Introduction to Ion Beam Cancer Therapy

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(with some slides from David Robin)

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1. History of Hadron Therapy (Cont)

A Time Line of Hadron Therapy

1938 Neutron therap(250 patients) by John Lawrence and R.S. Stone (Berkeley) "Distressing late effects"

1946 Robert Wilson suggests protons (Radiology **47**,487 (1946))

1948 Extensive studies at Berkeley confirm Wilson

1954 Protons used on patients in Berkeley

1957 Uppsala duplicates Berkeley results on patients

1961 First treatment at Harvard (By the time the facility closed in 2002, 9,111patients had been treated.)

1968 Dubna proton facility opens

1969 Moscow proton facility opens

1972 Neutron therapy initiated at MD Anderson (Soon 6 places in USA.)

1974 Patient treated with pi meson beam at Los Alamos (Terminated in 1981) (Starts and stops also at PSI and TRIUMF)

1. History of Hadron Therapy (Cont)

A Time Line of Hadron Therapy

1975 St. Petersburg proton therapy facility opens
1975 Harvard team pioneers eye cancer treatment with protons
1976 Neutron therapy initiated at Fermilab. (By the time the facility closed in 2003, 3,100 patients had been treated)
1977 Bevalac starts ion treatment of patients. 2/3 on biology and medicine; 1/3 on nuclear physics (By the time the facility closed in 1992, 223 patients had been treated.)
1979 Chiba opens with proton therapy
1988 Proton therapy approved by FDA
1989 Proton therapy at Clatterbridge
1990 Medicare covers proton therapy and Particle Therapy Cooperative Group (PTCOG) is formed:
www.ptcog.web.psi.ch
1990 First hospital-based facility at Loma Linda (California)
1991 Protons at Nice and Orsay

1. History of Hadron Therapy (Cont)

A Time Line of Hadron Therapy

1992 Berkeley cyclotron closed after treating more than 2,500 patients
1993 Protons at Cape Town
1993 Indiana treats first patient with protons
1994 Ion (carbon) therapy started at HIMAC (By 20088 more than 3,000patients treated.)
1996 PSI proton facility
1998 Berlin proton facility
2001 Massachusetts General opens proton therapy center
2006 MD Anderson opens
2007 Jacksonville, Florida opens
2008 Neutron therapy re-stated at Fermilab (due to an ear mark).

1. History (Cont):

Summary Comments on Hadron Facilities

Present facilities (*roughly*):

Sub-atomic physics labs doing some therapy: 12
Hospital based proton therapy centers: 10
Under construction:14

Patients treated:

To date about 50,000 patients have been treated with hadrons. (mostly with protons)
At HIMAC 3,000 patients treated with carbon beams
At GSI 300 patients treated with ions

2. X-Ray Machines

A modern system for treating a patient with x-rays produced by a high energy electron beam. The system, built by Varian, shows the very precise controls for positioning of a patient. The whole device is mounted on a gantry. As the gantry is rotated, so is the accelerator and the resulting x-rays, so that the radiation can be delivered to the tumor from all directions.

2. X-Ray Therapy

From Varian alone: The clinical installed base is about 5,200 units, and they are shipping new ones at the rate of 2-3 per day. There business is growing at roughly 10% per year.

Thus their machines are treating on the order of 200,000 patients daily, or 50 M treatments per year, so (about) 2 M patients/year. World-wide 10,000 linacs and treat 4 M patients/year

Compare this with hadron therapy which has a total of 50,000 patients treated in all the years. (Nevertheless Varian bought out ACCEL.)

3. Why Hadrons? Which Hadrons?

Primarily because the radiation can be deposited, because of the Bragg peak, directly where the tumor is located (in all three dimensions). Thus minimal is done to surrounding healthy tissue (and also to the skin, which is the limit in X-ray treatment).

Carbon is determined to be the best (Bragg peak like Z^2, but nuclear fragmentation for the higher ions causes range straggling). Require 200 MeV protons or 400 MeV/u carbon. Also carbon scatters less than protons so the "knife is sharper" and the kill mechanism is different and hence more effective in killing oxygen depleted tumors.

Radiation Therapy

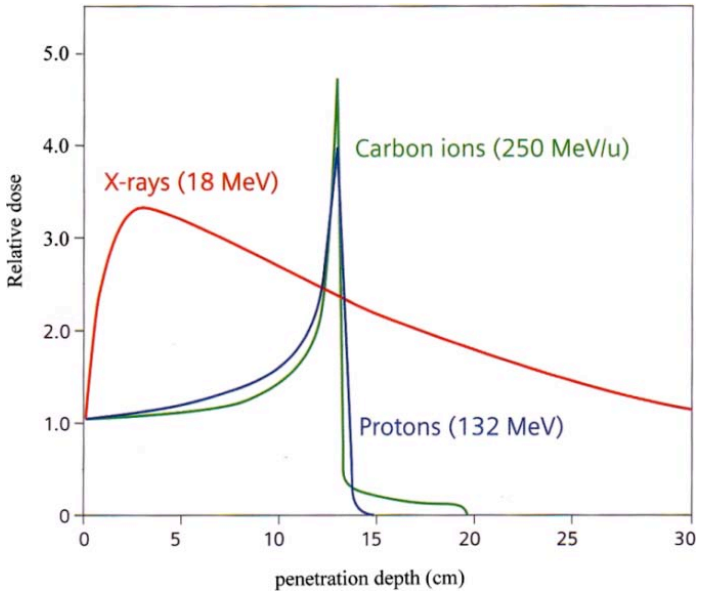
Goal of radiation therapy is to use radiation to kill cancer tumor tissues while minimizing damage to healthy tissue

Dose is a measure of energy deposited by the radiation in the body

This energy generates ionization of cell molecules that ultimately leads to cell death

