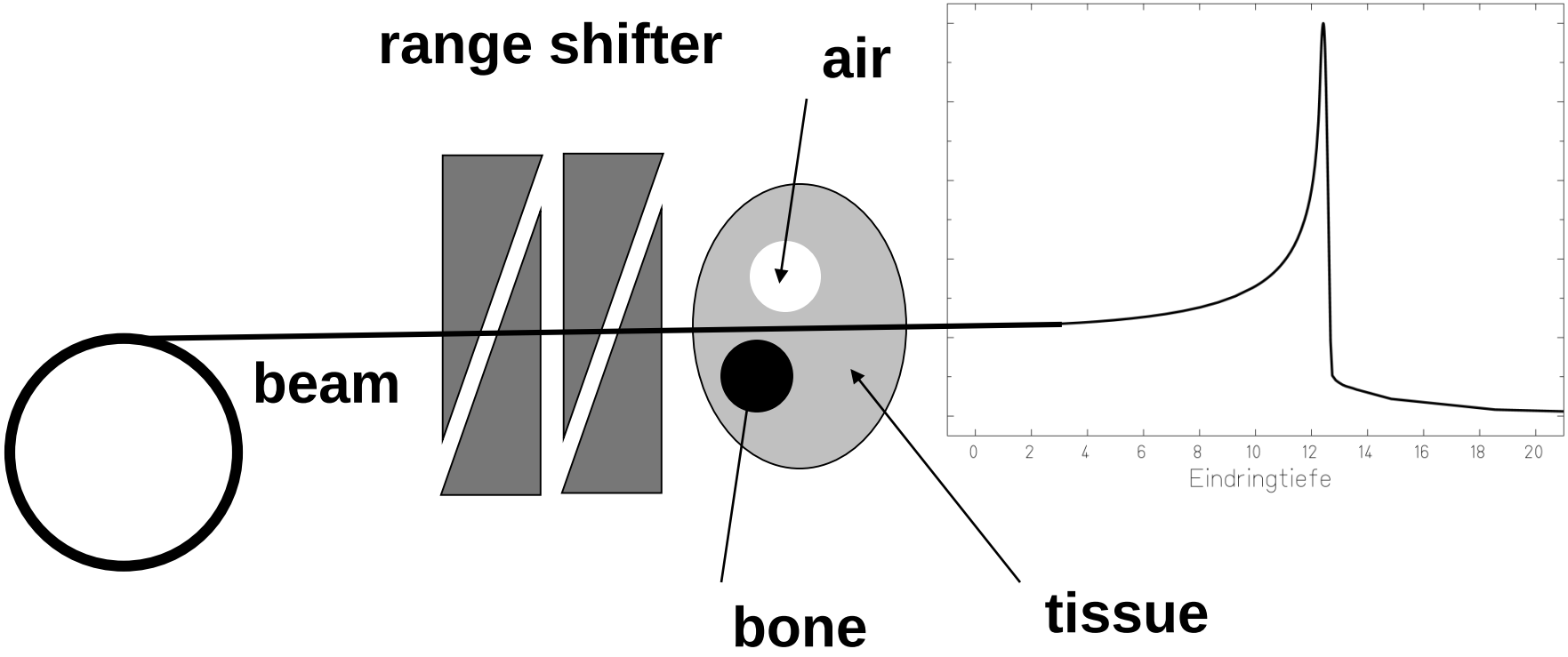
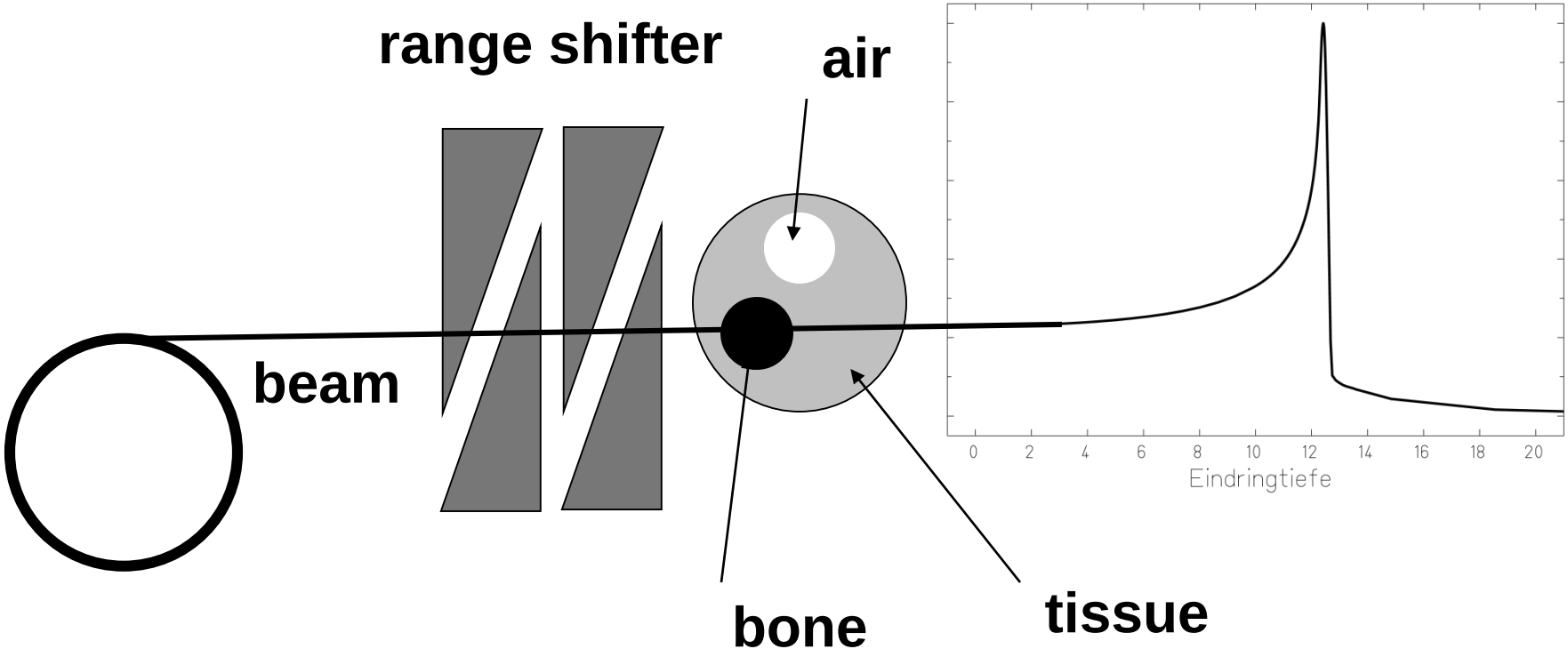


