Relativistic Ion Beams for Treating Human Cancer

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Outline of the Presentation

Ion-Beam Therapy

- Rationale and History
  - Berkeley Lab legacy
- Clinical Requirements
  - Technical Specifications
- Current Status of Ion-Beam Therapy Facilities
- Future Perspectives

Next Presentation

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    - **Berkeley Lab legacy**
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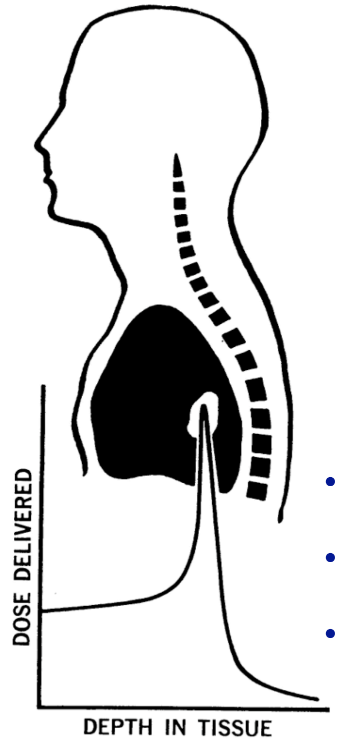
R.R. Wilson and Particle-Beam Therapy



- Dose localization
- Low entrance dose
- No or low exit dose

1946: Robert Wilson proposed the use of Bragg Peak for radiation therapy*

* RR Wilson, Radiology, **47**: 487-491 (1946).

The Wilson's Seminal 1946 Article

R.R. Wilson, "Foreword to the Second International Symposium on Hadrontherapy," in Advances in Hadrontherapy, (U. Amaldi, B. Larsson, Y. Lemoigne, Y., Eds.), Excerpta Medica, Elsevier, International Congress Series **1144**: ix-xiii (1997).

Radiological Use of Fast Protons

ROBERT R. WILSON
Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly, used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in ...e part, been due to the very short ...ation in tissue of protons, deut... particles from prese... ...r-energy mach... ... how...

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate inten...ly a strictly localized region ... but little

Radiology 47: 487-491, 1946

The Beginning of Particle Beam Therapy

184” Synchrocyclotron

- 1948- Biology experiments using protons
- 1955- Human exposure to accelerated protons and alphas
- 1956 - 1986: Clinical Trials– 1500 patients treated

Cornelius A. Tobias

CA Tobias, et al., *Cancer Res*. **18,** 121 (1958).
CA Tobias, et al., *Science* **174**, 1131-1134 (1973).
CA Tobias, “*Radiology* **108**, 145-158 (1973).

Bevatron at Berkeley

Bevatron construction (1949)

(l to r) Lloyd Smith, Ed McMillan, Ernest Lawrence, Ed Lofgren, Bill Brobeck, and Duane Shell.

Bevalac and Ion-Beam Therapy

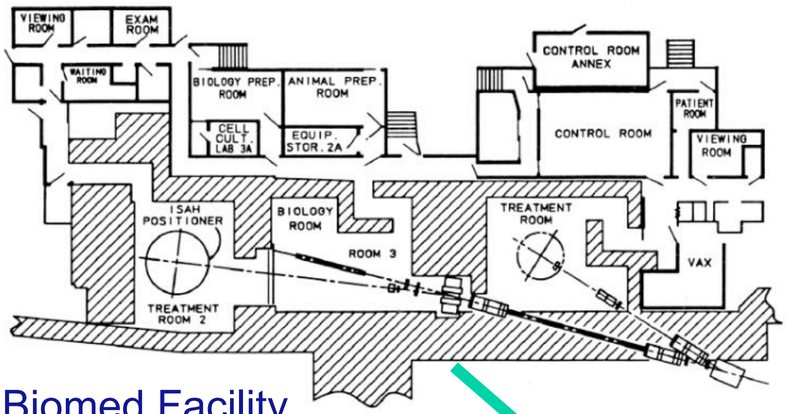
Harry Heckman, Ed McMillan, Cornelius Tobias, Tom Budinger, Ed Lofgren, Walt Hartsough (l. to r.)

Biomedical users advocated the Bevalac initiative.

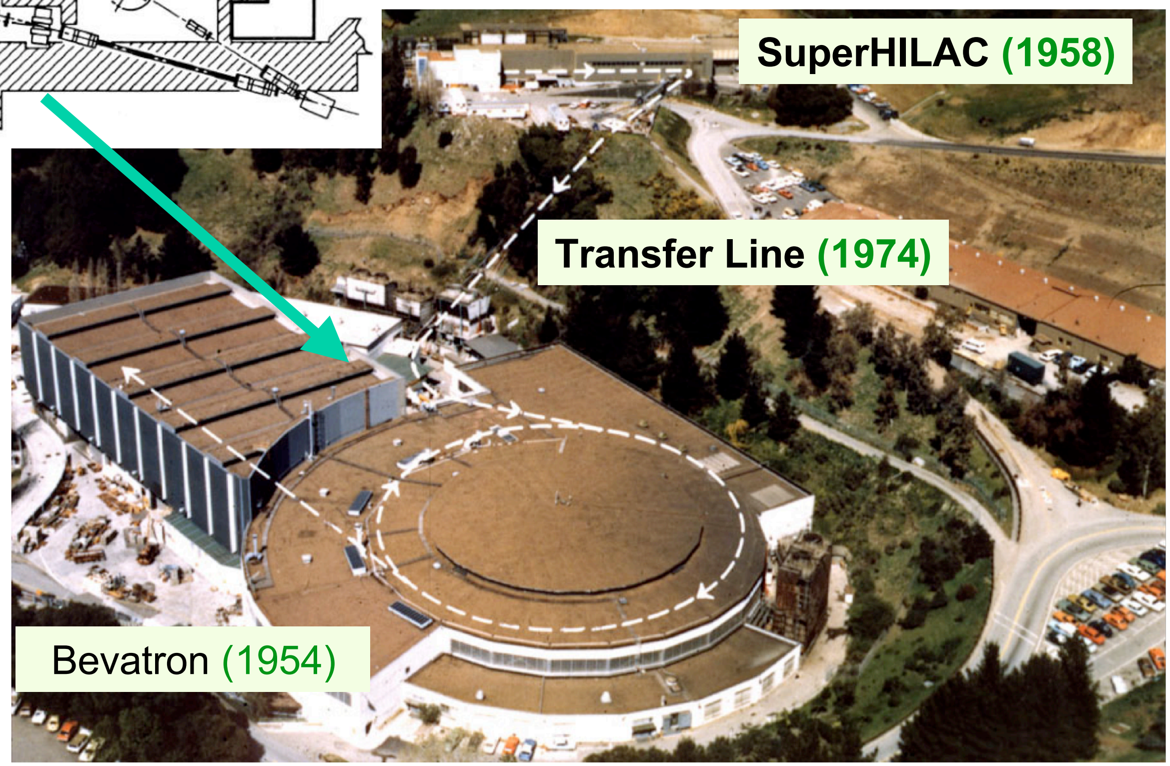
Press conference announcing the acceleration of heavy ions in the Bevatron (1971).

HA Grunder, WD Hartsough, EJ Lofgren, *Science* **174**, 1128-1129 (1971).

Clinical Research at the Bevalac



Biomed Facility



The Bevalac ceased operations in 1993.

Clinical Trials at LBNL, 1975–1992

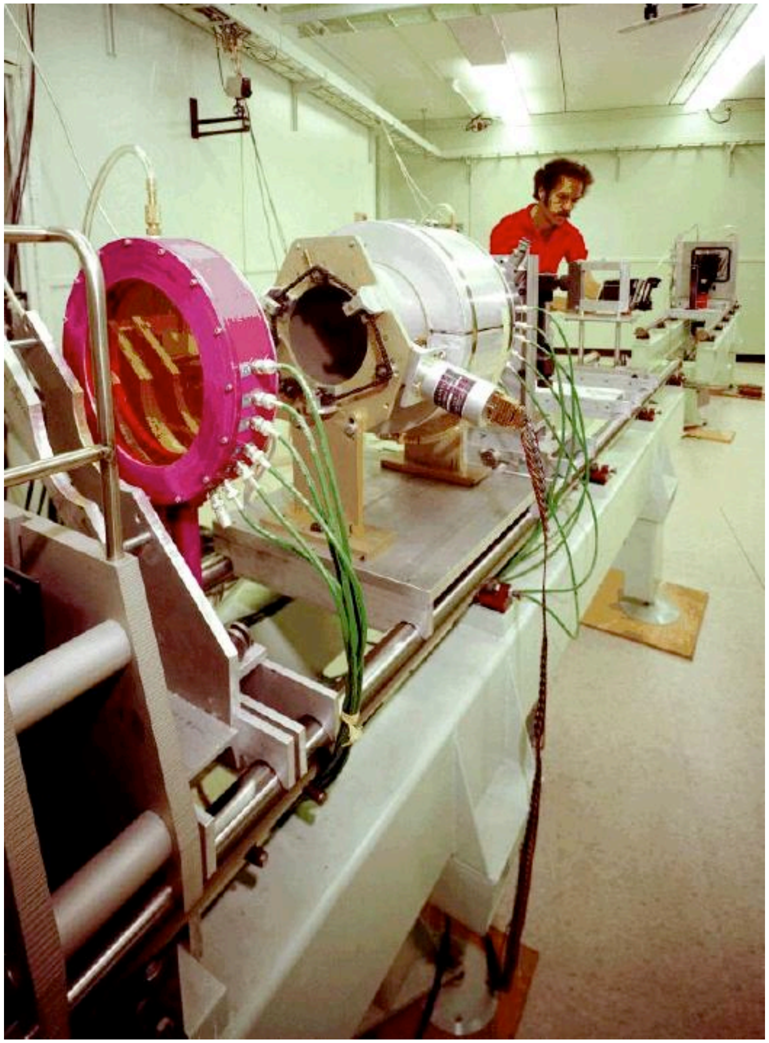
J.R. Castro, MD, UCSF, conducted the LBNL clinical trials.

1st He patient	6/75
1st C patient	5/77
1st Ne patient	11/77
1st Ar patient	3/79
1st Si patient	11/82

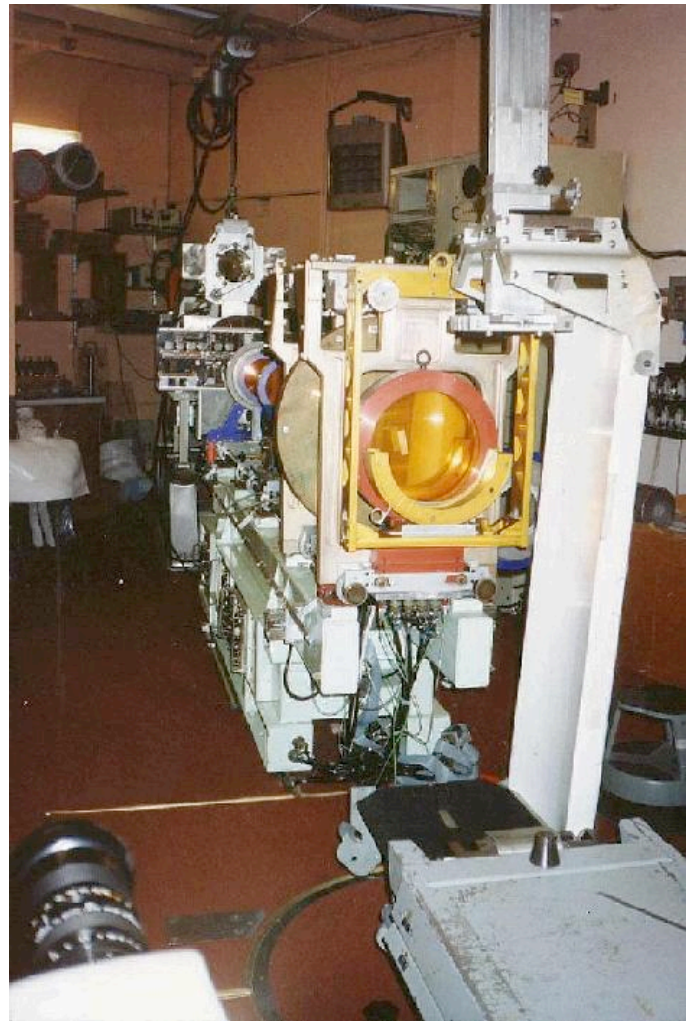
Total patient treated 1977–1992	1314
He patients	858
Heavier ions	456