Energy deposited by different ionizing radiation

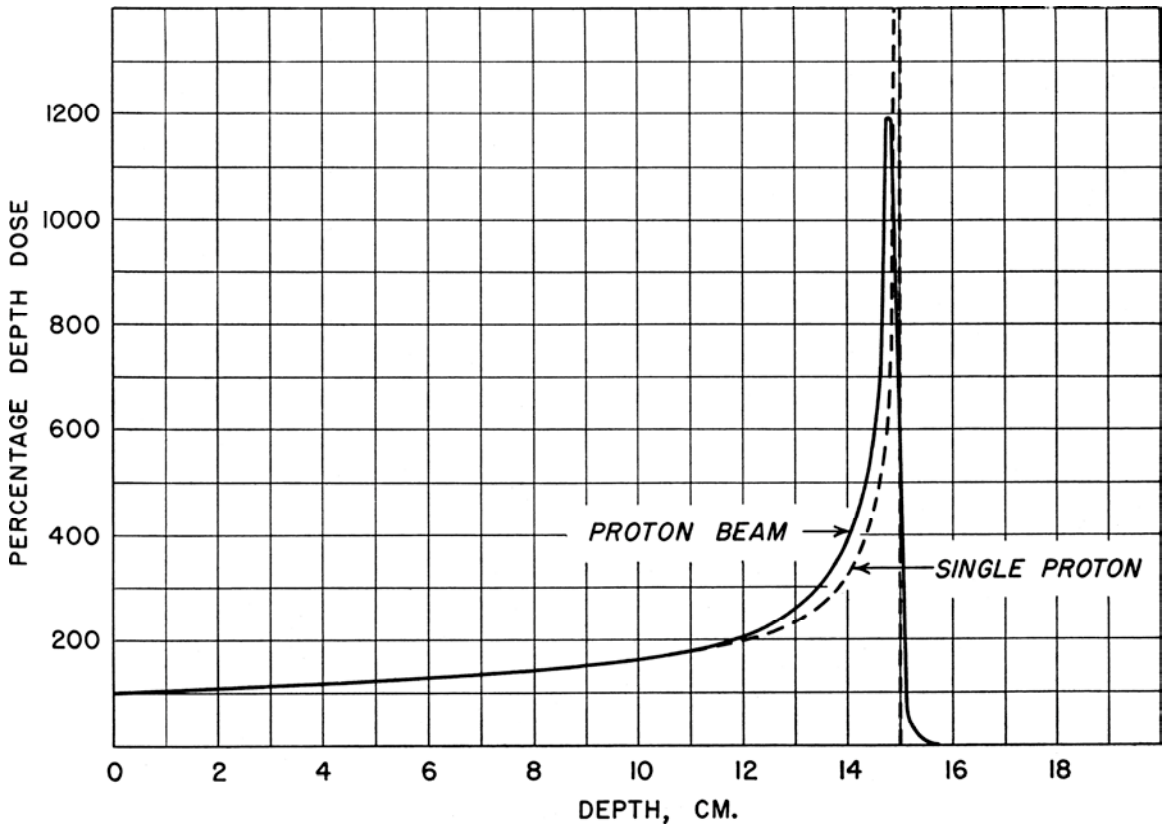
Dose versus depth



- X-rays deposit most of their energy near the body entrance.
- Ions (such as protons and carbon) concentrate more dose at the tumor
  - Less in front
  - Little or none beyond

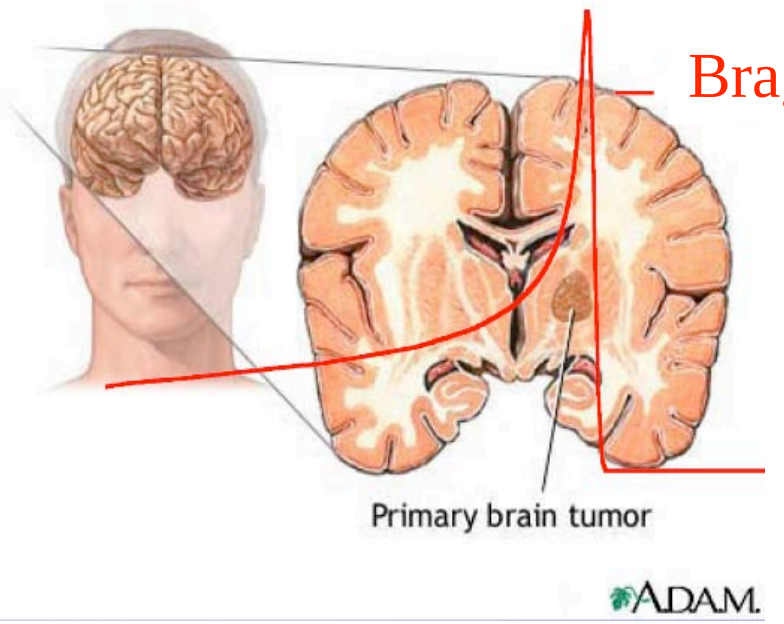
This is a fundamental advantage of ions because it allows minimizing the damage on healthy tissue. Called “toxicity”.

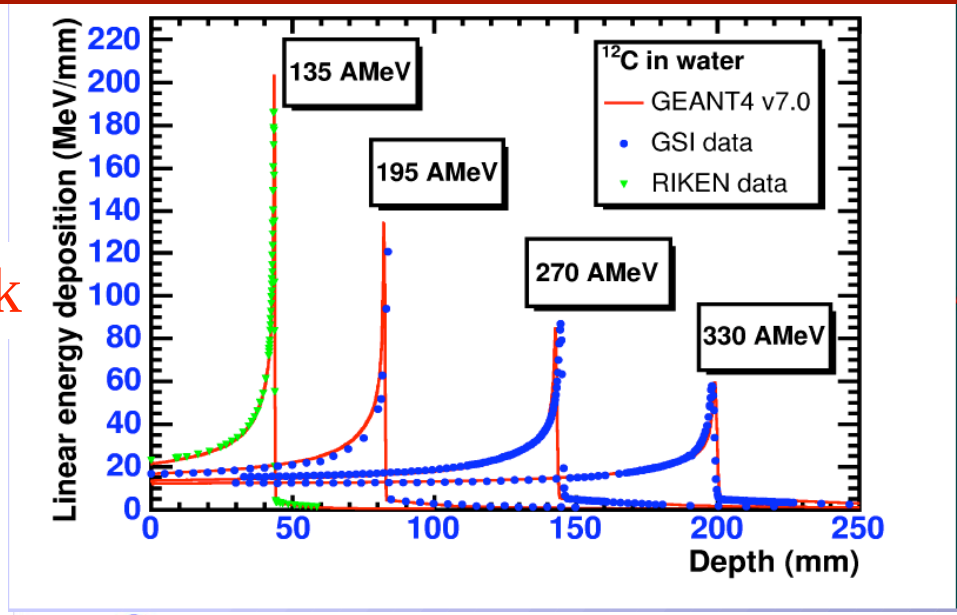
In what follows we will consider only protons and carbon ions.

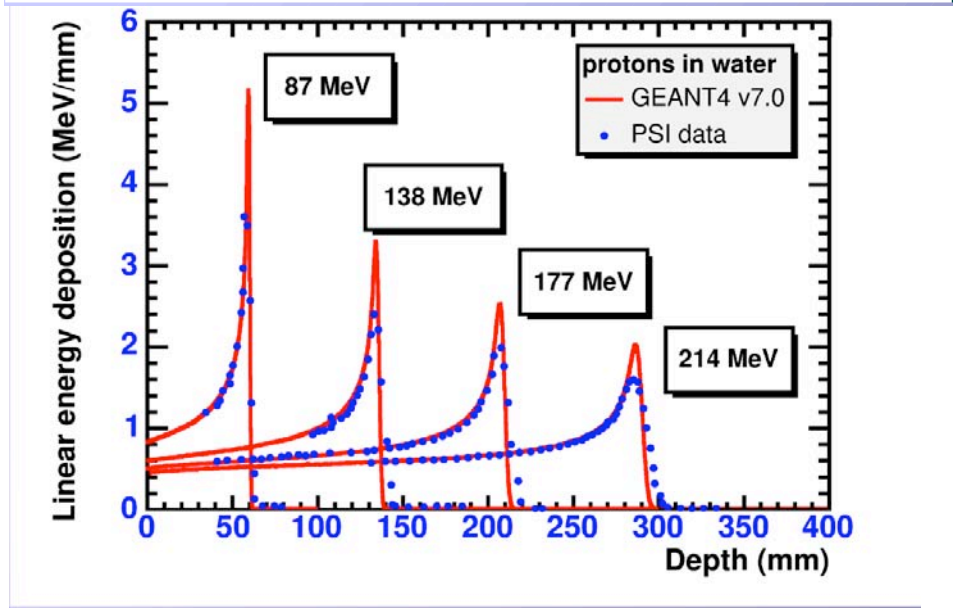


The Bragg peak curve from the original Wilson paper.