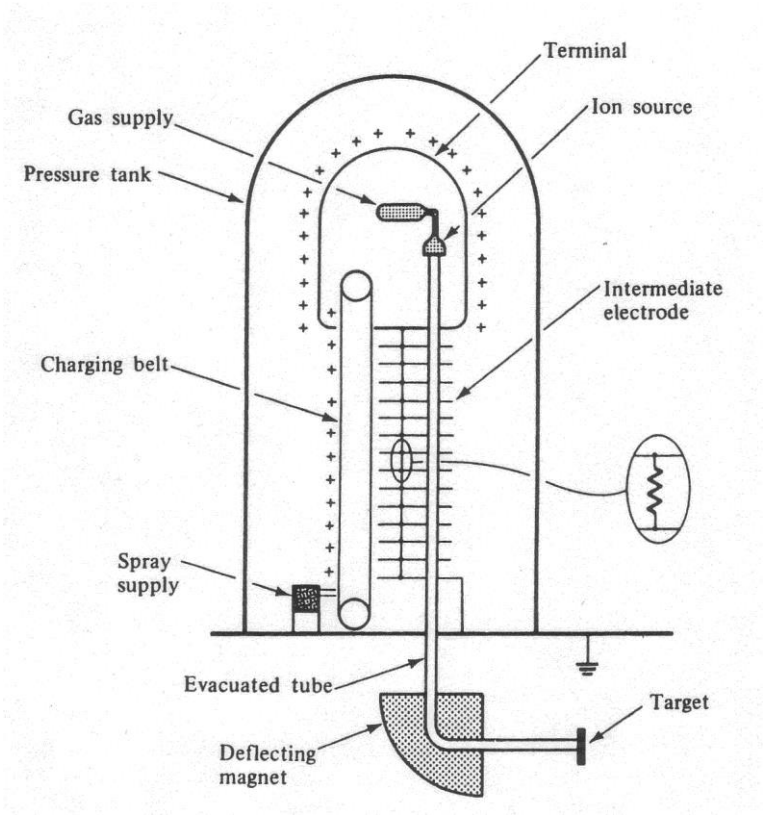
Range adaptation



Range adaptation

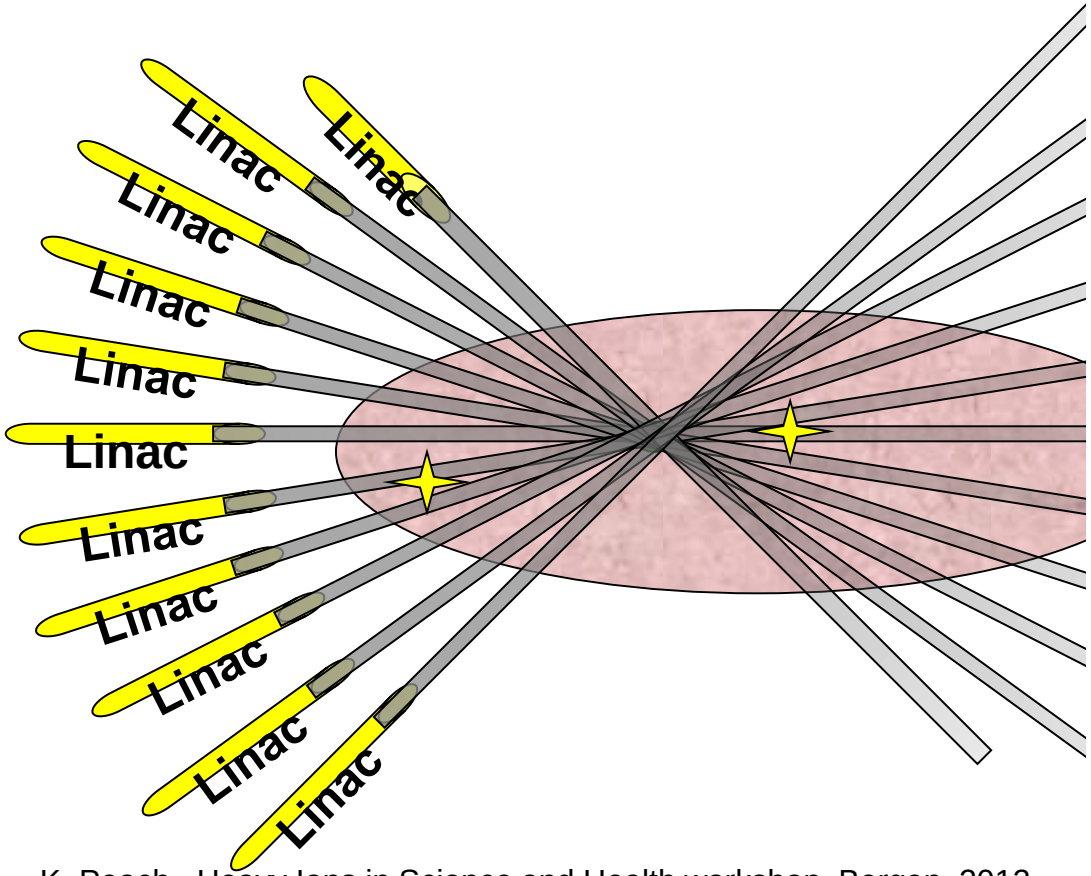


Example of Electrostatic Accelerator: Van de Graaf Accelerator



Radiotherapy with photons

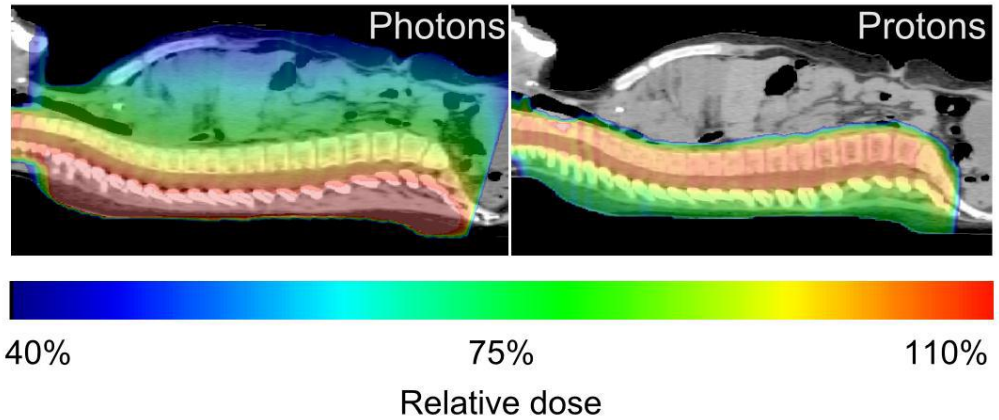
- **Curing cancer with multiple beams of MV X-rays**



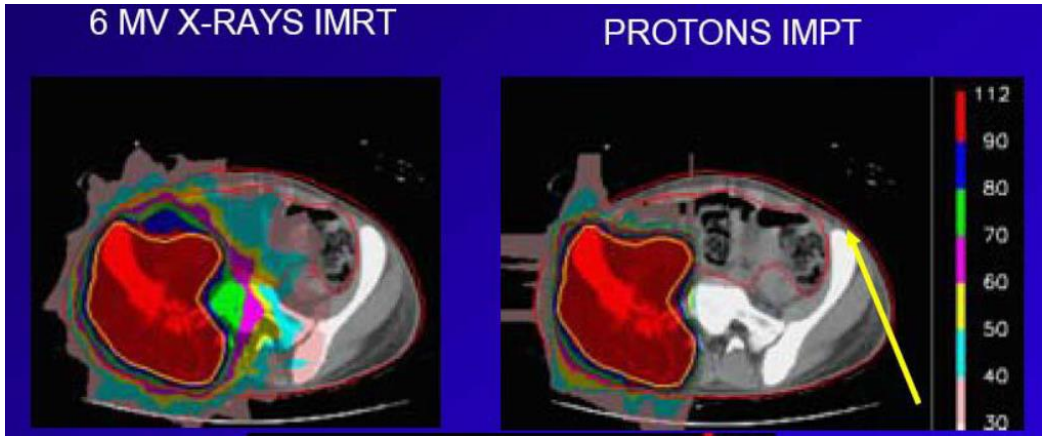
K. Peach, Heavy Ions in Science and Health workshop, Bergen, 2012

Radiotherapy – photons vs hadrons (II)

- **Treatment goal**
  - **Effective eradication of all tumor cells <-> avoid injury to healthy tissue**
- **Do we achieve the goal in the clinical routine?**
  - **Treatment plans for cancer in the central nervous system (Medulloblastoma)**



  - **Dose distribution Ewing's Sarcoma**



K. Ytre-Hauge, PhD, Bergen, 2013
C. Stokkevåg, PhD, Bergen
S. Kvinnsland, Heavy Ions in Science and Health workshop, Bergen, 2012