Ion-Beam Treatment Facility at Bevalac

1975



1990



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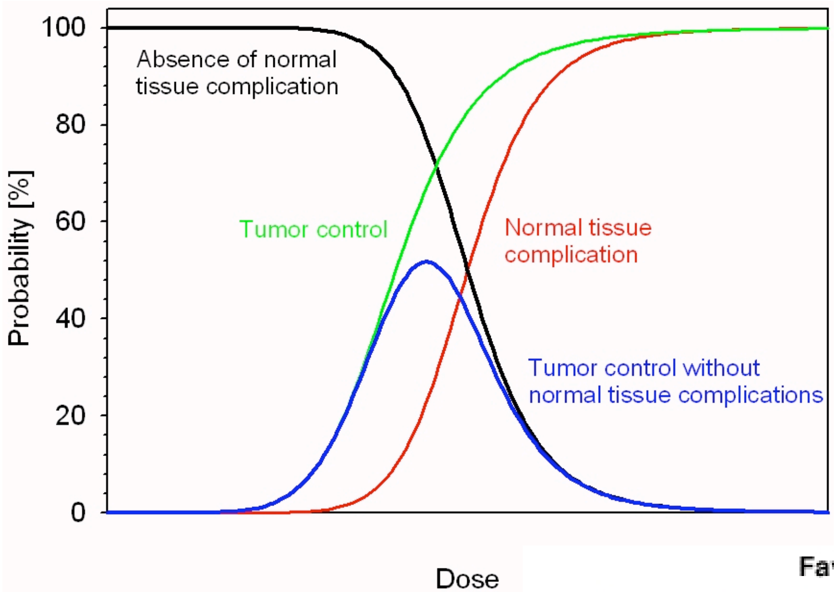
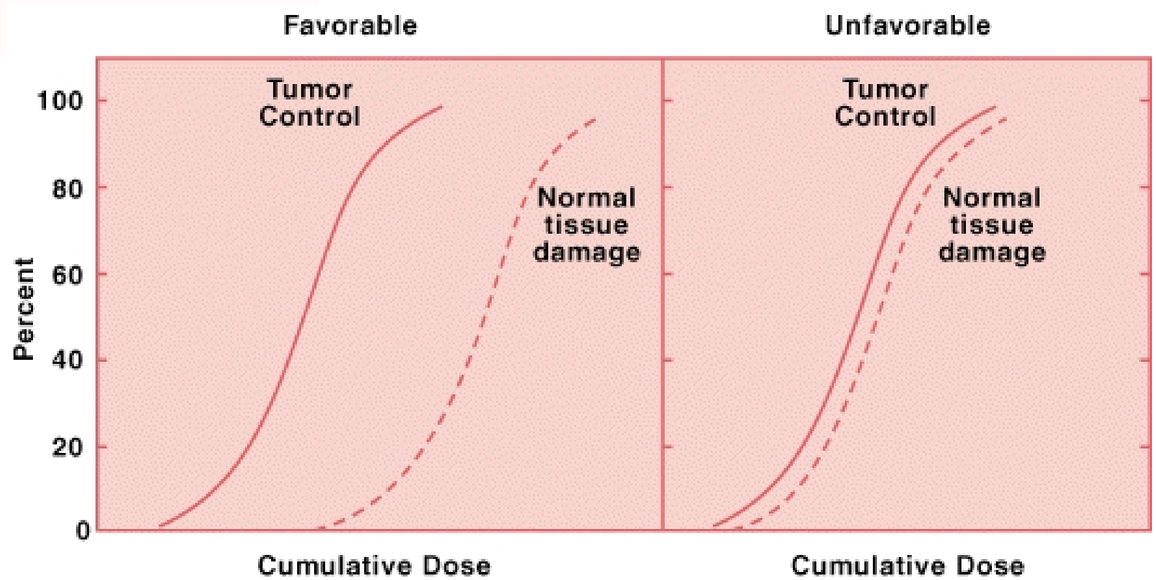
TCP, NTCP, Tumor Control without Normal Tissue Complication



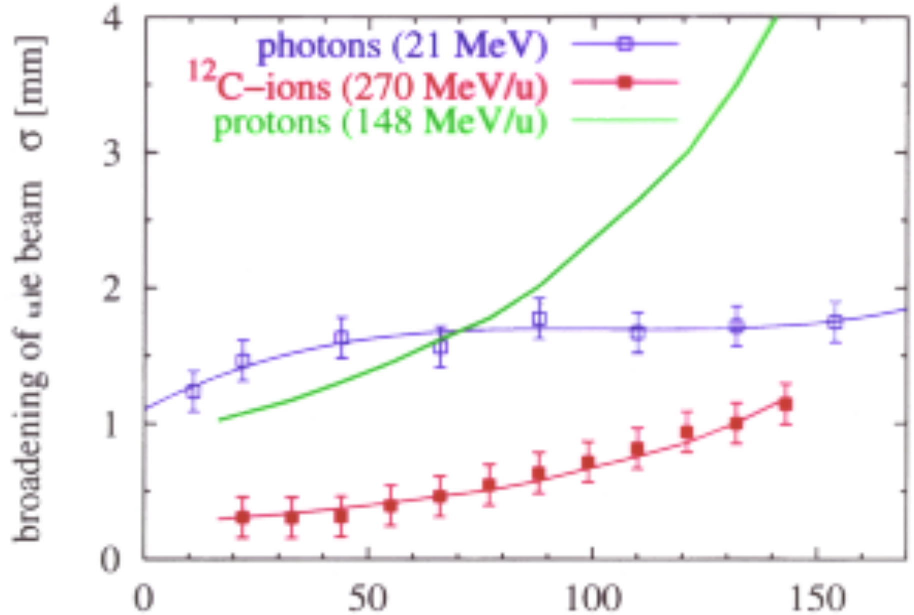
Desirable radiation

- Sharp penumbra
- High ionization density inside the Target
- TCP and NTCP far apart