Tuning the penetration depth with ions







- **The depth of the energy deposition peak (Bragg peak) can be efficiently tuned by changing the ion energy**

Gantries are important even for hadrons

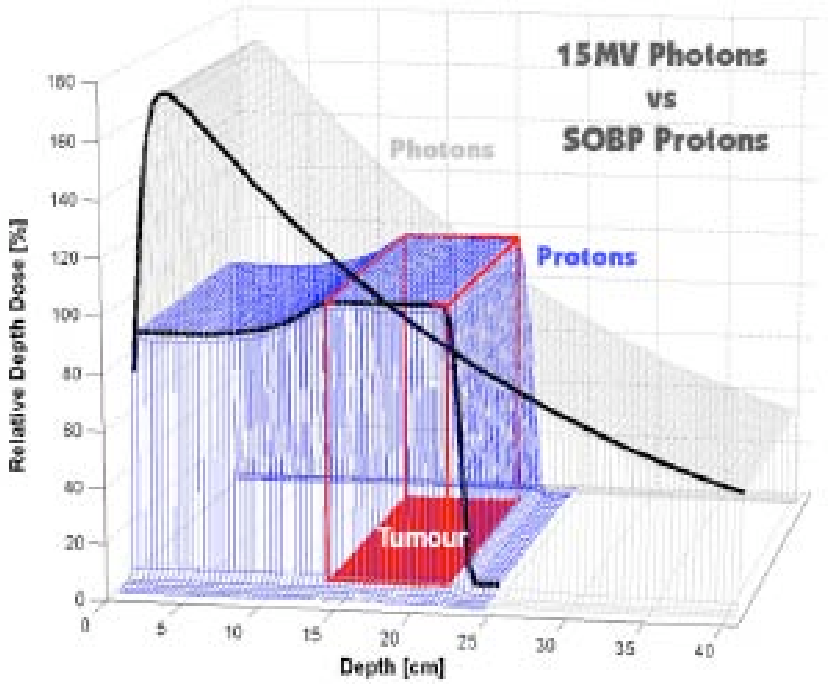


Figure 1. A comparison of depth doses for 15 MV photons and range/intensity modulated protons of variable energy. The proton spread-out Bragg peak (SOBP) has been developed so as to provide a region of high, uniform dose in at the tumour target shown in solid red. The red lines indicate an "ideal" dose distribution that is uniform within the tumour region and zero elsewhere. The proton SOBP shows much better conformality to the tumour target than does the photon dose distribution. The advantage of protons is that the dose proximal to the tumour target is lower than that for photons and the dose distal to the tumour target falls rapidly to zero while the photon dose continues to decrease exponentially.

Cell Killing Mechanism

Induce significant DNA damage to prevent cell replication

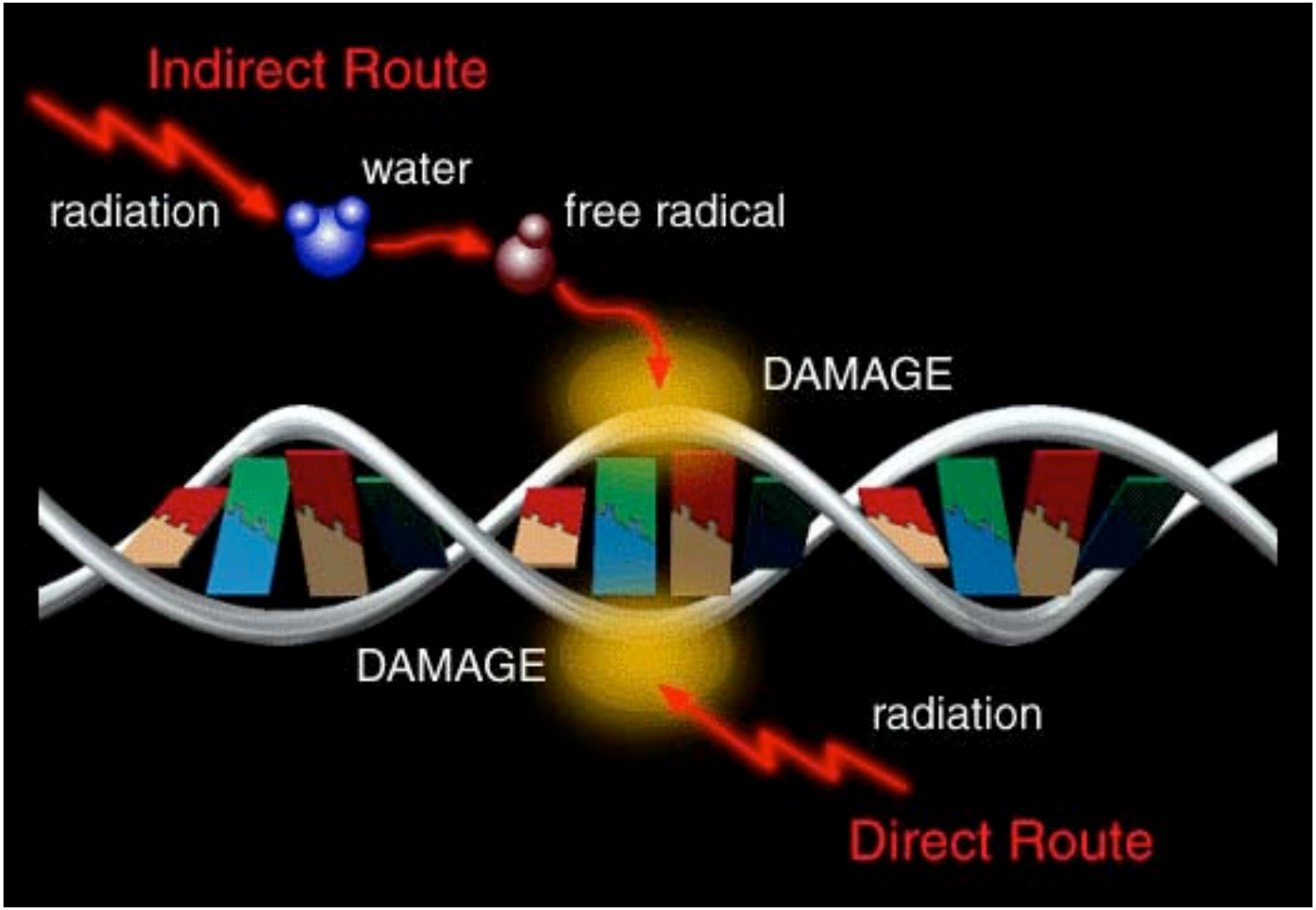
- **Requires Double Strand Break of the DNA**
  (Cells are very efficient at repairing Single Strand Breaks)

Double Strand Breaks can happen by two main mechanisms

1. **Direct Route**
   - **Ionization of DNA directly from the radiation**

2. **Indirect Route**
   - **Radiation interacts with water (H_2O) to create free radicals HO which then induce DNA damage**

Direct and indirect mechanisms



Advantage of Carbon vs Proton

Carbon has two properties that should yield a higher tumor control probability when compared with X-rays and protons

Carbon Properties

- **Sharper knife (Sharper *Penumbra*)**
- **Higher rate of energy deposited versus depth (High *Linear Energy Transfer*)**

Consequences

- **Less dose to healthy tissue**
- **More effective against tumors resistant to X-rays and proton radiation (hypoxic tumor cells)**
- **Shorter overall treatment course**

