Title
Treatment of Human Cancer Using Relativistic Hadron Beams

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Treatment of Human Cancer Using Relativistic Hadron Beams

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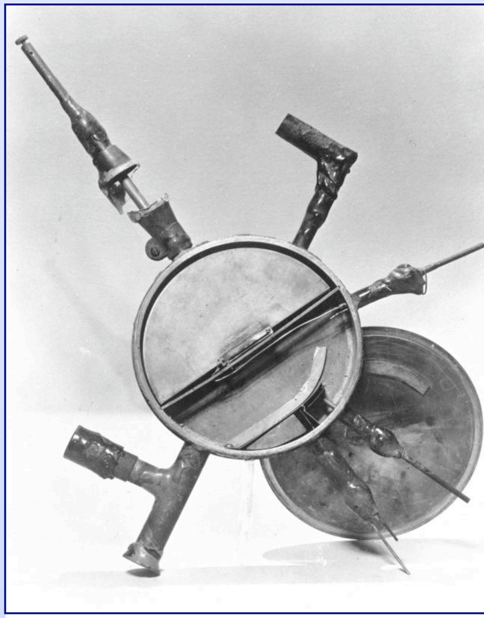
Outline of the Presentation

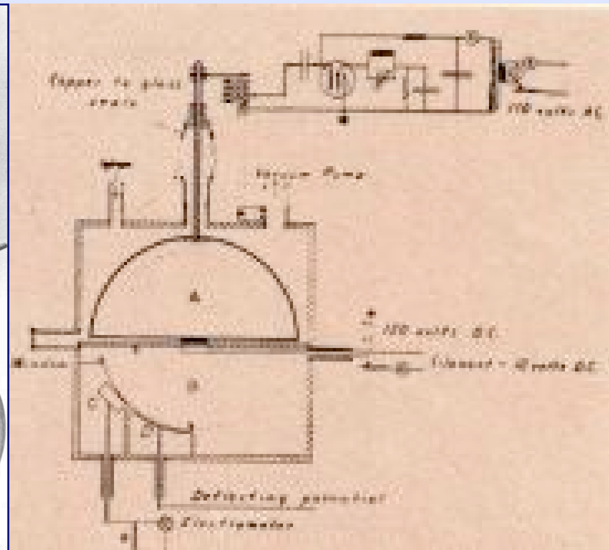
Hadron Beam Therapy*

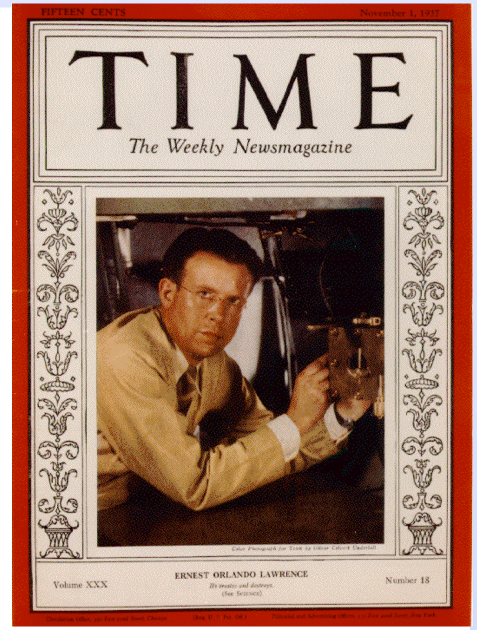
- Rationale and History
  - Berkeley Lab legacy
- An Overview of Proton Therapy Facilities.
- Future Development
  - Beam scanning (IMpT)
  - pCT, pPET, etc
  - Carbon-ion therapy

* Proton and light-ion beam therapy.

E. O. Lawrence and Cyclotron (1930)







The first cyclotron- Lawrence and M. S. Livingston (1930).

The single dee is 12 cm in diameter.

The old Radiation Laboratory ('31)

Early Work at Berkeley

E.O. Lawrence placed strong emphasis on medical uses of his cyclotrons.

His brother John H. Lawrence, M.D., became the Father of Nuclear Medicine.

184-Inch Cyclotron and proton Therapy

The first beam, November 1947

Robert R. Wilson
1914–2000

Cornelius A. Tobias
1918–2000

LBNL Pioneers of Hadron Therapy

184-Inch Cyclotron and Hadron Therapy

1956- Pioneered proton therapy
Clinical trials to 1986
1500 patients treated


Patient treatment on ISAH (Irradiation Stereotaxic Apparatus for Humans).


Closure of the 184-Inch, 1986.

Rationale of Bragg Peak Therapy

The stopping power S (or dE/dx) in MeV/cm–

$S=0.307(z^2 Z\rho)/(\beta^2 A)\,L(\beta)$

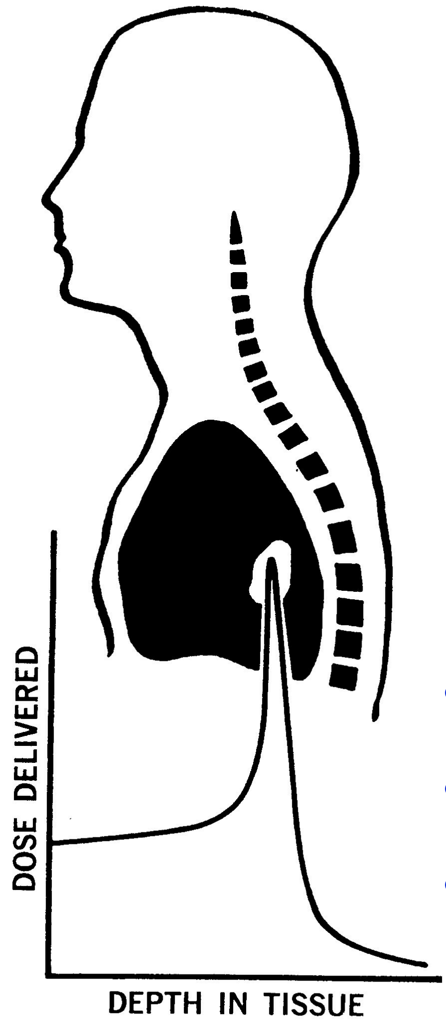
where

for projectile-particle –

- z: charge number and
- β: v/c

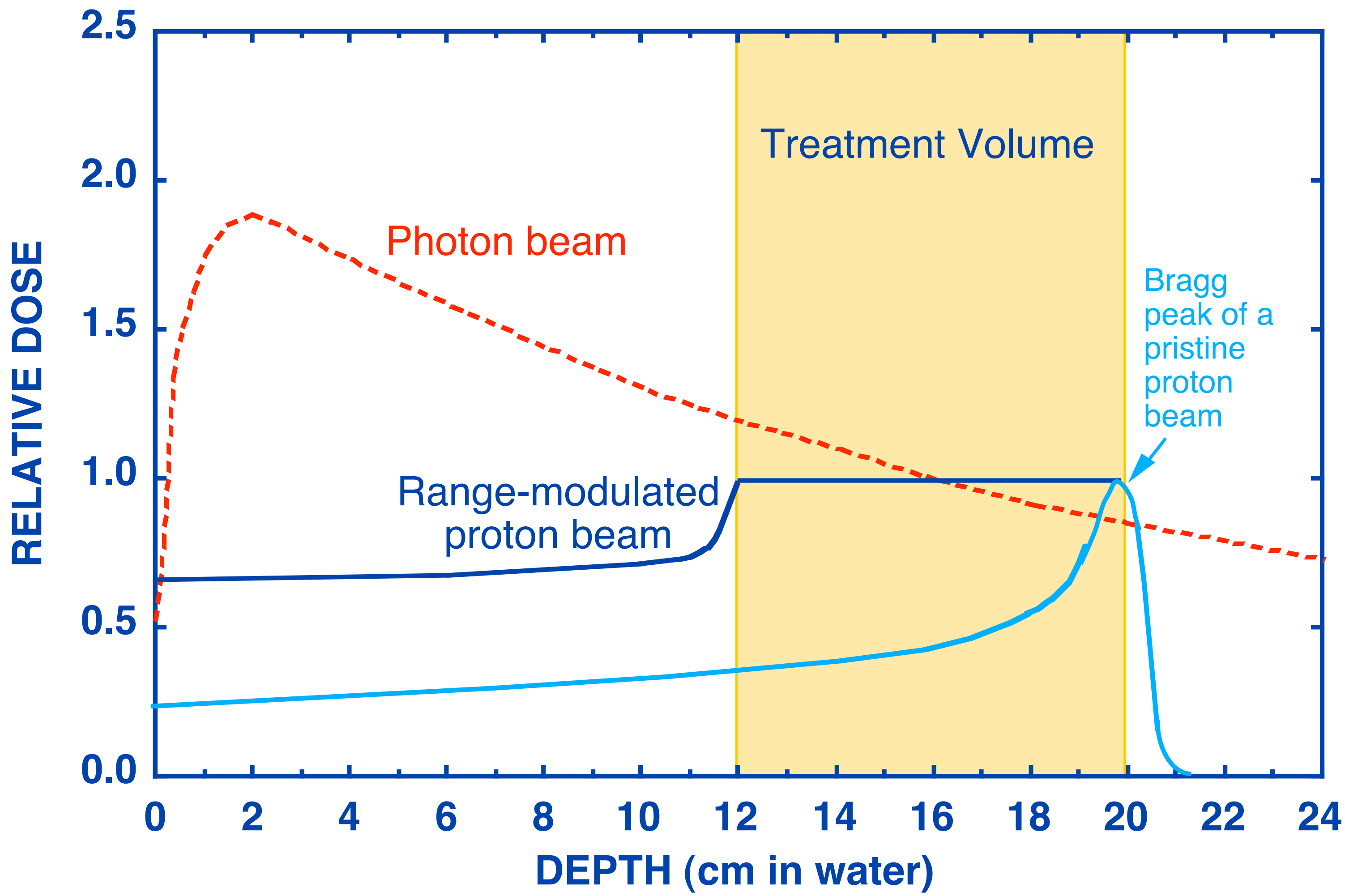
for medium

- Z: the nuclear charge
- A: the atomic weight
- ρ: the density
- L: the stopping number per unit mass

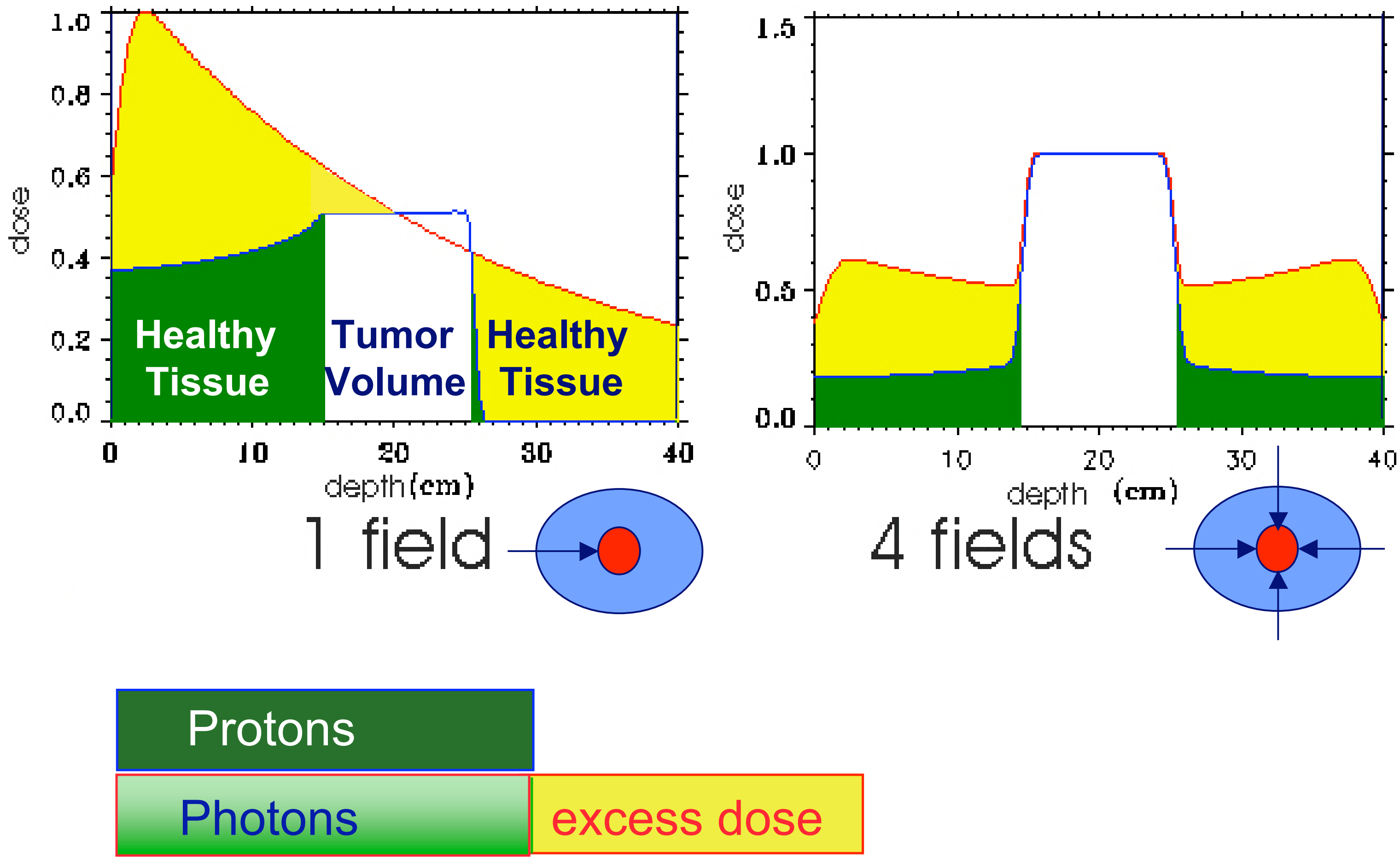


- Superior localization
- Lower entrance dose
- No or low exit dose

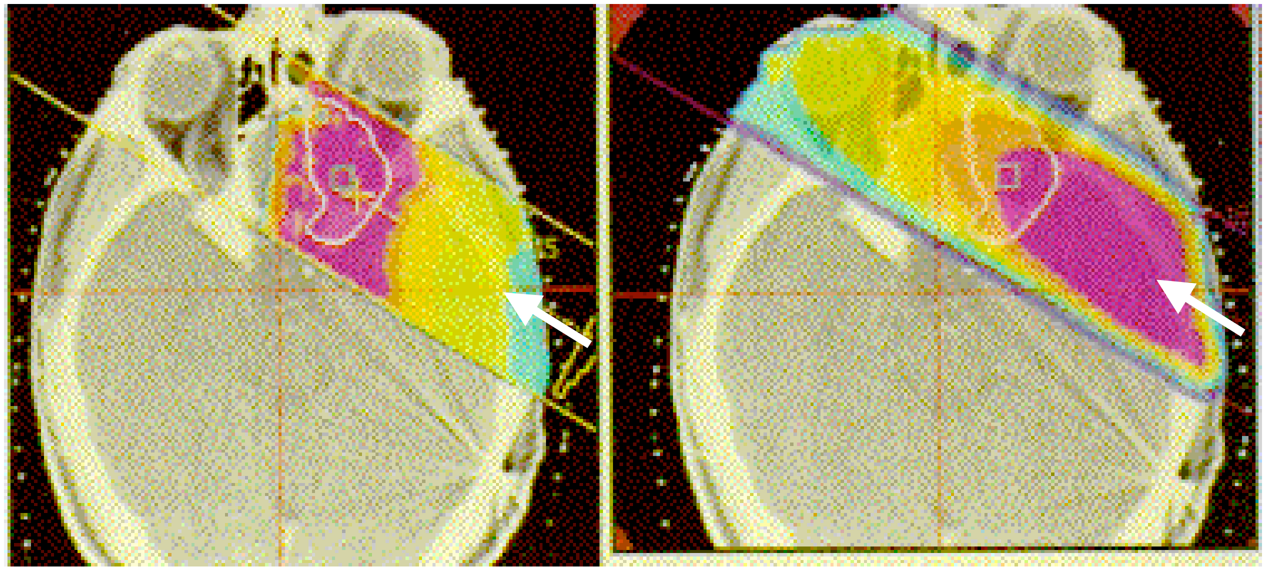
Depth-Dose Curves for Proton and Photon Beams



Dose Sparing: Protons vs. Photons



Clinical Advantage: Protons vs. Photons



Proton Beam　　　　　　　　Photon Beam

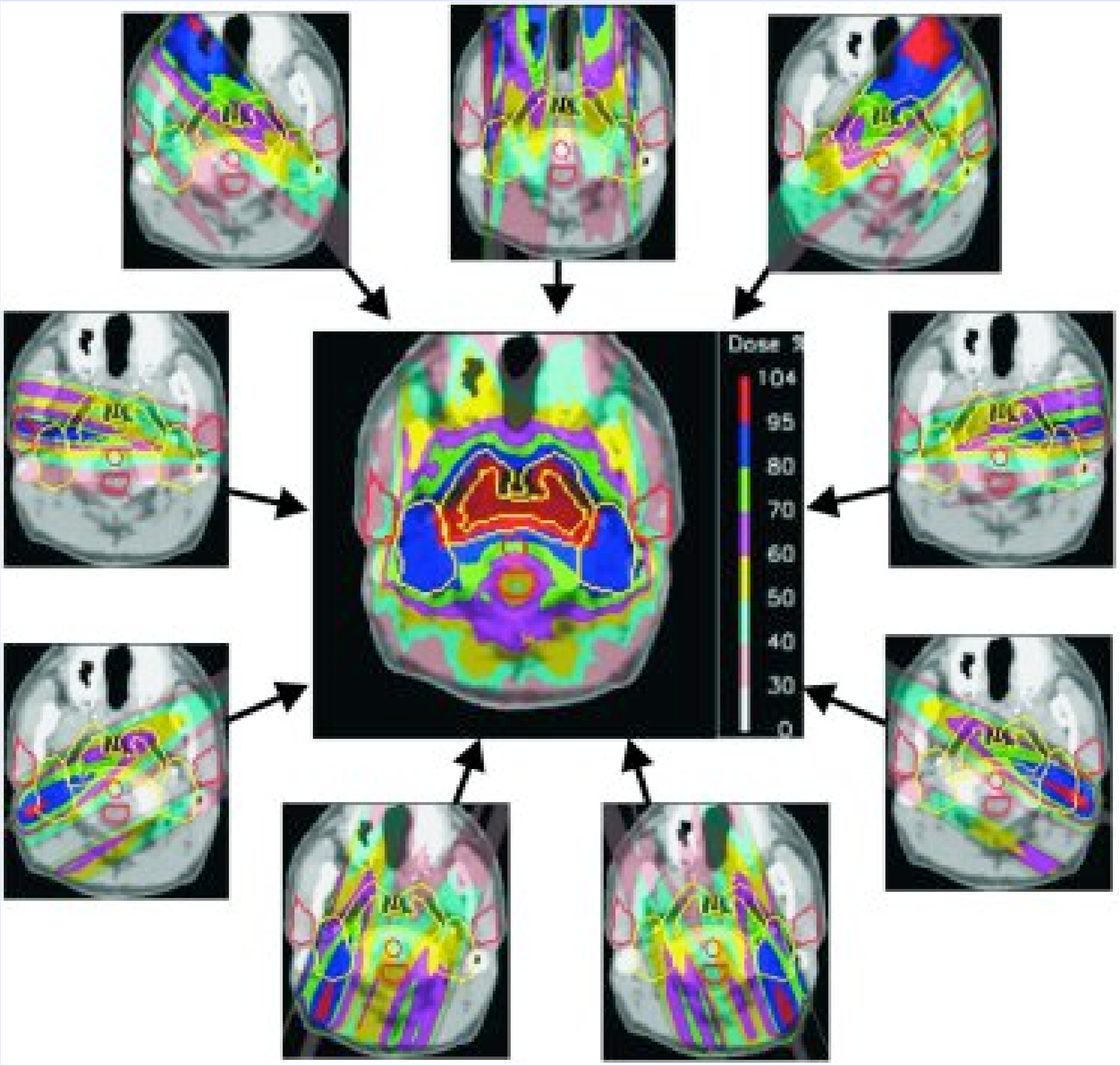
Proton vs. Photon Beams

- protons– lower entrance dose; no exit dose

Intensity Modulated Radiation Therapy (IMpT vs. IMRT)

- proton beams always produce superior dose distribution
  (protons provide higher cure rate with lower complication rate)
- fewer proton ports are needed than for a comparable photon treatment
  (the cost per cure is lower for proton therapy)

IMRT Therapy Planning- x rays



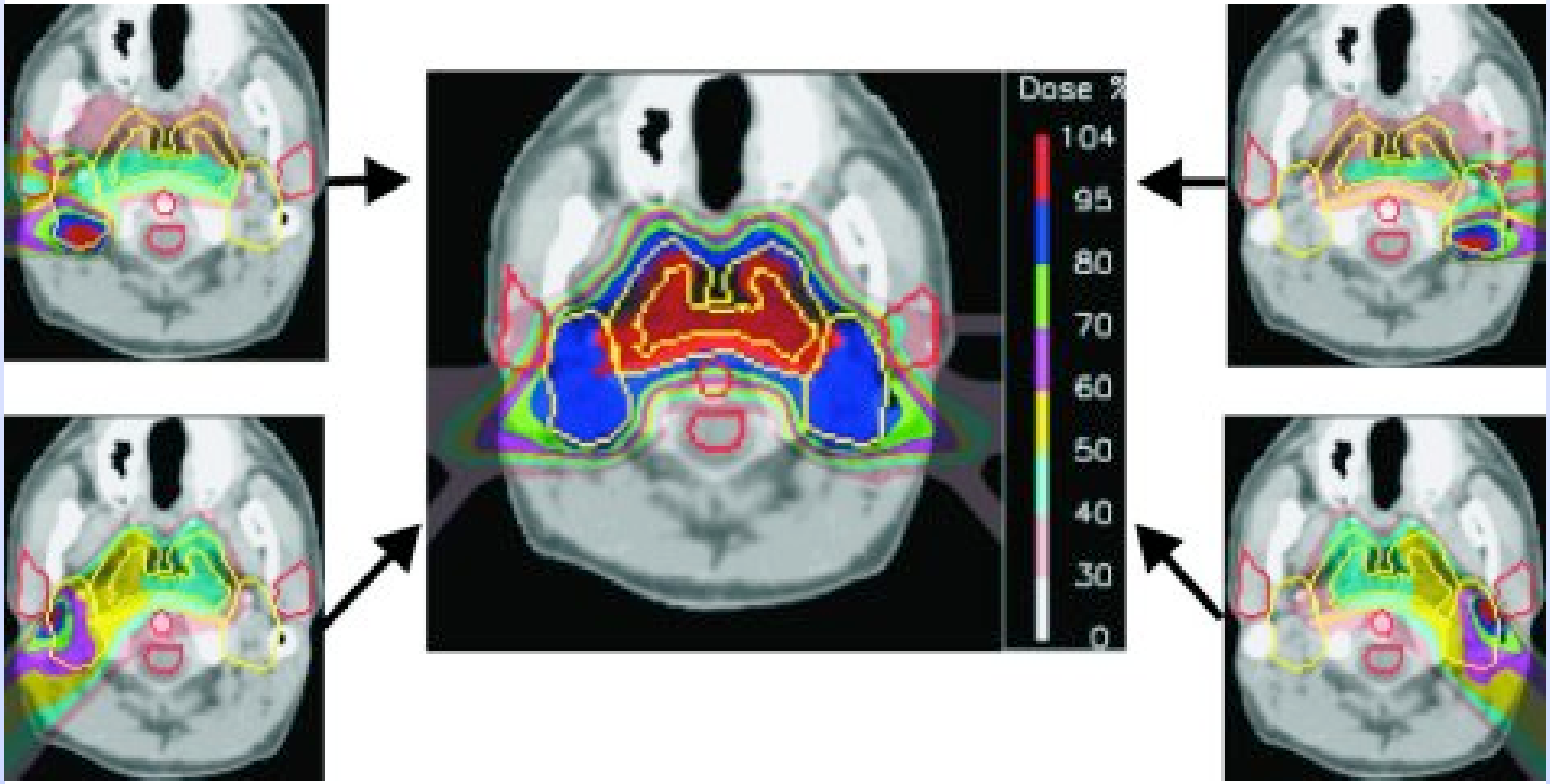
Example:

IMRT with photons

Use 9 fields to construct a highly conformed dose distribution with good **dose sparing** in the region of the brain stem.