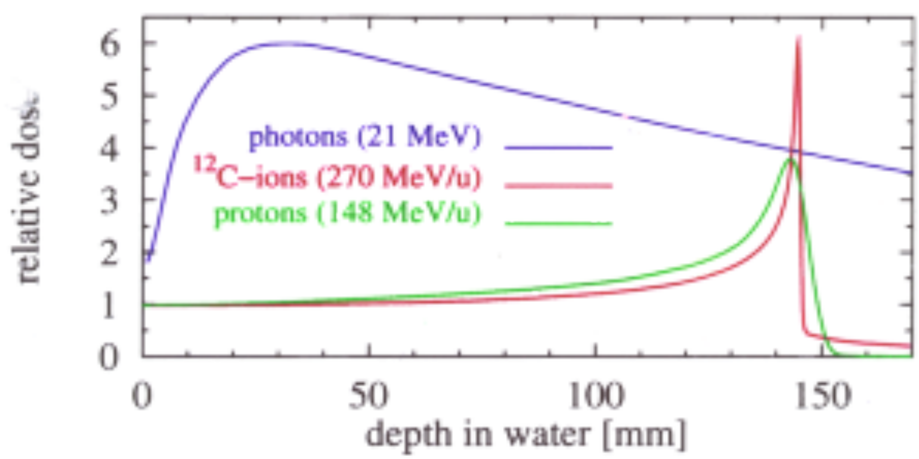


Photon, Proton and Carbon-ion Beams

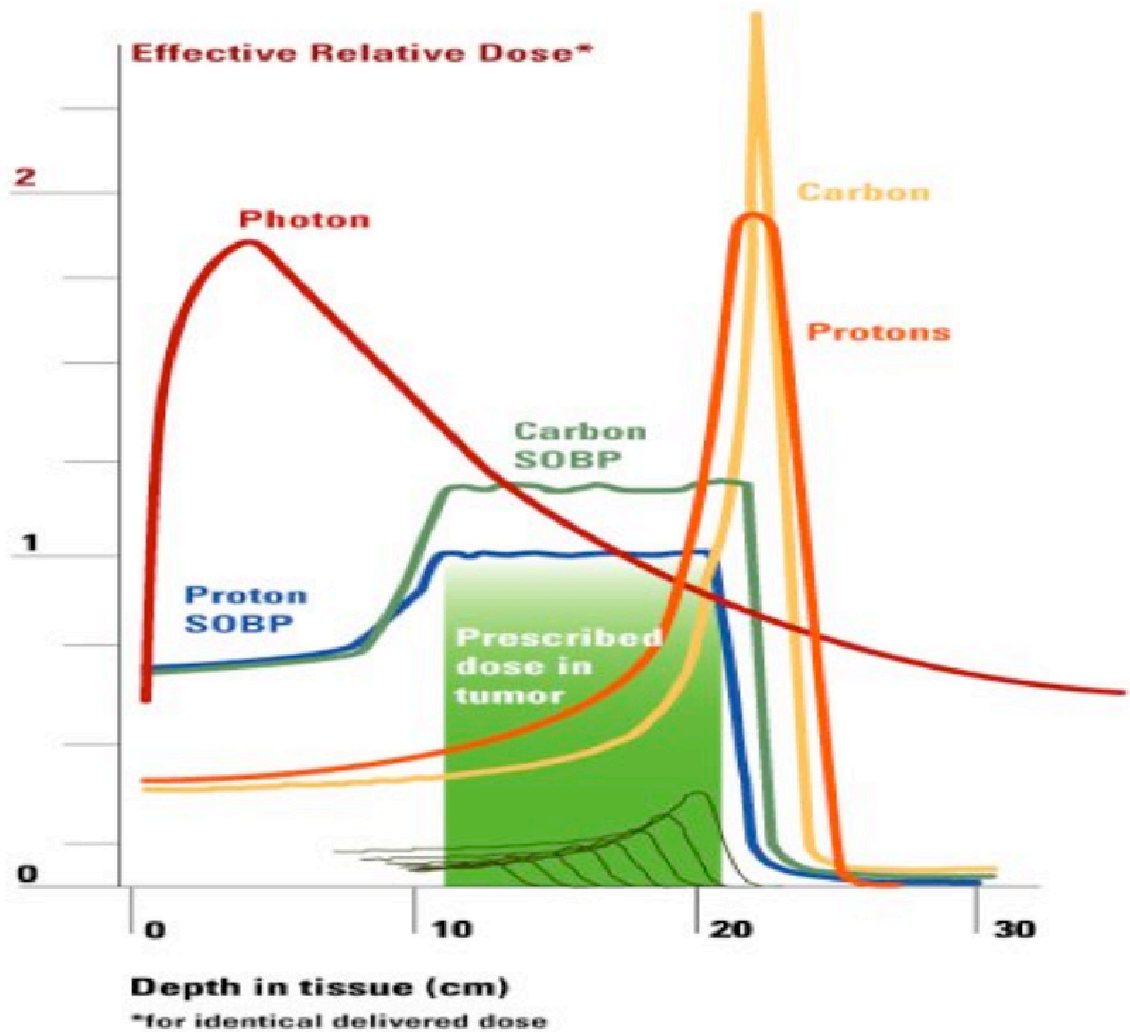
Broadening of pencil beams in water



Depth dose curves of photon, proton and carbon-ion beams



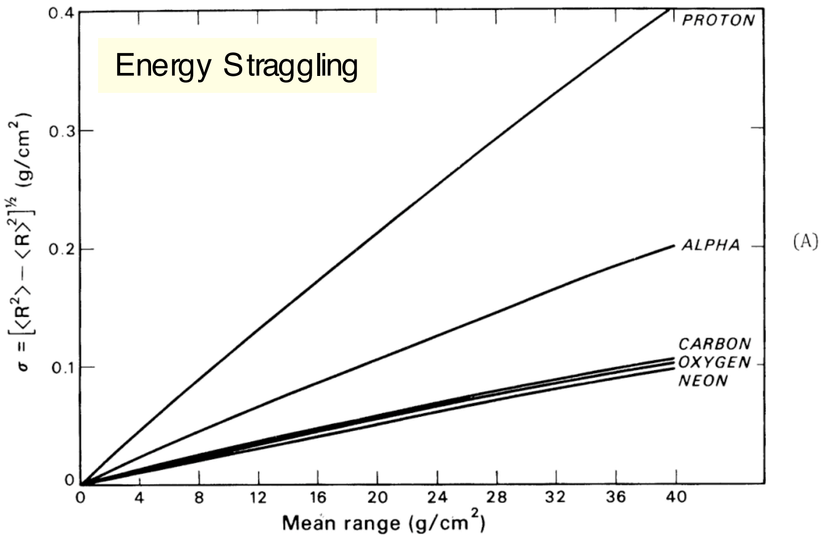
Photon, Protons vs. Ion Beams

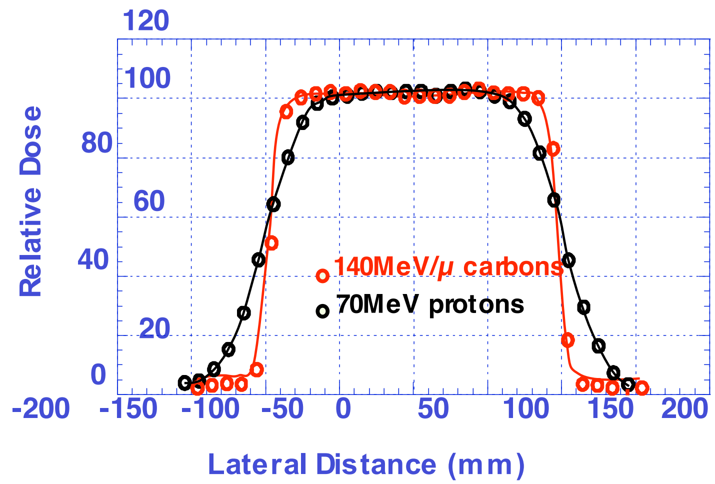


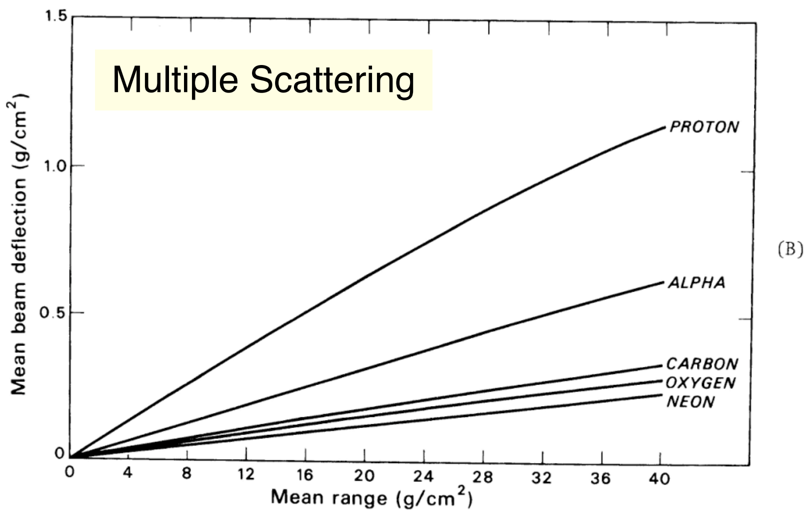
Advantages of ion beams

- Physical selectivity
- High-LET effect
- Reduced integral dose

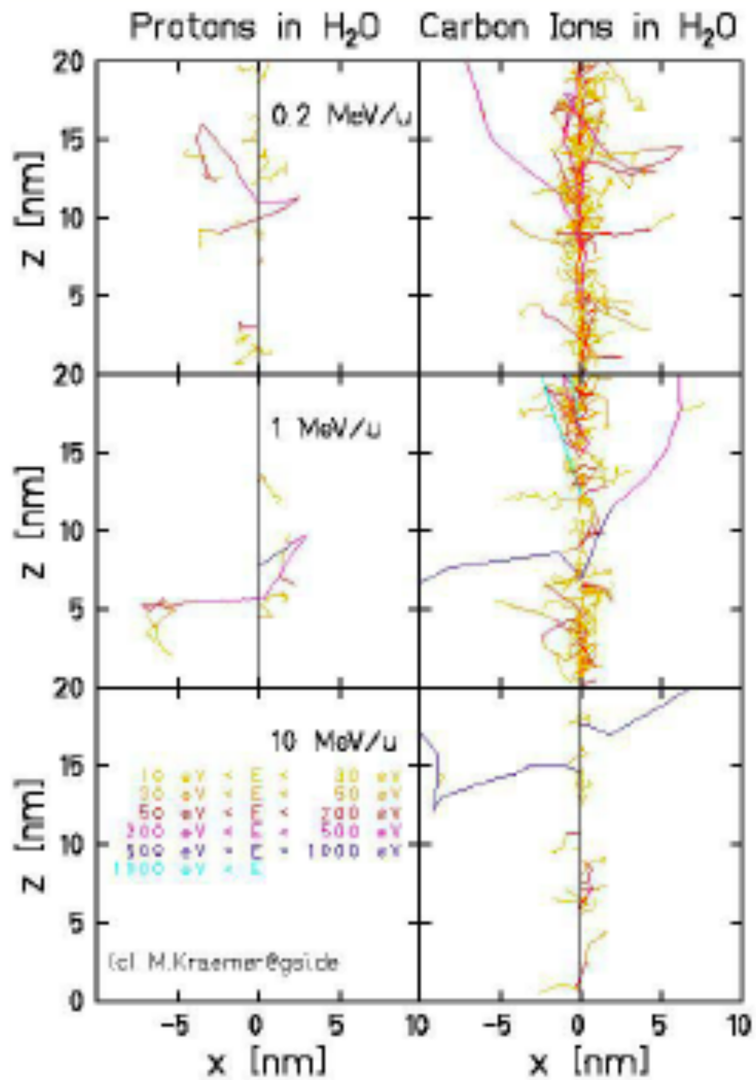
Scattering & Straggling of Ions







Track Structure of Ions



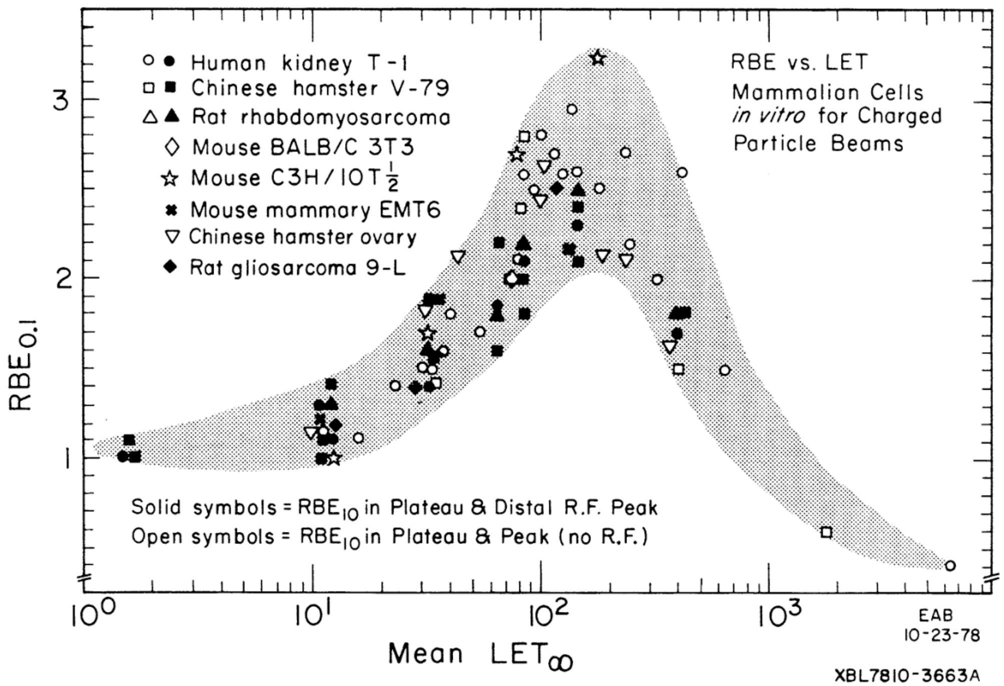
C ions are superior to protons–

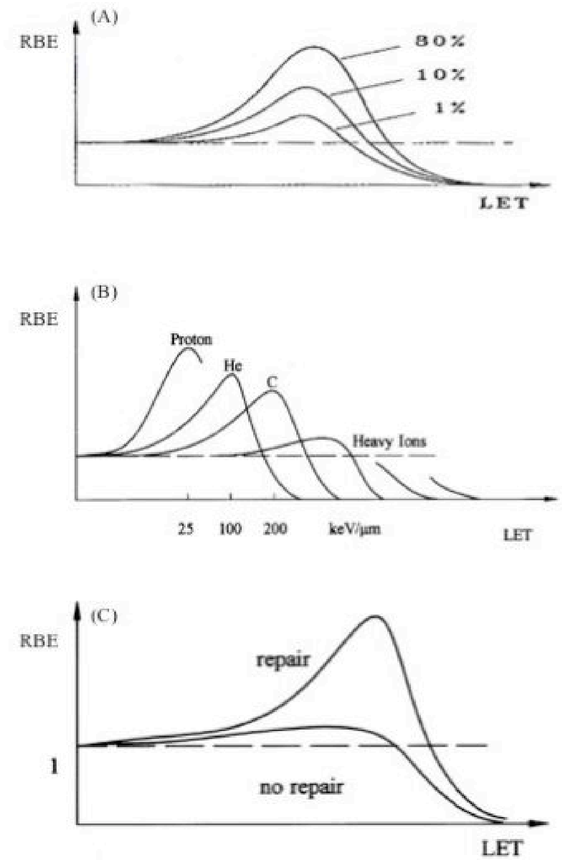
- Dose localization
- Biological advantages:
  - high LET* to provide significant differences in DNA damages
  - suppression of repair of sublethal radiation damages
  - Acceptable late effects

*Linear Energy Transfer (LET) = E absorbed per length tissue (keV/μm).

• LET is related to dE/dx

RBE vs. LET for Ion Beams

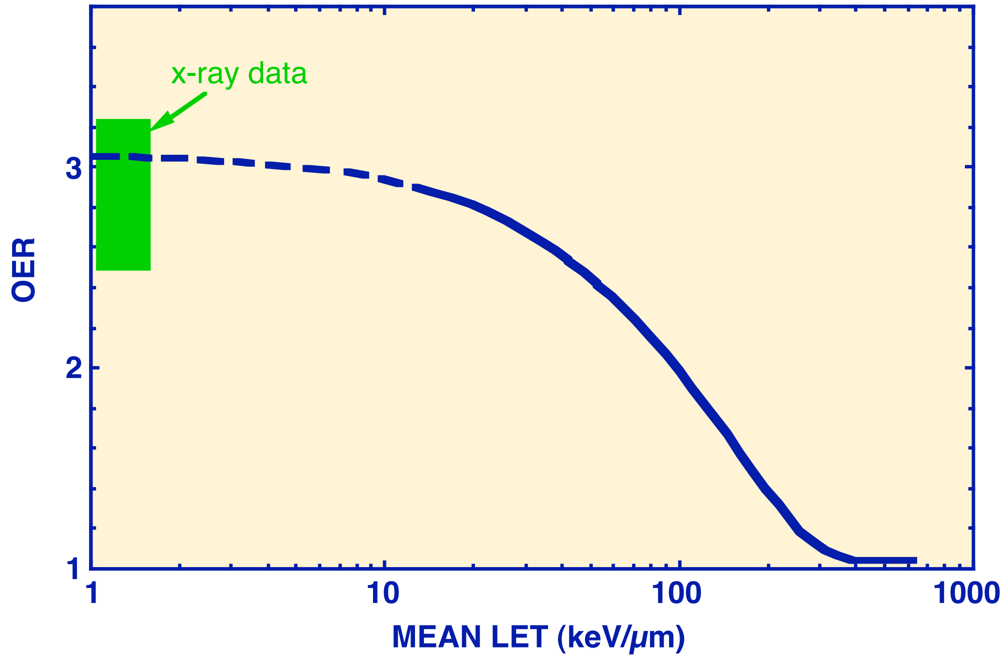


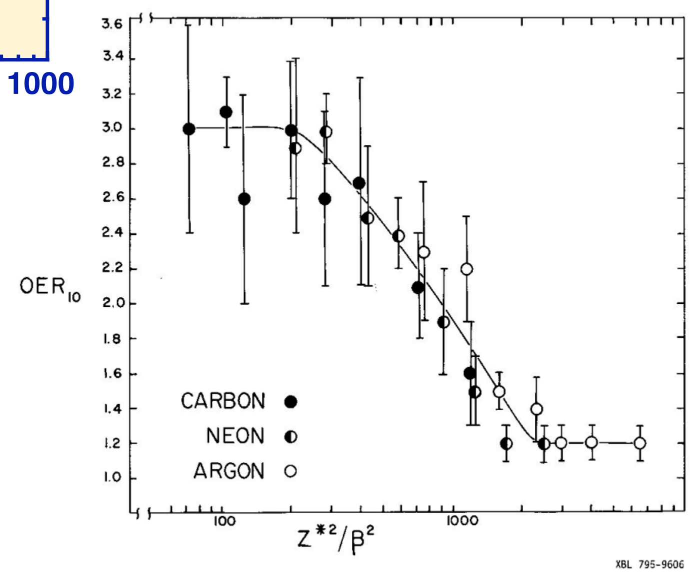


Relative Biological Effectiveness

RBE= D_x/D_i for same cell killing

Oxygen Enhancement Ratio (OER)



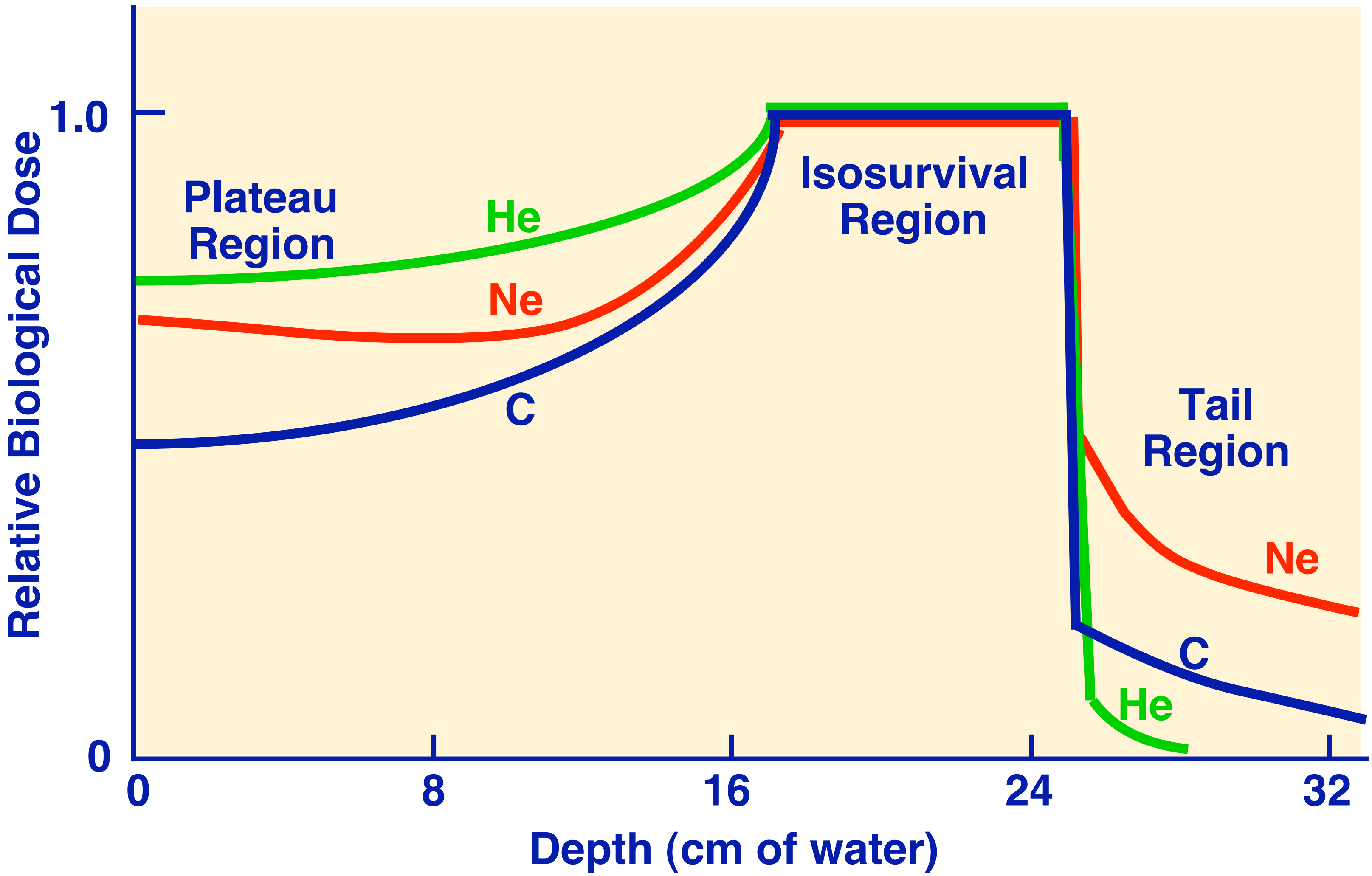


Anoxic cells are radioresistant, and require higher dose to kill.