Carbon vs. protons

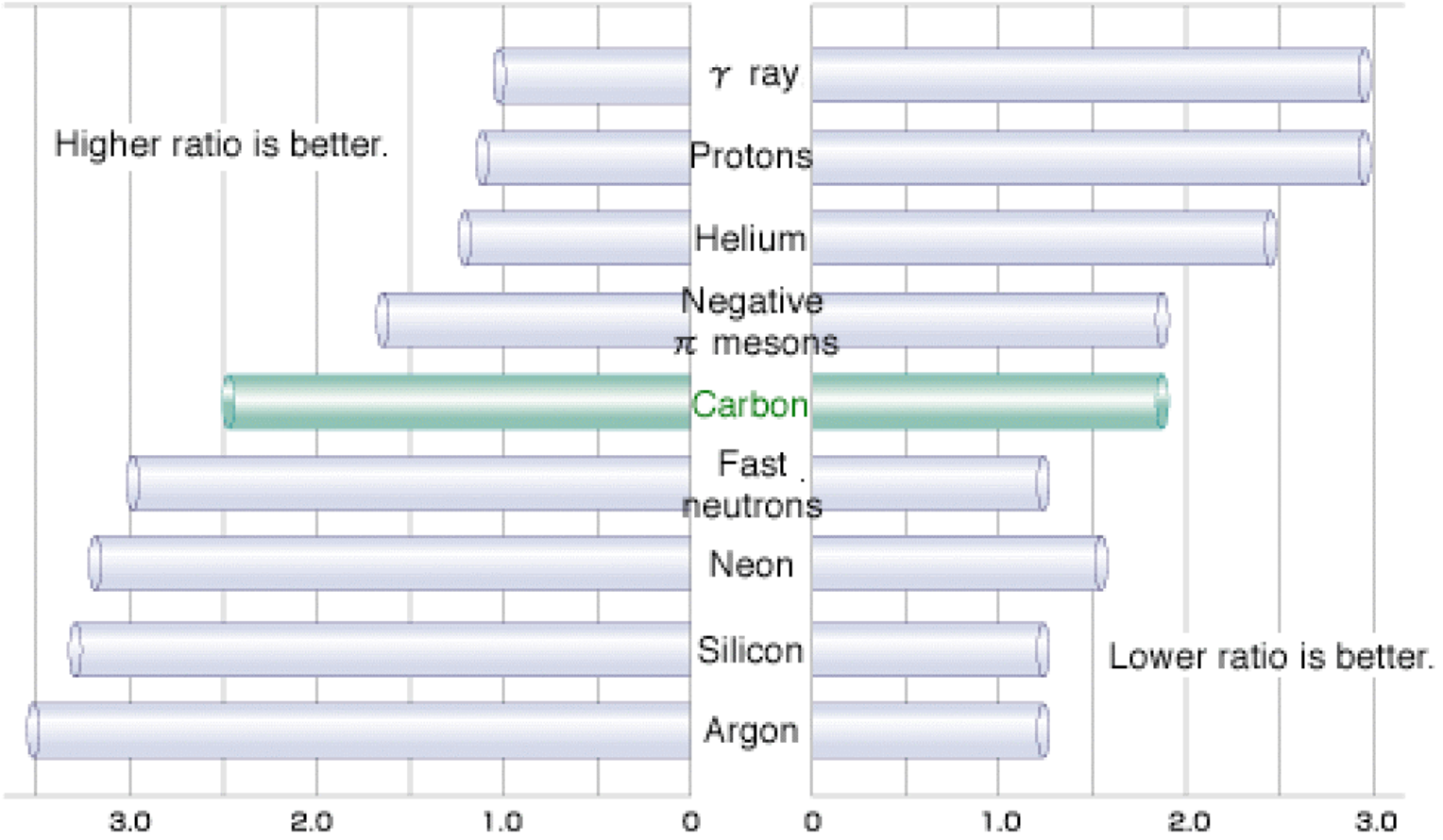
Comparison between proton and carbon therapy is only theoretical at this point, with a difference of "cost" of the accelerator and gantry of a factor of 4 and an overall facility difference of still a factor of 2. Much clinical experience, but so far no double blind comparisons.

The carbon is more spatially localized. The carbon is more than twice as effective (RBE) and the OER is more than 3/2 times better. (See next slide.)

Bone and soft tissue tumors can be treated, by carbon, but not even by protons and certainly not with X-rays.

RBE and OER

Relative biological effectiveness (RBE) and
oxygen enhancement ratio (OER) of various radiation types



RBE represents the biological effectiveness of radiation in the living body.
The larger the RBE, the greater the therapeutic effect on the cancer lesion.

OER represents the degree of sensitivity of hypoxic cancer cells to radiation.
The smaller the OER, the more effective the therapy for intractablecancer cells with low oxygen concentration.

Summary of Potential Benefits of Carbon

- Less dose to healthy tissue
- More effective against tumors resistant to X-rays and proton radiation (hypoxic tumor cells)
- Shorter overall treatment course
- An additional potential benefit is the verification of the location of the absorbed dose using PET detection. (Real time dosimetry is an important matter and no method (either for carbon or protons) is clinical yet.)