(T. Lomax, PSI)

Proton Conformal Therapy Planning

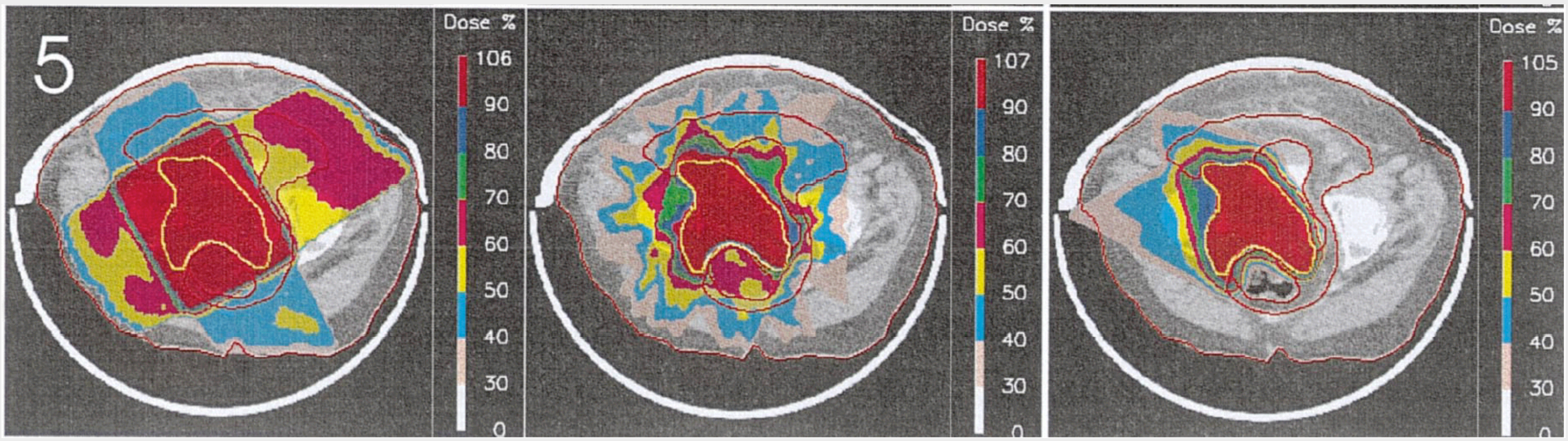


Example: **Proton therapy planning** using 4 dose fields.
The advantage compared with photon IMRT is the **general reduction of dose burden outside of the target volume**. (T. Lomax, PSI)

Photons vs. IMRT vs. Protons– Example

Cervix Cancer

Photons	IMRT	Protons



LAO,RAO,LPO,RPO*	9 fields	2 x RAO,RPO

	Photons	IMRT	Protons
Minimum significant dose in target (%):	95	81	93
Vol. (cm^3) receiving >30% of D:	4403 (x2.8)	3374 (x2.2)	1563

OAR and Tolerance Dose (% of mean target dose):

1 Rectum	65
2 Bladder	85
3 Large bowel	85
4 Total pelvis	

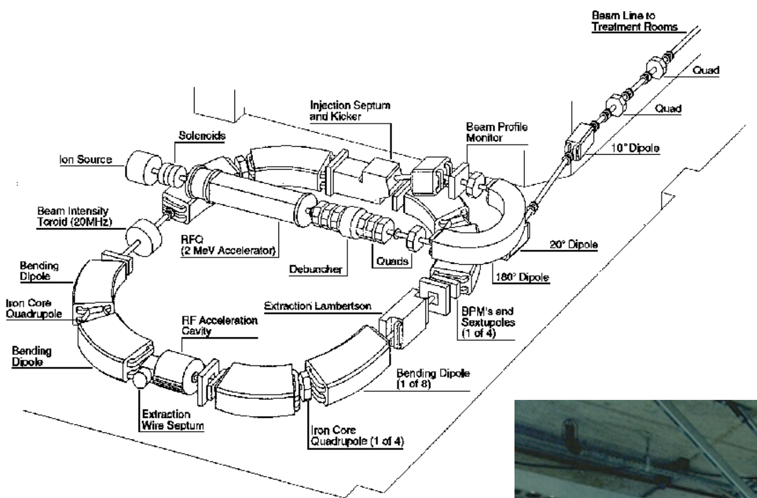
* **L**, lateral; **O**, oblique; **L**, left; **R**, right; **A**, anterior; **P**, posterior; **S**, superior

An Overview of Proton Therapy Facilities

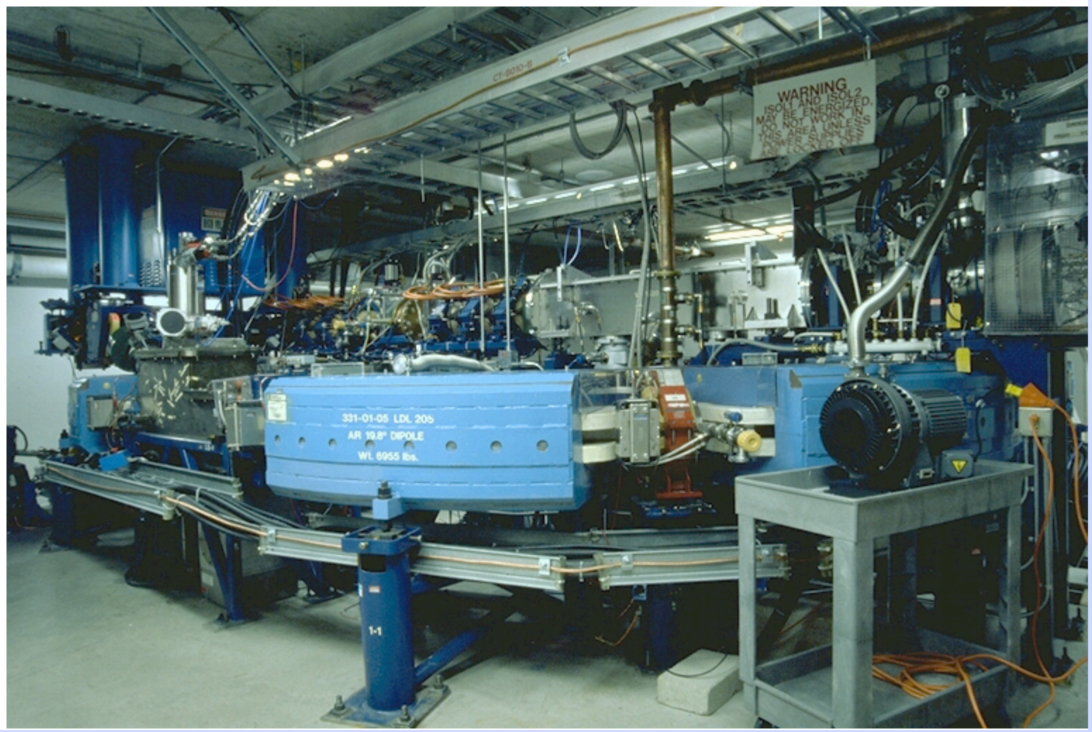
Clinical Specifications (LBNL/UCD/MGH)

ITEM	SPECIFICATIONS
Range in Patient	max = 32 gm/cm^2, min = 3.5 g/cm^2
Range Modulation	continuously adjustable
Range Adjustment	continuously adjustable
Average Dose Rate	2 Gy/min for 25 x 25 cm^2 field at 32 g/cm^2 full modulation
Spill Structure	scanning ready
Field Size	fixed: 40 x 40 cm^2, gantry: 40 x 30 cm^2
Dose Uniformity	˜2.5% over treatment field
Effective SAD	scattering: 3 m from the first scatterer wobbling: 2.6 m from the center of magnet
Lateral Penumbra	<2 mm over penumbra due to multiple scattering in patient

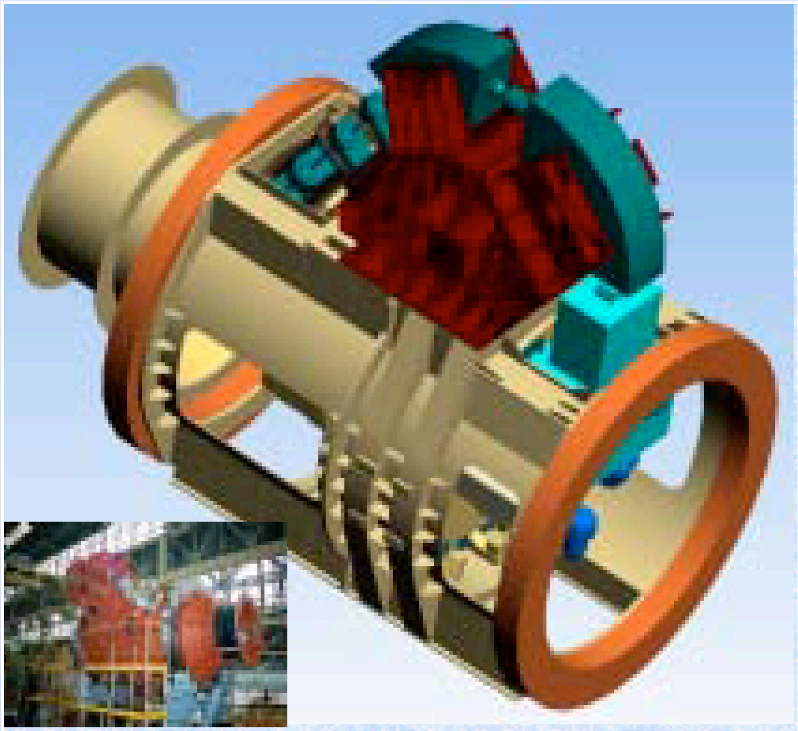
Medical Synchrotron, Loma Linda / Fermilab



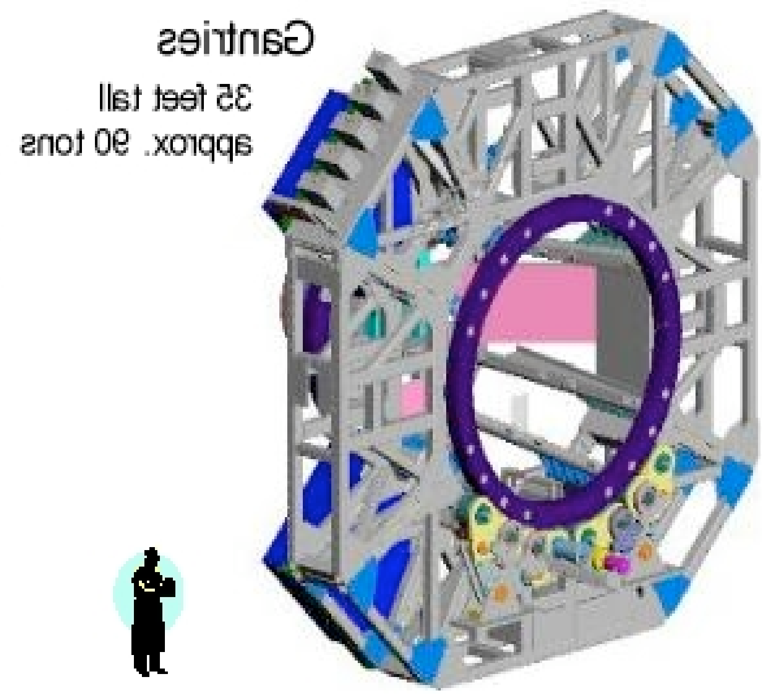
2 MeV RFQ, 250 MeV ZGS



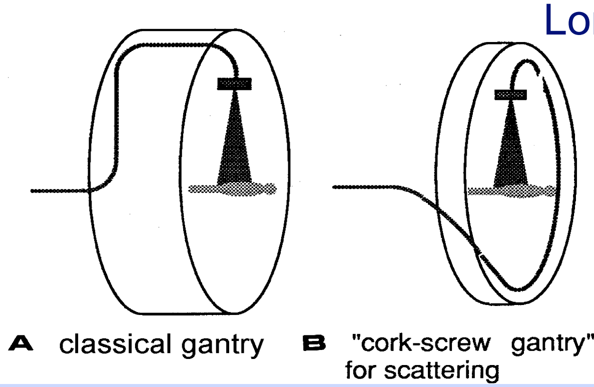
Rotating Gantries for 4π Treatment



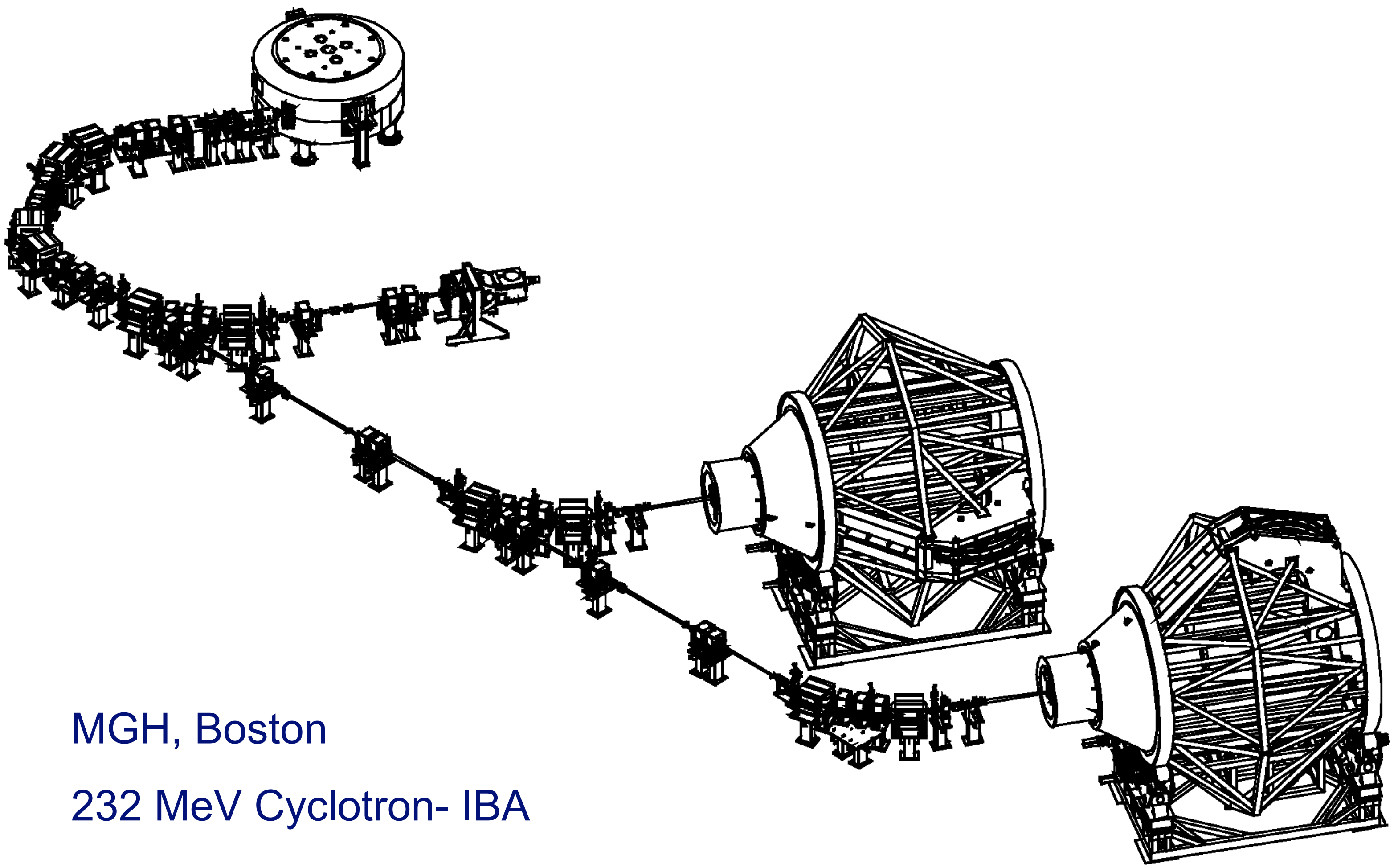
Tsukuba / Hitachi



Loma Linda / General Atomics



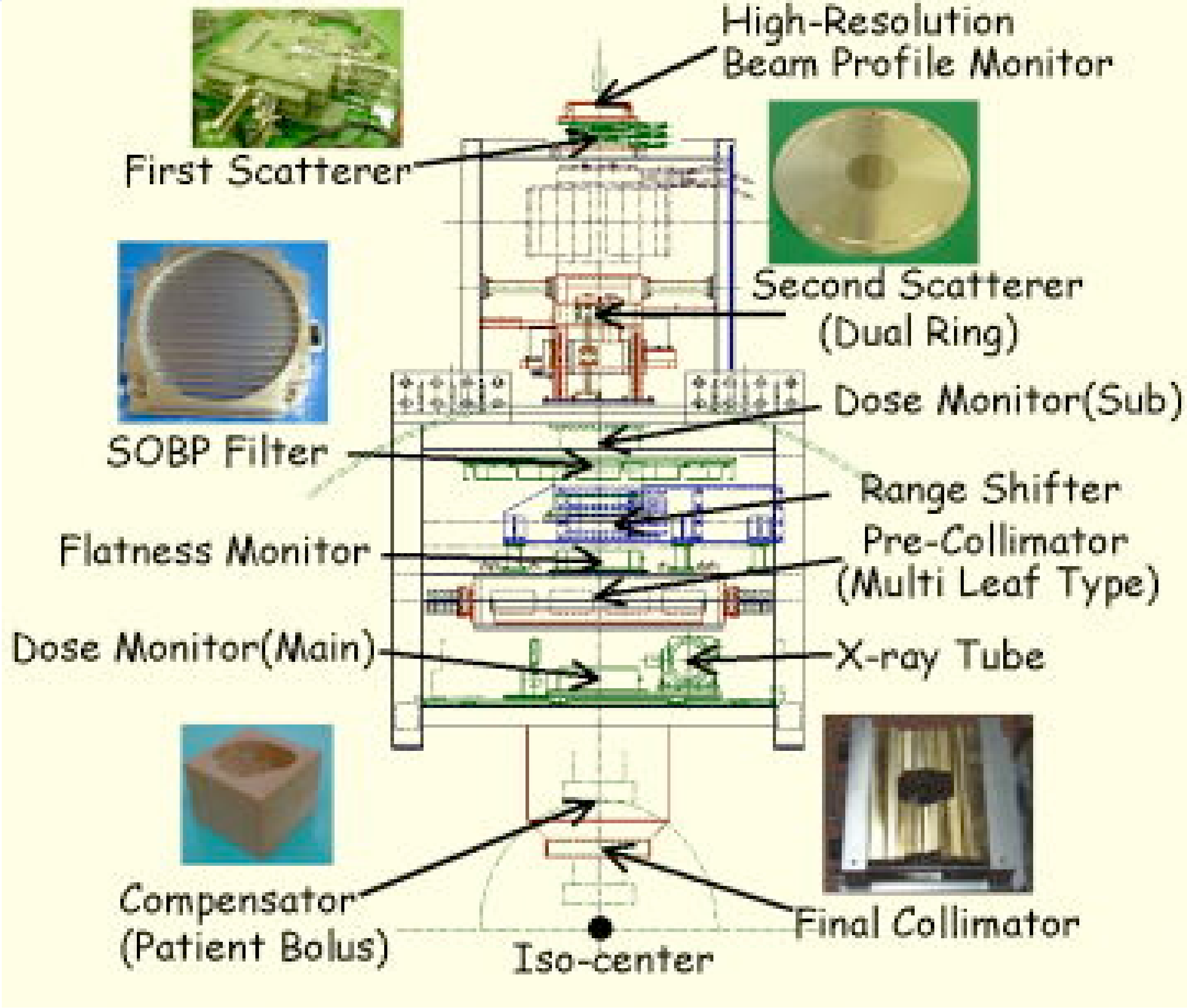
Accelerator Physicist's View of the Treatment Facility