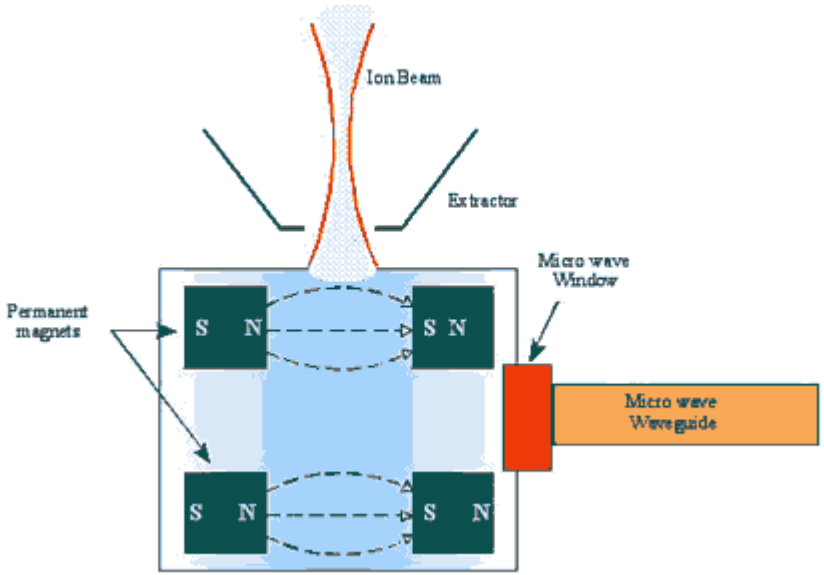
Accelerator complex – ion source

- **Electron Cyclotron Resonance (ECR) source**
  - **gas inside static B-field**
  - **inject RF-field with cyclotron frequency**

