An Introduction to Cancer Therapy With Hadron Radiation

Andrew M. Sessler

Lawrence Berkeley National Laboratory

Berkeley, CA 94720

April, 2008

Contents

1. History of Hadron Therapy

1. First treatment by the Lawrence's of their mother (X-rays)(1937). Seemed to cure an inoperable uterine cancer, but probably the malady was mis-diagnosed. Nevertheless it started the field of radiation treatment of cancer.

2. J.S. Stone and John Lawrence (both MDs) used neutrons for therapy in patients, starting in late 1938, with a major program (250 patients) starting in 1940. Quoting Stone: "Distressing late effects" and "Neutron therapy…should not be continued"

   No further neutron work for 25 years…

1. History of Hadron Therapy (Cont)

Review article, Alfred Smith, "Proton Therapy", *Phys. Med. Biol.* **51**, R491 (2006)

3. Linacs for X-rays built by Siemens and Varian in the US

4. Most patients are treated by X-rays. World-wide there are 10,000 linacs and 4 million patients a year treated.

5. Hadron therapy (Bragg peak) suggested by Bob Wilson in *Radiology* **47**, 487 (1946)

Pioneered in Berkeley and Harvard.

Now 6 hadron (proton) facilities in US; two under construction, more to come.

1. History of Hadron Therapy (Cont)

Review article: Joseph Castro,
LBL-35418 (1993)

6. Heavy ions carefully developed at the Bevalac in the 70's. From basic biology to patient treatment. All was really R&D. Even on patients: What cancers responded best? What doses? Etc.
Many scientists:
Joe Castro, Bill Chu, John Lyman,Cornelius Tobias, Eleanor Blakely, Ted Philips, and many others.

Bevalac was used 2/3 for medicine and only 1/3 for nuclear physics (but laid the basis for RHIC, LHC).

1. History of Hadron Therapy (Cont)

7. On the basis of the Berkeley work HIMAC was constructed. It is the first dedicated facility to ion treatment. There are none in US, but more are being built in Japan (eventually 50) and some are being built in Europe.

8. Pion and neutron therapy have been employed in the past and are not the method generally of interest. (Although neutron treatment has just started again at Fermilab)

1. History (Cont): 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), Wanje (China)
Almost completed: Hyogo (Near Kobe)(carbon)
Planned facilities: (all carbon)Sendei, Tokyo, Nagoya,
Hiroshima and Kyushu, Seoul, Austron (Australia).

In Europe:
Nice (protons) (and plans to go to higher energy), PSI (protons),
Orsay (France), ITEP (Moscow), Svedbog (Sweden), Dubna and
St. Petersburg (Russia),

Almost completed:Heidelberg (carbon)
Under construction:Munich, Lyon, Wiener Neustadt, Pave, etc.

Particle therapy facilities in operation:

WHO, WHERE	COUNTRY	PARTICLE	MAX. CLINICAL ENERGY (MeV)	BEAM DIRECTION
ITEP, Moscow	Russia	p	250	horiz.
St.Petersburg	Russia	p	1000	horiz.
PSI, Villigen	Switzerland	p	72	horiz.
Dubna	Russia	p	200***	horiz.
Uppsala	Sweden	p	200	horiz.
Clatterbridge	England	p	62	horiz.
Loma Linda	CA.,USA	p	250	gantry,horiz.
Nice	France	p	65	horiz.
Orsay	France	p	200	horiz.
iThemba Labs	South Africa	p	200	horiz.
MPRI(2)	IN.,USA	p	200	horiz.
UCSF	CA.,USA	p	60	horiz.
HIMAC, Chiba	Japan	ion	800/u	horiz.,vertical
TRIUMF, Vancouver	Canada	p	72	horiz.
PSI, Villigen	Switzerland	p**	250*	gantry
G.S.I. Darmstadt	Germany	ion**	430/u	horiz.
HMI, Berlin	Germany	p	72	horiz.