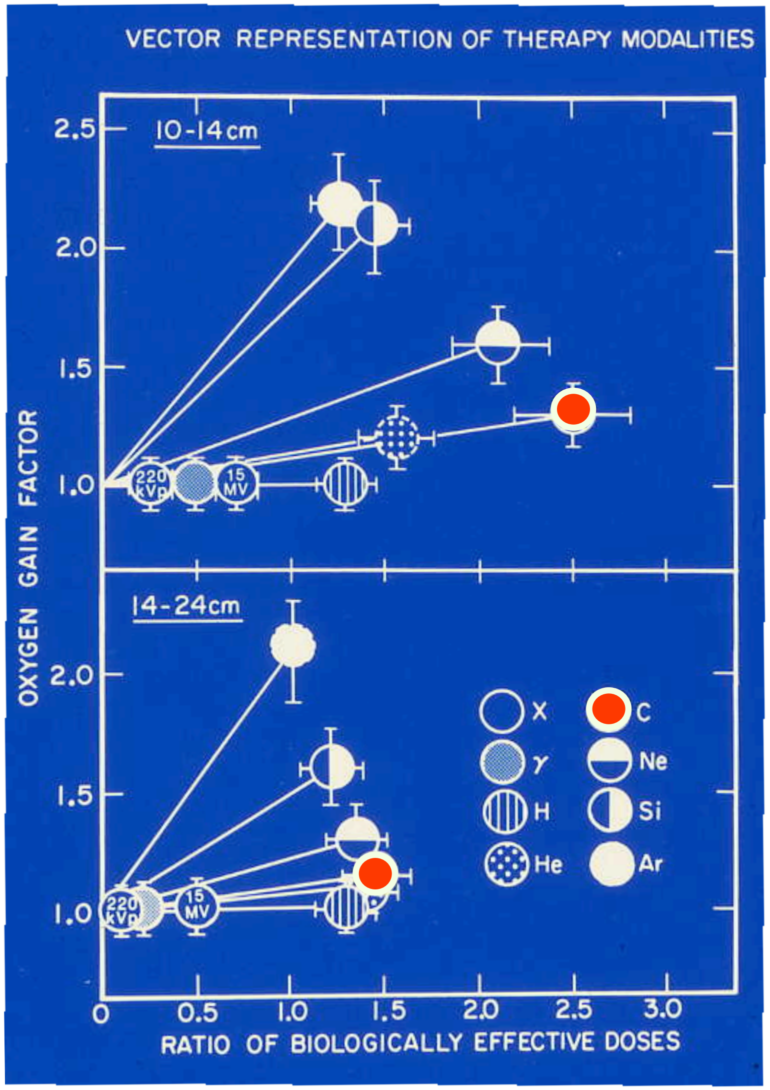
For photons, OER ≈ 3

For carbon ions, OER <<3

Biological Dose Distribution of Ion Beams



Therapeutic Gains of Ion Beams



RBE and Oxygen Gain Factor*
of various hadrons

* Oxygen Gain Factor

$= OER_p / OER_{ion}$

Hypo-fractionated Irradiation in C Ion RT (NIRS)

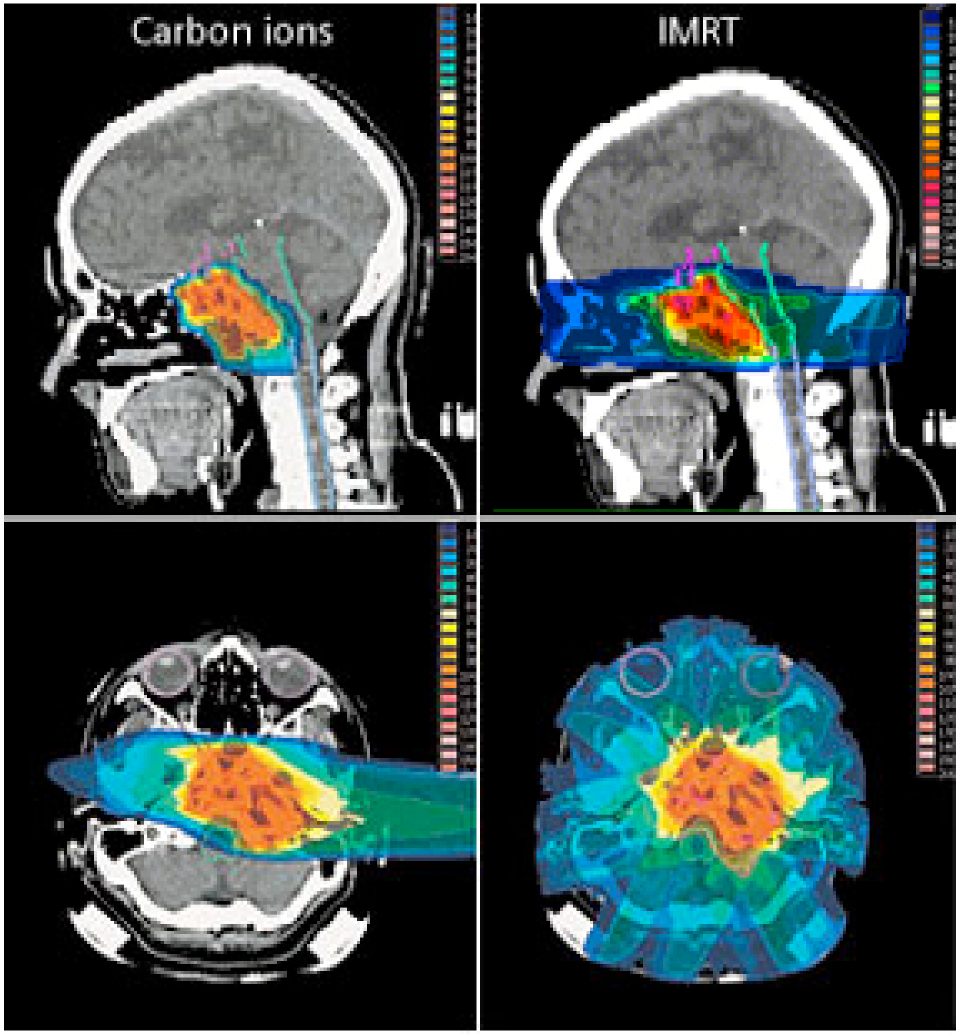
- Increasing dose per fraction lowers the RBE for both the tumor and normal tissues. But, the RBE for the tumor does not decrease as rapidly as the RBE for the normal tissues.
- Therapeutic ratio increases when the fraction dose is increased. (Similar with fast neutrons.)
- Fewer fractions result in short-courst treatment, which increases the patient throughput.

Koike S, et al: Radiat Prot Dos. 99: 405-408, 2002.
Ando et al. : J.Radiat.Res.,46:51-57, 2005.
Denekamp J: Int J Radiat Biol. 71: 681-694, 1997.

Therapeutic Advantage of Ion Beams

- Compared with proton beams, ion beams produce even higher dose conformation to the tumor volume
  - Reducing unwanted radiation in surrounding healthy tissues, which results in higher cure rates with lower complications
- Ion beams (higher LET radiation) are more efficient in killing anoxic tumor cells and significantly lower the chance of tumor recurrence
- Proton-beam treatments are usually delivered in 32 fractionations or more. Safe and effective ion beam treatments are delivered in fewer fractionation numbers, such as 8 or 4 or even 1
  - This implies higher patient throughput in a given facility, which lowers the cost of treatment and enhances the patient comfort

Photon vs. Carbon Beam Therapy Plans



Example:
head-and-neck tumor

<Left panels> A plan using **one carbon ion beam**

< right panels>
Most advanced photon treatment, **IMRT, that employs multiple beams**

Courtesy of Heidelberg University, Dept. Clinical Radiology and German Cancer Research Center (DKFZ).

Clinical Results of Photon and C-ion Treatments

		Photons	Carbon ion	Carbon ion
Indication	End point		NIRS-HIMAC	GSI
Chordomas	Local control rate	30-50%	65%	70%
Chondrosarcomas	Local control rate	33%	88%	89%
Nasopharynx carcinoma	5 year survival	40-50%	63%	
Glioblastoma	Av. survival time	12 months	16 months	
Choroid melanoma	Local control rate	95%	96%(*)	
Paranasal sinus tumors	Local control rate	21%	63%	
Pancreatic carcinoma	Av. survival time	6.5 months	7.8 months	
Liver tumors	5 year survival	23%	100%	
Salivary gland tumors	Local control rate	24-28%	61%	
Soft-tissue carcinoma	5 year survival	31-75%	52-83%	

* Preservation of vision

From U. Amaldi, "Hadrontherapy and its Accelerators- Part II," EPFL-30.10.2008 – UA; Table by G. Kraft, 2007.

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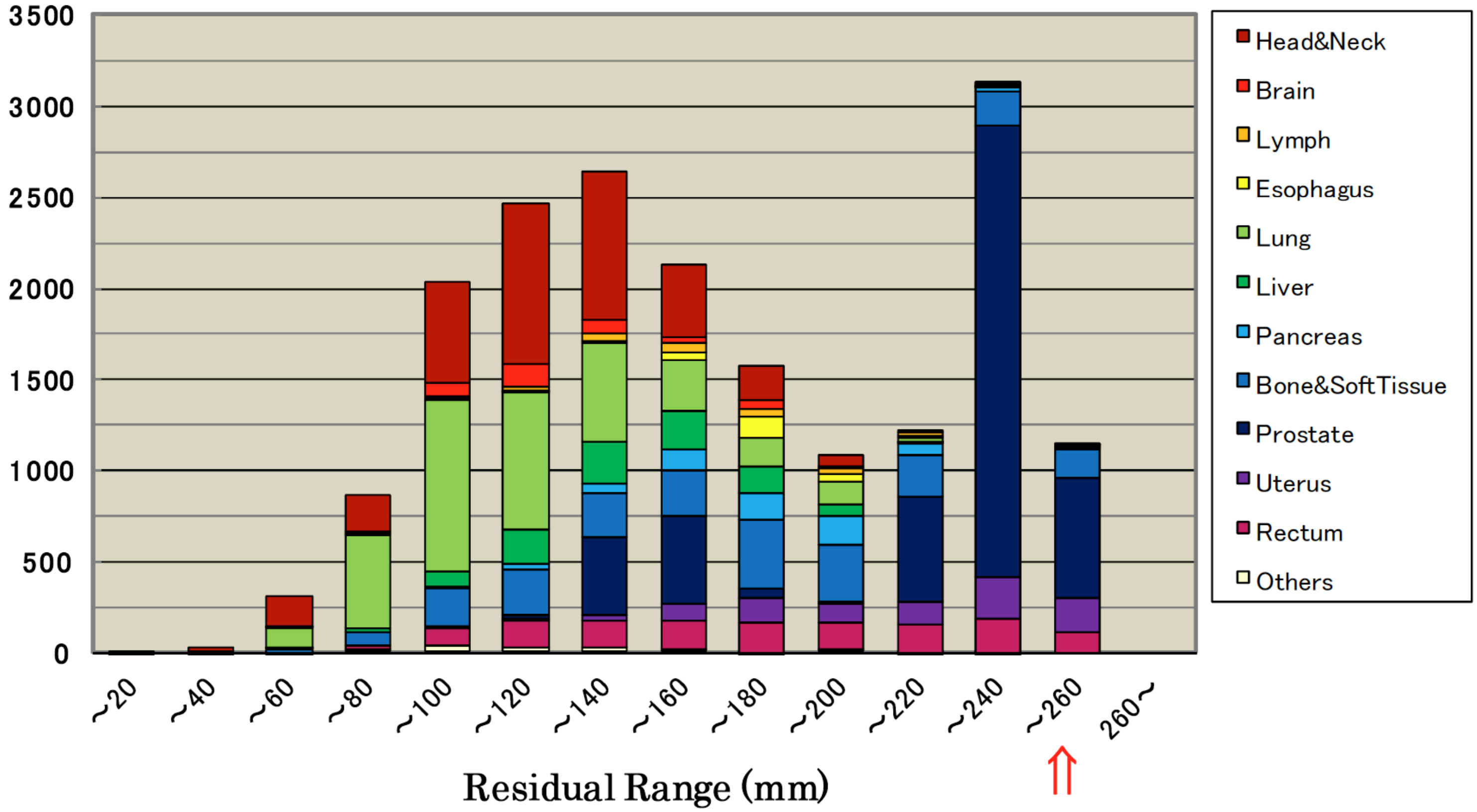
Clinical Requirements (LBNL/UCD/MGH)

ITEM	Clinical Requirements
Range in Patient	3.5 – 32 gm/cm^2
Range Modulation	Steps of 0.5 g/cm^2 over full depth
	Steps of 0.2 g/cm^2 for range< 5 g/cm^2
Range Adjustment	Steps of 0.1 g/cm^2
	Steps of 0.05 g/cm^2 for range< 5 g/cm^2
Average Dose Rate	2 Gy/min for 25 x 25 cm^2 field
	at 32 g/cm^2 full modulation
Spill Structure	Scanning compatible
Field Size	Fixed: 40 x 40 cm^2, gantry: 26x 20 cm^2
Dose Compliance	±2.5% over treatment field
Effective SAD	Scattering: 3 m from the first scatterer
	Scanning: 2.6 m from the center of magnets
Distal Dose Falloff (80-20%)	0.1 g/cm^2 above range straggling
Lateral Penumbra	<2 mm over penumbra due to multiple scattering in patient
Dose Accuracy	±2%