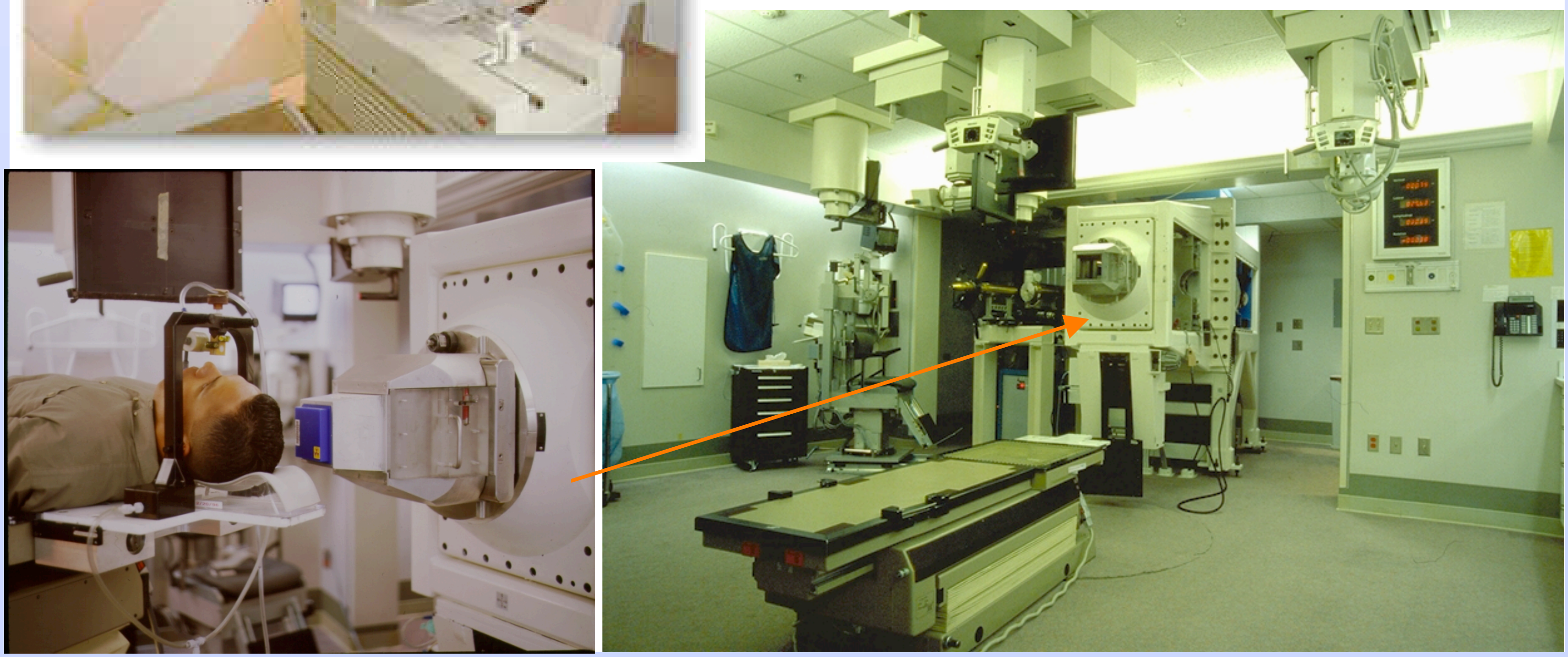
MGH, Boston

232 MeV Cyclotron- IBA

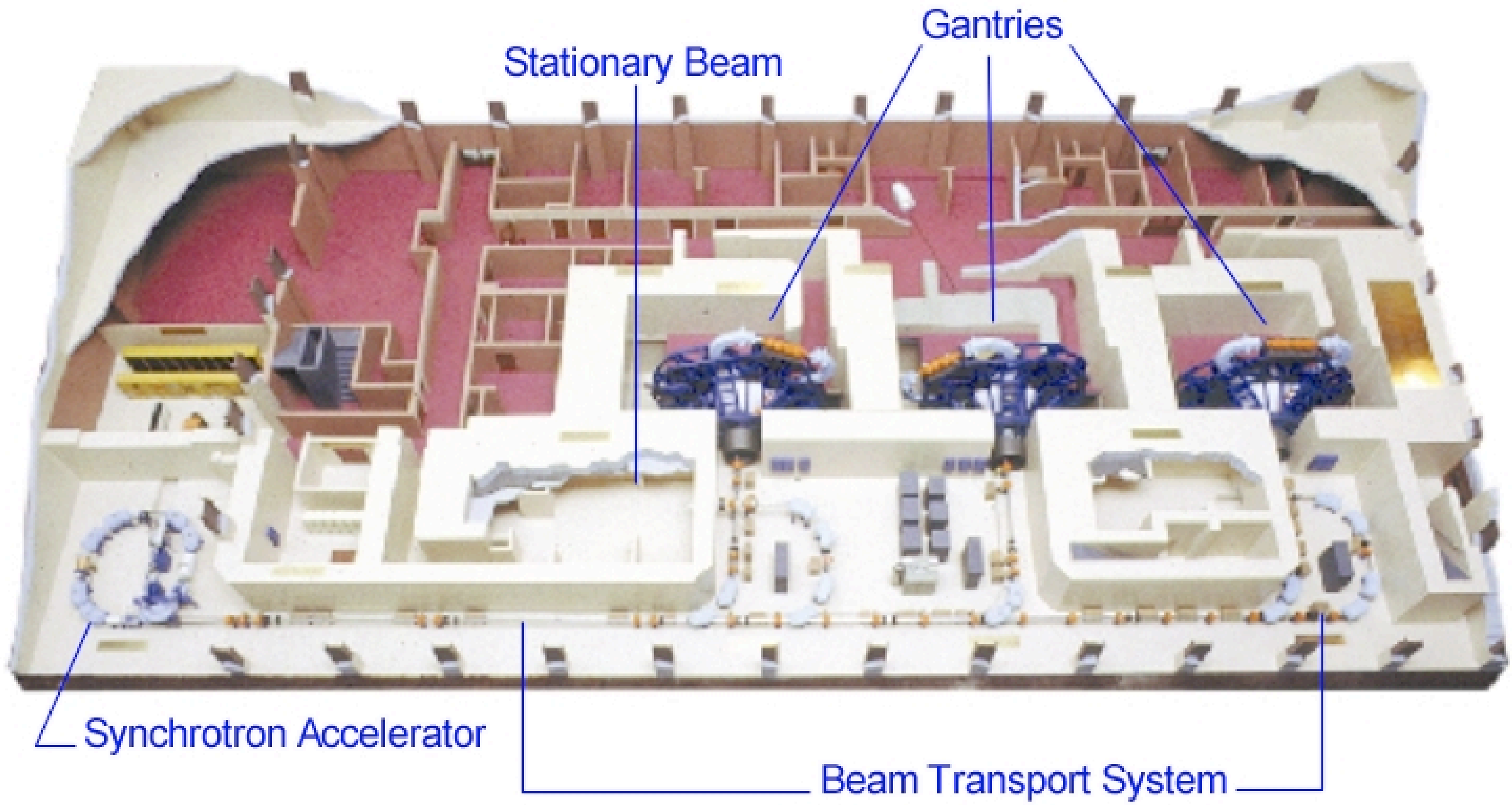
Physicist's View of the Treatment Facility



Physician/Patient’s View of the Treatment Facility



Builder's View of the Treatment Facility

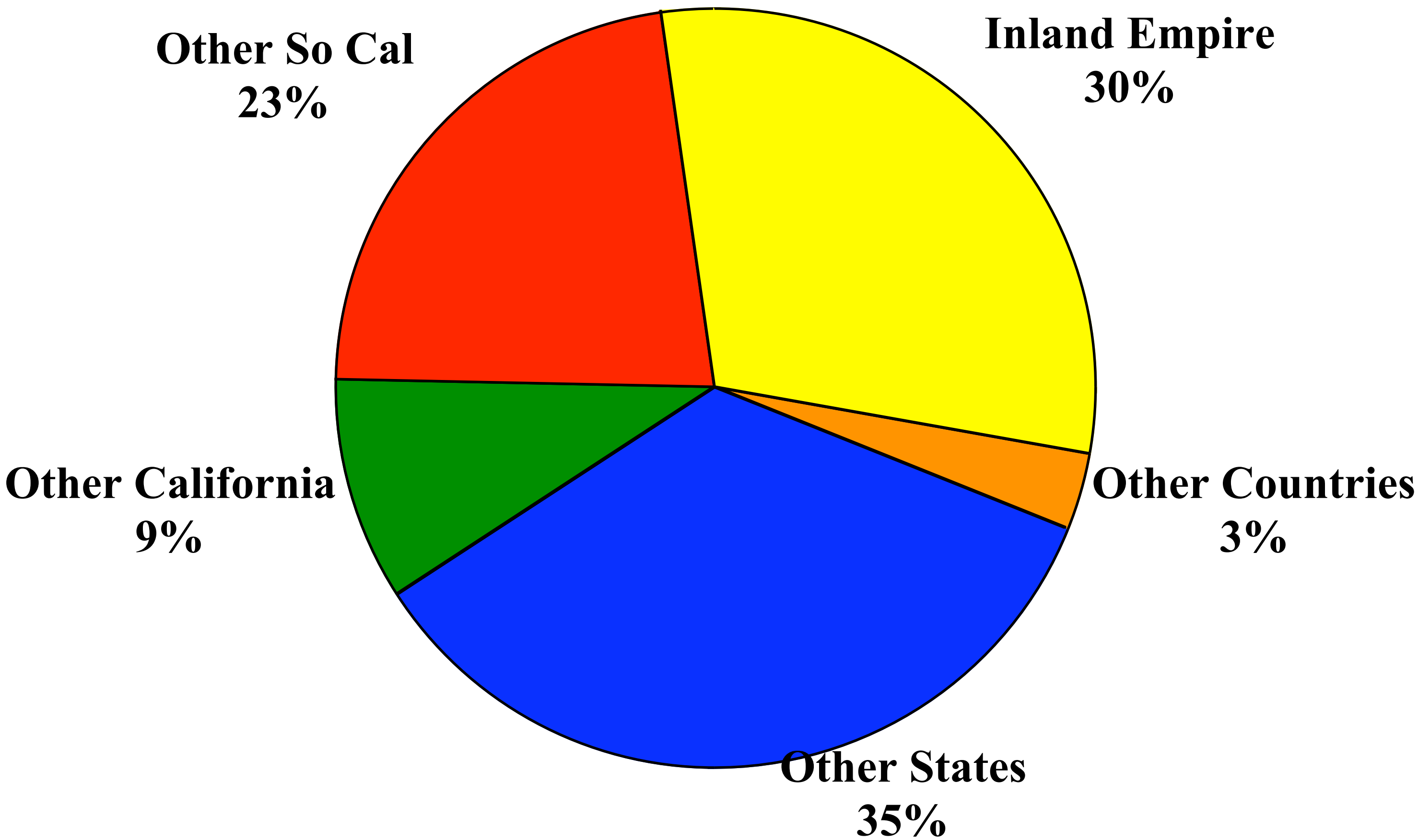


The Loma Linda University Medical Center Proton Therapy Facility was commissioned in 1991, and has successfully treated more than 7200 patients.

Diseases Treated Usin Protons (Loma Linda)

Brain and Spinal Cord	Gliomas (intermediate and low-grade) Isolated brain metastases Pituitary adenomas Arteriovenous malformations
Base of Skull	Meningiomas Acoustic neuromas Chordomas Chondrosarcomas
Eye	Uveal Melanoma Macular degeneration
Head and Neck	Nasopharynx (primary and recurrent) Oropharynx (locally advanced)
Chest and Abdomen	Stage A lung cancer (medically inoperable) Chordomas and chondrosarcomas
Pelvis	Prostate Unresectable pelvic cancers Chordomas and chondrosarcomas
Pediatrics	Brain and spinal cord tumors Orbital and ocular tumors Sarcomas of the base of skull and spine Abdominal and pelvic malignancies

Demographics of Patients (1990-2000, Loma Linda)



Diseases Treated at Loma Linda (to 6.01)

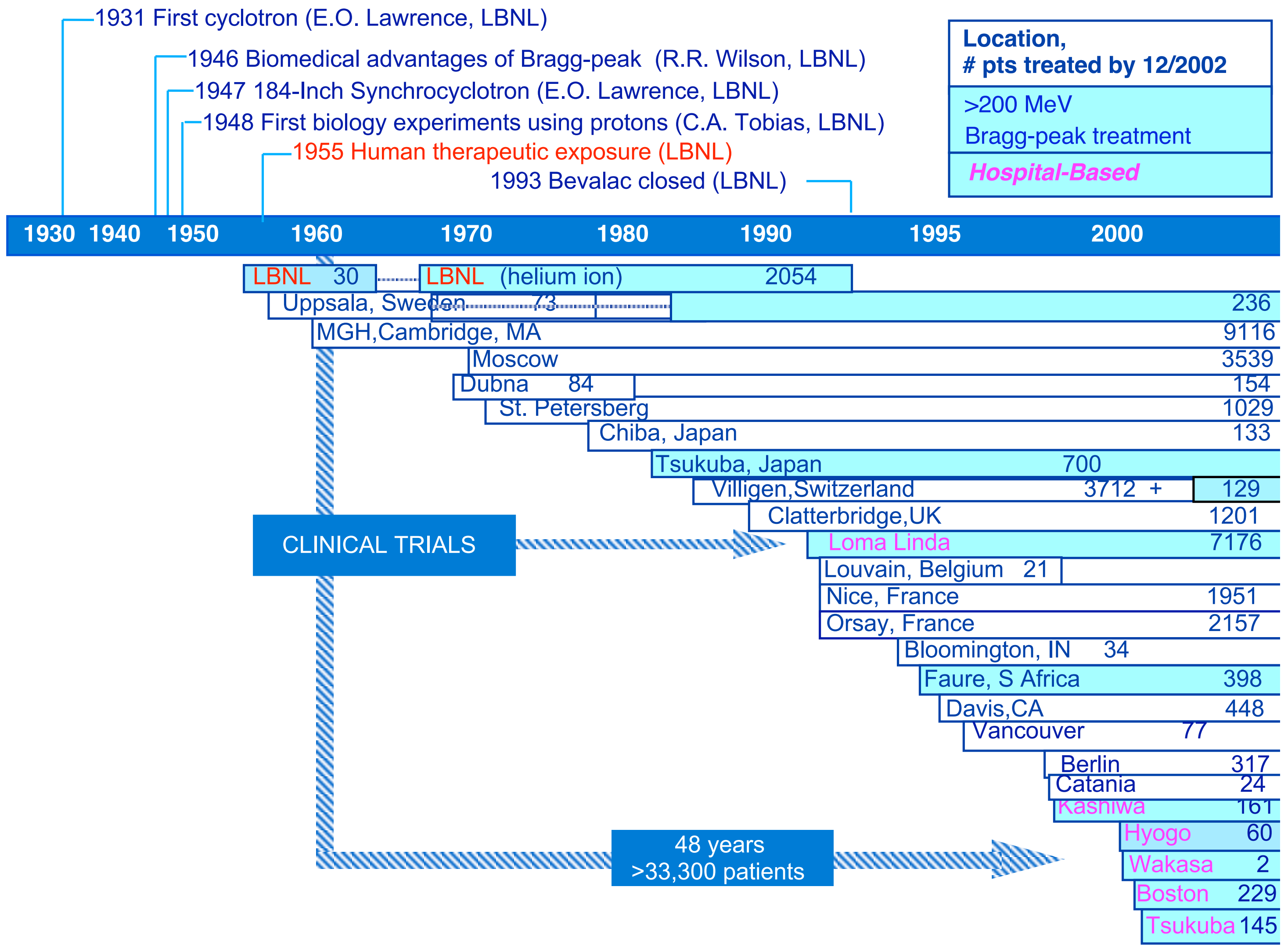
LOMA LINDA UNIVERSITY MEDICAL CENTER
COMPLETED PROTON PATIENT SUMMARY
FROM INCEPTION THROUGH JUNE 2001

DIAGNOSIS CATEGORY	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	TOTAL	%
Choroidal Melanoma	3	7	13	4	13	8	8	13	9	1	10	9	98	1.6%
Pituitary		10	17	6	5	1	7	2	2	7	6	8	71	1.1%
Acoustic Neuroma		3	3	0	3	3	4	2	2	9	7	5	41	0.7%
Meningioma		8	16	8	8	7	7	19	12	9	17	4	115	1.8%
Astrocytoma		4	26	4	6	5	17	9	7	10	13	10	111	1.8%
Other Brain		6	6	7	9	15	3	17	31	36	41	19	190	3.0%
Head & Neck		3	26	20	26	27	49	41	43	55	65	30	385	6.2%
Prostate		4	198	234	234	308	476	507	631	447	491	344	3874	61.9%
Other Pelvis		1	8	10	4	0	8	3	8	5	7	8	62	1.0%
Craniopharyngioma		0	3	0	1	1	2	4	4	2	2		19	0.3%
Orbital		3	2	0	0	1	2	11	13	12	0	4	48	0.8%
Paraspinal Tumors		1	11	8	6	4	7	7	12	15	14	4	89	1.4%
Chordoma/Chondrosarcoma		0	13	26	21	25	28	38	51	44	34	22	302	4.8%
Sarcoma		3	3	3	12	2	4	8	15	9	17	2	78	1.2%
Other Chest		0	0	7	11	34	16	34	44	27	49	20	242	3.9%
AVM				1	31	17	14	6	21	12	12	6	120	1.9%
Other Abdominal					5	7	9	4	9	23	13	14	84	1.3%
SNVM					21	29	20	35	30	57	101	37	330	5.3%
TOTAL BY YEAR	3	53	345	338	416	494	681	760	944	780	899	546	6,259	100.0%

Clinical Outcome of Prostate Treatments (Loma Linda)

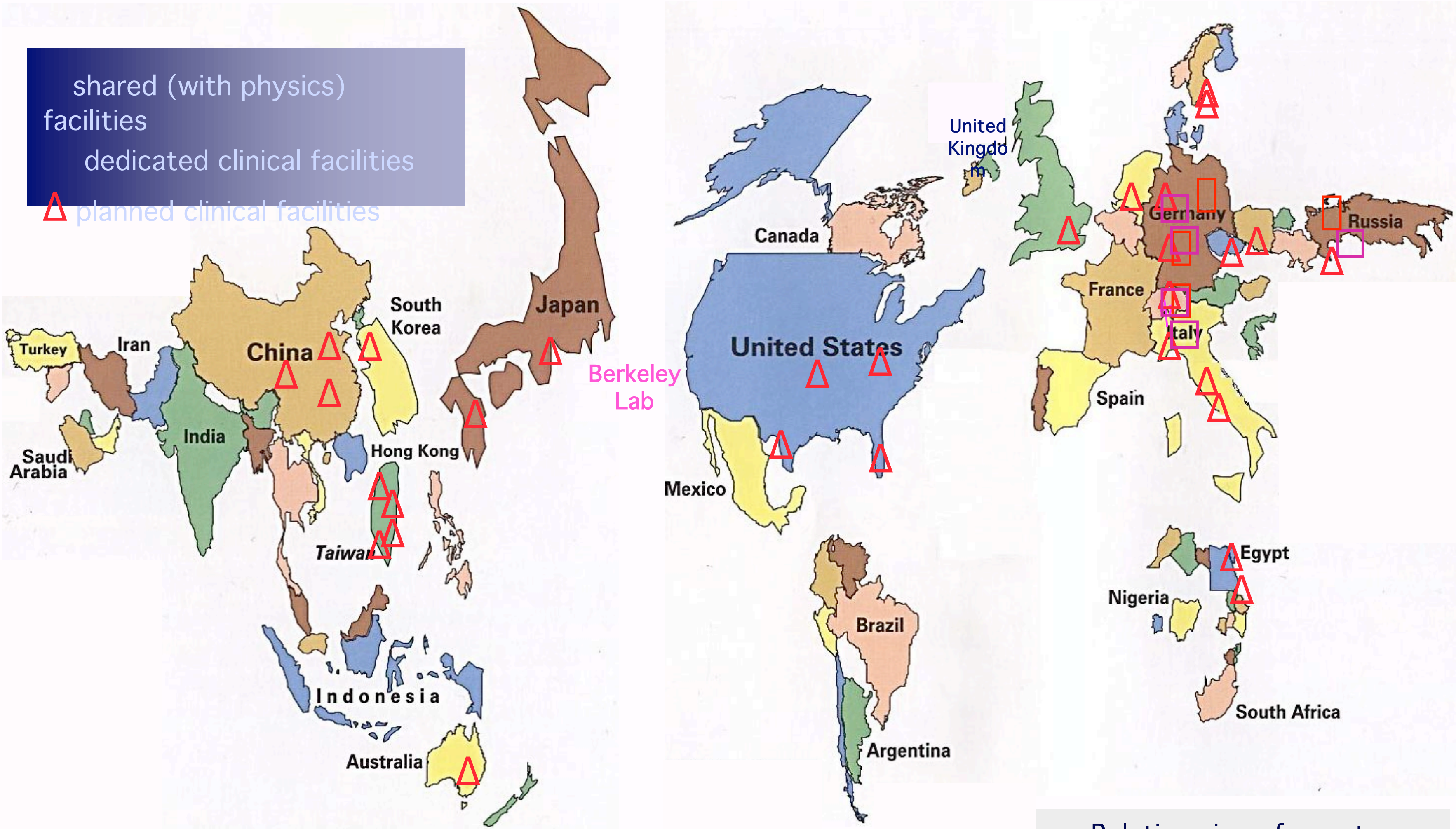
		Prostatectomy	Photon Radiation (75 Gy)	Proton Beam Treatment (75 CGE)
Clinical Outcome	Survival @ 5 years	>95%	>95%	>95%
Morbidity	Incontinence	≤8%	≤5%	≤1%
	Grade III/IV GI/GU Toxicity	0	≤10%	≤1%
	Impotence	≤60%	≤31%	Under study Expected ≤30%
Quality of Life		Requires hospital stay; treatment of side effects	Often requires treatment of side effects	Typically return to home or work

Proton Therapy Scientific Milestones



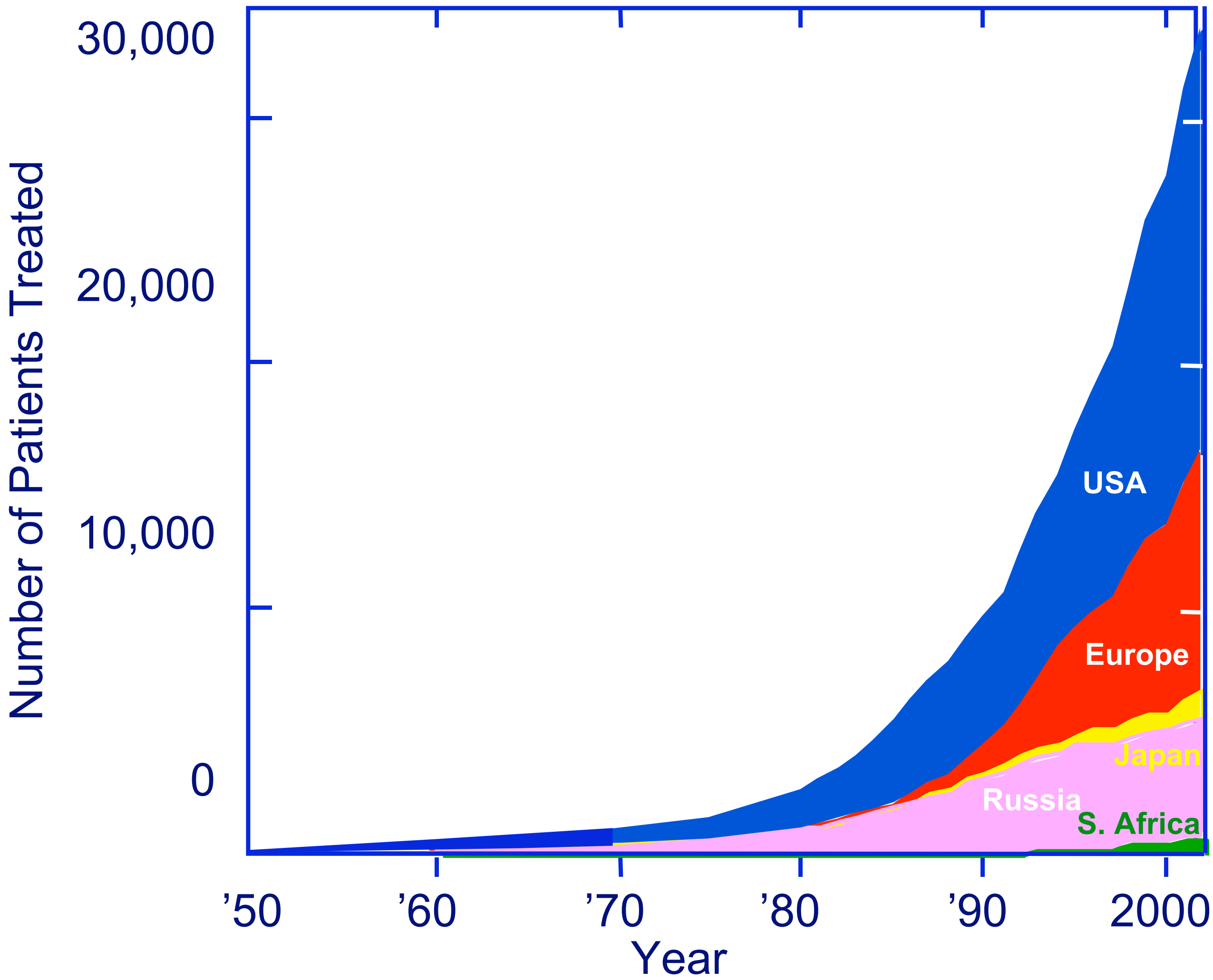
Proton Therapy Facilities Around the World (2001)

shared (with physics) facilities
dedicated clinical facilities
planned clinical facilities



Relative size of country indicates relative size of Gross Domestic Product.