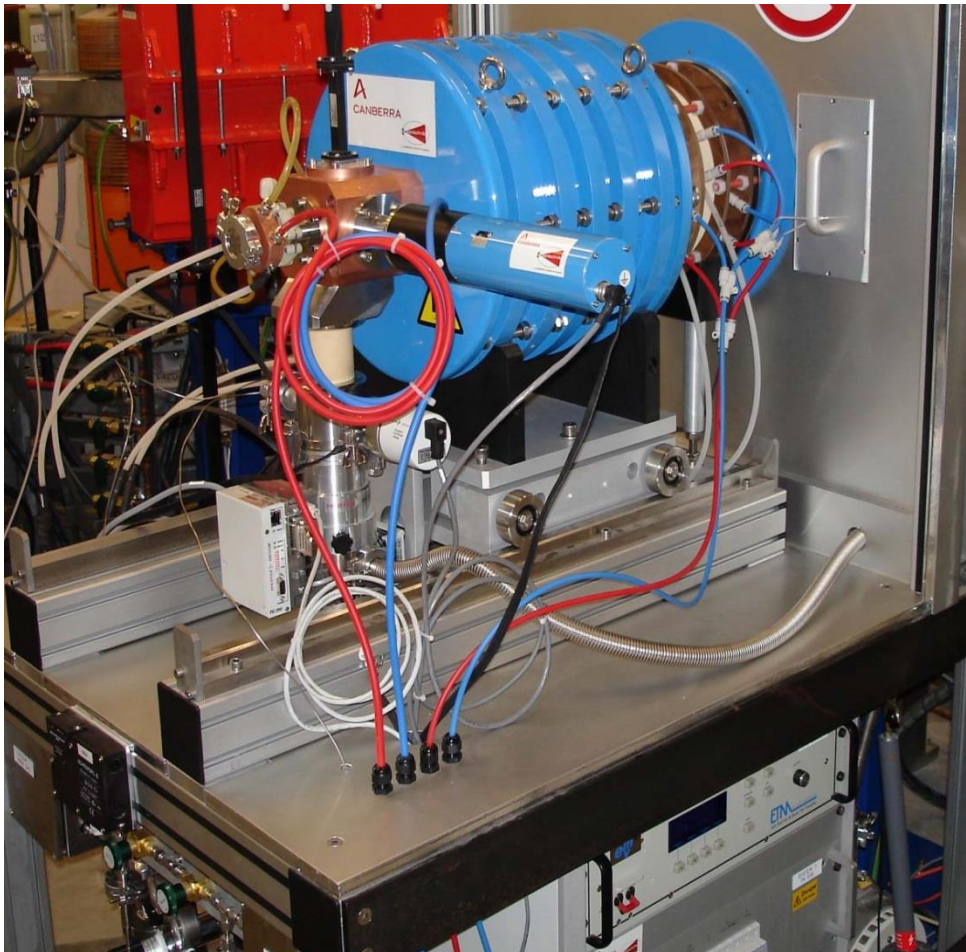
  → accelerate electrons

  → ionize atoms by electron impact

  → trap plasma in sophisticated magnetic field configuration

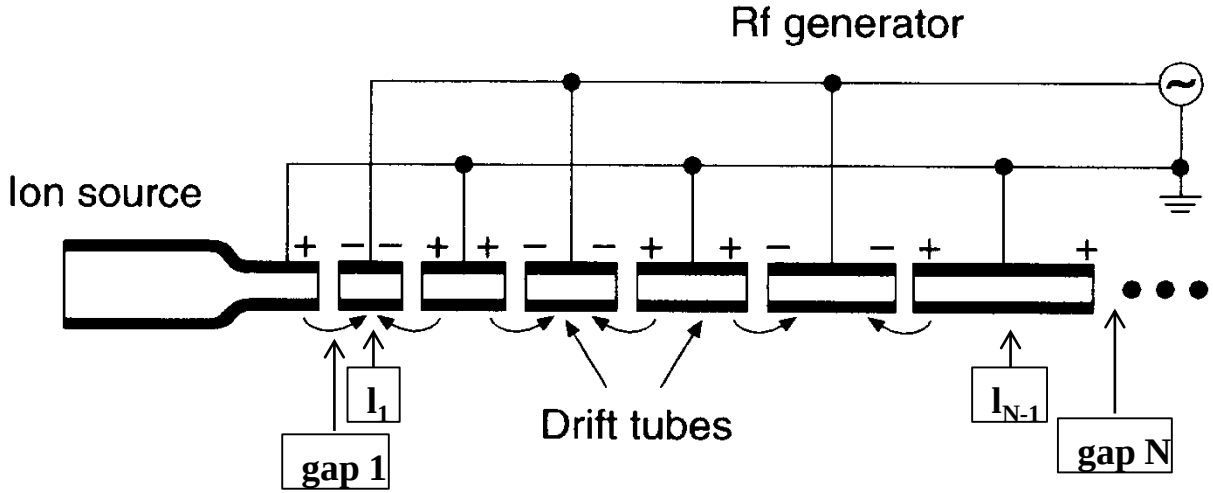


HIT



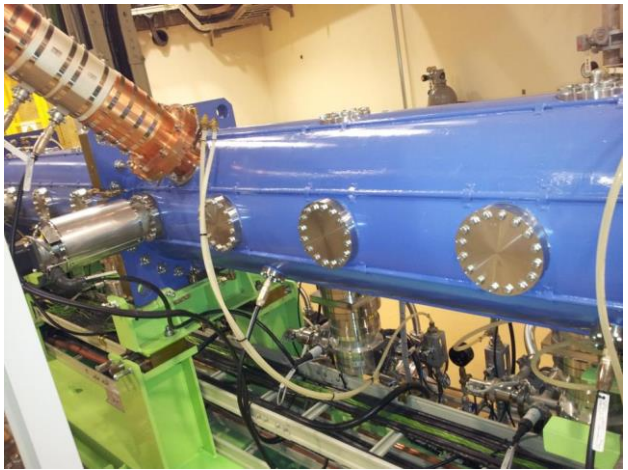
Accelerator complex - LINACS

- **Drift tube linac – Widerøe**
  - **Energy gain: $\Delta E = e \cdot N_{gap} \cdot V_{RF}$**
  - **Period length increases with velocity $l = v/2 \cdot f$**
  - **RF phase changes by 180° while the particles travel inside the tubes, i.e. while the electric fields point in the "wrong direction" the particles are shielded by the drift tubes**