Particle therapy facilities in operation:
(Continued)

WHO, WHERE	COUNTRY	PARTICLE	MAX. CLINICAL ENERGY (MeV)	BEAM DIRECTION
NCC, Kashiwa	Japan	p	235	gantry
HIBMC,Hyogo	Japan	p	230	gantry
HIBMC,Hyogo	Japan	ion	320	horiz.,vertical
PMRC(2), Tsukuba	Japan	p	250	gantry
NPTC, MGH Boston	USA	p	235	gantry,horiz.
INFN-LNS, Catania	Italy	p	60	horiz.
Shizuoka	Japan	p	235	gantry, horiz.
Wakasa WERC,Tsuruga	Japan	p	200	horiz.,vertical
WPTC, Zibo	China	p	230	gantry, horiz.
MD Anderson Cancer Center, Houston, TX	USA	p	250	gantry, horiz.
FPTI, Jacksonville, FL	USA	p	230	gantry, horiz.

Particle therapy facilities in a planning stage or under construction:

WHO, WHERE	COUNTRY	PARTICLE	MAX. CLINICAL ENERGY (MeV)	START OF TREATMENT PLANNED
RPTC, Munich*	Germany	p	250 SC cyclotron	2007
PSI, Villigen*	Switzerland	p	250 SC cyclotron	2007/08 (OPTIS2/ Gantry2)
NCC, Seoul*	Korea	p	230 cyclotron	End of 2007
UPenn*	USA	p	230 cyclotron	2009
Med-AUSTRON	Austria	p, ion	synchrotron	2011?
Trento	Italy	p	? cyclotron	2010?
CNAO, Pavia*	Italy	p, ion	430/u synchrotron	2009?
Heidelberg/GSI Darmstadt*	Germany	p, ion	430/u synchrotron	2008
iThemba Labs	South Africa	p	230 cyclotron	2009?
RPTC, Koeln	Germany	p	250 SC cyclotron	?
WPE, Essen*	Germany	p	230 cyclotron	2009
CPO, Orsay*	France	p	230 cyclotron	2010
PTC, Marburg*	Germany	p, ion	430/u synchrotron	2010
Northern Illinois PT Res.Institute, W. Chicago, IL	USA	p	250 accelerator	2011

1. History of Hadron Therapy (Cont)

A Time Line of Hadron Therapy

1938 Neutron therapy by John Lawrence and R.S. Stone (Berkeley)

1946 Robert Wilson suggests protons

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. (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
2008 Neutron therapy re-stated at Fermilab (due to an ear mark).

1. History (Cont): Summary Comments on Hadron Facilities

In summary:

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, shipping new ones at the rate of 2-3 per day and treating on the order of 200,000 patients daily, or 50 M per year.

Compare with hadron therapy which has a total of 50,000 patients treated in all the years.

2. X-Ray Therapy (Cont)
(Comments from D.Whittum)

The key problem with X-rays, and also with hadron therapy, is Real Time Position Management (RPM) and Image Guided Radiation Therapy (IGRT). In fact there is a 2-1/2 day seminar, twice a year, at Stanford, on just this subject. For example, in the old days (and still a lot these days) radiation treatment of a lung nodule would have to be 1-2 cm larger than the nodule because of breathing motion. A 3D movie made with a CT is used in so called Four Dimensional Computerized Tomography (4DCT) to gate the radiation. (But the movie is made days or weeks earlier and when the breathing pattern may be very different.) IGRT is still in its infancy, but is THE crucial topic in radiation treatment (and will be easier to solve with hadrons than with X-rays).

2. X-Ray Therapy (Cont)

Bad side-effects are just now being seen (40 year gestation). (children cancer, women breast cancer). Most serious are cardio-vascular. We are studying this at the National Academy.

In January and February of 2005 I had treatment with X-rays.
Proton therapy would involve living in LA or Boston for 2 months, and I elected not to do that.

I was given 72 Gy in 36 partitions (5 a week), so 2 Gy each time
with radiation directed from 6 directions. (Full body radiation of 3 Gy results in a 50% probability of death.)

The radiation field is defined by aperture definition close to the
X-ray source. The new procedure is Intensity Modulated Radiation
Treatment (IMRT). I didn't have it.

3.Why Hadrons? Which Hadrons?

Primarily because the radiation can be deposited directly where the tumor is located (in all three dimensions) (and damage is not done to the skin).
Also, because of the Bragg peak, the radiation is localized (and damage is not done to surrounding healthy tissue).