Growth of Proton Treatments



National Needs of Proton Therapy (USA)

- Needs for clinical proton facilities in the US*
  - ~375,000 cancer patients will turn to radiation therapy (conventional) for curative treatments
  - ~130,000 of the above will benefit if treated using 3D conformal radiation therapy (which is best delivered using proton beams)
  -

	IMRT	Proton
# pts trreated per year	**250**	**1000**
# fractions treated per year	**8000**	**16000**
Treatment per day	**32**	**64**
Facilities needed	**520**	**130**

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* Based on the **Final Report of a Select Panel** (chaired by Lester J. Peters, Univ. Texas, M.D. Anderson Cancer Center, 1992; no proton advocators in the panel) to the **National Cancer Advisory Board**.

Proton Therapy Facilities Built by Industries

Name of Institution	Main Accelerator	Particle	Energy MeV/u	Oper.	Beam Courses				
					Horizon	Vertical	45?	Rotating Gantry	Research
Loma Linda	Synchrotron	proton	250	1990	1			3	1
HIMAC / NIRS Chiba	Synchrotron D~40 m x 2	p~Xe	800 (q/m=1/2)	1994	2 ^{12}C	2 ^{12}C			5 p~Xe
PTF/ NCC-HE Kashiwa	Cyclotron D ~4 m	proton	235	1998	1			2	
HARIMAC Hyogo	Synchrotron D~30 m	proton 12C	230 320	2001	1 ^{12}C	1 ^{12}C	1 ^{12}C	2	1
PTF, PMRC U. Tsukuba	Synchrotron D~7 m	proton	250	2001				2	2
W-MAST Wakasa-Bay	Synchrotron D~10 m	proton	200	2001		1			1
NPTC / MGH Boston	Cyclotron	proton	232	2002	1			2	
PTF / CC Shizuoka	Synchrotron D~6 m	proton	235	2002	1			2	
Zibo, China	Cyclotron	proton	232	2002	1			2	
Ilsan, Korea	Cyclotron	proton	232	2002	1			2	
MDACCr, Houston, TX	Synchrotron	proton	250	2006	1			5	1
HUP, Philadelphia	Bids accepted	proton	250	2006	1			3	1
Palermo, Sicily	RFP	proton	250	2006	1			1	1

Planned: ETOILE, Lyon (France); Yokohama City University; Kanagawa Cancer Center; Kyushu University; Ibaraki-ken; Gifu-ken; Aichi-ken CanceR Center; Hukui-ken Hospital (Japan); Iksan, Jeonbuk (Korea)

Construction Costs of Proton Therapy Facilities*

Proton Therapy Facility	Major Contractor	Facility Descriptions -accelerator	-gantry	-fixed	Tech Comp Cost	Tech + Bldg Cost
Loma Linda (1991)	SAIC/FNAL	250 MeV synchrotron	3	2/3		$76M
NPTC, Boston (2001)	IBA	232 MeV cyclotron	2	2 empty	$24M	$49M
NCC, Kashiwa, Tokyo (1999)	Sumitomo	235 MeV cyclotron	2	1		$60M
Tsukuba (2001)	Hitachi	250 MeV synchrotron	2	1/2		$67-70M
Wakasa Bay (2002)	Hitachi	200 MeV synchrotron	0	1 H/V	acc $20M beam $15M	$43-45M
Shizuoka (2003)	Mitsubishi	210 MeV synchrotron	2	1		

* Based on data supplied by James Slater (Loma Linda); Michael Goitein (MGH); and Sadayoxhi Fukumoto (Japanese facilities).

Cost Analysis for Protons vs. Photons – 1

	Proton	IMRT	Multiplicative factor for photon facilities to equal the capability of one proton facility
BASIC COST Tech. components Conventional facility Facility TOTAL	 ~ $37M ~ $35M ~ $72M	 ~ $3M ~ $5M ~ $8M	**Wrong conclusion**: Proton cost ~ 9 X IMRT cost
# of therapy rooms	4 – 5	1	X4 - 5
# of ports for conformal therapy	2 - 3 ports	5 - 10 ports	The length of time to finish
Conformal therapy delivery per hour per room	3 (capable now)	2	each fraction X1.5
# of fractions per treatment	potentially fewer than 32 fx/tx	~ 32 fx/tx	X1.2
Useful life of the accelerator(s)	Useful life of synchrotron facility ~ 25 - 35 years	Useful life of linacs ~ 10 - 12 years	X2
NET MULTIPLICATIVE FACTOR			X14 - 18, take **X16** as a nominal figure

Conclusion: A proton facility may cost as much as 9 IMRT facilities; but, it can treat 16 times as many patients during its lifetime.
Protons are cost-effective!

Cost of Protons vs. Photons –2

	Proton	IMRT
Cost of Proton vs. IMRT Facilities		
Technical Components in 25 years	Useful life time is ~ 25 years: ~ $37M	8 linacs ~ $3 X 8 = $24M to be replaced after 10 to 12 years ~ 48M
Cost of conventional facility	For one: $35M	To house 8 linacs ~ $40M
Total cost of the therapy facility in 25 years	~ $72M	~ $88M
Labor Cost		
Maintenance	1 proton facility	8 linac facilities
Therapy planning	Proton conformal therapy requires 1-5 ports	IMRT requires 5-10 ports
Patient Preparation and Setup	Fewer ports and possibly fewer fractions	Larger number of ports and larger number of fractions

Conclusion:

- Costs per treatment for protons and IMRT are comparable.
- “Cure / no complication”probability– lower for protons than IMRT.
- Cost-benefit ratio is advantageous for protons over IMRT.

Conformal Dose Delivery- Beam Scanning

The most important attribute of hadron therapy --

- Dose localizing characteristics

To take a full advantage of this characteristics --

- Three-dimensional dynamic conformal therapy delivery

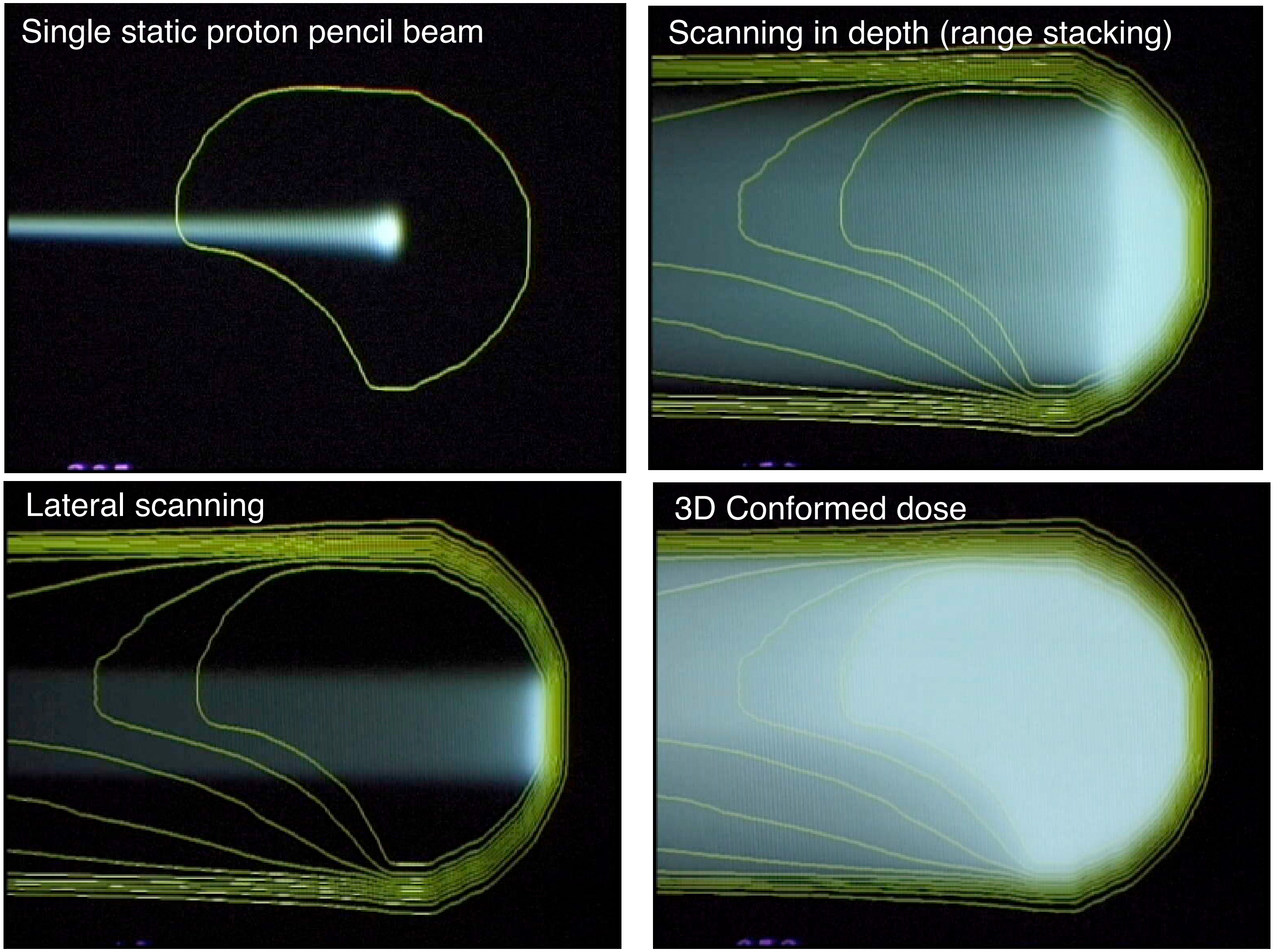
  - Intensity Modulated Proton Therapy

    (IMpT) ← compare → IMRT

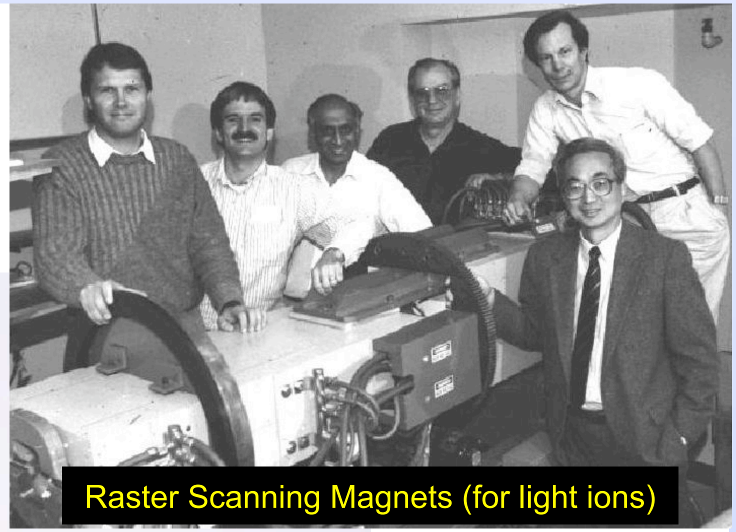
  - Raster-scanning- LBNL

  - Pixel scanning- PSI, GSI

Beam Scanning (PSI)

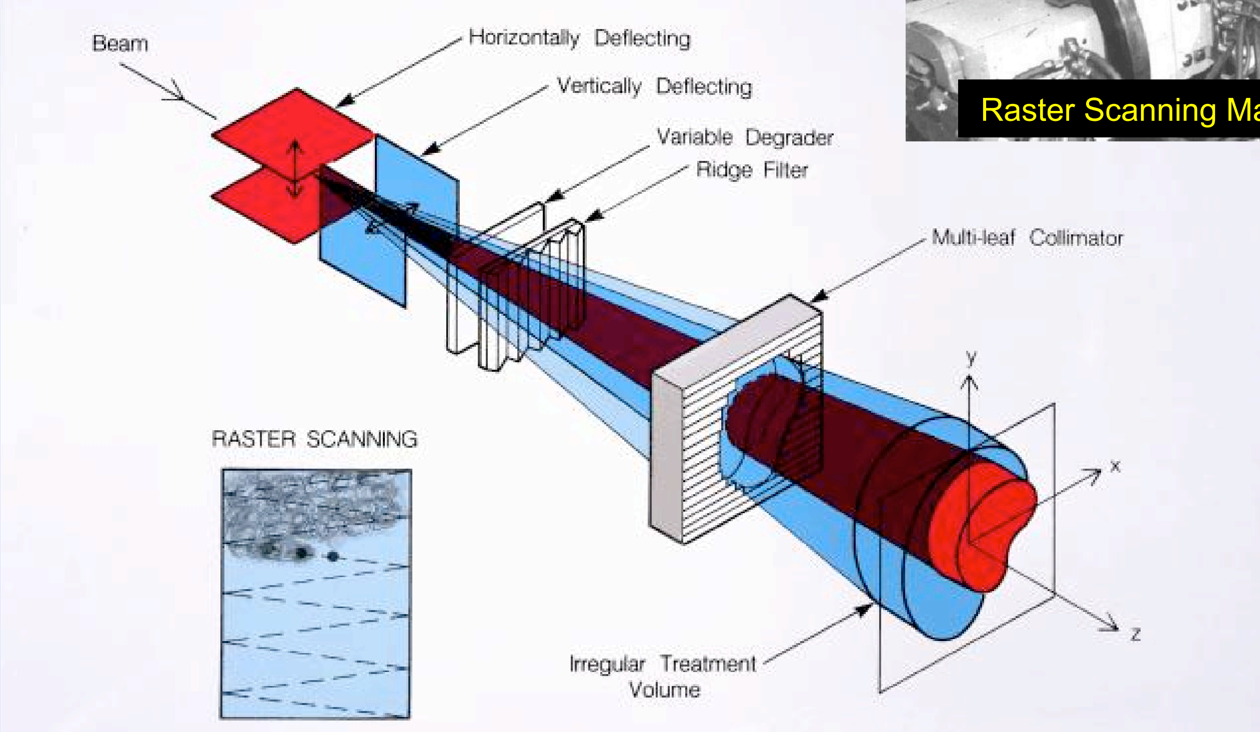


LBNL Raster Scanning System

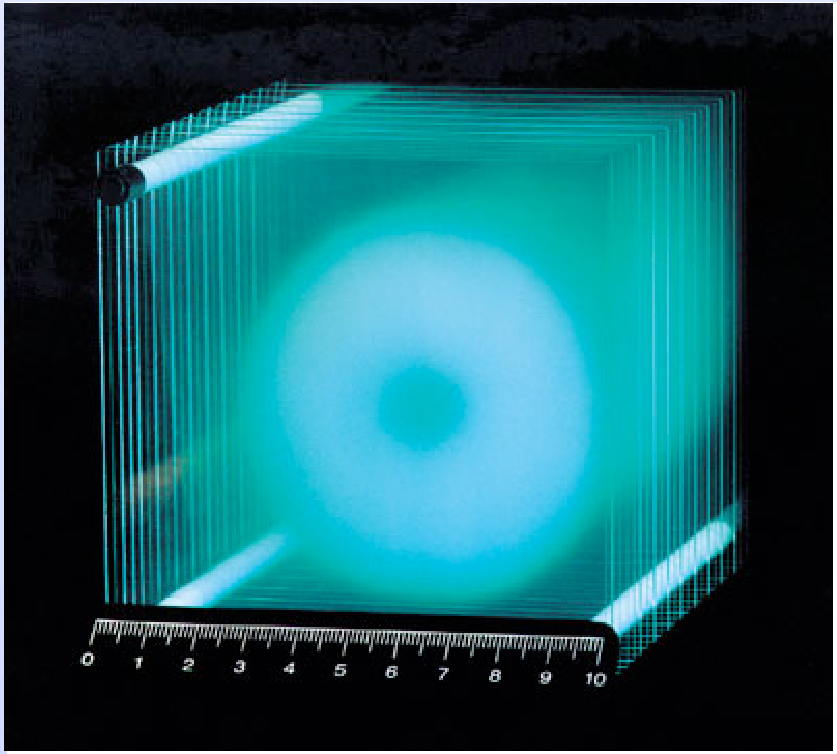


Raster Scanning Magnets (for light ions)

Commissioned for clinical use in 1991.

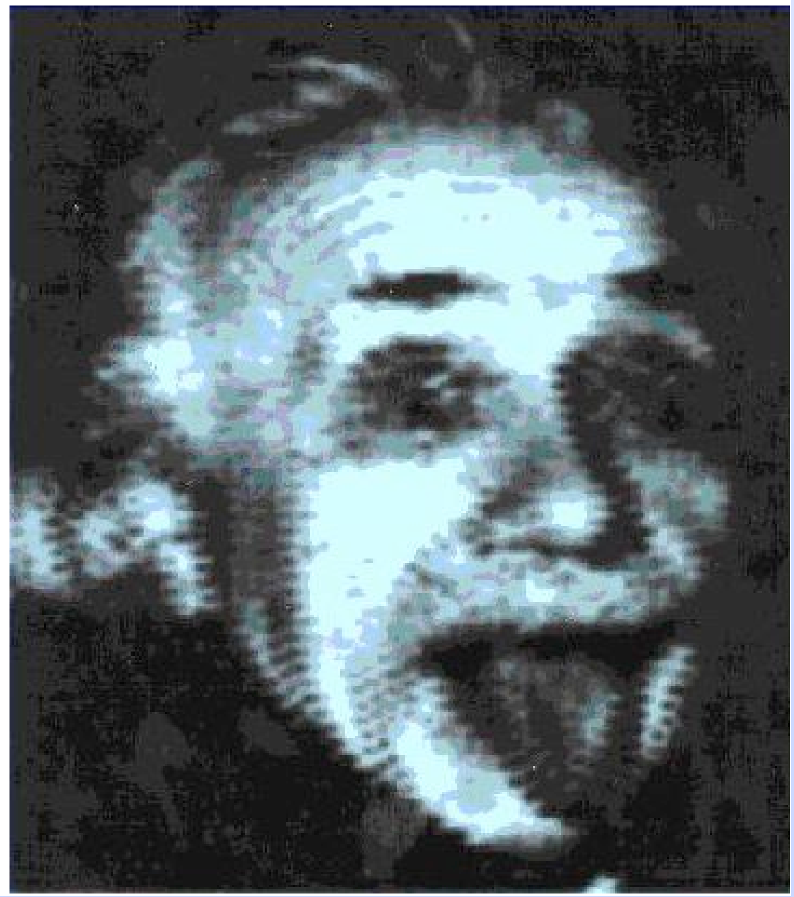


Carbon-Ion Beam Scanning – GSI

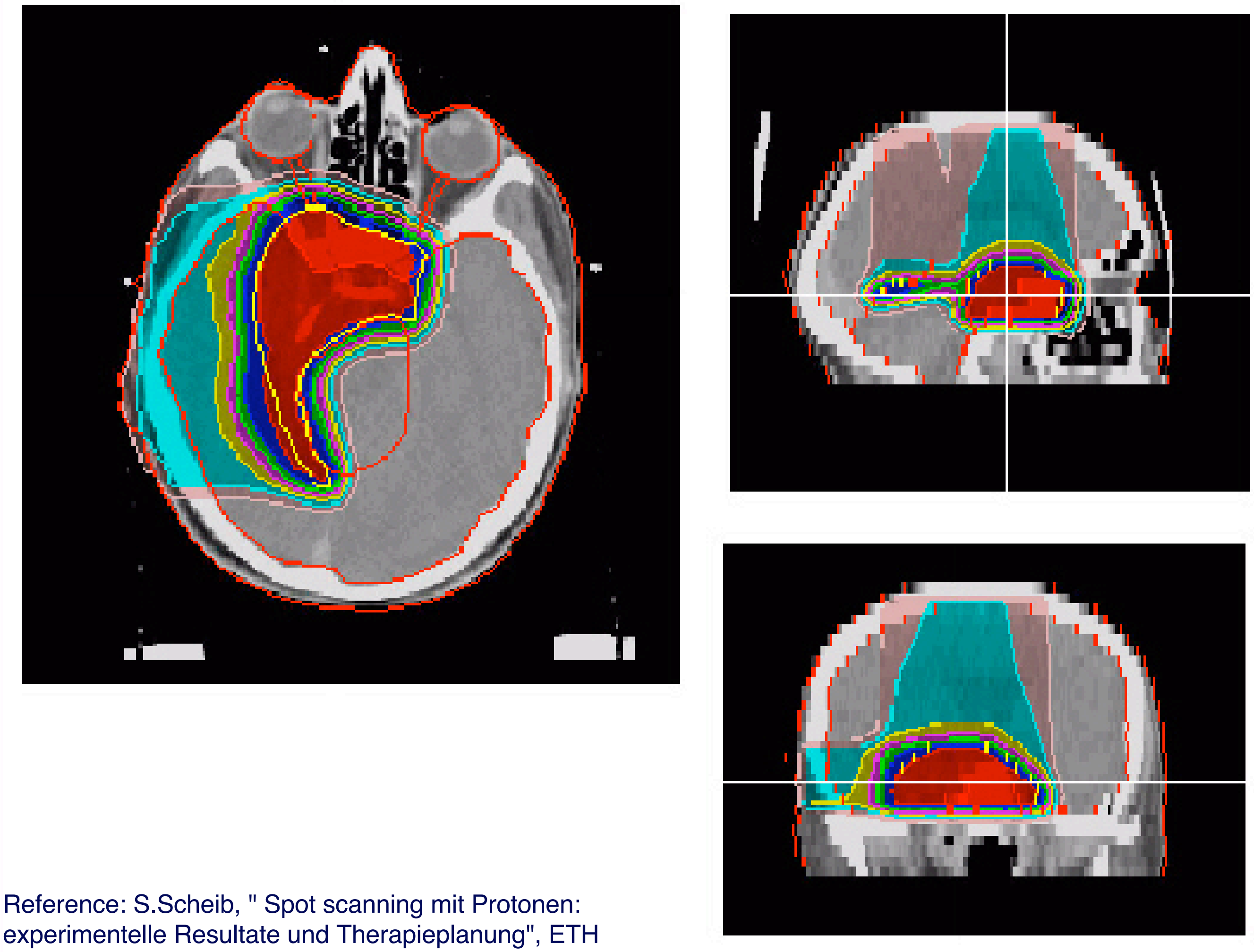


The GSI beam-scanning technique allows any shape to be irradiated. Here, plastic sheets immersed in water have been irradiated in a doughnut shape.