Range in Patient: 25 gm/cm^2

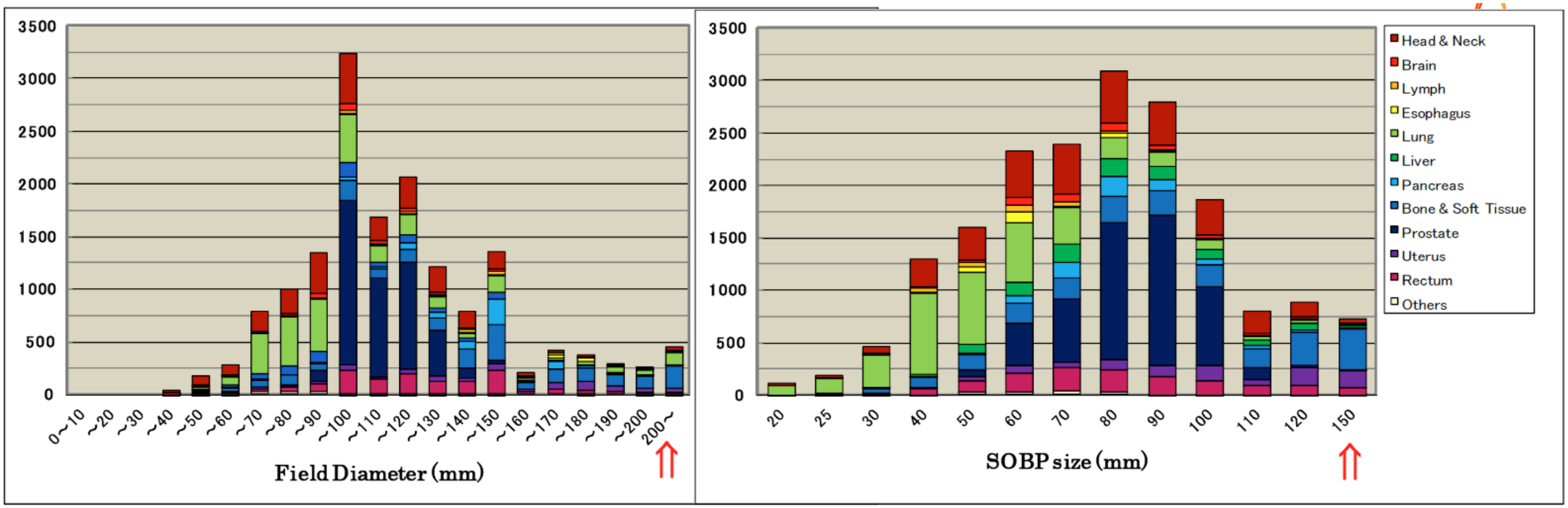


- Residual range of 25 cm
- Required energy: 400 MeV/n, with range loss of 2.5 cm in in-beam materials

K. Noda, 2010

Treatment Volume

- Range Modulation: Steps of 0.5 g/cm^2 over full depth
- Range Adjustment: Steps of 0.1 g/cm^2
- Field Size: Fixed: 40 x 40 cm^2, gantry: 26x 20 cm^2

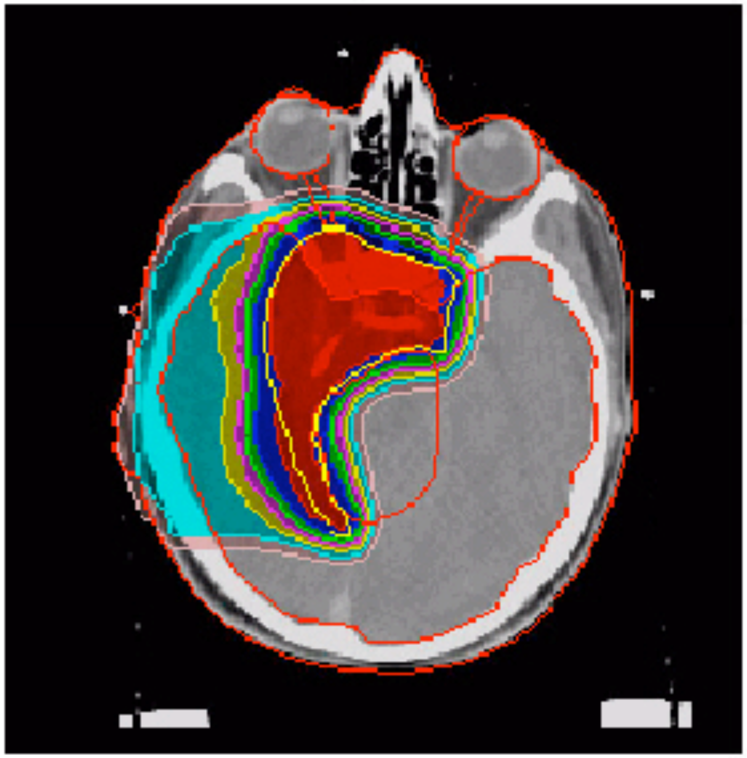


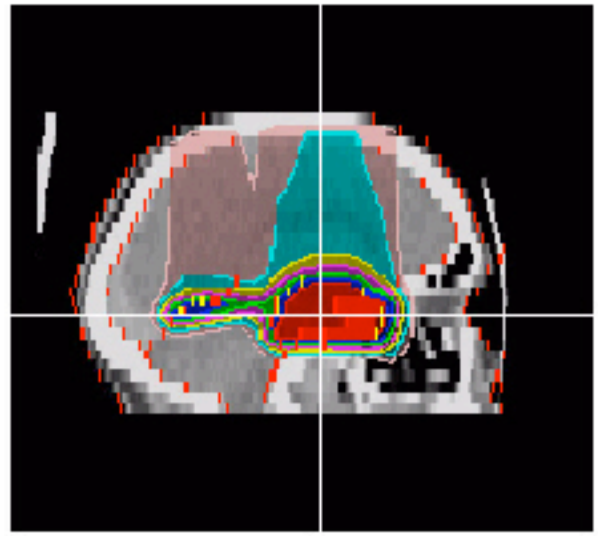
The field size = 20 x 20 cm^2

SOBP width = 16 cm

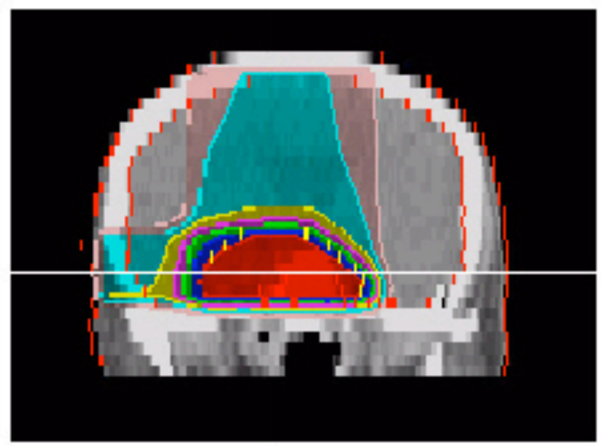
K. Noda, 2010.

Rational for Scanning - 1



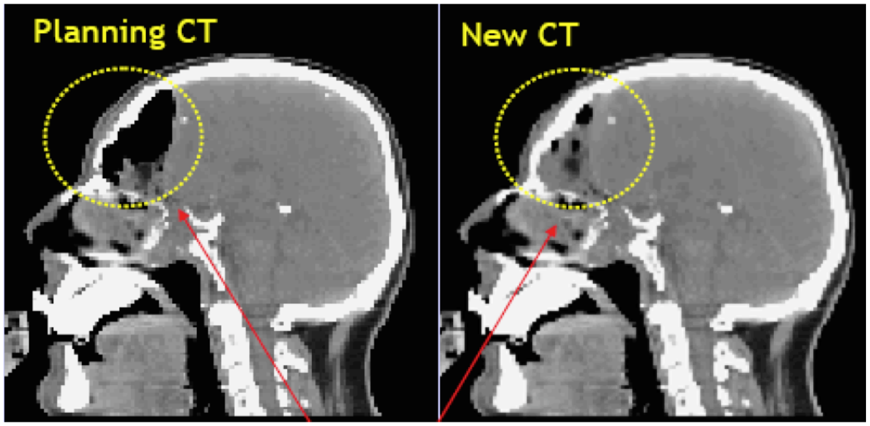


Carbon ion beam scanning (GSI)

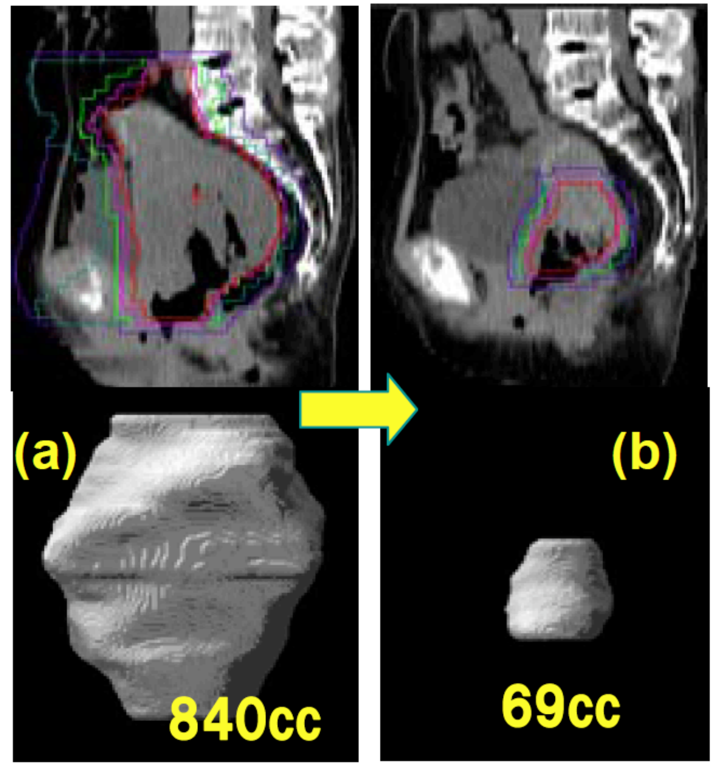


S.Scheib, " Spot scanning mit Protonen: experimentelle Resultate und Therapieplanung", ETH Zurich Dissertation Nr. 10451, 1993.

Rational for Scanning - 2



Infiltration of soft tissue into air cavity during treatment (@PSI)



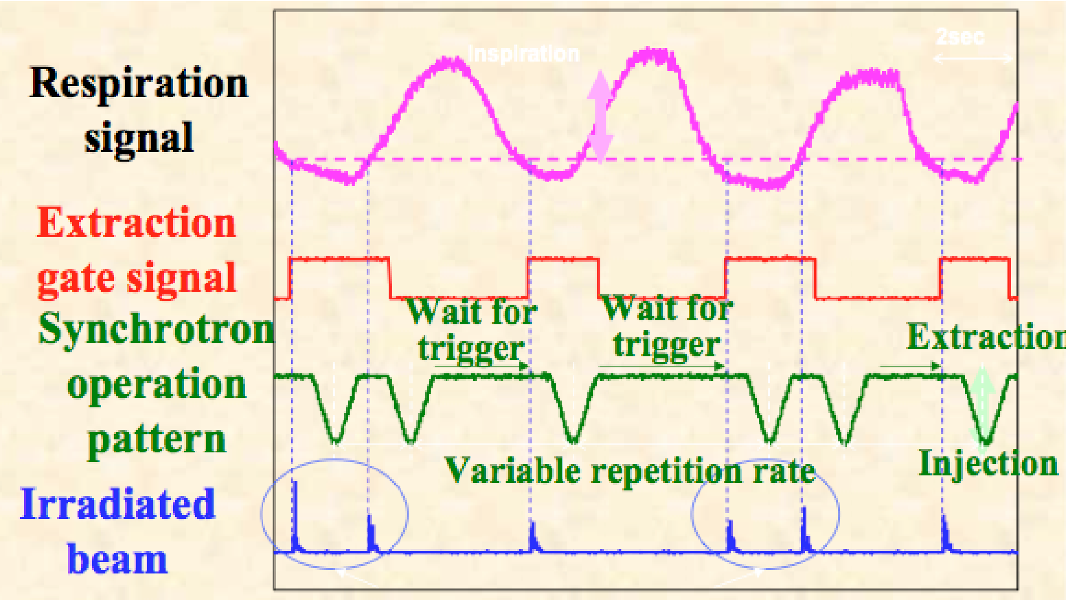
Large changes in target shape and size

Should modify treatment planning corresponding to changes of target during treatment
⇒ Adaptive Cancer Treatment ⇒ Beam Scanning

K. Noda, 2010.

Rational for Scanning - 3

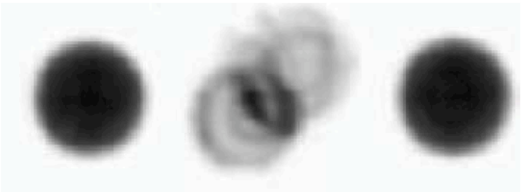
- Gating



Hiramoto, PTCOG, May 2007.