In the 70's we did the basic science at the Bevalac (2/3 of the time devoted to biology and medicine) to determine if heavy ions were advantageous and to carefully determine the proper dose for treatment. Carbon was 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.

Proton and Carbon Cancer Therapy

The cancerous tumors are removed most efficiently by the ion radiation as it had been previously (1946) recognized by R. Wilson.
[Radiological use of fast protons. Radiology 47:487-91, 1946].

The Relative Biological Efficiency RBE is at least 2 times better with ions compared to the X-rays.

[A new method of treating leukemia at the Sloan Hospital in New York is by short lived **α-emitters.** They have to stick to the cancerous cells (??) and the energy deposited by radiation destroy the DNA].

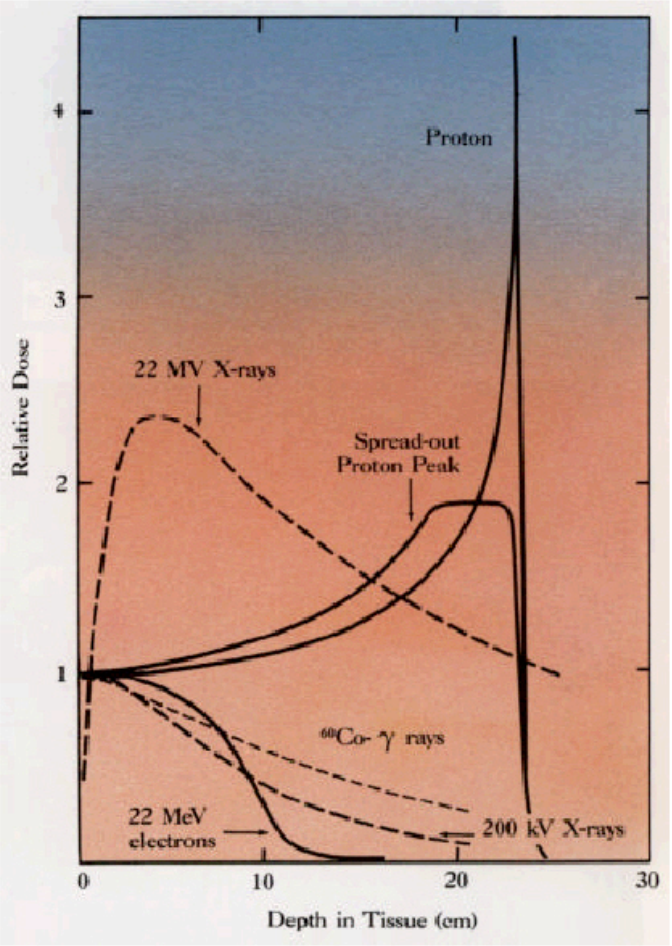


Figure 1: Depth dose curves for an unmodulated proton beam (Bragg peak), a modulated proton beam (spread-out Bragg peak – SOBP), 22 MeV X-rays, 22 MeV electrons, ^{60}Co γ-rays and 200 kV X-rays.

3.Why Hadrons? Which Hadrons? (Cont)