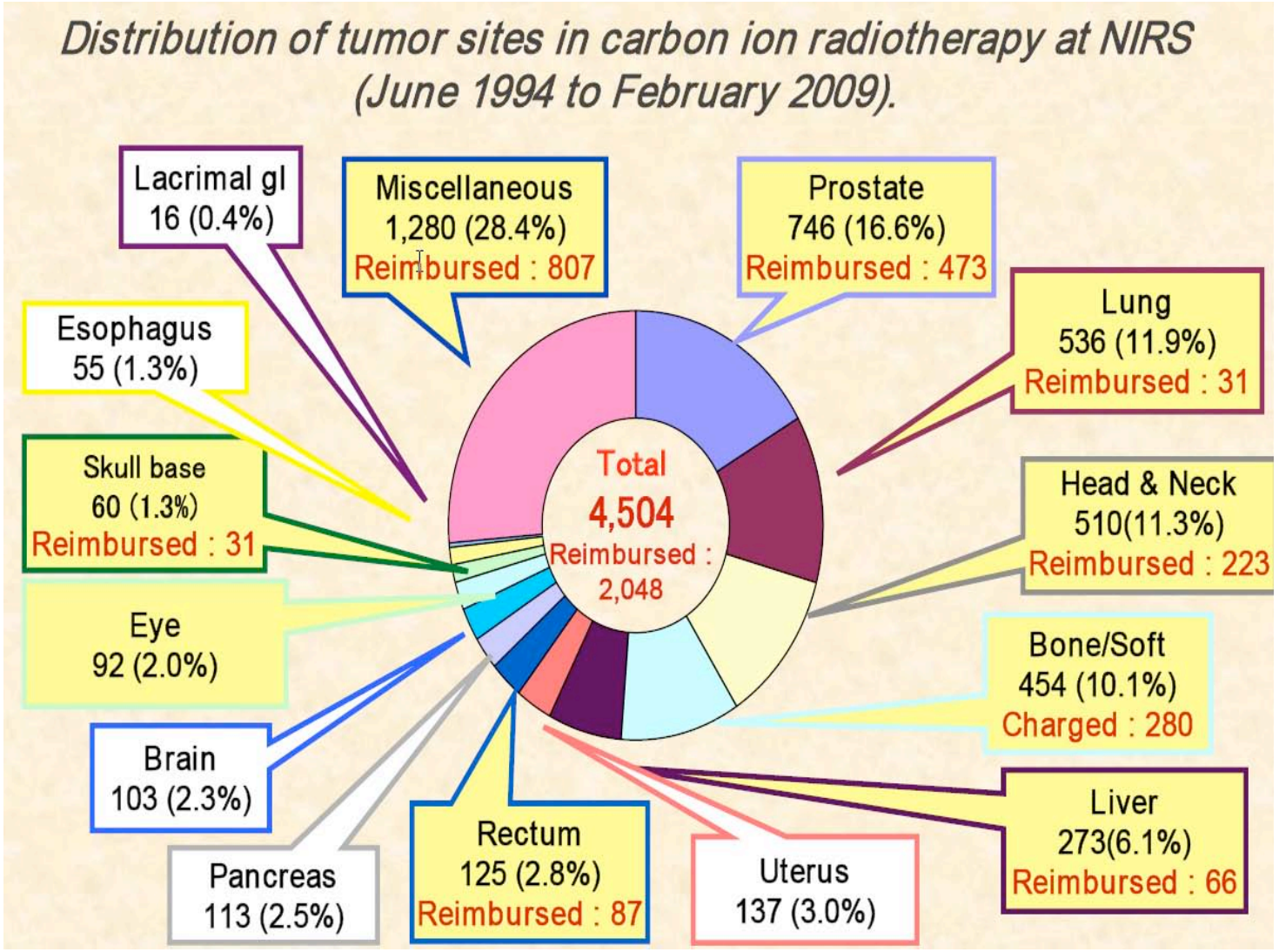
Conversion Factors and Needs

1Gy = 1Joule/Kg, a 250 MeV proton has 5 x 10^{-11}Joules, so 1 Gy is deposited by 2 x 10^{10} protons, if the protons stop inside 1 Kg. Typically 1/2 to 2/3 the energy is deposited outside the tumor.)

Physician want 2 to 10 Gy.

For spot scanning, consider a voxel as 4x4x4 mm^3 (multiple scattering precludes a smaller voxel and larger is less good). Take a typical tumour volume of 250 cm^3 (a grapefruit and 1/4 Kg). With a voxel-volume 0.064 cm^3, there are 4,000 elements, which with 10 pulses for each voxel needs 40k pulses in around 30 seconds, or a cycle rate of 1.3 kHz. A number of pulses per cycle is possible, but requires fast kickers. (The factor of 10 is because of the need for careful intensity control; an English facility talks of a factor of 100 as the physicians want dose control to 1 %.)

Japanese Have Extensive Experience With Carbon



4. Various Hadron Facilities

A Partial List of Hadron Facilities

In the US & Canada (All proton facilities):
Loma Linda (Fermilab), Mass General (IBA), Crocker (Davis)
Jacksonville, Texas (Hitachi), Indiana (NSF), TRIUMF (Canada)

In Asia:
HIMAC, Chiba (carbon), Tsukuba (Hitachi), WPTC (China),
Hyogo (Near Kobe)(carbon), Tsukuba, Lanzhou (carbon)
*Planned facilities:*Sendei, Tokyo, Nagoya, Hiroshima and
Kyushu, Seoul, Austron (Australia), Taiwan.

In Europe:
Nice, PSI, Orsay (France), ITEP (Moscow), St. Petersburgh,
Dubna, Svedbog (Sweden), GSI(carbon), Heidelberg (carbon)
*Under construction:*Munich, Czech Rep., Austron (carbon),
Wiener Neustadt, Pavia (carbon), South Africa, China, 4 in
Germany(2 carbon)

4. Various Hadron Facilities (Cont.)

Patient Statistics (for the facilities out of operation):

WHERE		WHAT	FIRST PATIENT	LAST PATIENT	PATIENT TOTAL	
Belgium	Louvain-la-Neuve	p	1991	1993	21	ocular tumors only
Canada	Vancouver (TRIUMF)	π^-	1979	1994	367	
Germany	Darmstadt (GSI)	ion	1997	2009	440	
Japan	Tsukuba (PMRC, 1)	p	1983	2000	700	
Japan	Chiba	p	1979	2002	145	ocular tumors only
Russia	Dubna (1)	p	1967	1996	124	
Sweden	Uppsala (1)	p	1957	1976	73	
Switzerland	Villigen PSI (SIN-Piotron)	π^-	1980	1993	503	
CA., USA	Berkeley 184	p	1954	1957	30	
CA., USA	Berkeley	He	1957	1992	2054	
CA., USA	Berkeley	ion	1975	1992	433	
IN., USA	Bloomington (MPRI, 1)	p	1993	1999	34	ocular tumors only
MA., USA	Harvard	p	1961	2002	9116	
NM., USA	Los Alamos	π^-	1974	1982	230	
					14270	**Total**
				thereof	2054	He
					1100	pions
					873	ions
					10243	protons

4. Various Hadron Facilities (Cont.)

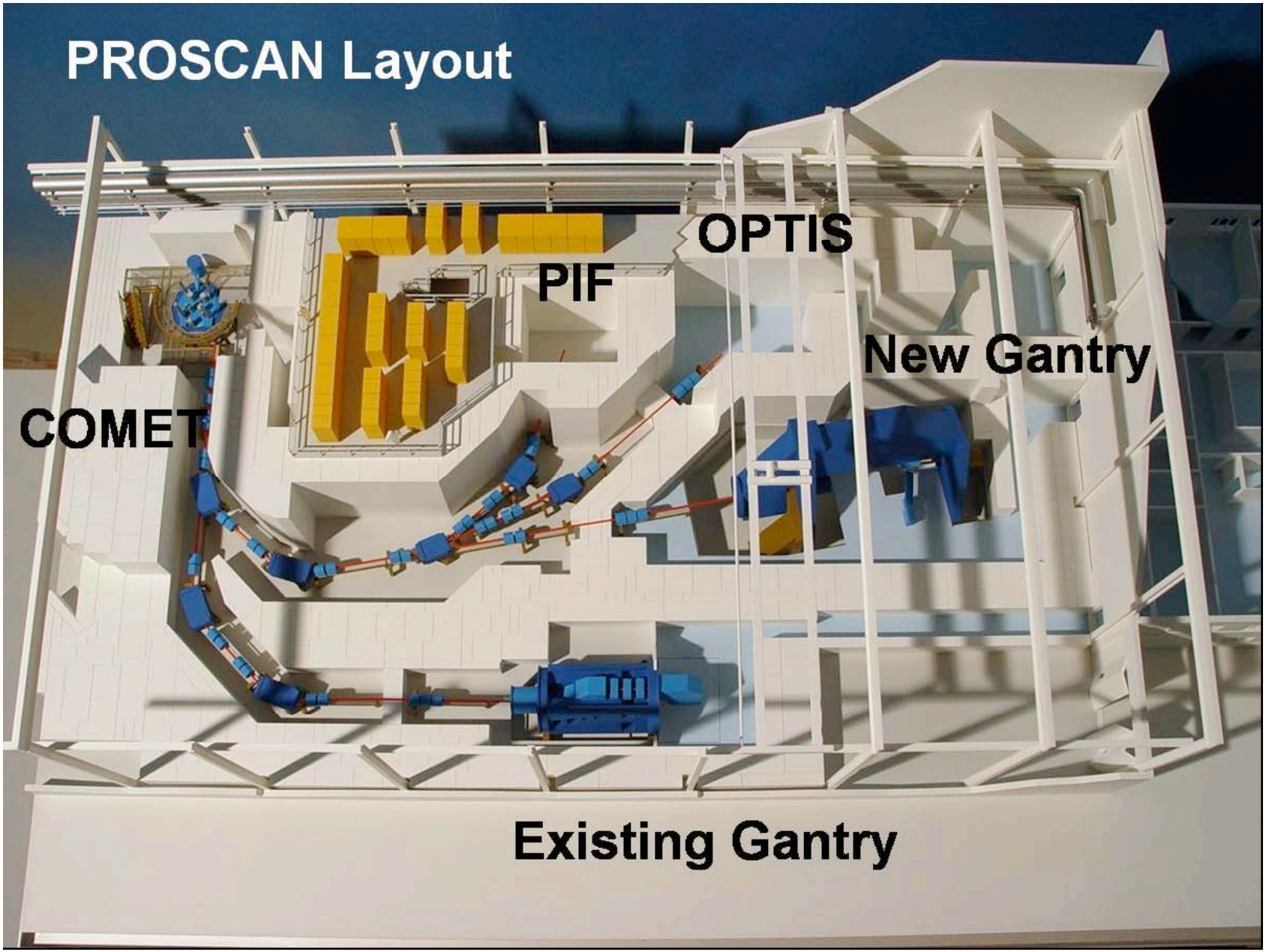
Patient Statistics (for the facilities in operation end of 2009):