GSI, carbon beam

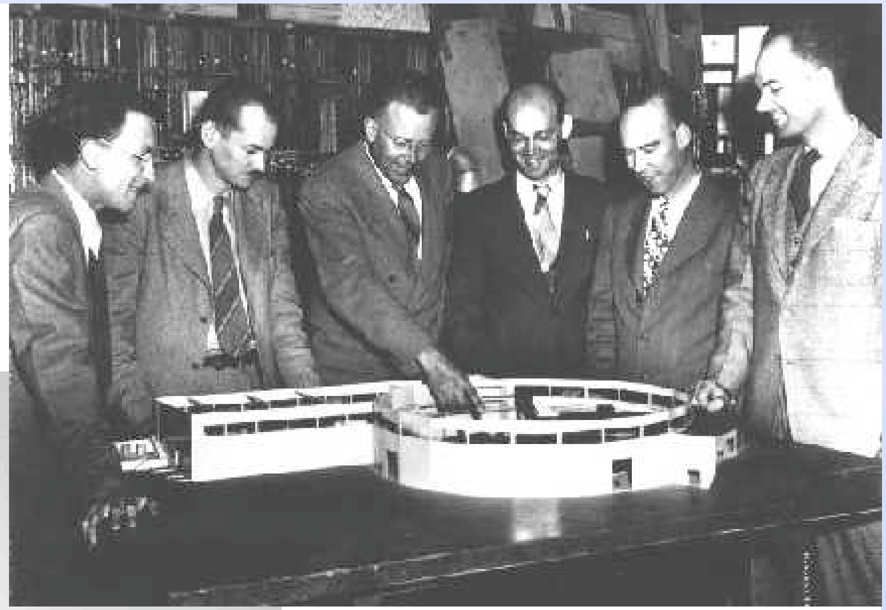


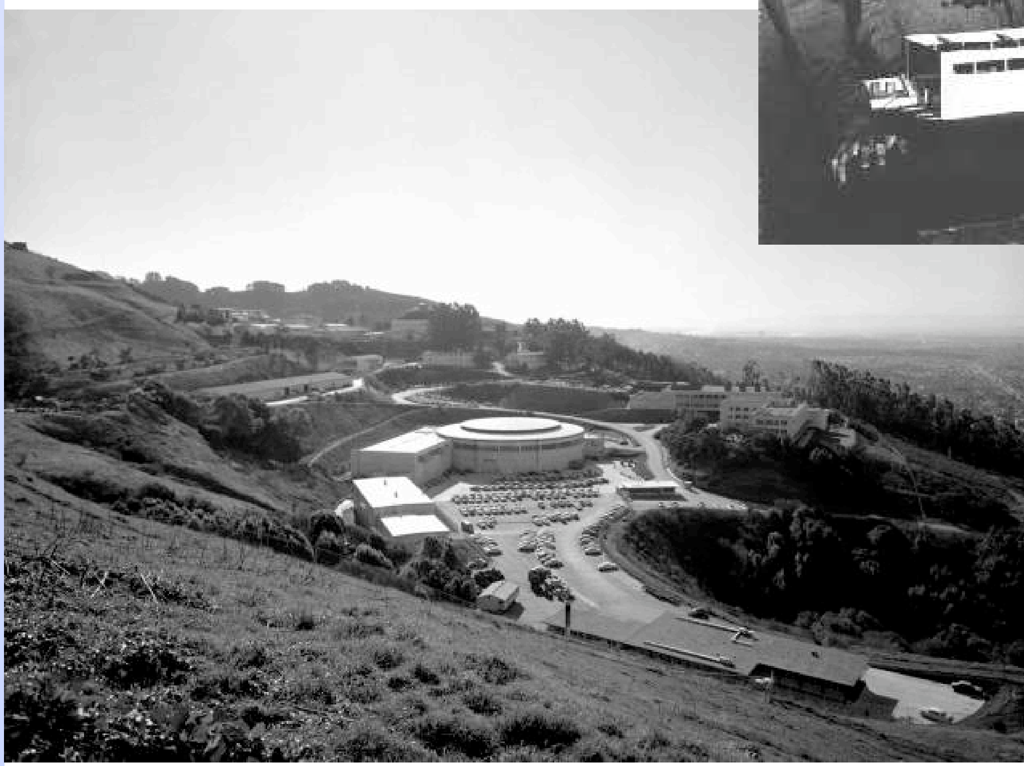
Spot Scanning for Carbon Beam (GSI)



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

Bevatron and Hadron Therapy



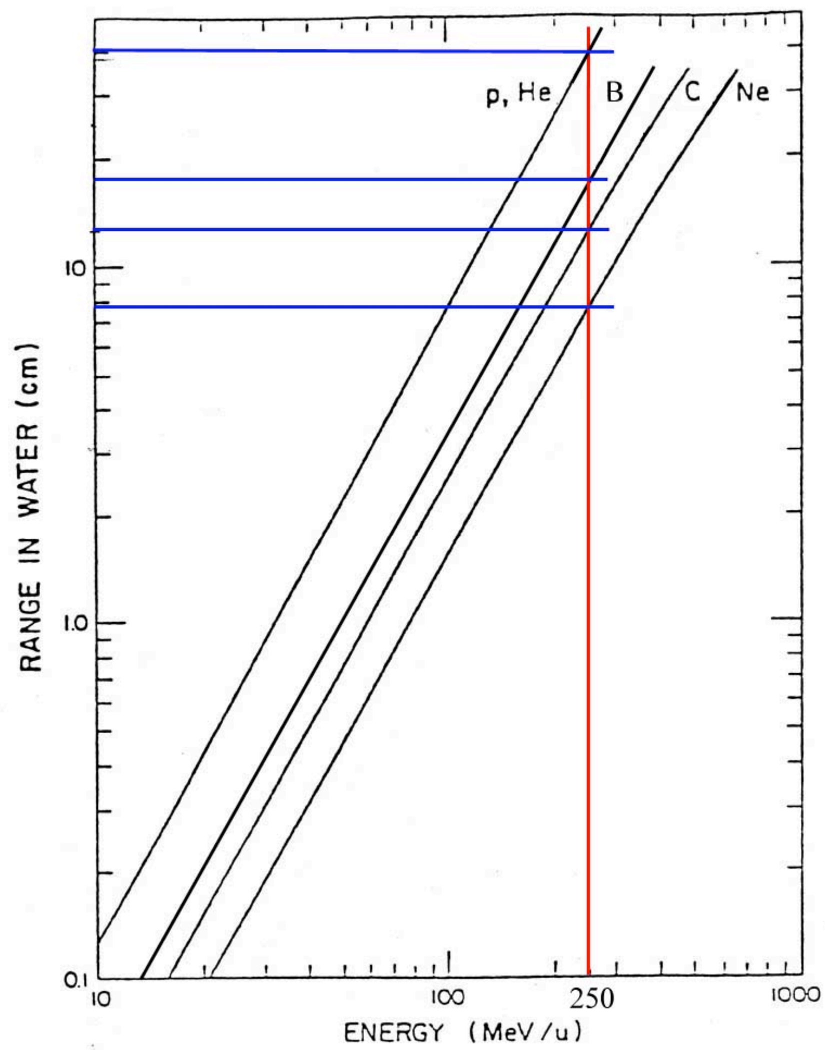


Bevalac (1971-1993) and Hadron Therapy

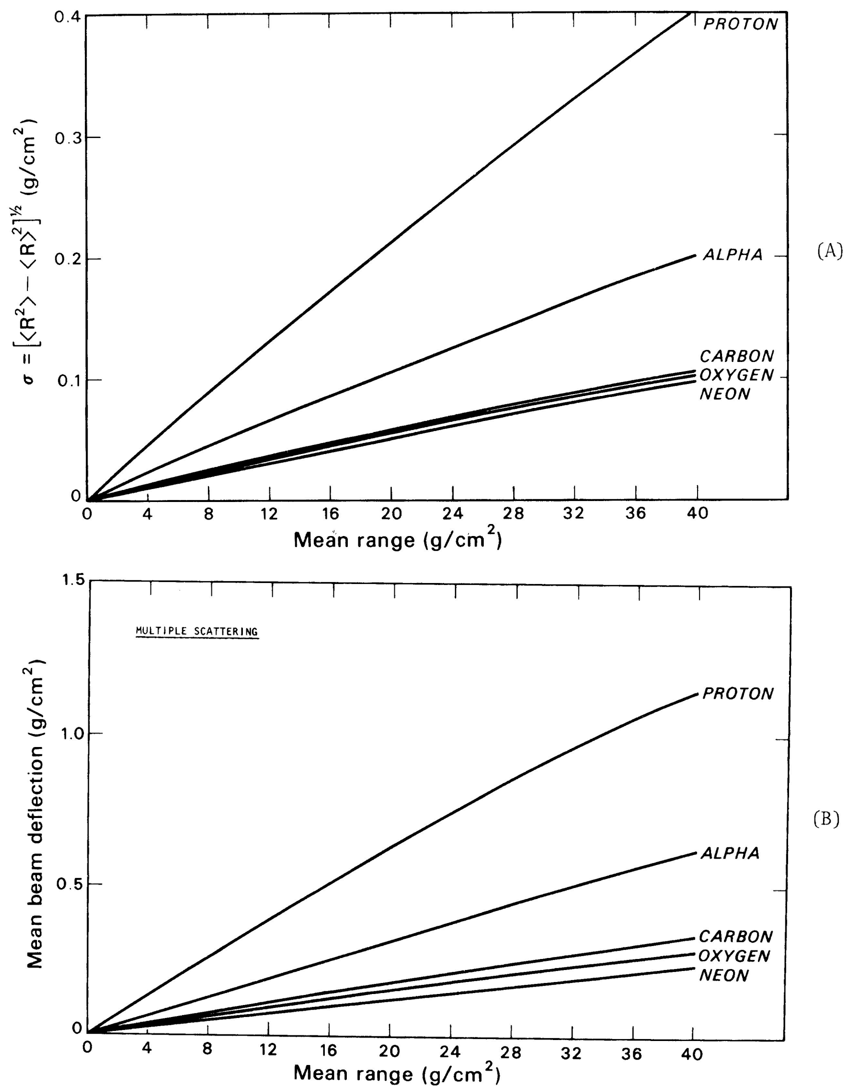
Harry Heckman, Ed McMillan, Cornelius Tobias, Tom Budinger, Ed Lofgren, Walt Hartsough (l. to r.)

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

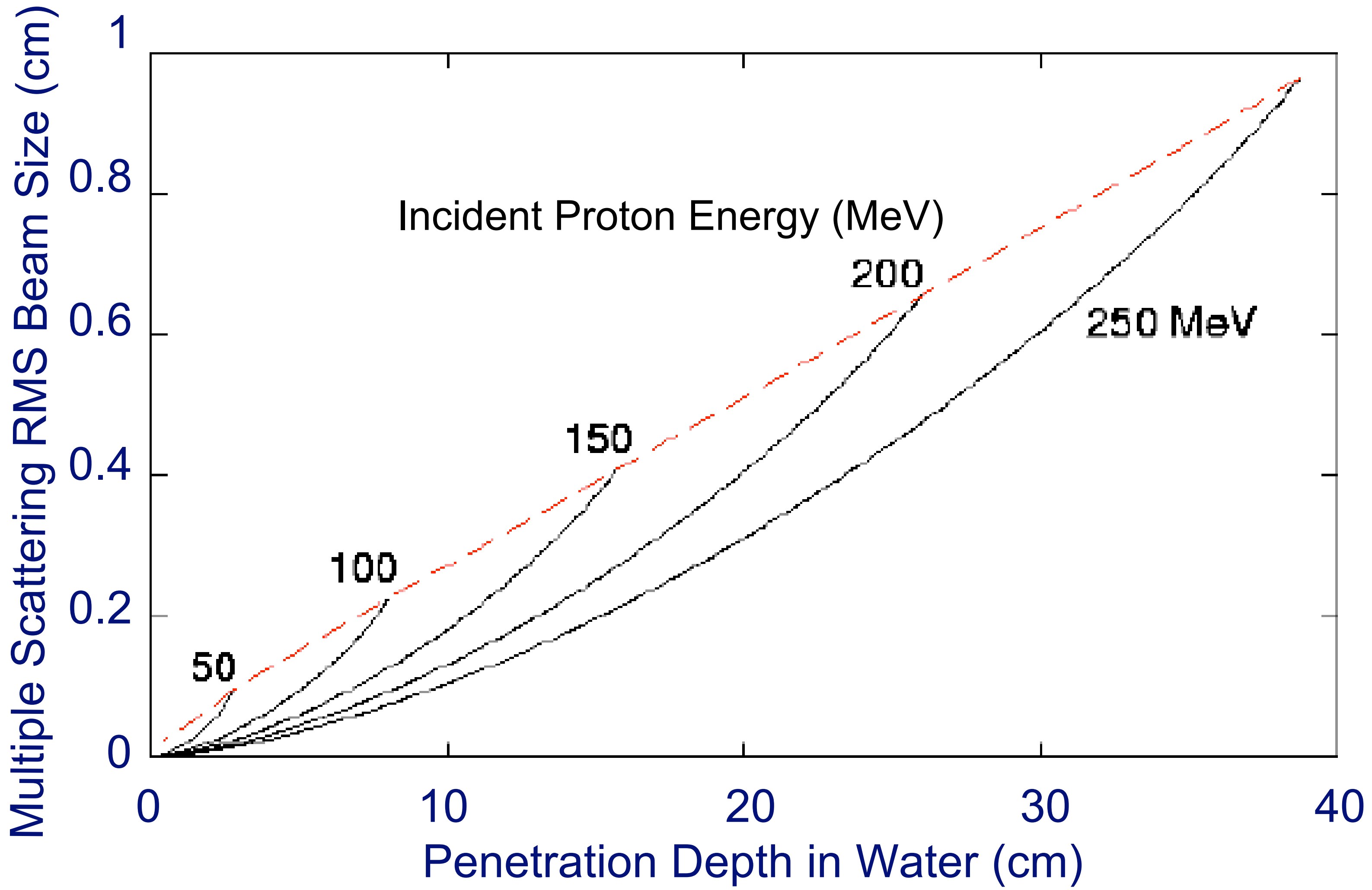
Hadron Energy vs. Range



Scattering & Straggling of Hadrons



Growth of Beam Size by Multiple Scattering



Beam Spots vs. Depth- protons and carbon ions

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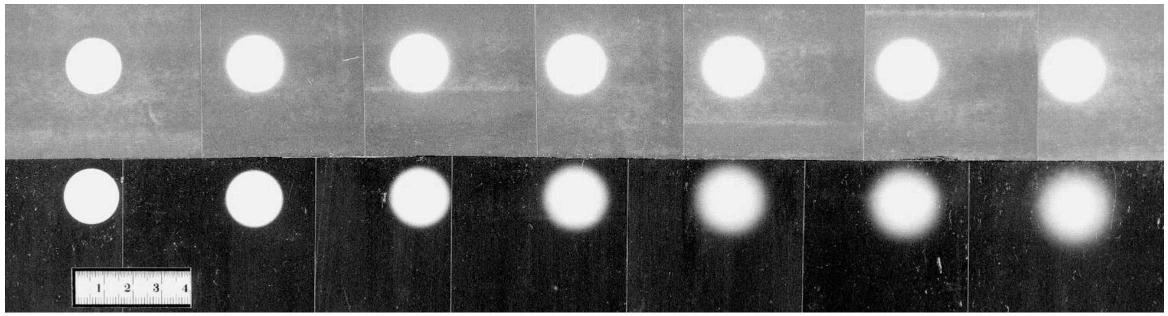
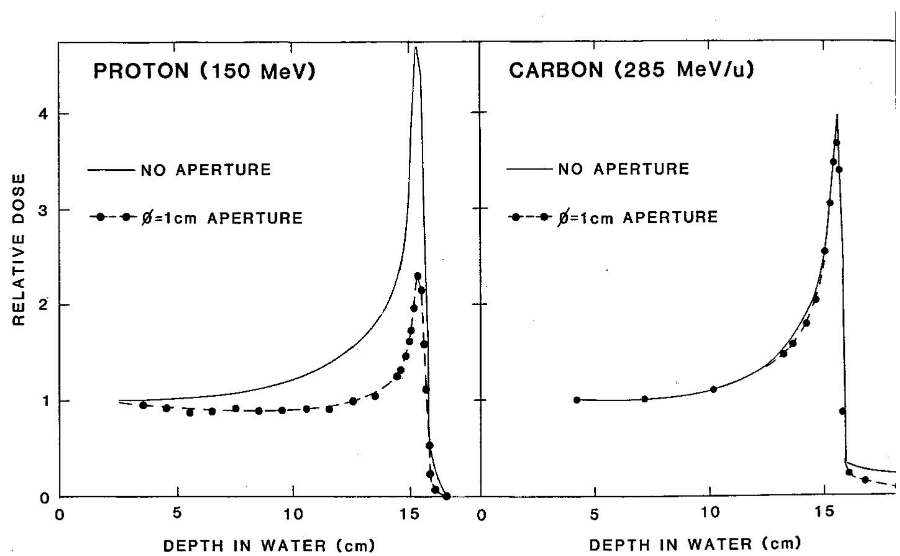
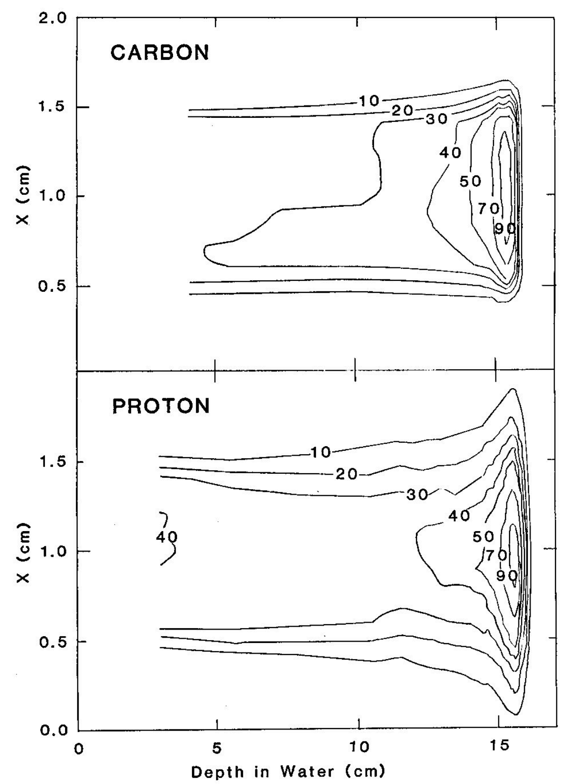
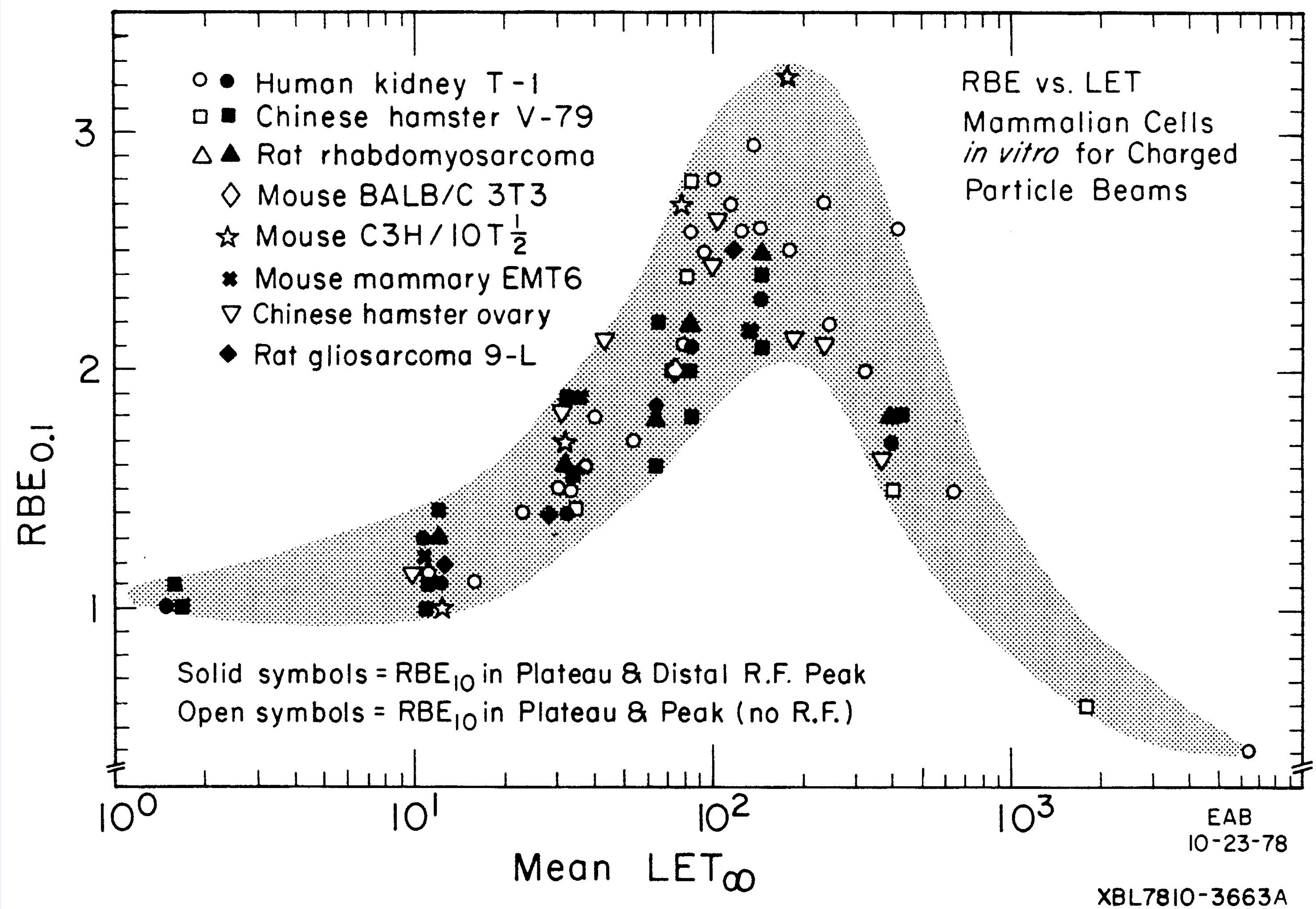






High LET Radiation- Clinical Rationale



RBE Values of Modulated Carbon-ion Beams

Modulated 290-mev/u Carbon-Ion Beams

Position	LET* (KeV/μ)	RBE Values: Single Fraction: Cell Culture	RBE Values: Single Fraction: Skin Reaction	RBE Values: Four Fractions: Skin Reaction
Entrance	22	1.8	2.0	···
SOBP (6 cm)				
Proximal	42	2.1	2.1	2.3
	45	2.2	2.2	···
Middle	48	2.2	2.3	···
	55	2.4	2.3	···
Distal	65	2.6	2.3	2.9
	80*	2.8	2.4	3.1
Distal fall-off	100	···	···	3.5

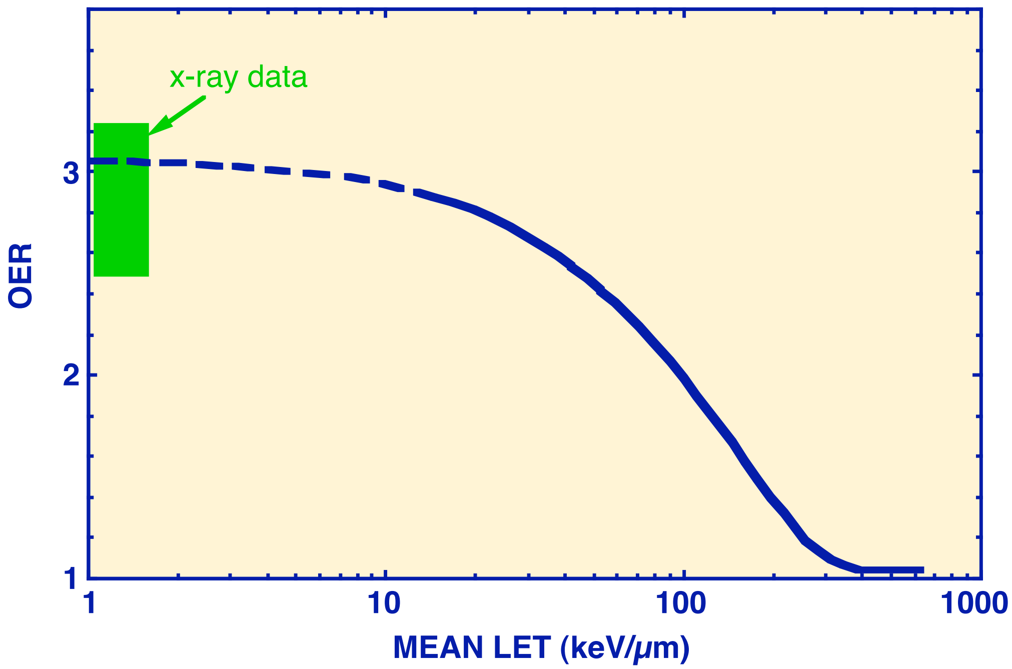
*Linear energy transfer (LET) value of fast neutrons used in cancer treatment at the National Institute of Radiological Sciences is also 80 keV/m.