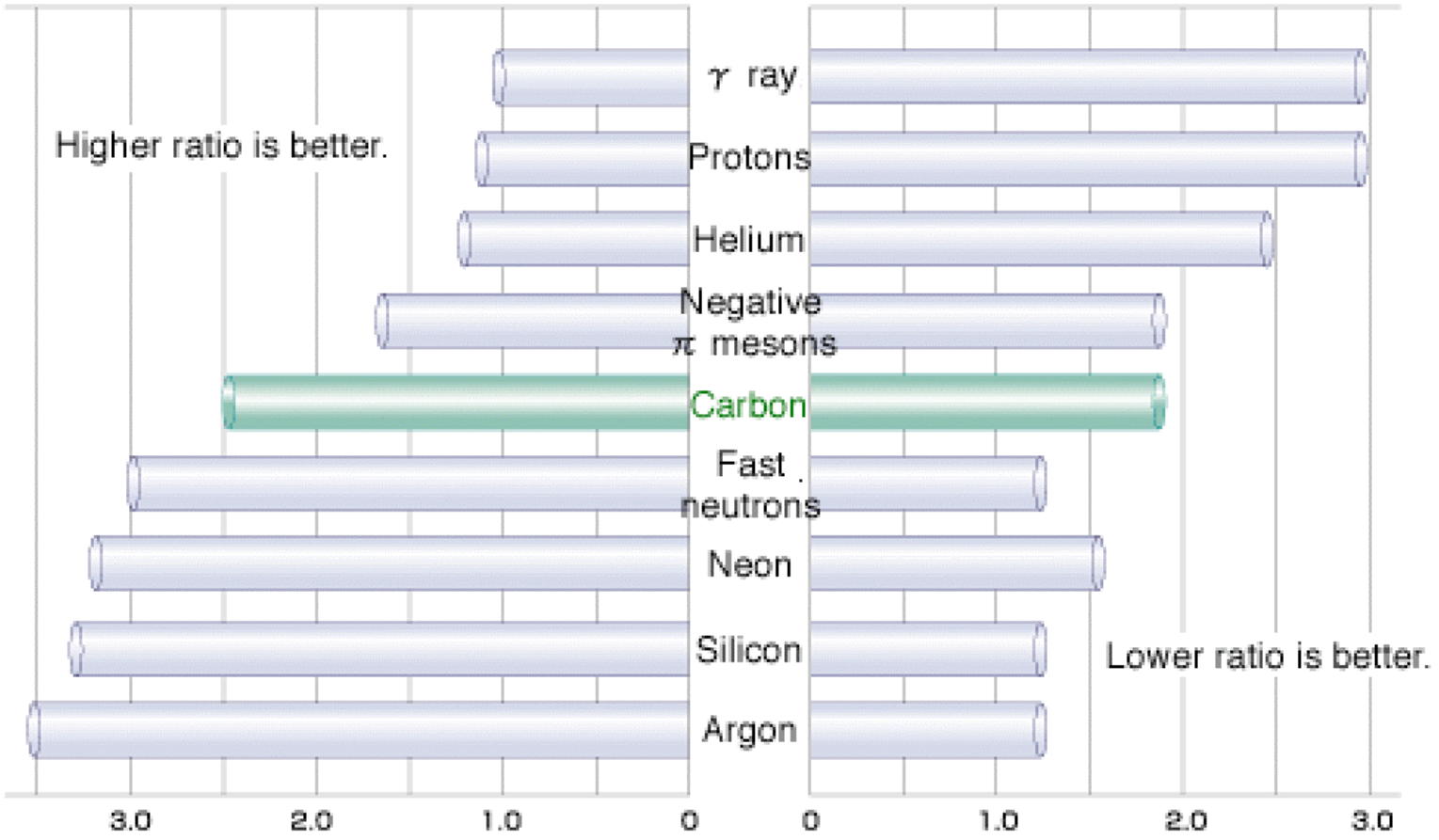
Comparison between proton and carbon therapy is only theoretical at this point, with a difference of cost of the accelerator and gantry of a factor of 4 and an overall facility difference of still a factor of 2. The carbon is more spatially localized (but it is unclear to me if this is medically important). 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. The post-operative PSA of prostate cancer patients remained significantly lower (did not increase in time) compared to those treated by either protons or X-rays.

Presumably the greater lethality of carbon kills the cancer resistant cells of X-ray or proton therapy; i.e., reduces cancer recurrence.

3.Why Hadrons? Which Hadrons? (Cont)

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.