- Tracking

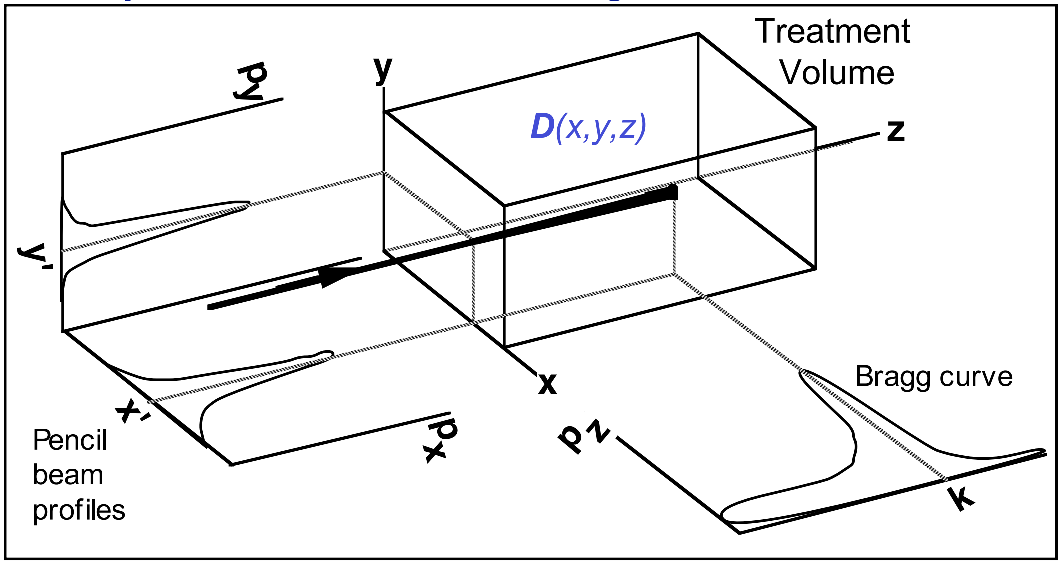
5-cm sphere inside water bath

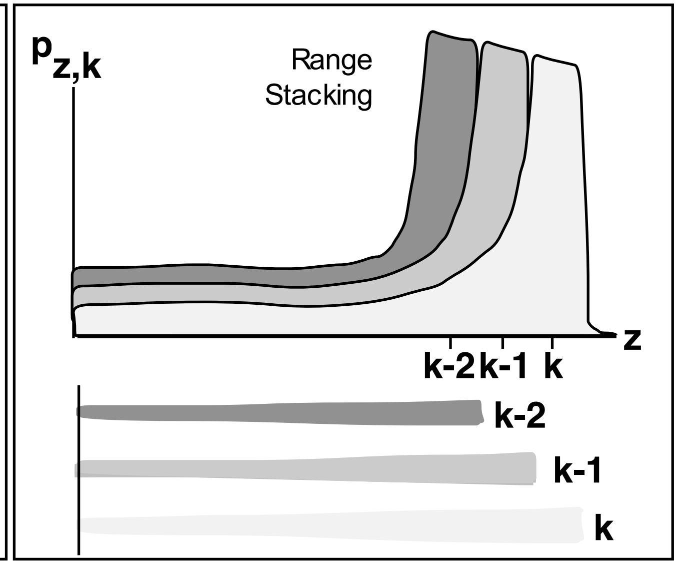


Stationar Breathing Tracking

Kraft, GSI

Physics of Beam Scanning





- Moves the pencil-beam distribution, ***p***
- Obtain the desired dose distribution, ***D***, in and out of PTV

  $\boldsymbol{p}_x$, $\boldsymbol{p}_y$, = lateral beam profile (beam divergence and scattering)

  $\boldsymbol{p}_z$ = Bragg-peak depth dose profile of a pencil beam

- ***D*** is obtained by convolving ***p*** with a scan density function, ***F***, viz.,

$$\boldsymbol{D} = \iiint \boldsymbol{F} \cdot \boldsymbol{p}$$

Beam Scan Algorithm – Scan Density Function

- Desired dose distribution, D_0, is specified in PTV and OAR
- p_i are known at all points
- The optimized dose distribution, D, is obtained by convolving p with F, an *occupation function* (also called *scan density*), symbolically:

$$D = F \otimes p$$

- F is determined through an iteration process:

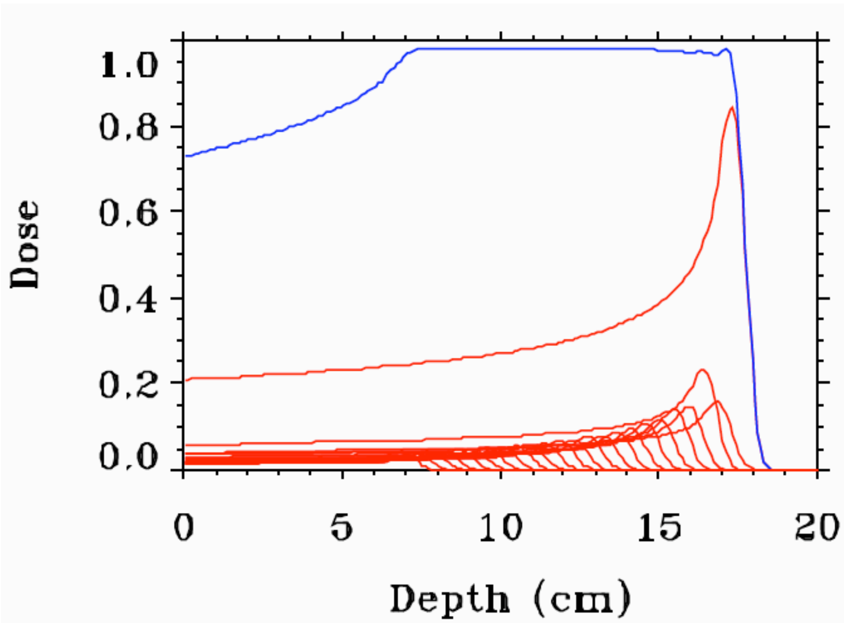
$$F_{n+1} = C\,[F_n + a(D_0 - F_n p)],$$

where C is a constraint operator ensuring non-negative occupation function amplitude, and a is a convergence-speed parameter. The initial guess of $F_0 = D_0$.

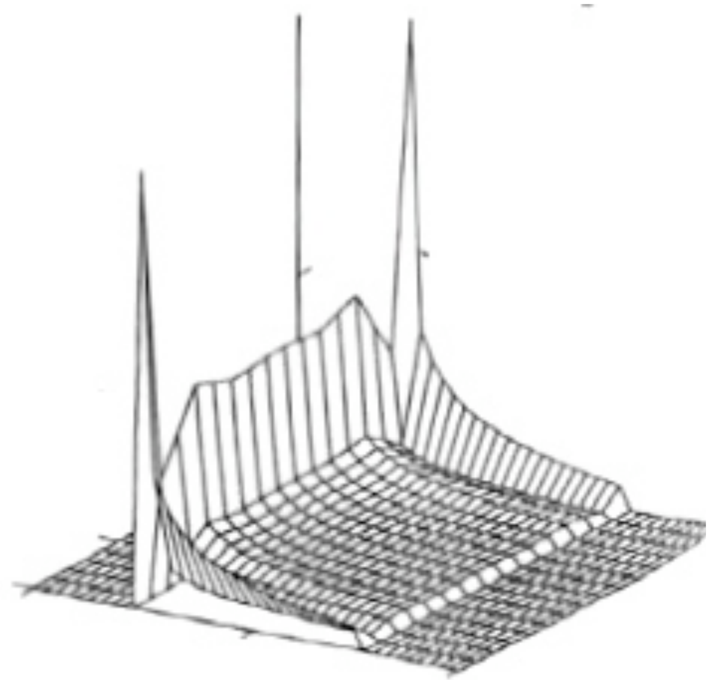
Staples and Ludewigt, Proc. of the 1993 PAC, 1759-1761.
Brahme, Kallman and Lind, 1990, Radiotherapy and Oncology, **15**: 189-197.

Optimization of Occupation Function, *F*

For sharp distal dose falloffs



A standard Spread-Out Bragg Peak (SOBP) is an optimized "range stacking" of Bragg peaks of transversely widened beams (not pencil beams).



The optimized density function (occupation function) in a plane perpendicular to the scan plane and the through the central axis of the radiation field.

* Staples and Ludewigt, LBNL,1993.

Occupation Functions and Beam Parameters

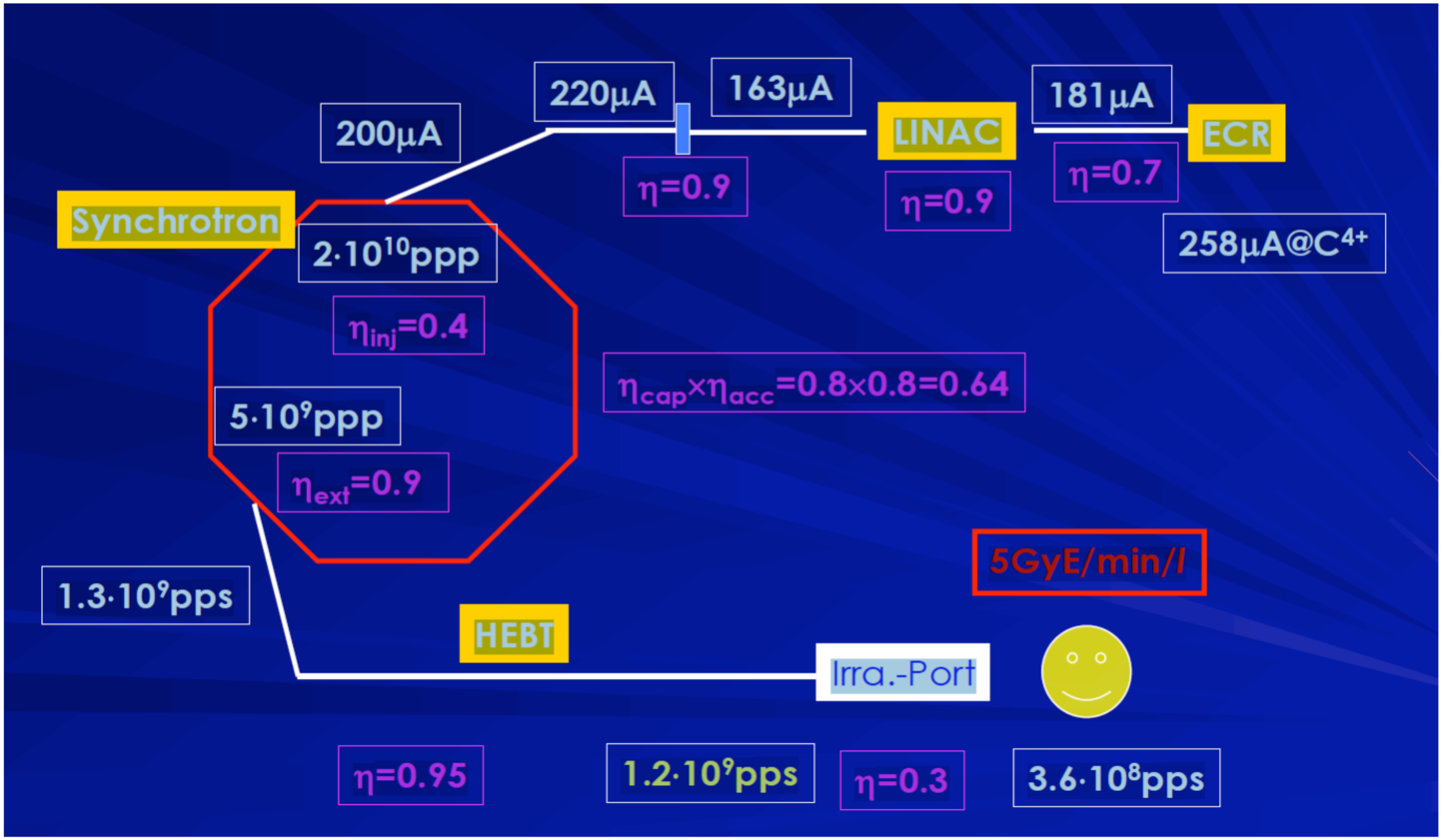
Requirements of ***F*** on—

- Accelerator parameters:
  - Beam extraction
    - Pixel-to-pixel beam intensity modulation < 1:7
    - Transient time for full intensity changes < 40 μsec
- Beam optics and beam spot parameters
  - beam emittance (divergence and size)
  - sharpness of distal dose falloffs (beam-energy spread)

Normalized emittance:
- $\varepsilon = 0.5\pi/0.777$ cm-mradians
- for $\sigma = 0.5$-cm beam spot the rms divergence $\theta_{rms} = 0.074°$