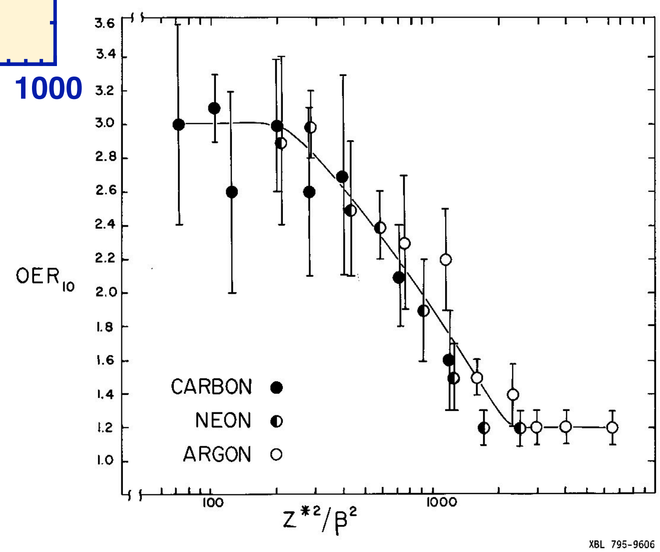
Local Control After Carbon-ion Therapy

Site	Dose	Period	
	GyE/Fractions	6 mo	12 mo
Head and neck	48.6/18	3/3	3/3
	54.0	2/3	2/2
	59.4	3/4	···
Brain			
Astrocytoma	50.4/24	3/3	3/3
Malignant glioma	66.8/33	3/7	1/3
Lung	59.4/18	6/6	2/5
	64.8	4/4	1/1
	72.0	3/3	···
Liver	49.5/15	2/2	···
	54.0	2/3	···
Prostate	54.0/20	2/2	···
Uterine cervix	52.8/24	3/3	···

Tsujii et al., 1997

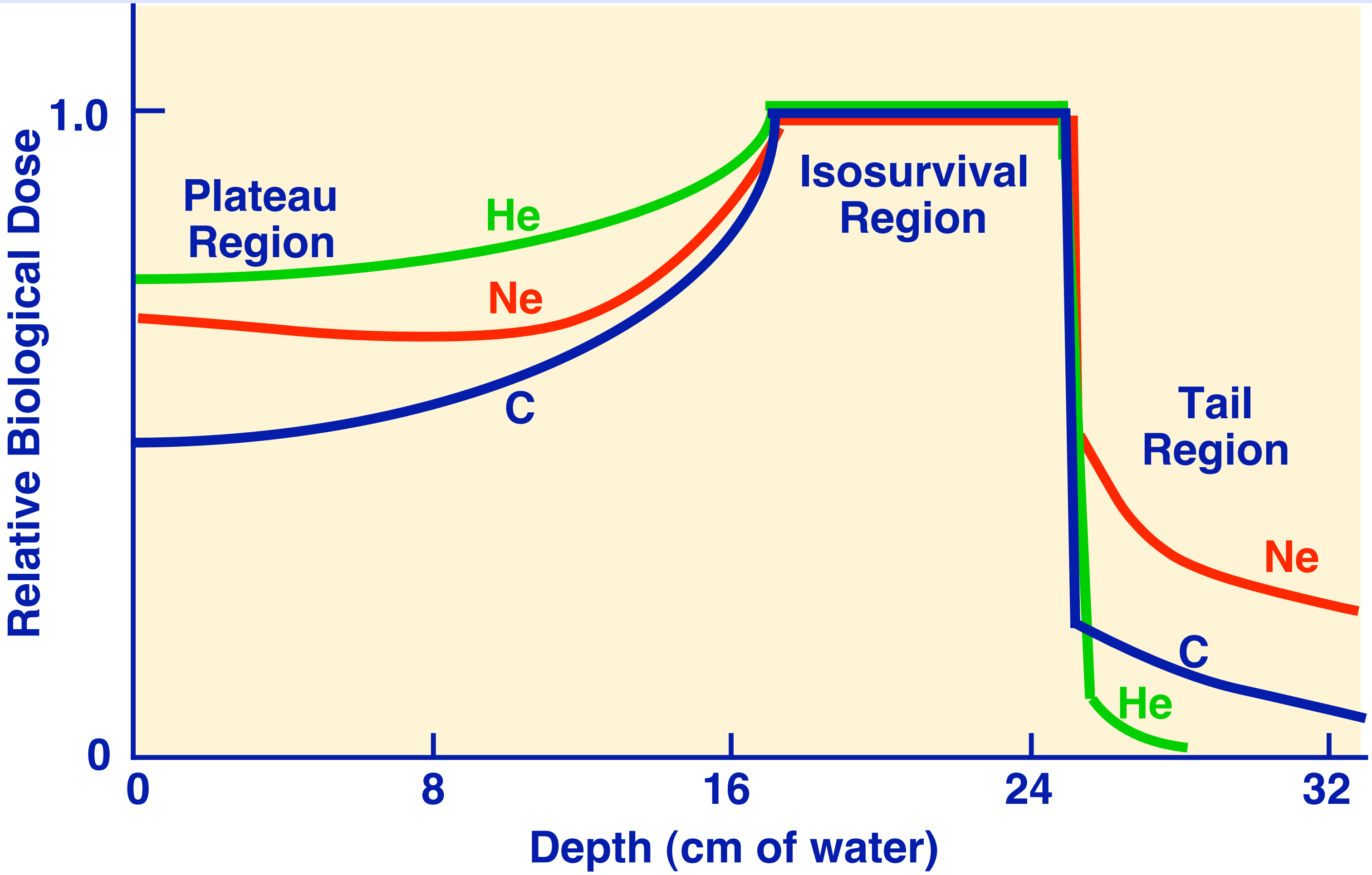
OER vs. LET





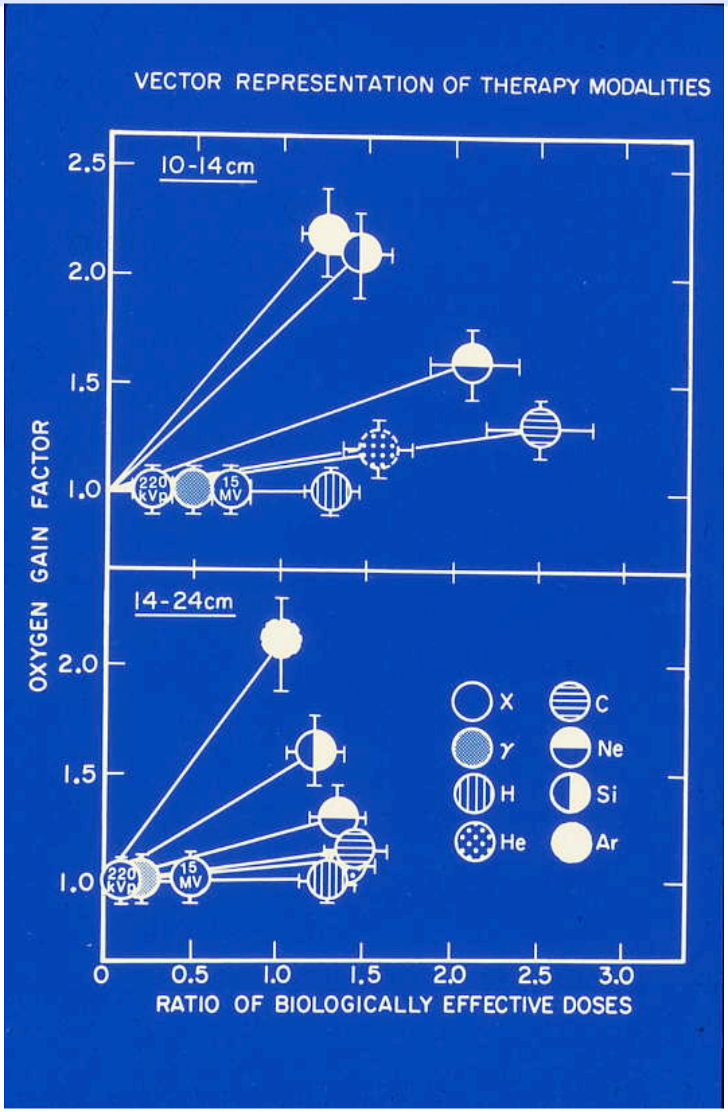
OER: Oxygen Enhancement Ratio

Relative Biological Dose Distributions

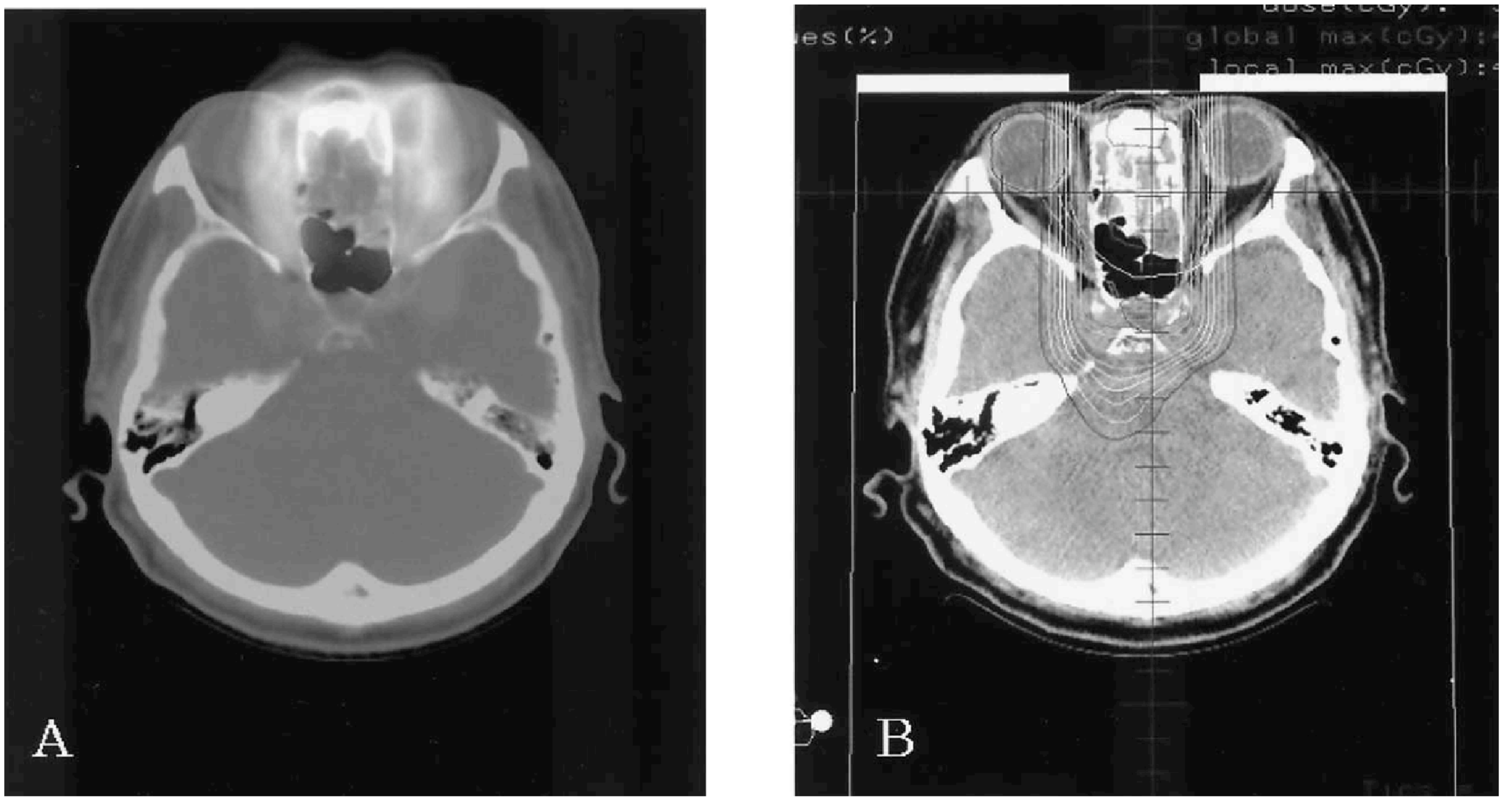


Relative biological dose distribution
over 'Spread-Out Bragg Peak' for various hadrons.

RBE and OER

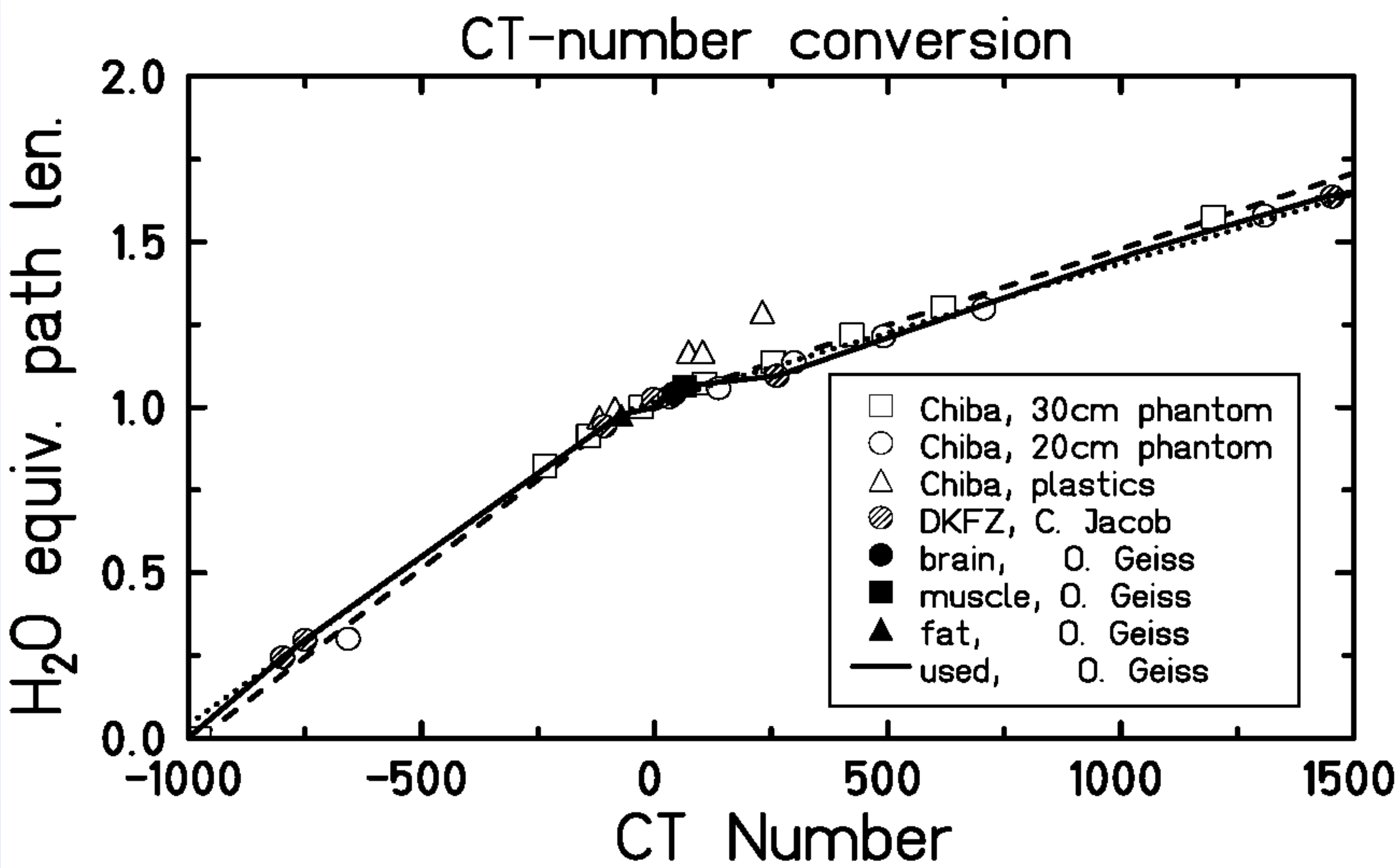


Relative Biological Effectiveness (RBE) and Oxygen Enhancement Ratio (OER) of various hadrons.

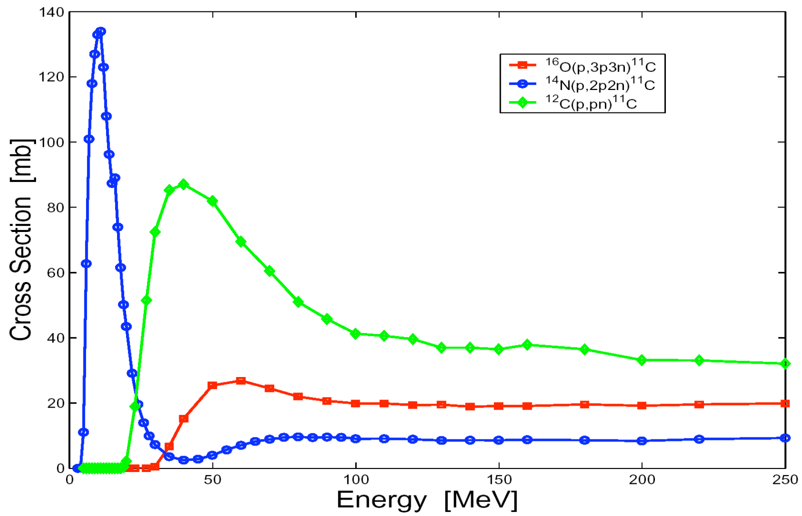


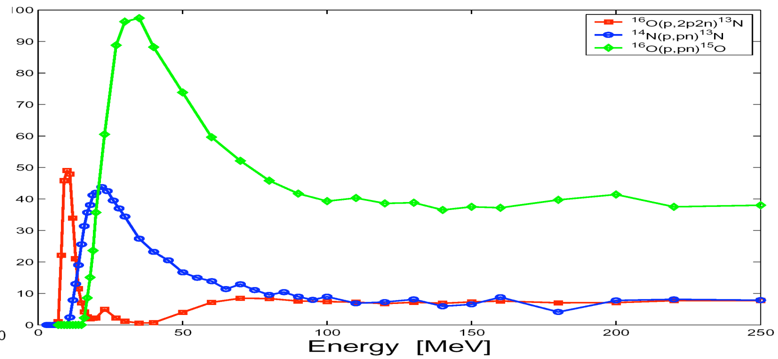
Comparison between the (A) CT-PET image and (B) treatment planning at the center slice of the treatment volume.

Proton Stopping Power and CT Number



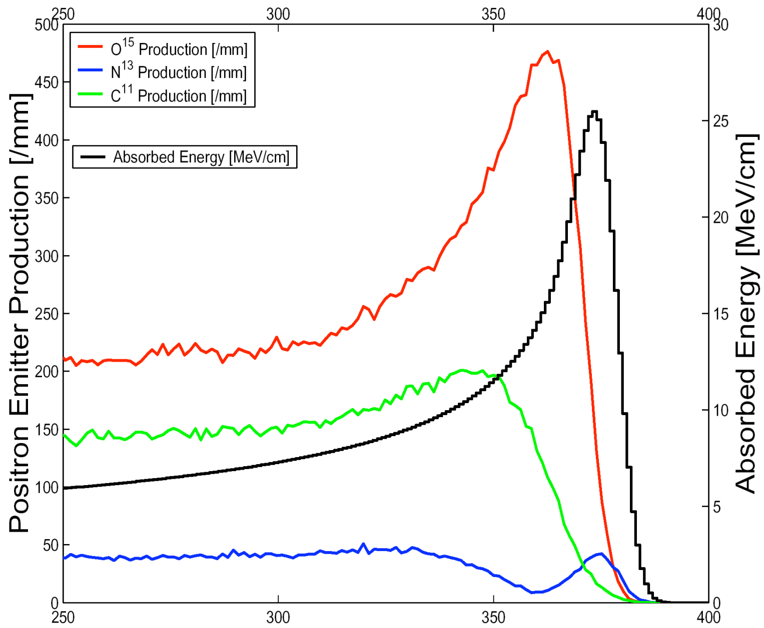
Radioactive Nuclei Production Cross-Sections vs. E_p



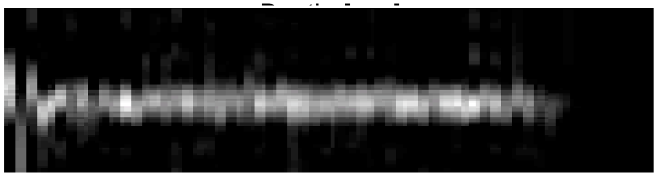


Radioactive nuclei production cross sections vs. proton energy

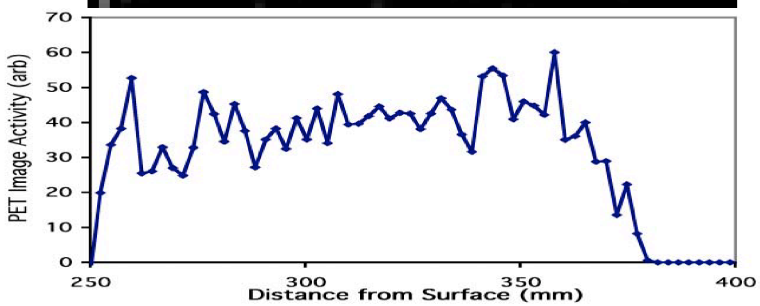
$^{12}C(p, pn)^{11}C$	$^{16}O(p, 2p2n)^{13}N$
$^{14}N(p, 2p2n)^{11}C$	$^{14}N(p, pn)^{13}N$
$^{16}O(p, 3p3n)^{11}C$.	$^{16}O(p, pn)\ ^{15}O$



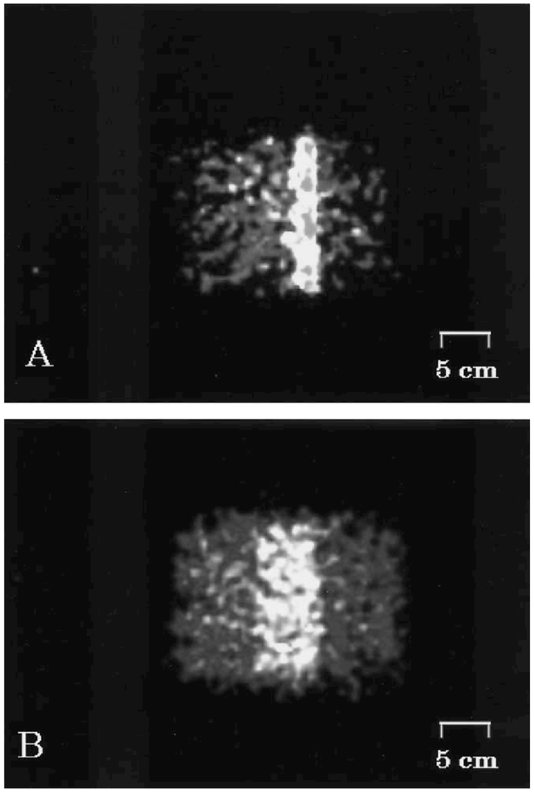
The simulation results of linear production densities of ^{11}C, ^{13}N and ^{15}O vs. depth. The absorbed energy by the tissue is superimposed using a right-side vertical scale for depth comparison.