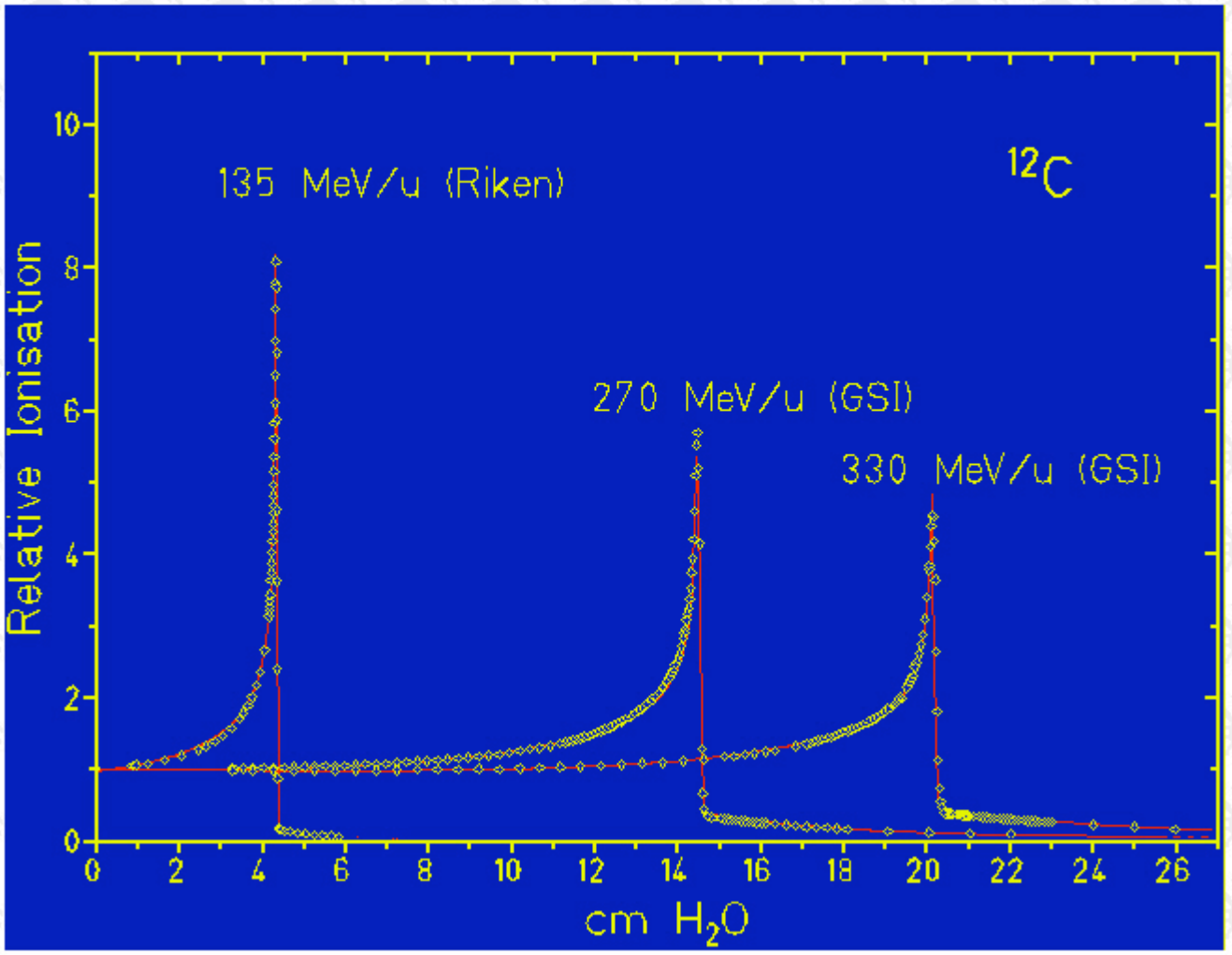
OER represents the degree of sensitivity of hypoxic cancer cells to radiation.
The smaller the OER, the more effective the therapy for intractablecancer cells with low oxygen concentration.

3.Why Hadrons? Which Hadrons? (Cont)

It is clear that hadron therapy is in the future.
Most impressive, is being able, for example to give 12 Gy in a single stage (three entry points) and so treat a patient in simply one visit (as is done at HIMAC). This should be contrasted with X-rays where the dose delivered in one location, and in one visit, is only 1/3 Gy. In all cases the number of fractionalizations is greatly reduced (typically one half) compared to X-rays and even protons. In some cases just one or two fractionalizations are adequate. Even the worst case (prostate cancer) only requires (about) 20 fractionalizations (compared to 36 for x-rays).