2 Gy/min for 25 x 25 cm^2 field

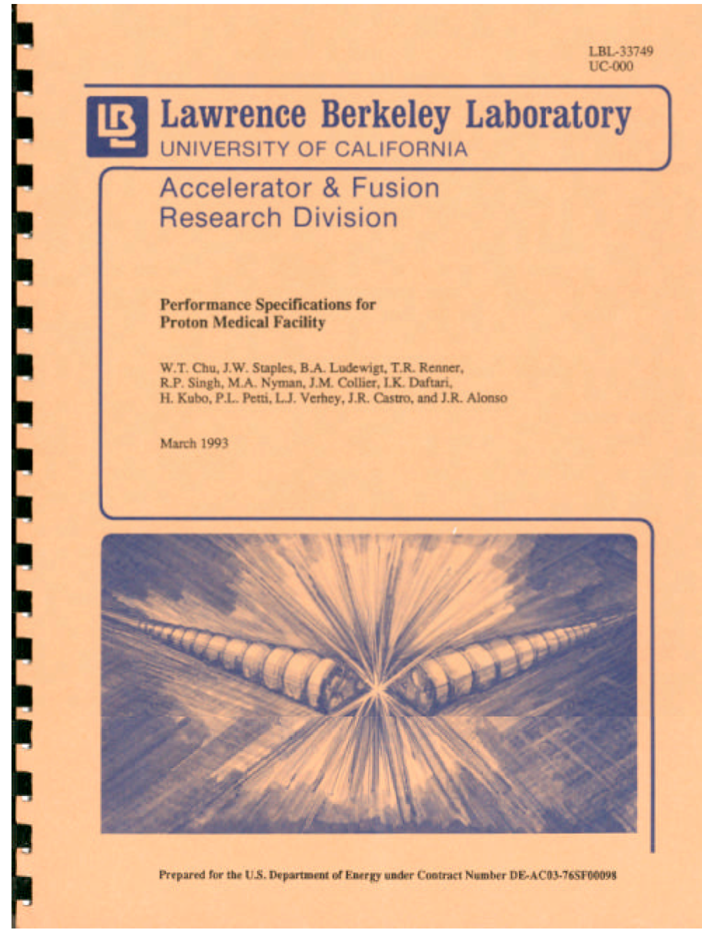
Beam Intensity Specifications



Y. Iwata (NIRS)

A Summary of Technical Specifications

Ion Species	Carbon - p, He, Li, Be, B,C and beyond (N, O, and Ne)
Energy	400 – 140 MeV/μ
Range/SOBP	250/150 – 40/20 mm
Lateral-Size	20 x 20 cm^2
Beam Intensity	1.2 x 10^9 pps
Beam Intensity Modulation (per pixel)	Dynamic Range 1 : 7
Beam Intensity Modulation Time	40 μsec
Treatment Rooms	3: H&V, H, V / Gantry
Irradiation Method	Pixel Scanning / with Gating / Tracking



W.T. Chu, et al., "Performance Specifications for Proton Medical Facility," LBL-33749 (1993).
http://www.osti.gov/energycitations/product.biblio.jsp?query_id=2&page=0&osti_id=10163935

3 Japanese Ion-Beam Therapy Accelerators

HIMAC of NIRS in Chiba, HIBMC in Hyogo, and GHMC of Gunma Univ., Gunma

Parameter	HIMAC	HIBMC	GHMC
Ion-source type	ECR	ECR	ECR
Ion species	C^{2+}	C^{2+}	C^{2+}
Injector type	RFQ & DTL	RFQ & DTL	RFQ & IH-DTL
Operation frequency	100 MHz	200 MHz	200 MHz
Extraction energy	6 MeV/u	4 MeV/u	4 MeV/u
Accelerator type	2 synchrotrons	synchrotron	synchrotron
Circumference	130 m	94 m	63 m
Number of Magnets	12	12	12
Deflection angle	30 deg	30 deg	30 deg
Energy at extraction	100 – 430	100 – 320	140 - 400
Beam intensity (pps)	2×10^9	1.2×10^9 2×10^{10} proton	2×10^9
Pulse repetition rate	3.3 s – 2 s	2 s	2 s
RF cavity frequency	1 – 6 MHz	1 – 6.5 MHz	0.90 - 6.97 MHz
RF power (Max)	10 kV	6 kV	2 kV

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Light Ion Facilities— Operational and Under Construction

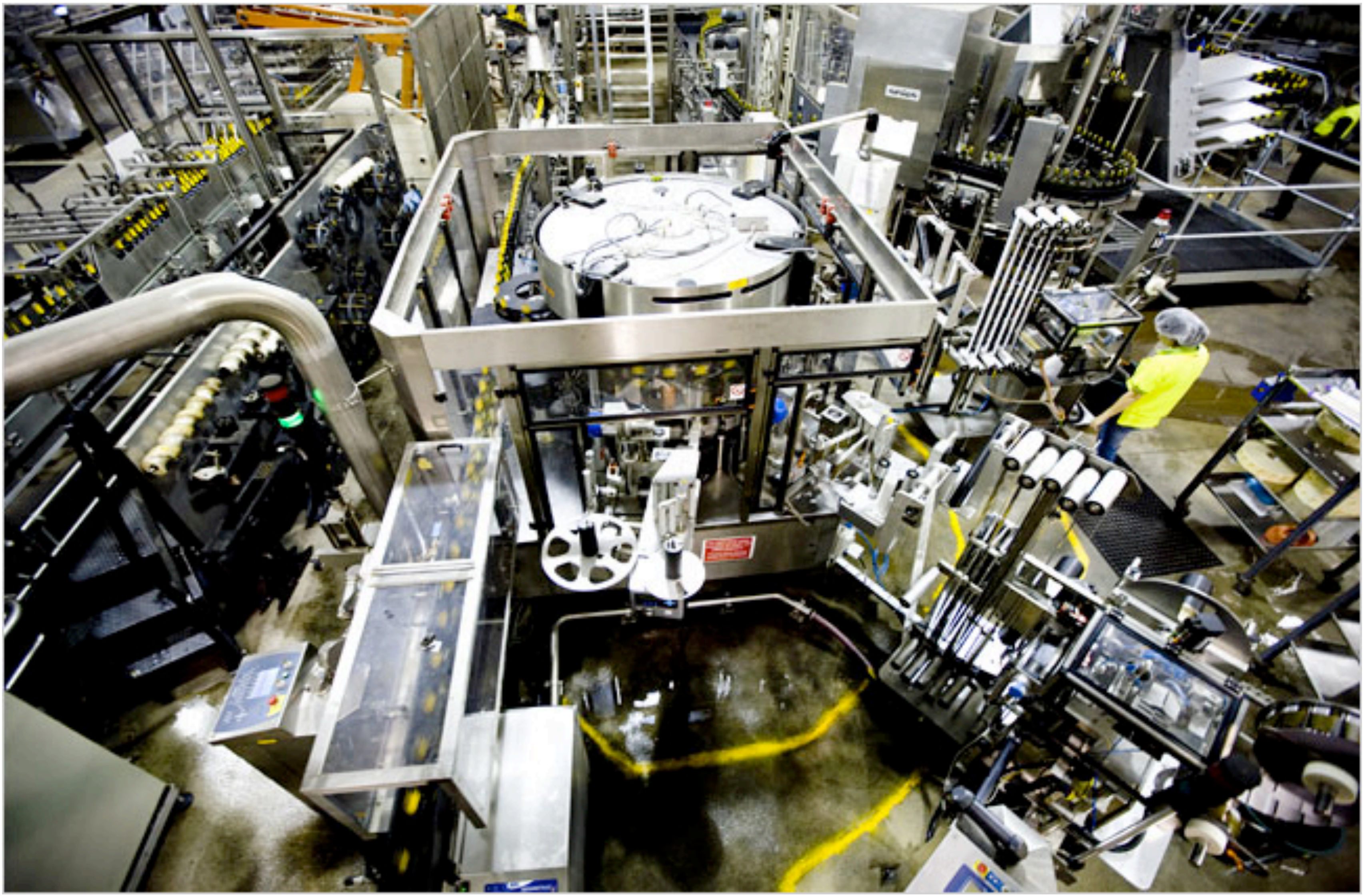
LOCATION	COUNTRY	ACCELERATOR	ION (ENERGY – MeV/u)	FIRST TREATMENT	PATIENTS TREATED (Feb 2009)
Berkeley CA[1]	**USA**	Synchrocyclotron Synchrotron	^{4}He (230)	1957 - 1992	2 054
Berkeley CA[1]	**USA**	Synchrotron	C, Ne, Si, Ar (670)	1975 - 1992	433
Chiba[2]	**Japan**	Synchrotron	C (400)	1994	4 504
Darmstadt[3]–	**Germany**	Synchrotron	C (430), Ar,	1997-2008	424
Hyogo[4]	**Japan**	Synchrotron	p, C (320)	2002	454
Heidelberg[5]–	**Germany**	Synchrotron	p, He, C, O (430)	2009	
Gunma[6]	**Japan**	Synchrotron	p, C (400)	2010	
Pavia[7]	**Italy**	Synchrotron	p, C (430)	2010	
Marburg[8]–	**Germany**	Synchrotron	p, C (430)	2010	
Kiel[9]–	**Germany**	Synchrotron	p, C (430)	2012	
Wiener Neustadt[10]	**Austria**	Synchrotron	p, C (420)	2013	
Lanzhou[11]	**China**	Synchrotron	p, C (120)	?	
				Light Ions	**5 815**
				He + LI	**7 869**

–**Scanning beam**

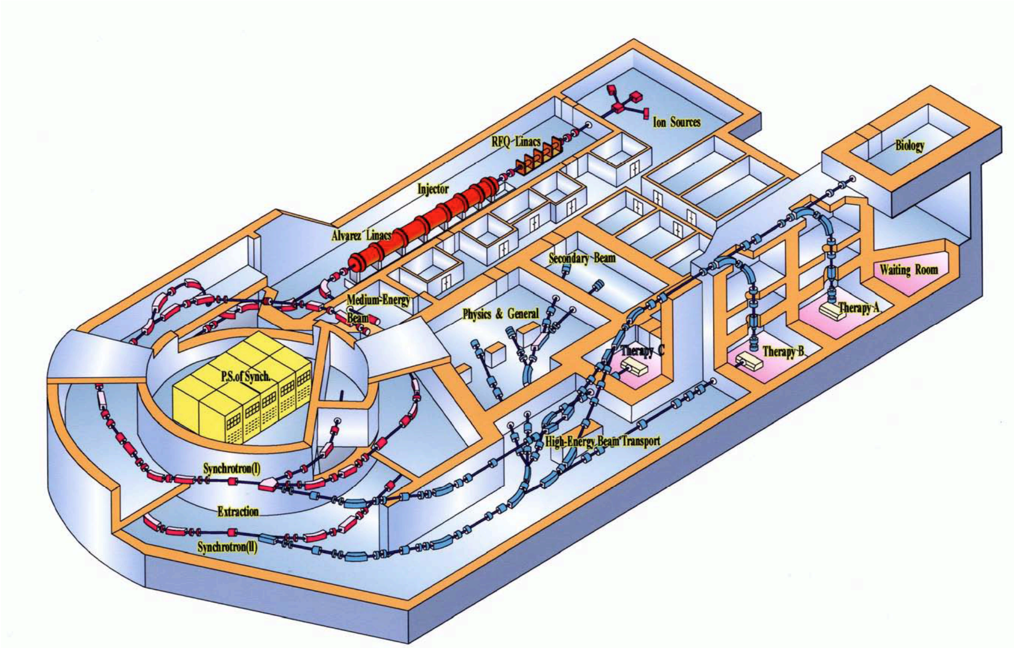
Under construction/ funded

1. Lawrence Berkeley National Laboratory (Bevalac, LBNL)
2. National Institute of Radiological Sciences (HIMAC, NIRS)
3. Gesellschaft für Schwerionenforschung (GSI, Helmholtzzentrum für Schwerionenforschung)
4. Hyogo Ion Beam Medical Center (HIBMC), Hyogo
5. Heidelberger Ionstrahl-Therapiezentrum (HIT)
6. Gunma University Heavy Ion Medical Center (GUHIMC)
7. Centro Nazionale di Adroterapia (CNAO)
8. Particle Therapy Center Marburg (PTCM), Rhon-Klinikum AG (RAK)
9. North European Radiooncological Center Kiel (NroCK)
10. MedAustron
11. Institute of Modern Physics (IMP)

An Ion-Beam Facility is complex like–

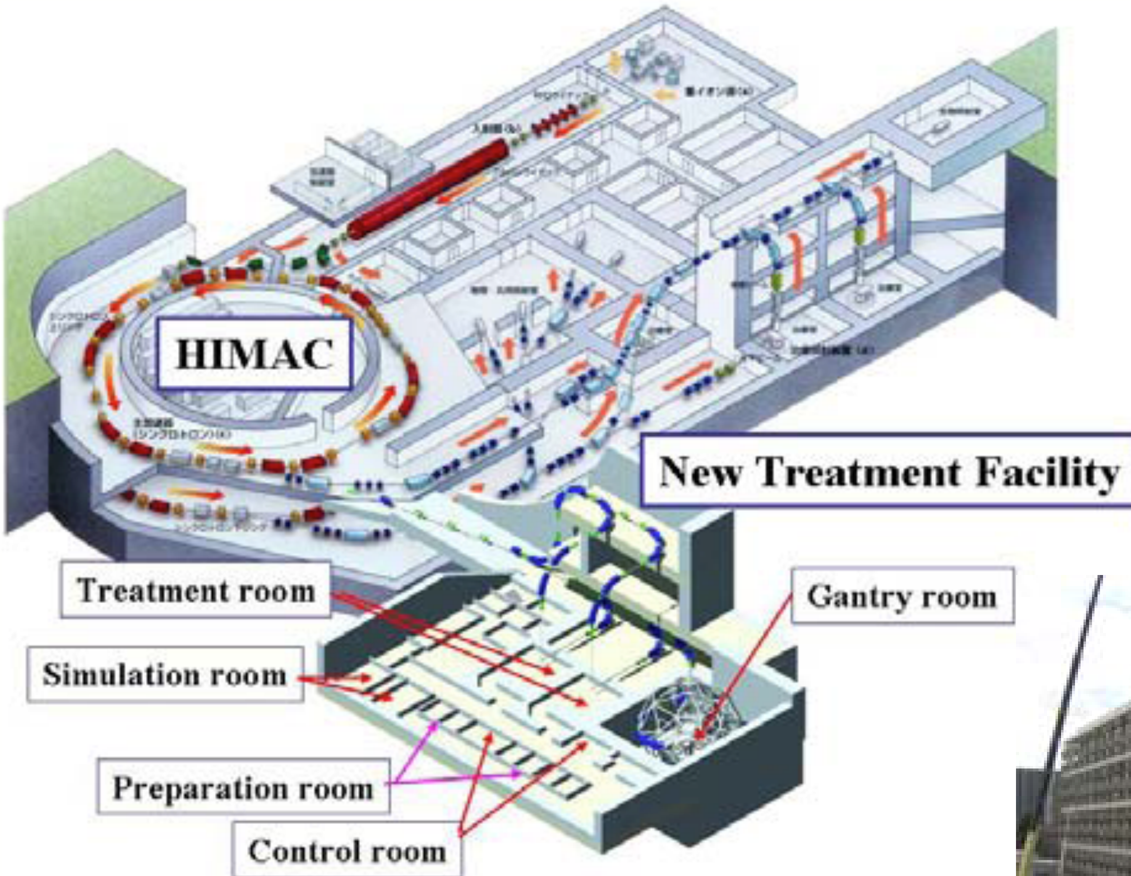


Heavy Ion Medical Accelerator in Chiba (HIMAC)