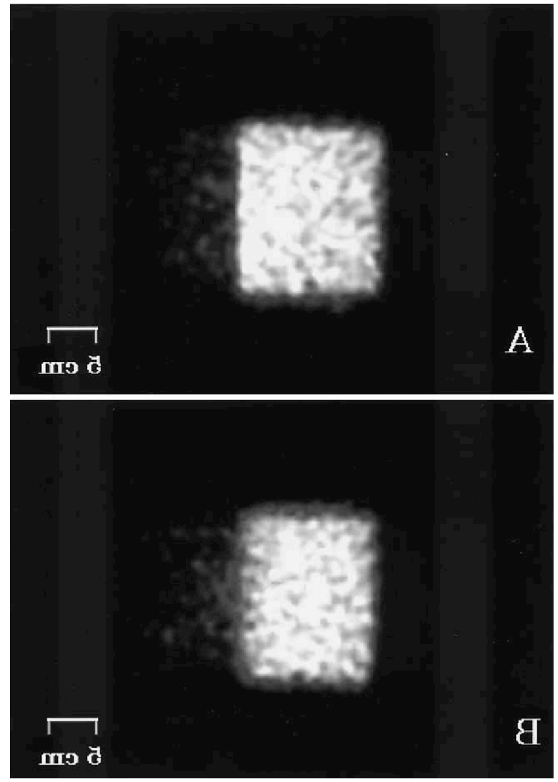
PET image



PET Image of Hadron Beams

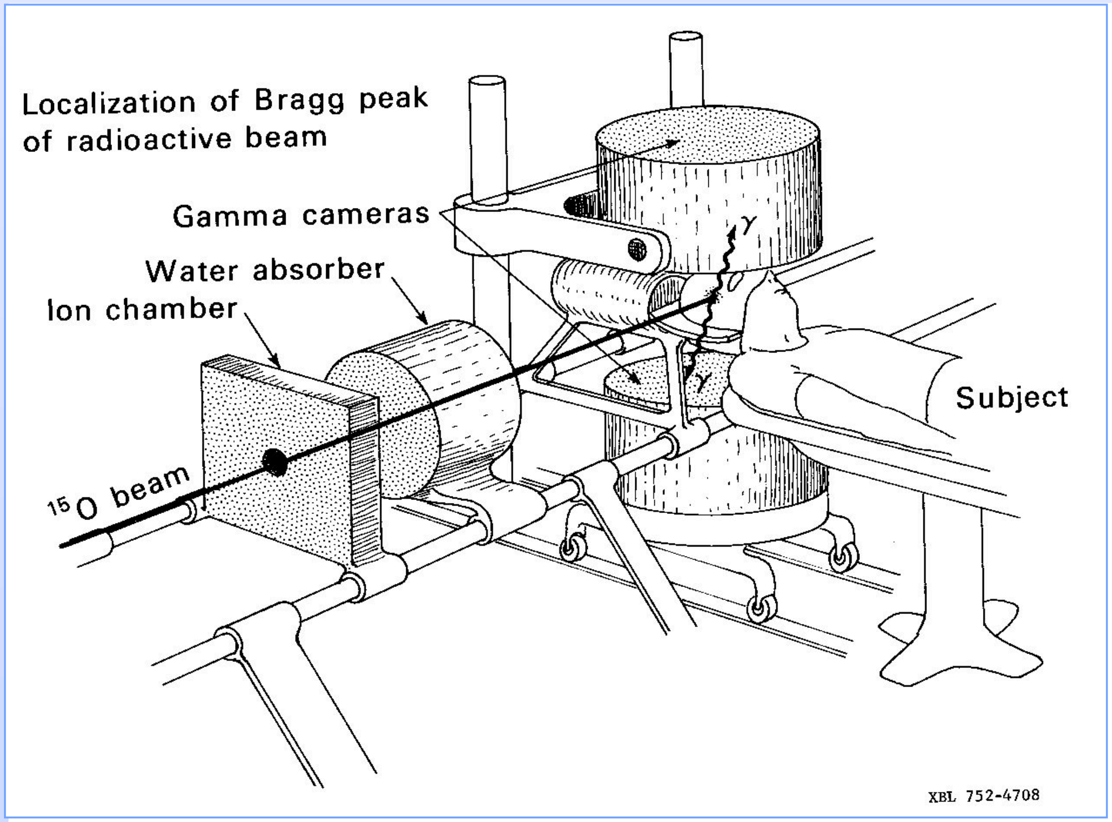


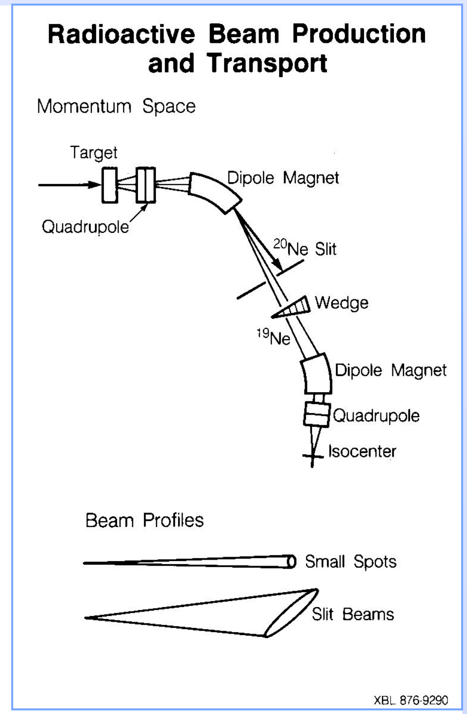
Carbon-ion beams in a phantom. High pixel counts are recognized (A) at the narrow Bragg peak of a monoenergetic carbon-ion beam and (B) at the 6-cm–SOBP.

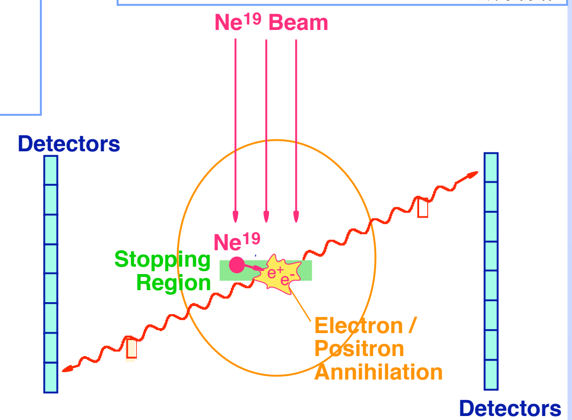


Proton beams in a phantom. High pixel counts are recognized throughout the proton beam track (A) in the monoenergetic beam and (B) also in the 6-cm–SOBP proton beam.

Tissue Ranging Using Radioactive Beam

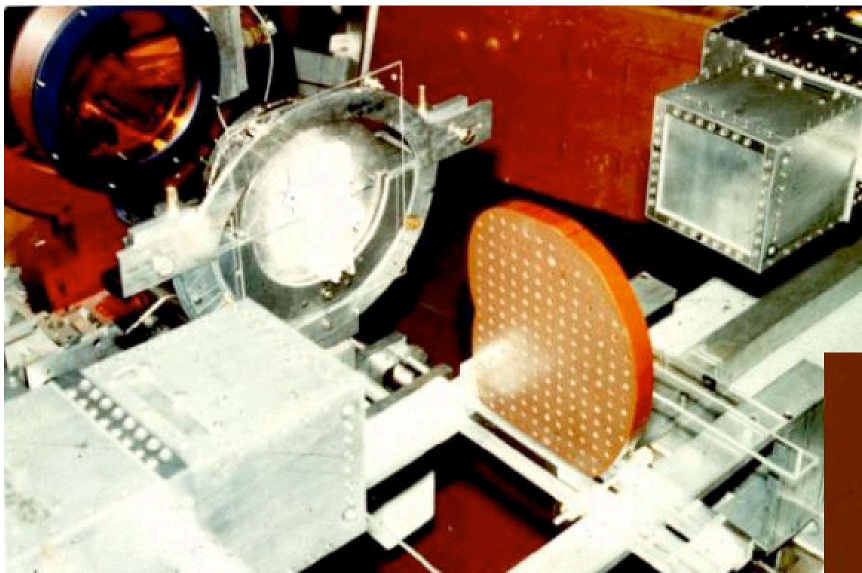




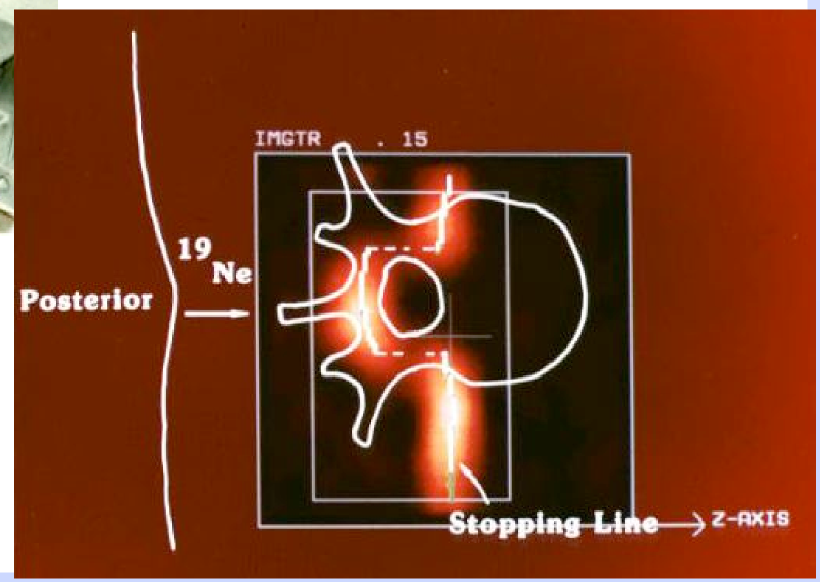


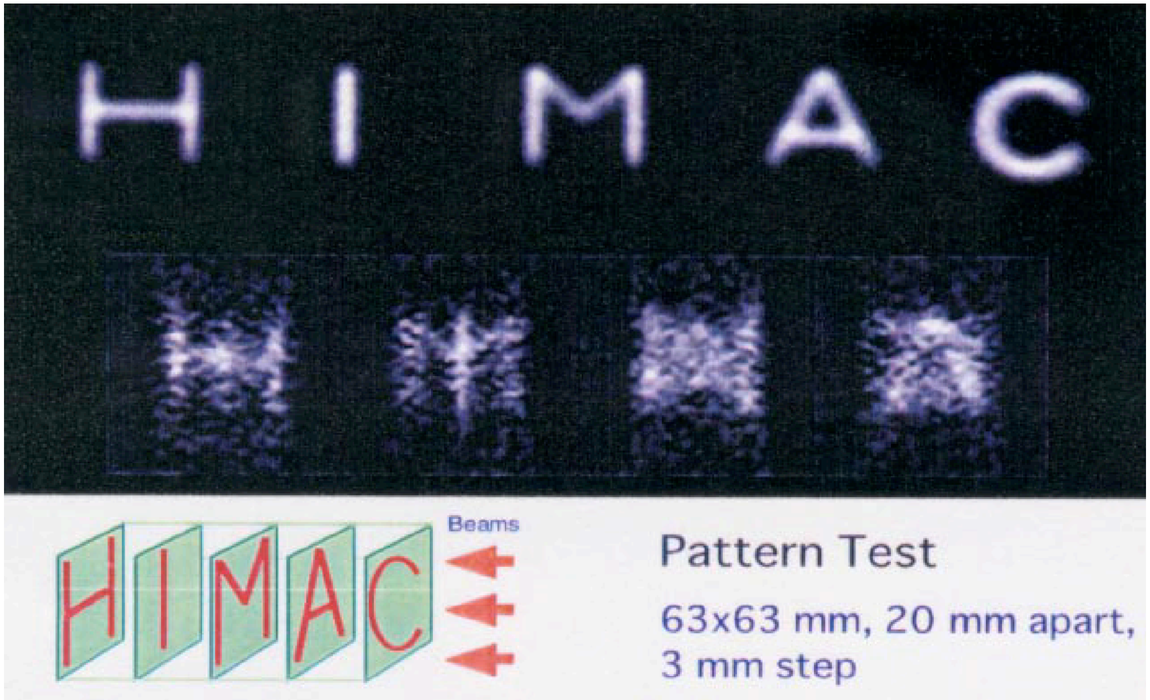
Stopping Region Determined by PEBA

The PEBA camera was used primarily to verify the stopping point of light-ion beams in phantoms and a few animals and to verify positioning of a few patients by low intensity irradiations with the patient in place.



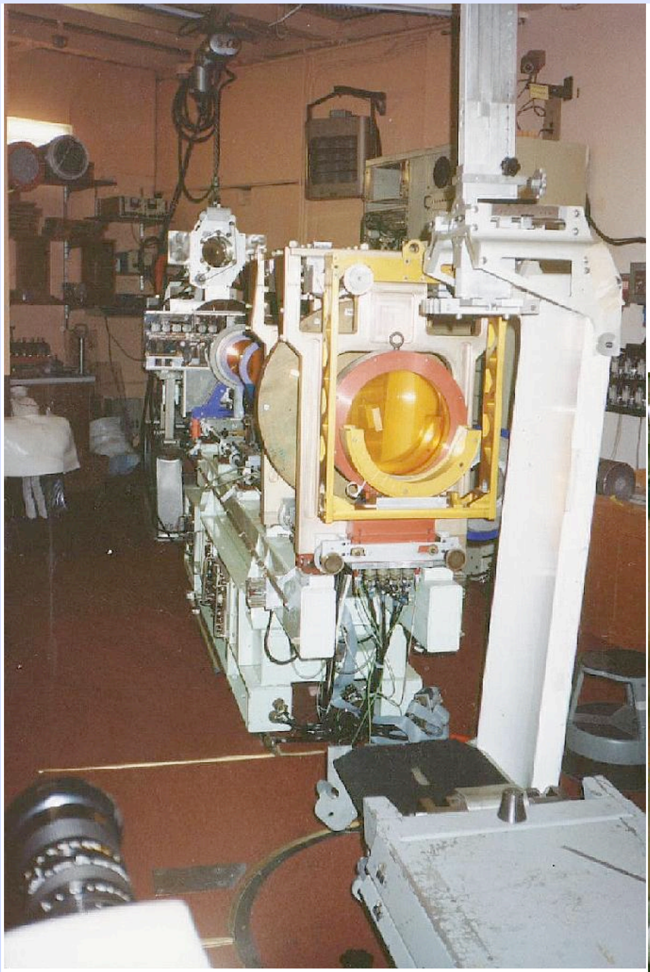
PEBA was also used to demonstrate the possibility of treating patients using radioactive beams.





An example of ^{11}C distribution measurements with a 3D spot scanning system.

Patient Treatments at Bevalac

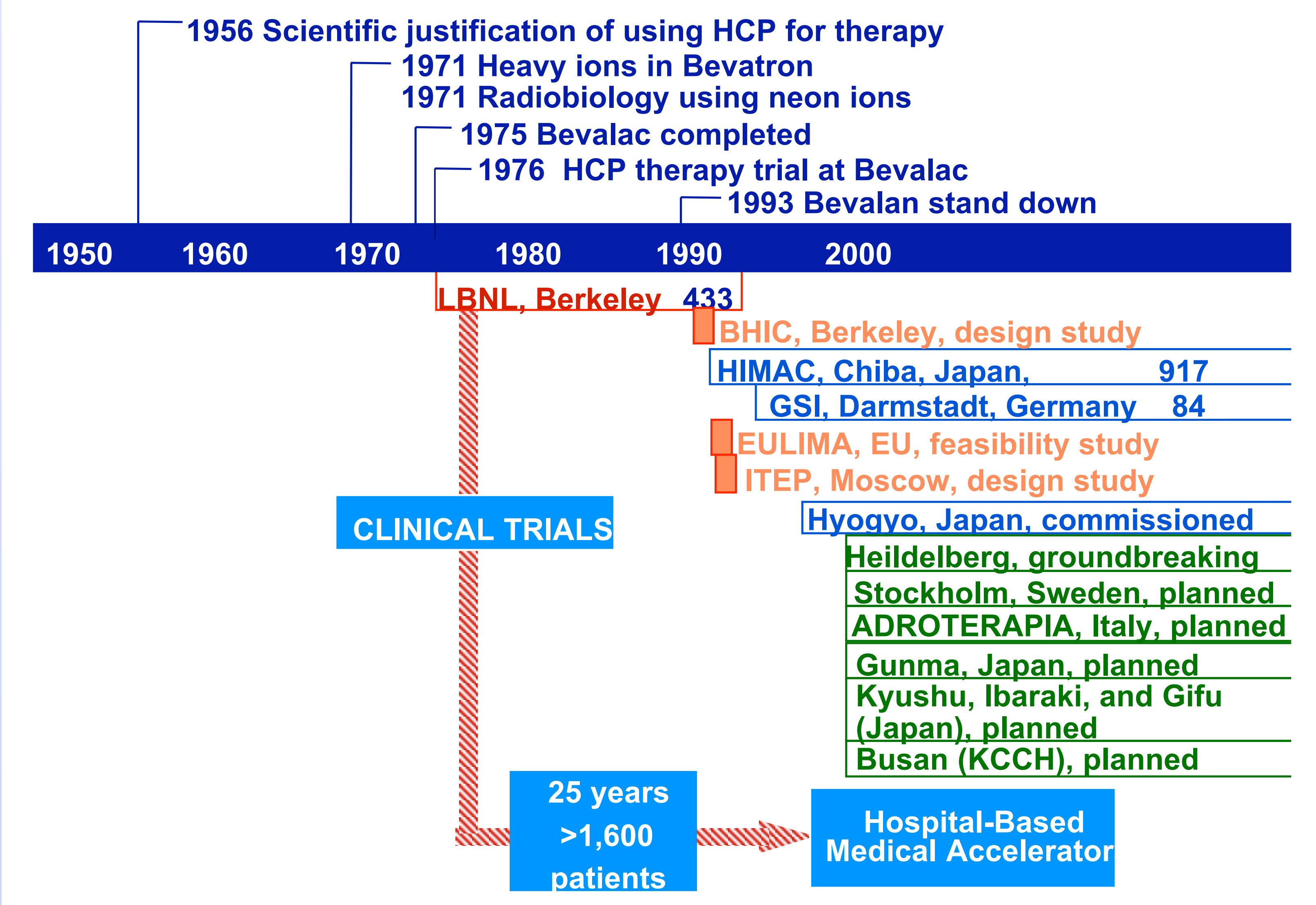


1975-1993

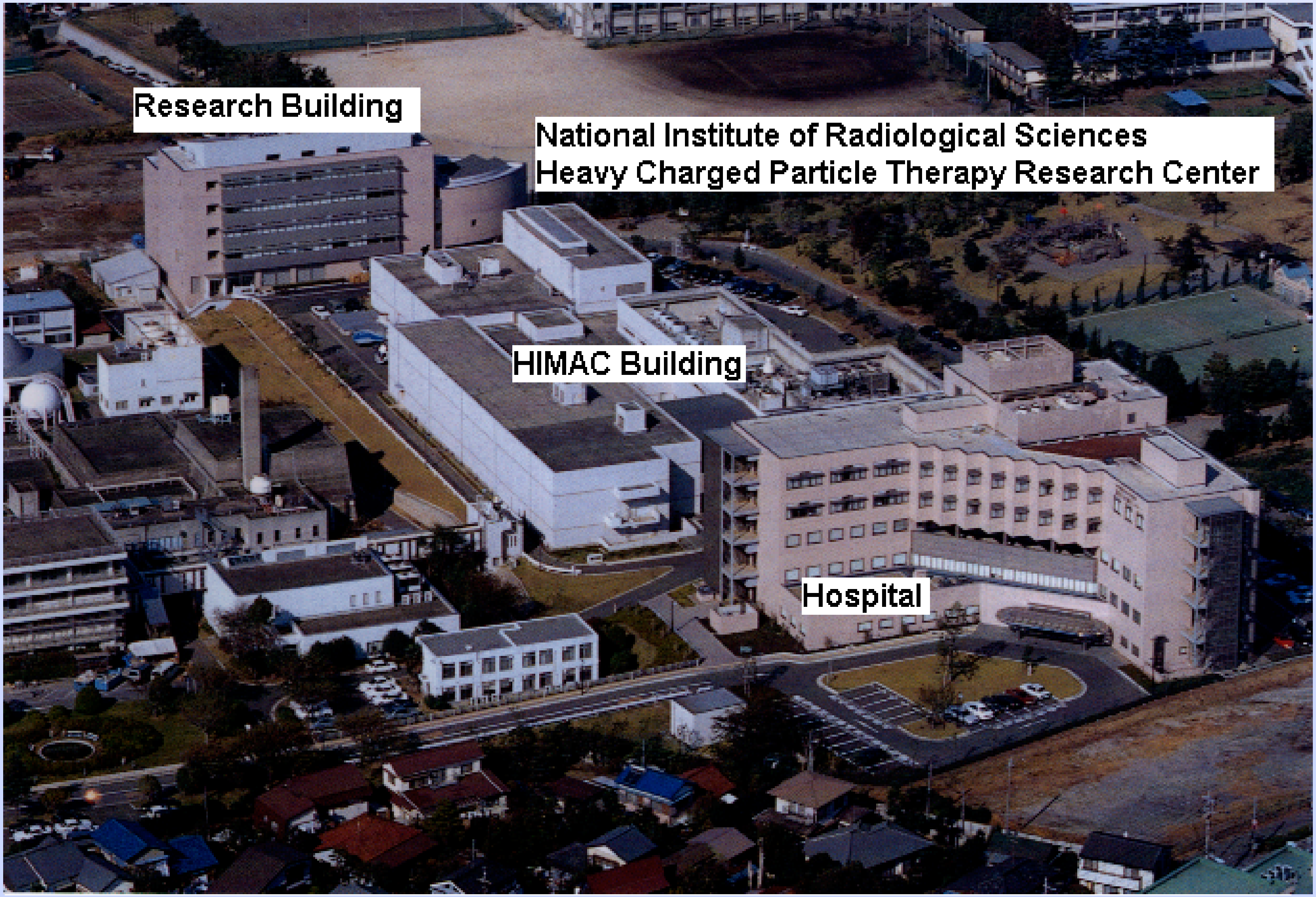
He ions 2054 patients

Neon ions 433 patients

High-LET Particle Therapy– Milestones

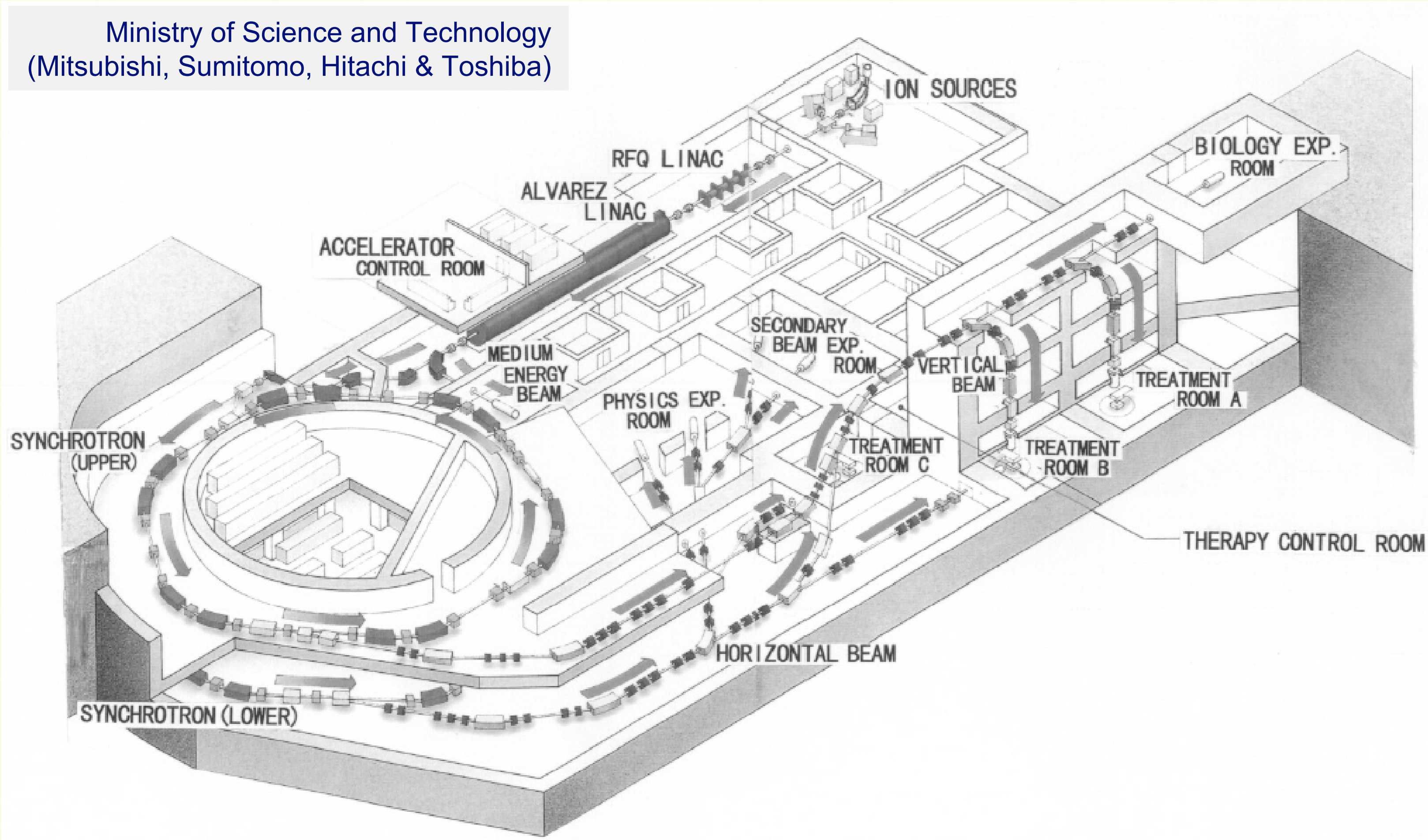


National Institute of Radiological Sciences (NIRS)