WHERE		WHAT	FIRST PATIENT	PATIENT TOTAL	DATE OF TOTAL
Canada	Vancouver (TRIUMF)	p	1995	145	Dec-09
China	Wanjie (WPTC)	p	2004	977	Dec-09
England	Clatterbridge	p	1989	1923	Dec-09
France	Nice (CAL)	p	1991	3935	Dec-09
France	Orsay (CPO)	p	1991	4811	Dec-09
Germany	Berlin (HMI)	p	1998	1437	Dec-09
Germany	Munich (RPTC)	p	2009	78	Dec-09
Italy	Catania (INFN-LNS)	p	2002	174	Mar-09
Japan	Chiba (HIMAC)	C ion	1994	4504	Feb-09
Japan	Kashiwa (NCC)	p	1998	680	Dec-09
Japan	Hyogo (HIBMC)	p	2001	2382	Nov-09
Japan	Hyogo (HIBMC)	C ion	2002	638	Nov-09
Japan	Tsukuba (PMRC, 2)	p	2001	1586	Dec-09
Japan	WERC	p	2002	56	Dec-08
Japan	Shizuoka	p	2003	852	Dec-09
Korea	Ilsan, Korea	p	2007	519	Dec-09
Russia	Moscow (ITEP)	p	1969	4162	Jul-09
Russia	St. Petersburg	p	1975	1353	Dec-09
Russia	Dubna (JINR, 2)	p	1999	595	Dec-09
South Africa	iThemba LABS	p	1993	511	Dec-09
Sweden	Uppsala (2)	p	1989	929	Dec-08
Switzerland	Villigen PSI (72 MeV-Optis)	p	1984	5300	Dec-09
Switzerland	Villigen PSI (230 MeV)	p	1996	542	Dec-09
CA., USA	UCSF - CNL	p	1994	1200	Dec-09
CA., USA	Loma Linda (LLUMC)	p	1990	14000	Oct-09
IN., USA	Bloomington (MPRI, 2)	p	2004	890	Dec-09
MA., USA	Boston (NPTC)	p	2001	4270	Oct-09
TX, USA	Houston	p	2006	1700	Dec-09
FL, USA	Jacksonville	p	2006	1847	Dec-09
OK, USA	Oklahoma City (ProCurePTC)	p	2009	21	Dec-09
				62017	**Total**
			thereof	7151	C-ions
				56854	protons

Total for all facilities (in operation and out of operation):

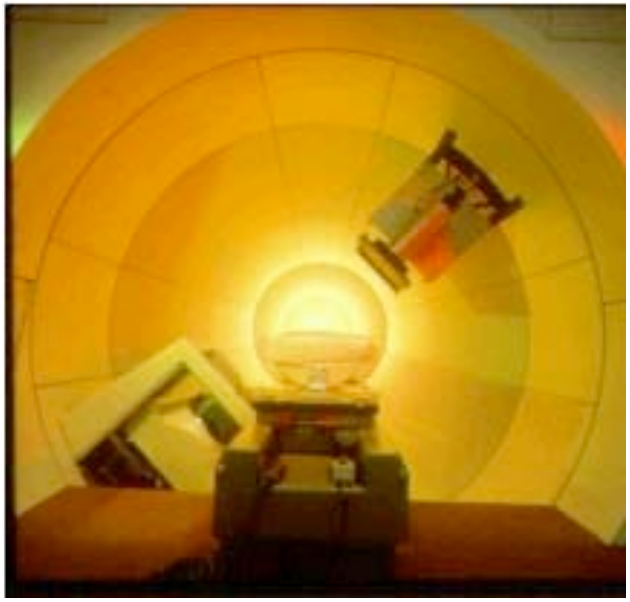
2054	He
1100	pions
7151	C-ions
873	other ions
67097	protons
78275	**Grand Total**

PSI Switzerland: Cyclotron Based Proton Facility



The PSI SC Accelerator. Diameter 3.25 m, 250 MeV protons
Built by ACCEL (based on design by Hank Blosser)