  - **higher frequencies (> 10 MHz) were not practical, because then the drift tubes would act more like antennas**
  - **when using low frequencies, the length of the drift tubes becomes prohibitive for high-energy protons, e.g. 3 m at 20 MeV**

Accelerator complex – synchrotron



Accelerator complex – extraction

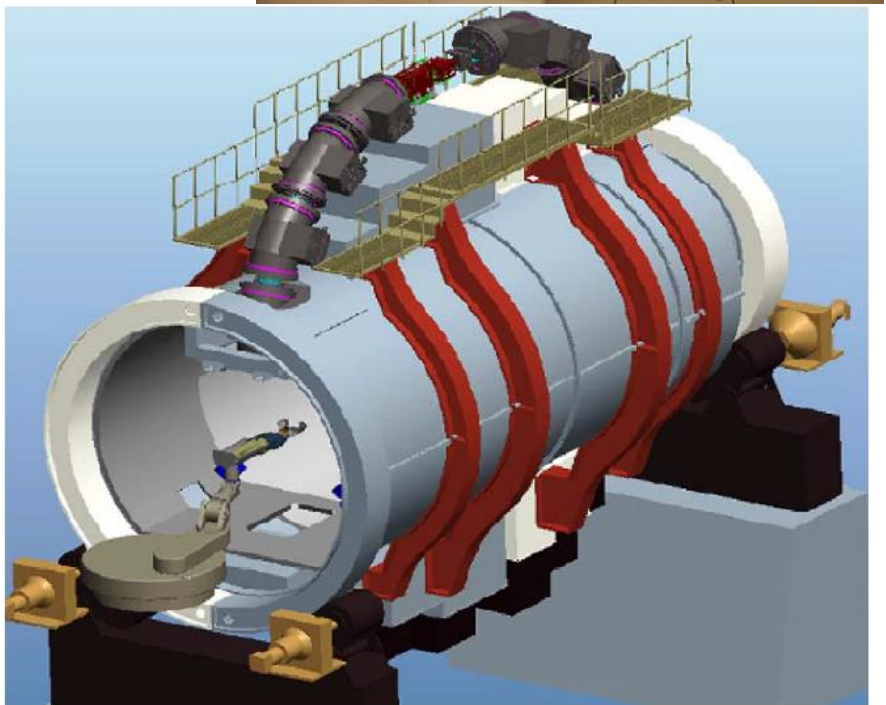
- **Extraction**
  - **stable beam spot and position**
  - **extraction during ramping -**
    "energy scan", future option for tracking moving targets

Beam transport systems – beam lines

- **Dose delivery to treatment rooms**
  - **fixed beam lines: 0°, (45°), 90°**

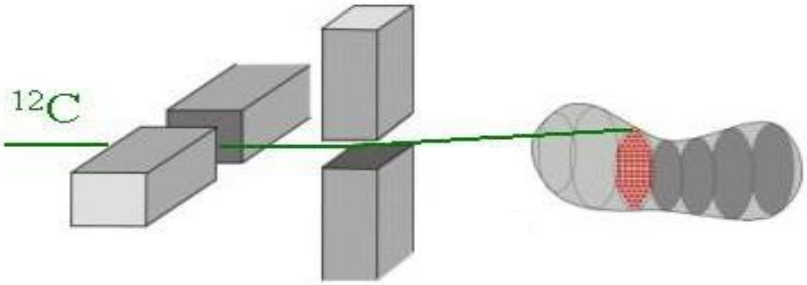
  - **movable beam line - superconducting gantry**