1984: Heavy ion therapy project started
1988-93: Construction of HIMAC.
1994: Carbon-ion RT started at 21st June 1994
2003: approved “Highly Advanced Medical Technology”
2010: Treated >5200 patients
2006-10: New Treatment Facility Project at HIMAC for further development of HIMAC treatment

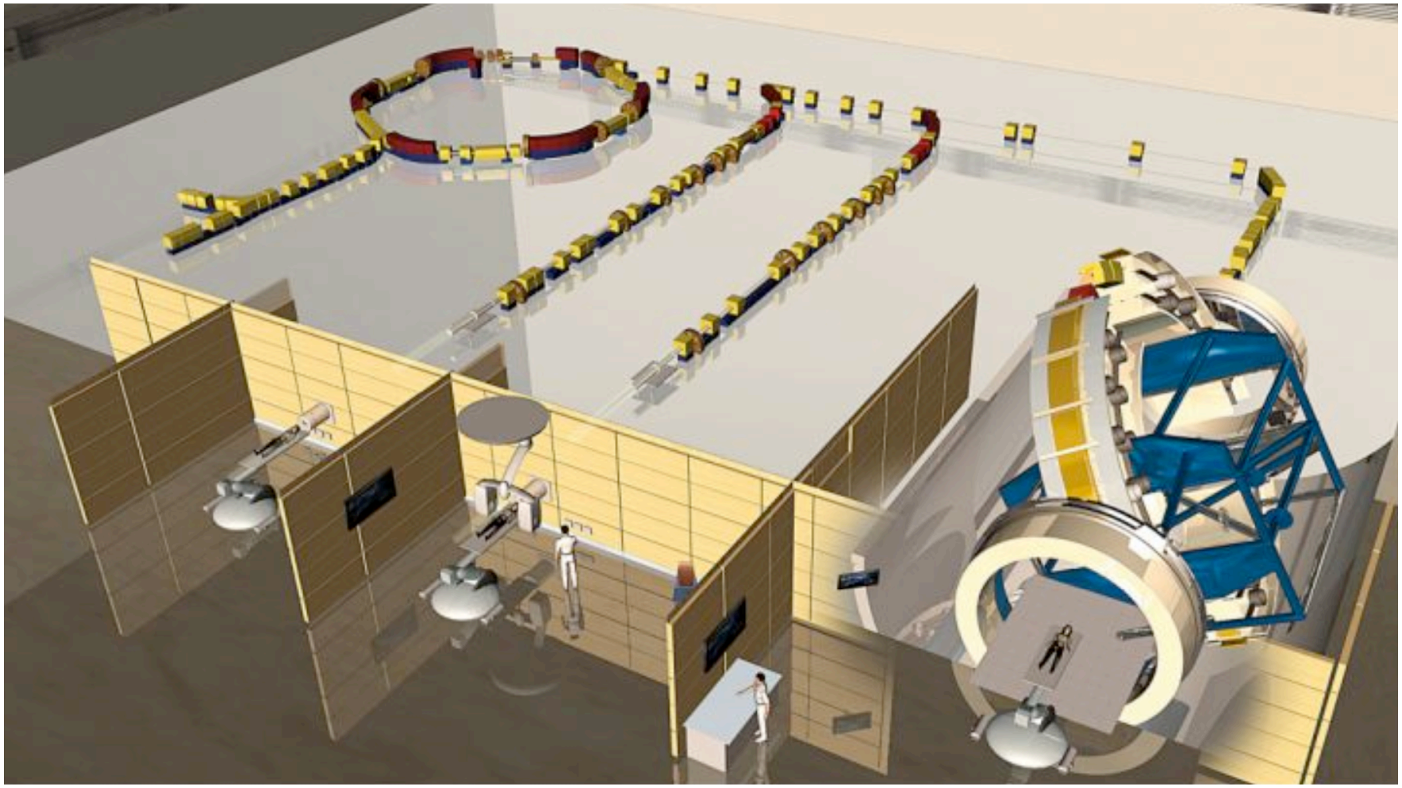
NIRS HIMAC Expansion



The first patient will be treated in March, 2011

Koji Noda (National Institute of Radiological Sciences)
2nd NIRS-CNAO Symp., Pavia, Italy, 21st March, 2010.

Heidelberg Ion Therapy Facility (HIT)

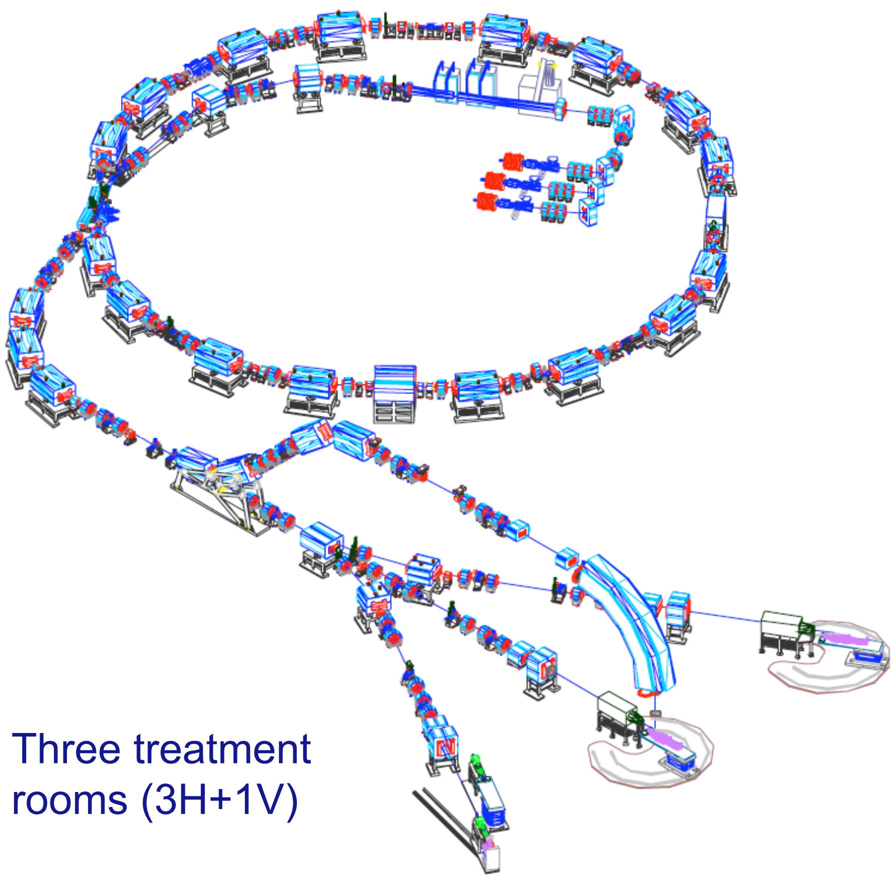


- Two ion sources, a linac and a synchrotron
- 2 fixed beam lines and one with a rotating gantry
- Effective area ≈ 5000 m^2
- 30,000 tons of concrete, 7,500 tons of construction steel

Commissioned in 11.2009

Th. Haberer, PTCOG 45, Houston (2004).

CNAO* Facility, Pavia, Italy



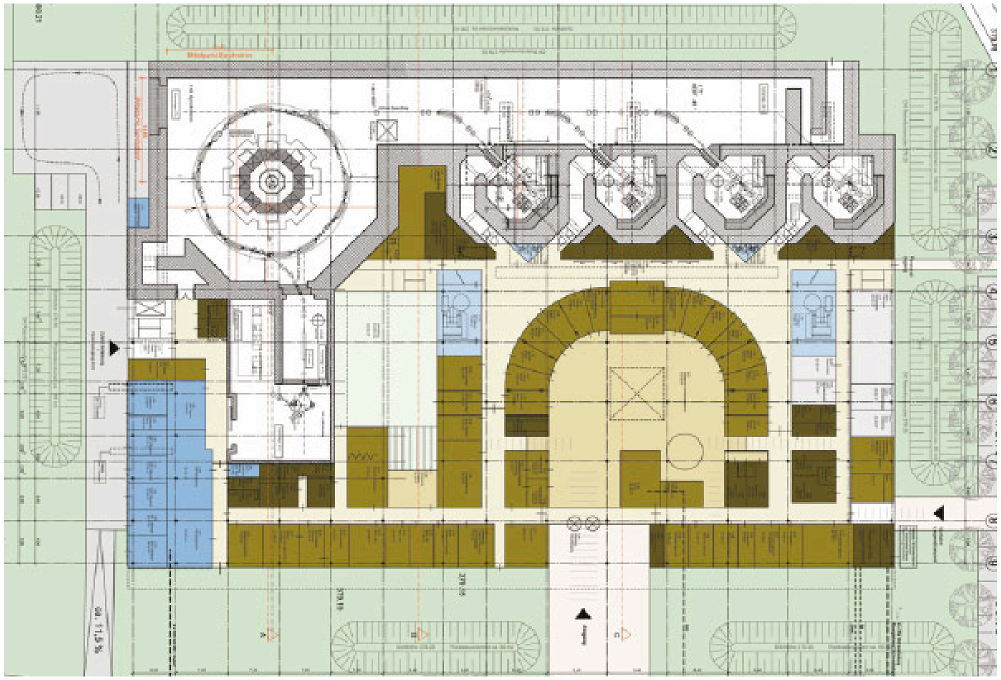
Three treatment rooms (3H+1V)

To be commissioned in 2010

Future implementation (2 gantries)

* Centro Nazionale di Adroterapia Oncologica (National Hadron Therapy Center)

Commercial Solutions



Proton and carbon-ion treatment facility (Siemens)

The Marburg ion-beam therapy facility is based on an extended study of the clinical workflow. Three treatment areas with a horizontal beamline and one with a 45° oblique beam will be optimized to shorten the treatment.

(Rhön–Klinikum–AG and architects Brenner and partners)

Physical Characteristics of Ion Beam Facilities

	HIMAC, Chiba	HIBMC, Hyogo	HIT, Heidelberg	CNAO, Pavia	GUNMA	Marburg
Particles	p, C, O, Ar, Xe	p, He, C	p, He, C, O	p, He, C, O		p, C
Accelerator Type	2 Synchrotrons	Synchrotron	Synchrotron	Synchrotron	Synchrotron	Synchrotron
Ion Sources	PIG for low Z; ECR for high Z	2 ECR	2 ECR sources	2 ECR sources	ECR source	2 ECR sources
Injector	RFQ (8 to 800 keV/u) and Alvarez LINAC (0.8 to 6 MeV/u) at 100 MHz	RFQ (1MeV/u) and Alvarez LINAC (5 MeV/u)	7 MeV/u linac injector	RFQ (8 to 400 keV/u) and IH-DTL LINAC (to 7 MeV/u)	RFQ and APFIH	
Particle Energy (MeV/u)	C (420), Ar (800)	p & He (70- 230), C (70 - 320)	50 - 430	p: -250 C: 60 - 400	C: 400	100-430
Beam Intensity, particles per spill (pps)		p: 7.3×10^{10} He: 1.8×10^{10} C: 1.2×10^{9}	p: 4×10^{10} He: 1×10^{10} C: 1×10^{9} O: 5×10^{8}	p: 2×10^{10} C: 4×10^{8}	C: 1.2×10^{9}	C: 3×10^{8}
Repetition Rate		p: 1 Hz He and C: 0.5 Hz				
Spill Length (msec)		400		250 - 10,000		
Dose Rate (Gy RBE/min)		5				
Beam Range (mm)		p, He: 40 - 300 C: 13 - 200				
Field Size		15cmx15cm for ports A, B				
		10cm diam. for port C				
		15cm diam. for gantry ports G1, 2				
Beam Spot Size (mm FWHM)			4 - 10	4 - 10		
Treatment Rooms	1 H, 1 V, and 1 H+V 1 gantry (planned)	p: 1 H and 2 gantry rooms C: 1 H+V and 1 45 degree	2 H and 1 gantry room	2 H and 1 H+V		3 H and 1 45 degree
Beam Delivery Technique	Passive scattering		Intensity controlled 3D raster scan	Intensity controlled 3D raster scan	Wobbler / Layer stacking	
Treatment Field Size (cm^2)			20 x 20	20 x 20		
# Patients Treated or Planned Per Year	4818 (2009.8)	515 (2009.3)	> 1,000			1500-2000
Year of first patient treatment	1994	2001	2009	2010	2010	2010

Next Presentation

Ion-Beam Therapy

- Rationale and History
  - Berkeley Lab legacy
- Clinical Requirements
  - Technical Specifications
- Current Status of Ion-Beam Therapy Facilities
- **Future Perspectives**

Ion-Beam Therapy– Future Perspectives

Window in Wixhausen's
baroque church

Running ion-beam therapy is a big effort like the military-industrial complex. It requires close cooperative efforts of medicine, physic, biology and engineering, and big money,.

Light-Ion Therapy– Future Perspectives

Ion-Beam therapy–

- Scientific rationale– impeccable
- Clinical results– very promising
- Health-care needs– strong
- Technology– advanced far
- Future– very bright

Thank You for Your Attention