PSI Treatment Room



The facility at PSI

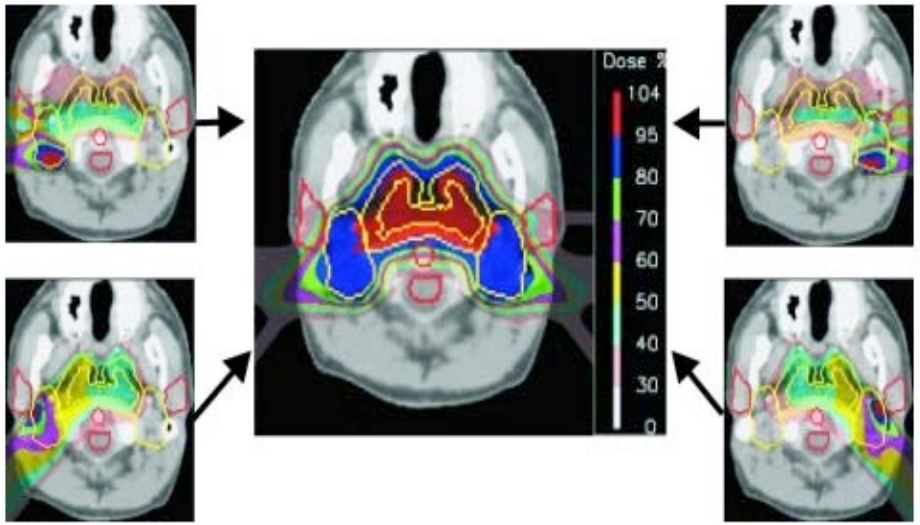
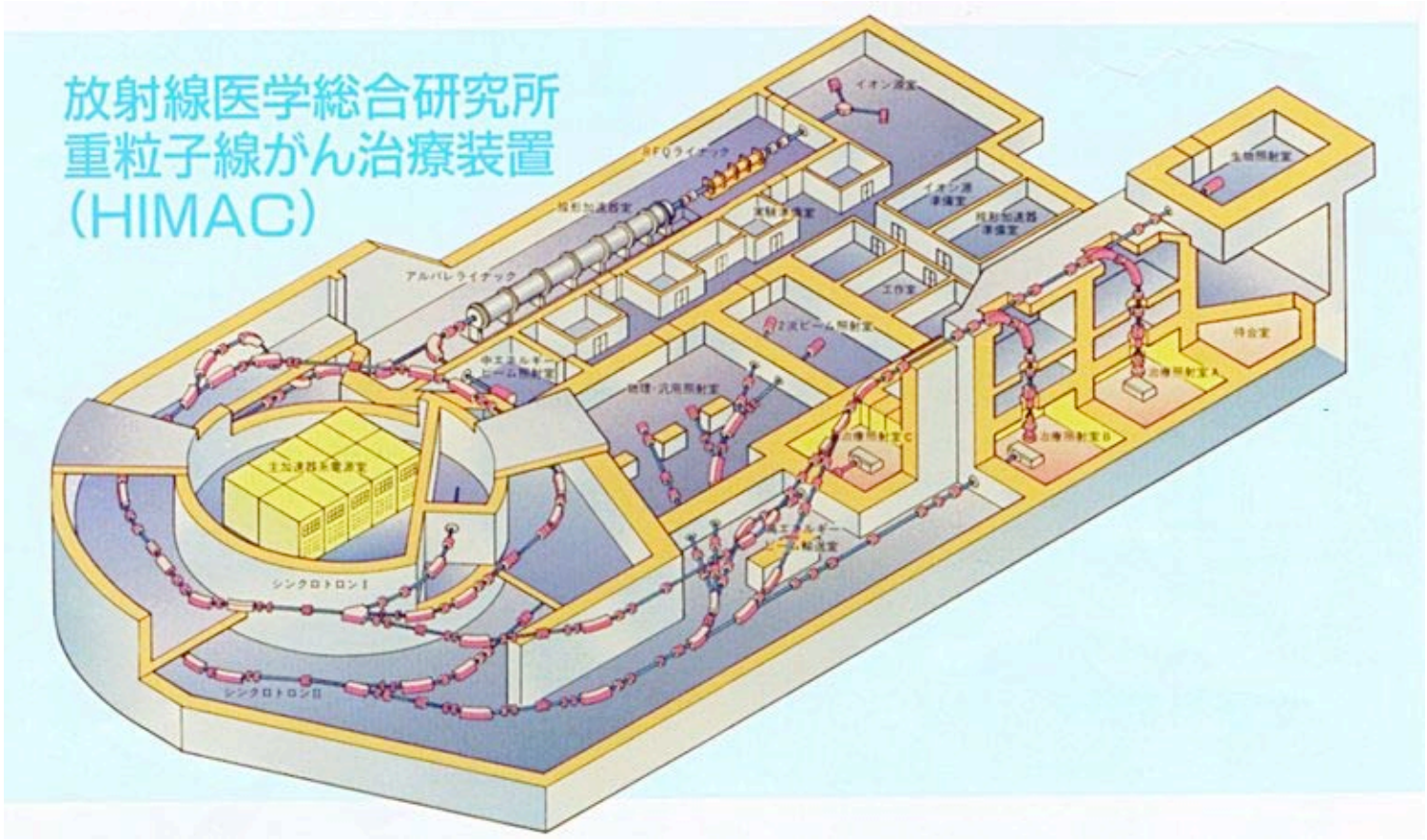


Fig 4 Example of intensity modulated therapy with protons. A high degree of conformity is achieved using a low number of dose fields. The advantage compared with photons is the general reduction of dose burden outside of the target volume (courtesy of T.Lomax, PSI)

Himac (Japan): Carbon Beam Facility

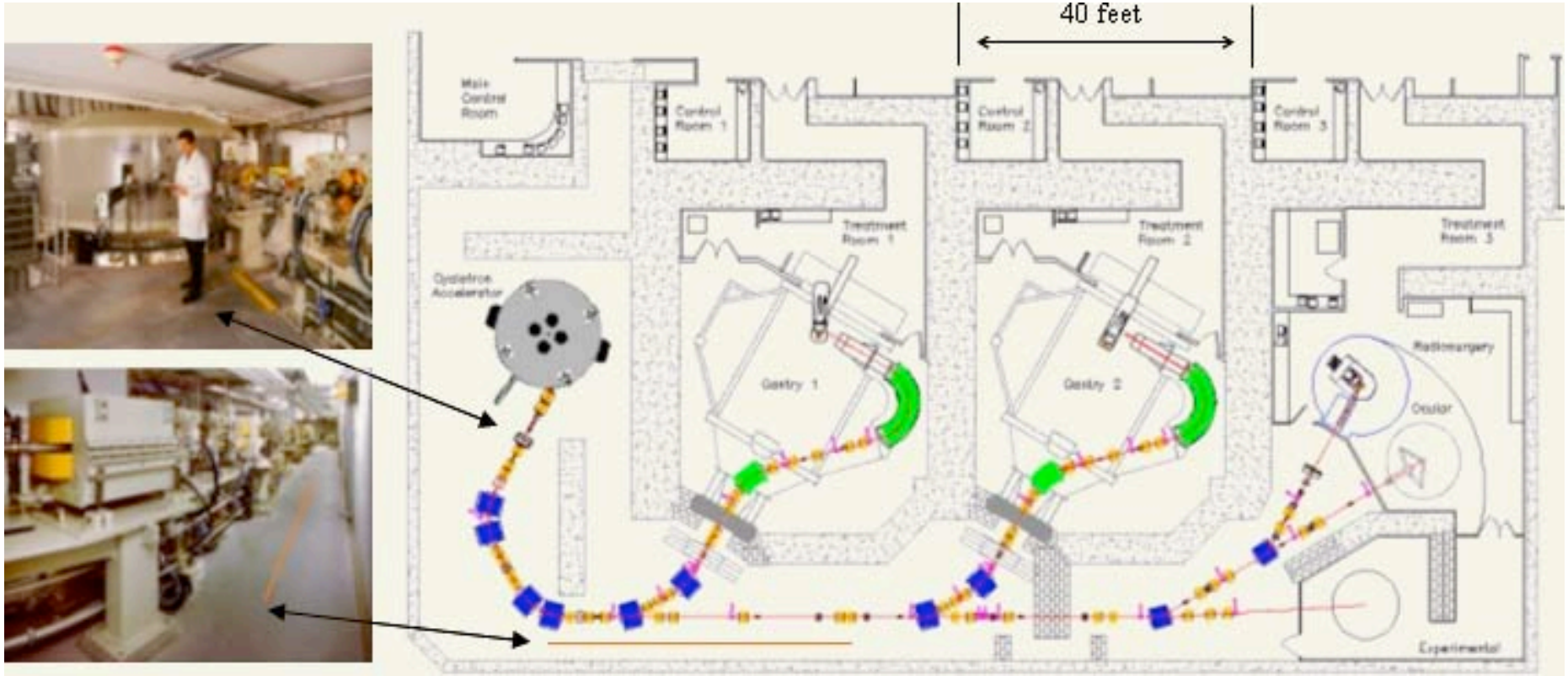


The Japanese two proton ion synchrotrons at HIMAC. The pulse of ions is synchronized with the respiration of the patient so as to minimize the effect of organ movement. The facility is being re-conditioned. A new one could be 1/3 as large (as in Hyogo).

Experience at the HIMAC

The HIMAC was started in 1987 and first treated patients in 1994. All patients have been treated with carbon (no protons used) and 3,000 patients have been treated. Last year: 500. About 50 are treated a day and the HIMAC treats patients 4 days a week. Typically a patient waits a month before starting therapy and only about 5% of those asking for treatment are accepted. Maintenance is done on Mondays and for one month in the summer and one month in the winter. The machine runs 24 hours a day, but patients are only treated from about 9 AM to 6 PM; night hours are used for nuclear physics. The HIMAC has three sources: Two ECR and one PIG, each producing 8 keV/u. There follows an RFQ and linac that results in carbon of 6 MeV/u, which is then injected into the synchrotron. The linac runs at Q/M = 1/3, so C^{4+} is accelerated. For therapy 2 x 10^9 carbon ions per second are used.