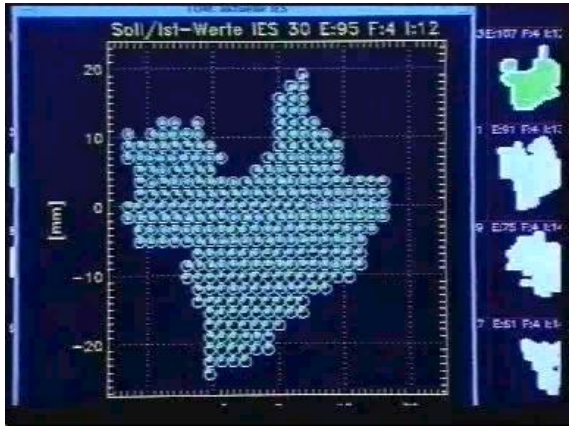
Rotating Gantry	
Ion species	^{12}C
Irradiation meth.	Scanning
Beam energy	430 MeV/n (max.)
Max. Field	18×18 cm^2
Magnet	Superconducting Combined function
Num. of magnets	10
Magnetic field	2.4 ~ 2.9 T
Gantry radius	5.5 m
Gantry weight	~200 t



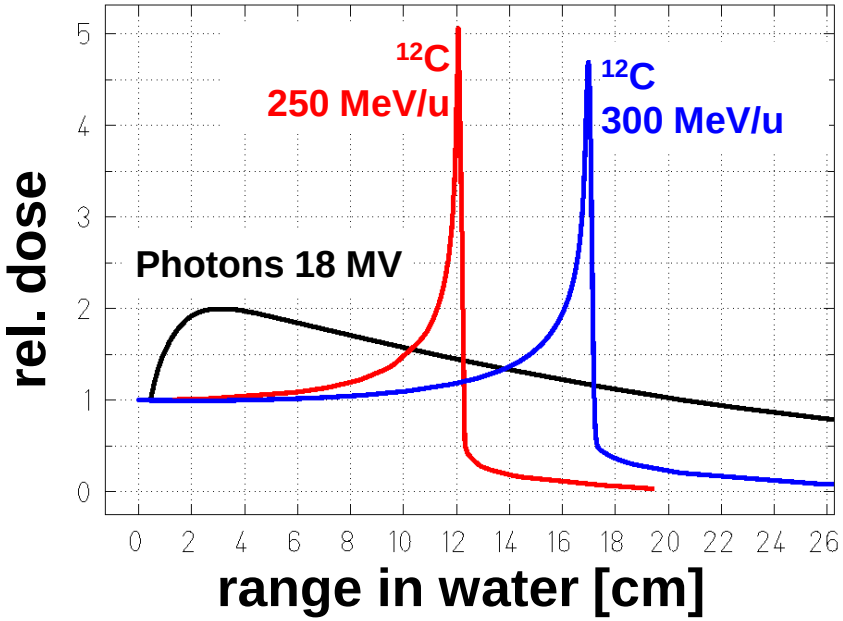
Beam delivery systems – scanning pencil beam

- **Raster scan method – scanning system**
  - **Deflection (x,y) of focused ion beams in fast dipole magnets**





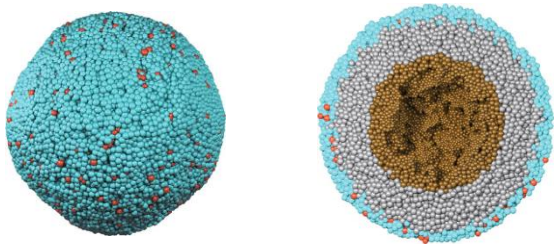
  - **Variation of the energy, focus and intensity in the accelerator complex and beam lines**



Haberer et al., NIM A , 1993

What remains to be done?

- **Improve treatment of moving targets**
  - **Current method: gating**
  - **Future: active beam tracking**
- **Improve treatment planning**
- **Improve online verification of dose delivery**
- **Improve understanding of RBE**
- **Improve modeling the dynamics of tumor growth after irradiation**