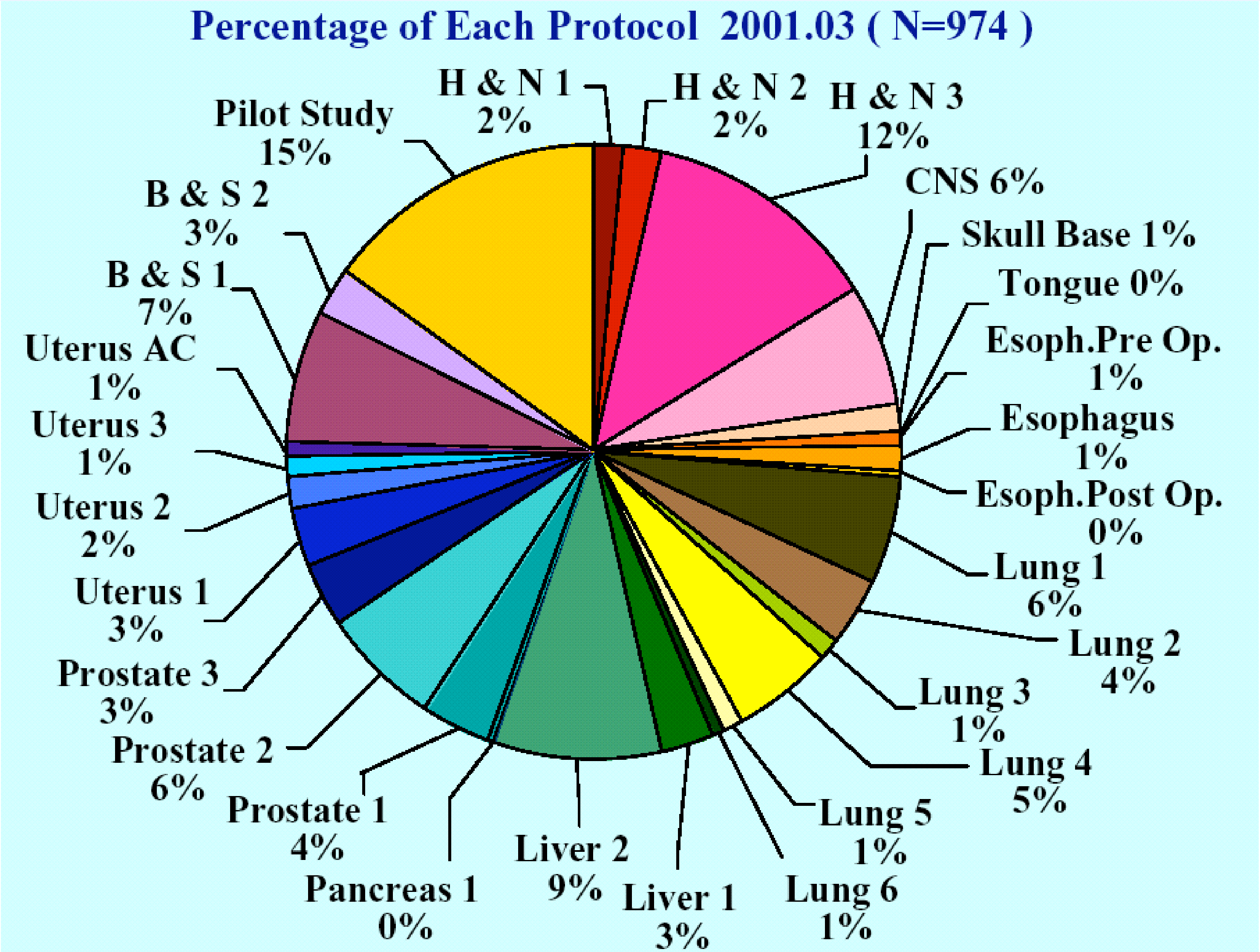
Heavy Ion Medical Accelerator at Chiba (HIMC)

Ministry of Science and Technology
(Mitsubishi, Sumitomo, Hitachi & Toshiba)

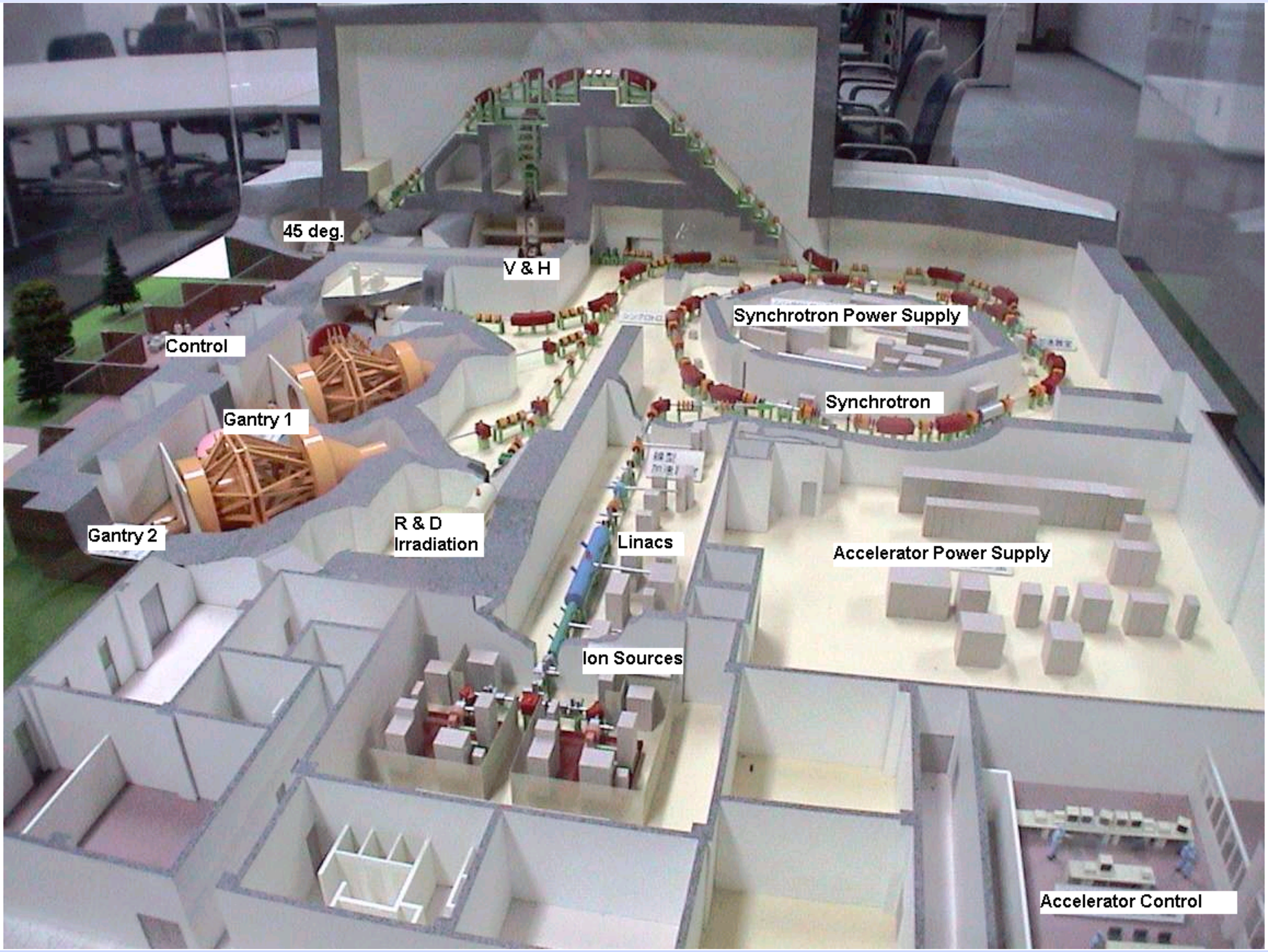


HIMAC was commissioned in 1994
and has successfully treated more than 1000 patients.

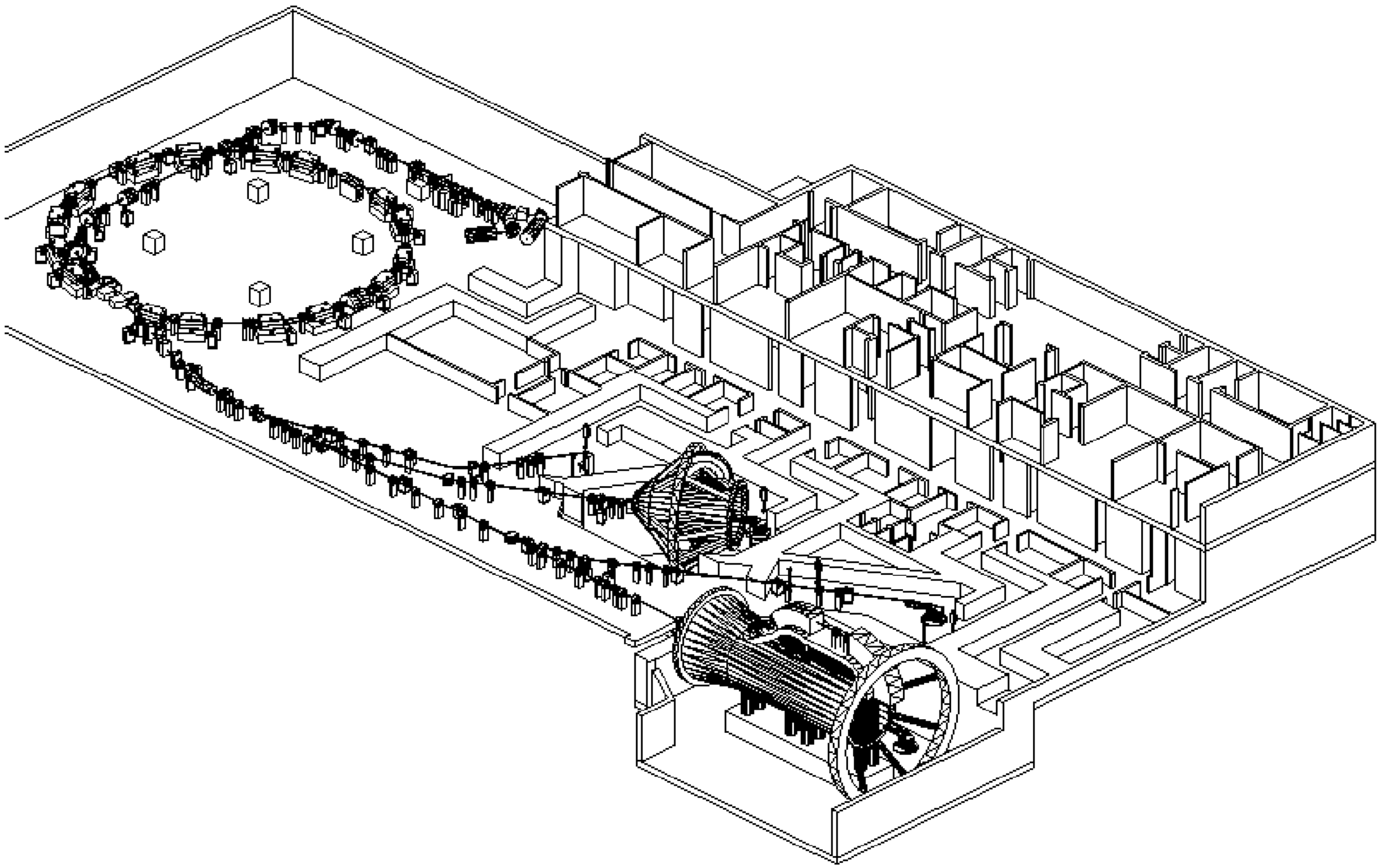
Patients Treated at HIMAC (March 2001)



PATRO Facility at Hyogo

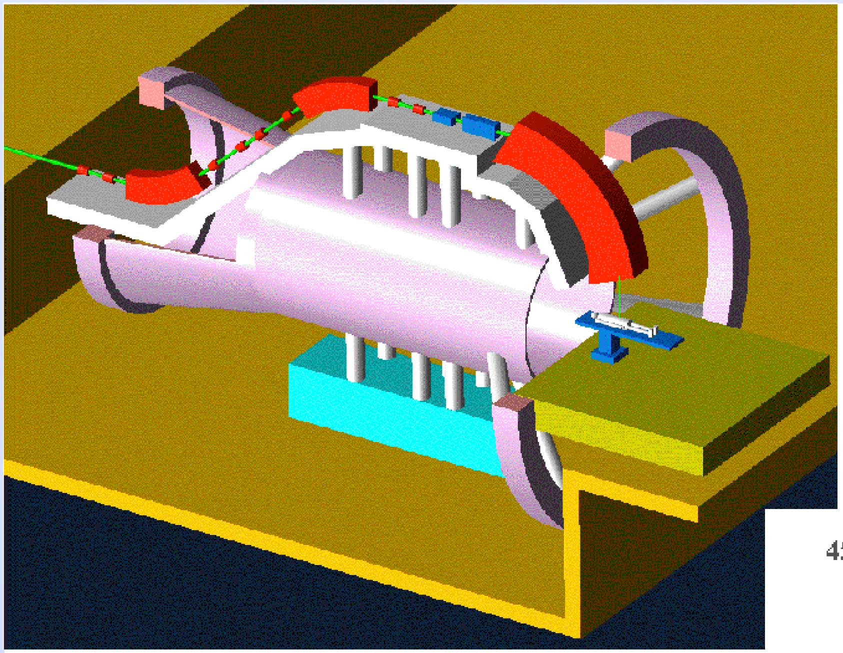


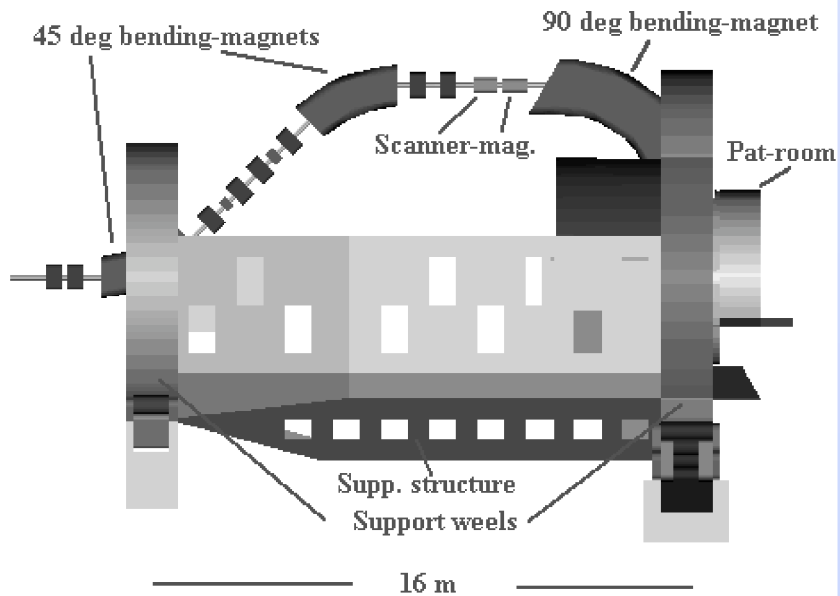
New Designs for Light-Ion Therapy



A light-ion therapy facility proposed by TERA Project (Italy), Karolinska Institute (Sweden), and Heidelberg-GSI (Germany).

Heidelberg Carbon-Ion Gantry





Proton vs. Light-Ion Therapy

	x ray	protons	Light ions
Bragg peak	none	+	++ (sharper)
Scattering (penumbra)	–	–	+
RBE*	– (1.0)	– (1.0-1.1)	+ (˜1.8-2.4)
OER†	– (3)	– (3)	+ (˜1.4)
Number of fx per tx‡	– (32)	– (32)	+++ (16, 8, 4, 2)
Capital investment	˜$10M	˜$50-100M	˜$250-350M

* Relative Biological Effectiveness
† Oxygen Enhancement Ratio
‡ Number of fractions per treatment

– standard or no advantages
+ good, ++ better, +++ best

Light-Ion Therapy Facilities

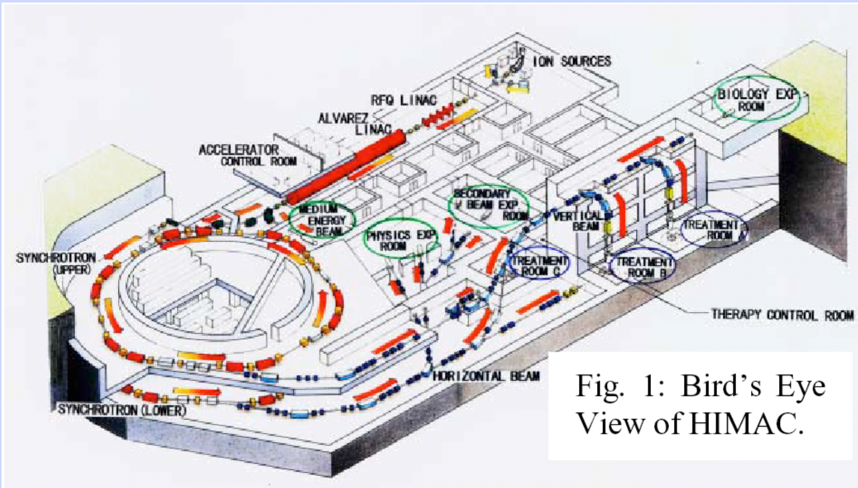
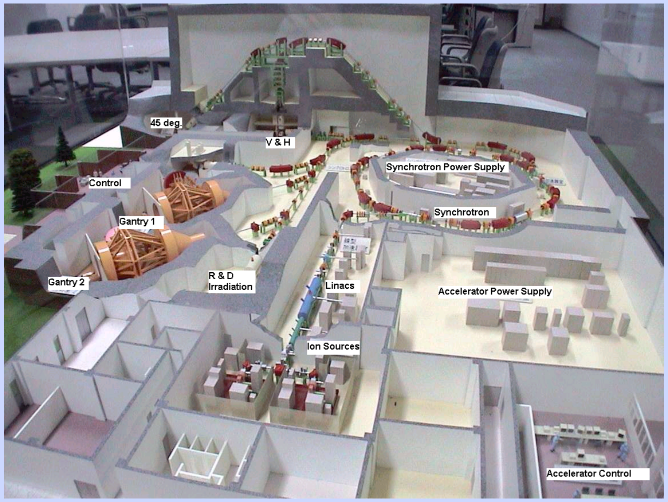
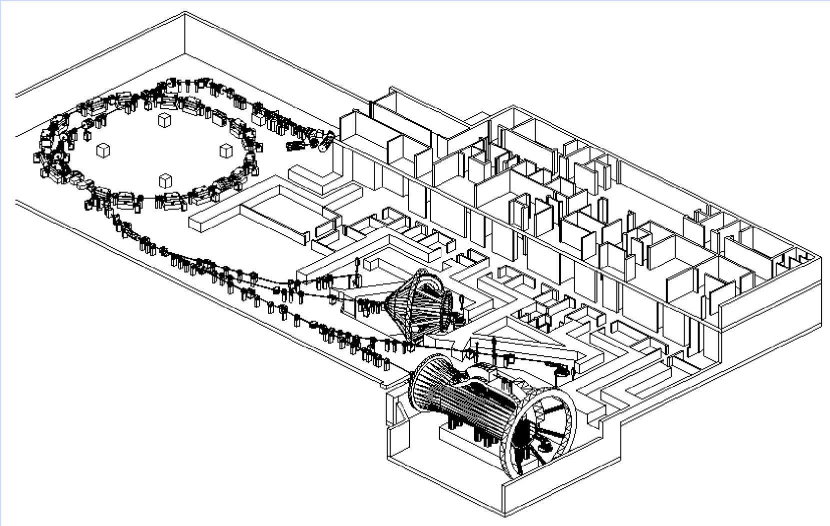


Fig. 1: Bird's Eye View of HIMAC.

HIMAC in Chiba- $350M



PATRO in Hyogo- $250M



A light-ion therapy facility proposed by

- TERA Project (Italy)
- Karolinska Institute (Sweden)
- Heidelberg-GSI (Germany) ground breaking, 2001
- Gunma, Kyushu, Ibaraki, Gifu (Japan)
- Busan (KCCH), Korea

International Outlook

- Protons- Commercialization by private sector
- Light-Ion Therapy
  - HIMAC, operating since 1994, has treated 1000 patients using carbon ions
  - Harima Facility in Hyogo started treating patients with carbon ions since 2001
  - GSI treating complex head/neck fields with advanced 3-d scanning system
- Exciting new developments add more solid evidence for Light-Ion Therapy
  - Hypofractionation studies at HIMAC can have significant impact on economic modeling
  - Effectiveness of precision treatments at GSI indicate maturity of advanced delivery technology for widespread application
  - Several new initiatives in carbon-ion therapy-
    - Heidelberg-GSI, Germany-- ground breaking, 2001
    - Karolinska Institute, Stockholm, Sweden
    - TERA Project, Milan, Italy
    - Gunma University, Kyushu, Ibaraki, Gifu (Japan)-- design
    - Busan, Korea– a proposal


Thank You