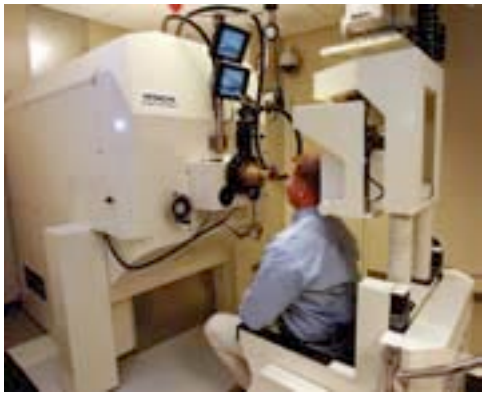
Massachusetts General Hospital: Cyclotron Based Proton Facility

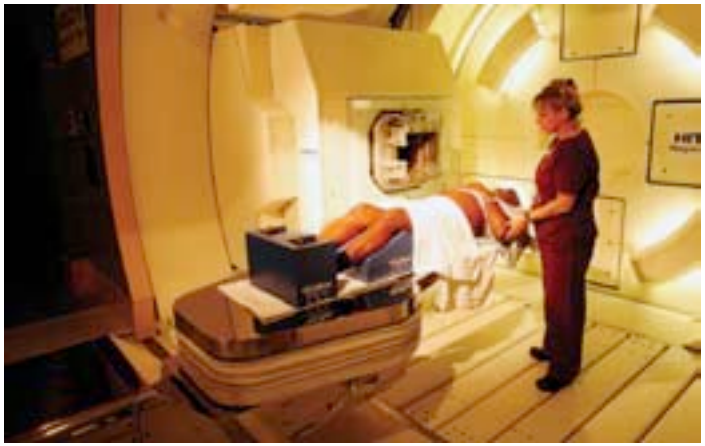


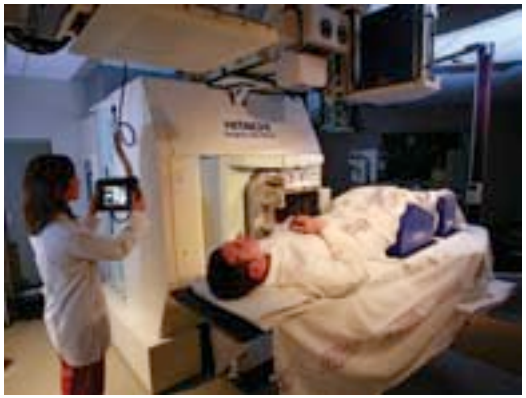
IBA built the accelerator (room temperature, but compact)

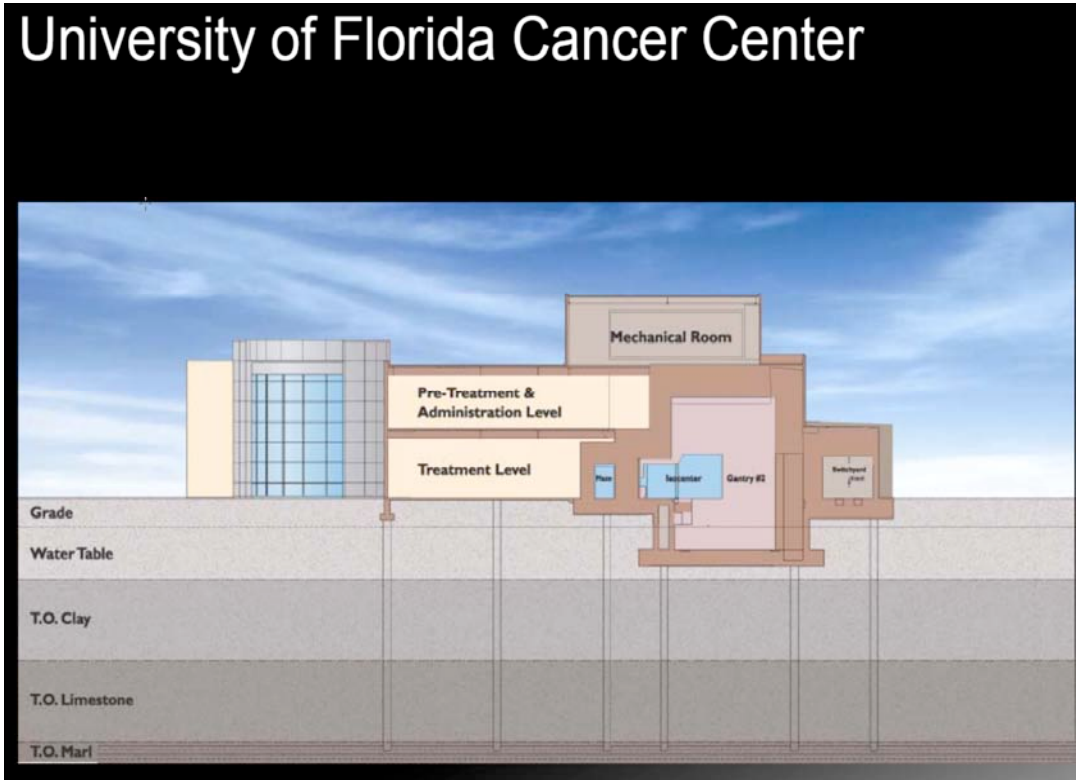
The Heidelberg Facility: Synchrotron Based Carbon Facility

MD Anderson: Synchrotron Based (Hitachi) Proton Treatment









Mix of a large accelerator facility (cyclotron)and a complex medical treatment facility

Protons.
Two Gantries,
One Horiz. Beam
Footprint: 98000 sq ft
$125M (Financially sound)

4. Various Hadron Facilities (Cont.)

Spot scanning seems advantageous (vary transverse position and energy (depth) and thus map out the tumor), but doing that within one patient breadth (so as to keep the location fixed) requires a cyclotron or a fast cycling synchrotron (at a rep rate of a few hundred Hz or higher).

Must be able to vary the energy by +/-20%, and transversely direct the beam over +/-10 cm so as to cover the tumor in any one patient.

Five companies supply turn-key proton therapy machines.Most of the hadron installations are proton facilities.

So far all carbon facilities (and a few proton facilities) are based upon synchrotrons.

Typically the accelerator is only 25% of a facility, with the beam handling (including gantries) another 25%. Much R&D happening on gantries. A bit of R&D is attacking the subject of real time dosimetry.

7. Conclusions

1. Hadron cancer therapy facilities are being built at a rapid rate. The efficacy of hadron therapy is accepted, but these facilities are expensive. ("The best and the worst of medicine.")
2. It is unclear if carbon is better than protons, but the Japanese are sold on it. The Americans have, so far, only gone for protons. Double blind studies do not exist.
3. Spot scanning may be medically advantageous, and it requires a cyclotron or fast cycling synchrotron, and seems to be the way the world is going.
4. The accelerator is only about 25% of the cost of the facility.
5. Gantries are about 25% of the cost of the facility (and improve the treatment, although much therapy can be done even without them).
6. All present facilities are synchrotrons or spiral ridge cyclotrons, but a linac is under construction in Italy.
7. R&D on many aspects should be most valuable.

Thank you for your attention.