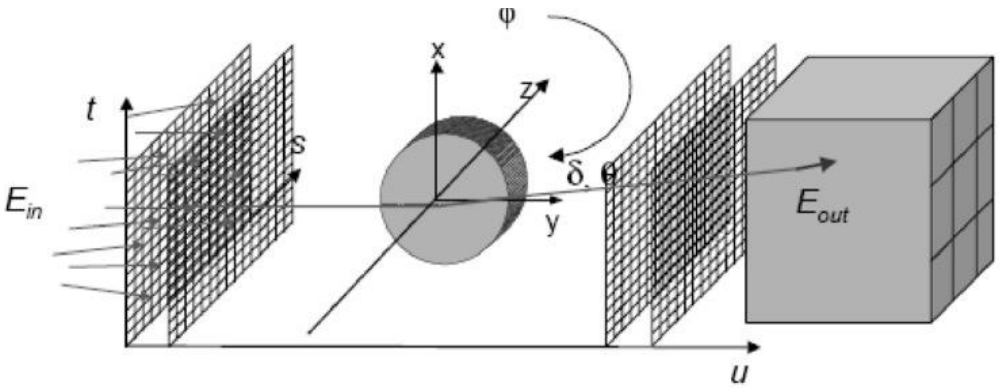


- **…**

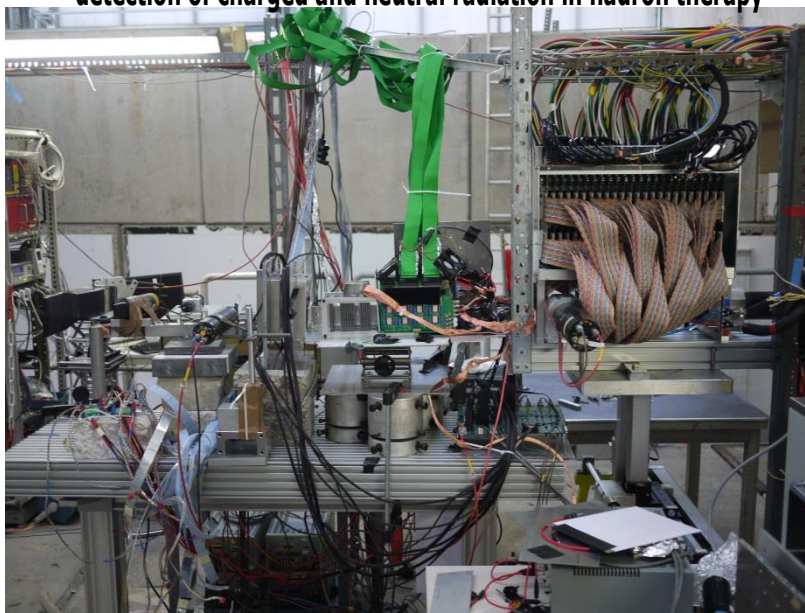
Verification of dose delivery (II)

- **Quasi-online dose verification**
  - **proton-CT**
    - **high energetic proton beam (800 MeV) quasi simultaneously with therapeutic beam**
    - **Measurement of scattered protons: position (->multiple scattering) and energy (-> energy loss dE/dx)**
    - **3D map of electron density in target -> online verification of dose plan**

the principle and the prototype (UiB, Utrecht)



Extremely high-granularity digital tracking calorimeter for the detection of charged and neutral radiation in hadron therapy



Clinical studies at NIRS

1) C-ion RT is successful in the not treatable by other means(radio-resistant tumors)

- Advanced Head & Neck cancers (non-SCC)
- Large skull base cancers
- Post-op recurrent rectal cancer
- Inoperable sarcoma
- Re-irradiation after photon radiotherapy

16 fractions in 4 weeks

2) Promising results are obtained in C-ion hypo-fractionated RT(common cancers)

- Lung cancer (Single irradiation)
- Liver cancer (Single & Two fractions)
- Pancreatic cancer (8~12 fractions)
- High risk prostate cancer (12~16 fractions)

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013

Clinical results (NIRS) – skull base chordoma (I)

Pre-treatment

Dose distribution

67 months later

T. Kamada, Carbon Ion Radiotherapy at NIRS, Chiba, 2013

Clinical results (NIRS) – skull base chordoma (II)

Clinical characteristics of the reported cases of skull base chordoma

	Authors	N	Median dose	Median f/u (y)	Local control rate (%)		
					3-y	5-y	10-y
Photon	Catton et al . 1996	24	50	5.2		23	15
	Romero et al. 1993	18	50	3.1		17	
	Forsyth et al. 1993	39	50	8.3		39	31
	Magrini et al. 1992	12	58	6		25	25
Proton (+/- photon)	Munzenrider et al. (MGH) 1999	169	66-83	3.4		73	54
	Noel et al. (CPO) 2003	100	67	2.6	86 (2y)	54 (4y)	
	Igaki et al. (Tsukuba) 2004	13	72	5.8	67	46	
	Ares et al. (PSI) 2009	42	73.5	3.2 (mean)		81	
Helium	Castro et al. (LB) 1994	53	65	4.3		63	
Carbon	Shults-Ertner et al. (GSI) 2007	96	60	2.6 (mean)	81	70	
	Present study	44	60.8	4.8	91	88	79

Norwegian prospects (I)

Protokoll frå føretaksmøte Helse Vest RHF

27. september 2013

Føretaksmøtet la til grunn at alternativet med etablering av mindre, regionale protonanlegg er eit godt alternativ for raskt å kunne tilby protonbehandling i Noreg og på lengre sikt mogeleg etablering av eit felles karbonanlegg i Noreg.

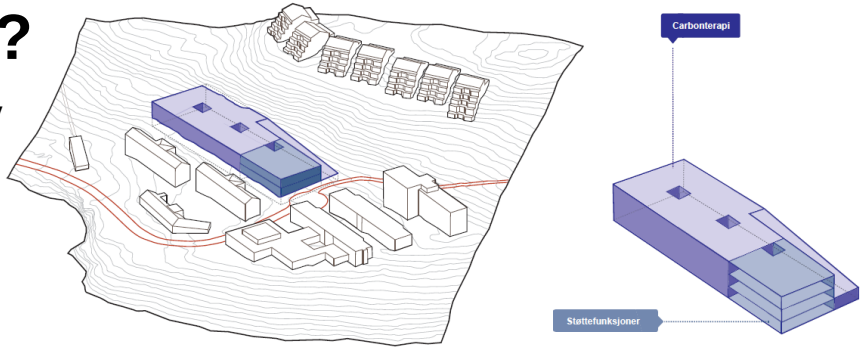
Føretaksmøte vedtok:

Føretaksmøtet ber dei regionale helseføretaka i fellesskap gjennomføre idéfase for etablering av regionale protonsenter lokalisert i Oslo, Bergen, Trondheim og Tromsø. Føretaksmøtet ber Helse Vest lede arbeidet med bidrag frå dei andre regionale helseføretaka. Frist for oppdraget vert sett til 1.desember 2014.

Norwegian prospects (II)

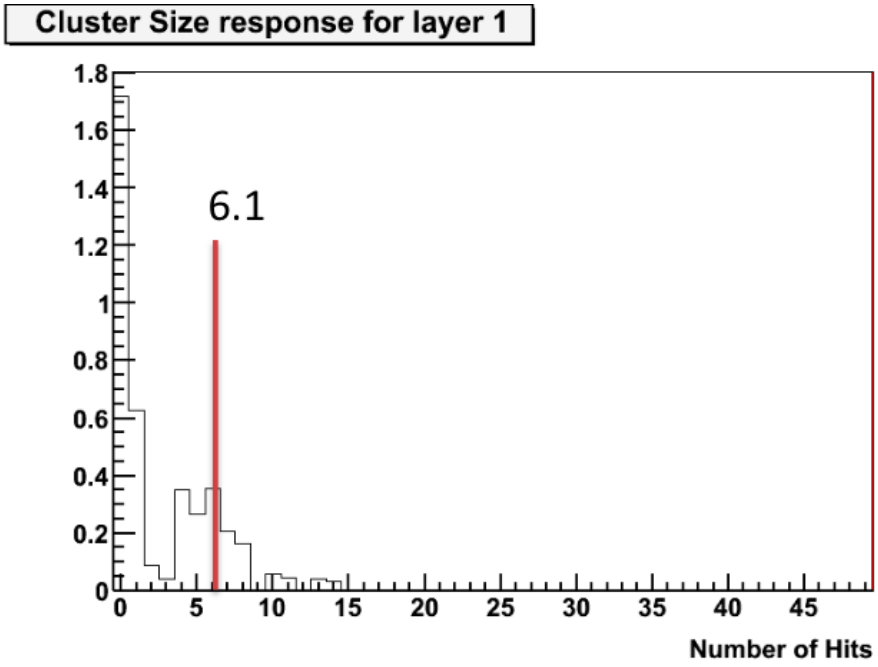
What can we hope for in Bergen?

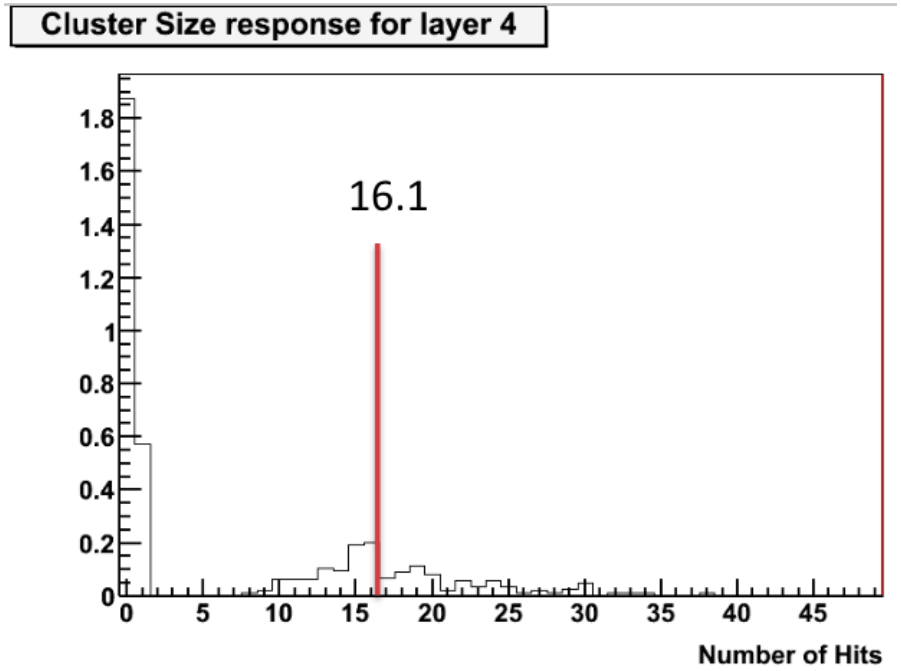
- Combined proton and carbon facility
- State-of-the-art technology
  - fast scanning/repainting system
  - active energy modulation
  - beam gating system
  - several treatment rooms
  - superconducting gantry for carbon ions



Digital tracking calorimeter – rangemeter (IV)

- **Validation of sensor simulation**
  - **Cluster sizes vs energy deposition - cluster sizes are larger than expected**





Digital tracking calorimeter – rangemeter (V)

- **Mean cluster size vs layer (range) for different beam energies**
  - **clear Bragg peak**
  - **170 MeV:**
    Bragg peak close to sensitive layer 5
  - **180 MeV:**
    Bragg peak located inside absorber
  - **190 MeV:**
    Bragg peak located between sensitive layer 6 and 7

-> to be compared with MC