Bragg Peaks

Physical beam model for carbon ion radiotherapy



Gantries are important even for hadrons

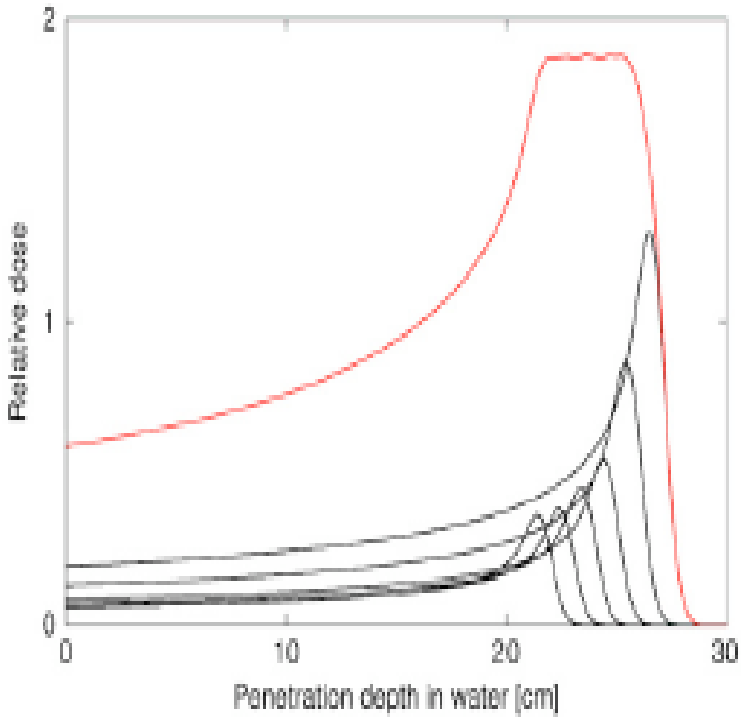


Figure 2. Range and intensity modulation of Bragg peaks to achieve a spread-out Bragg peak (SOBP). SOBPs can be produced by use of a physical device (ridge filter or modulation wheel) or by energy selection from the accelerator in conjunction with variable weighting of each individual Bragg peak. SOBPs can be produced for variable widths.

Gantries are important even for hadrons (Cont)

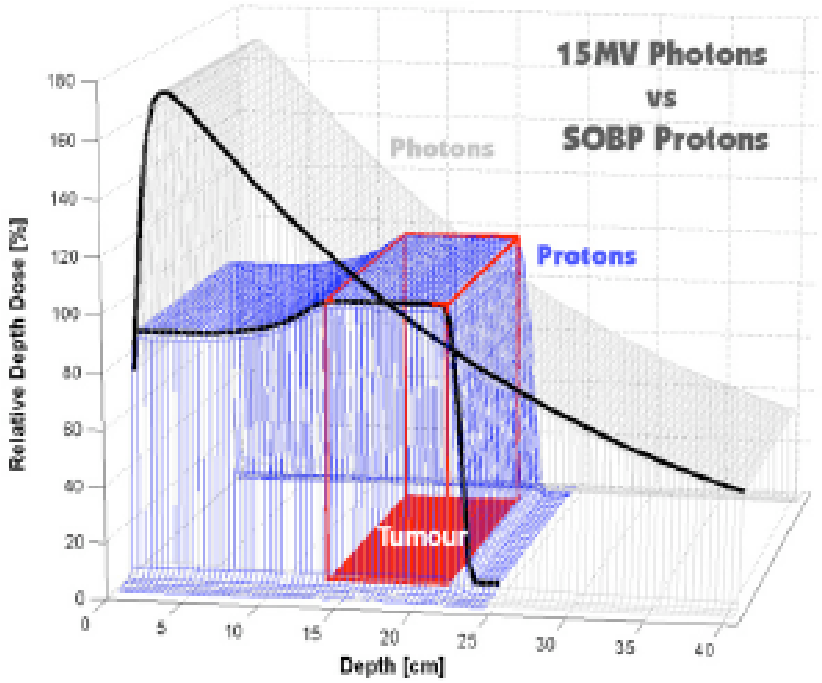


Figure 1. A comparison of depth doses for 15 MV photons and range/intensity modulated protons of variable energy. The proton spread-out Bragg peak (SOBP) has been developed so as to provide a region of high, uniform dose in at the tumour target shown in solid red. The red lines indicate an 'ideal' dose 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.

Conversion Factors and Needs

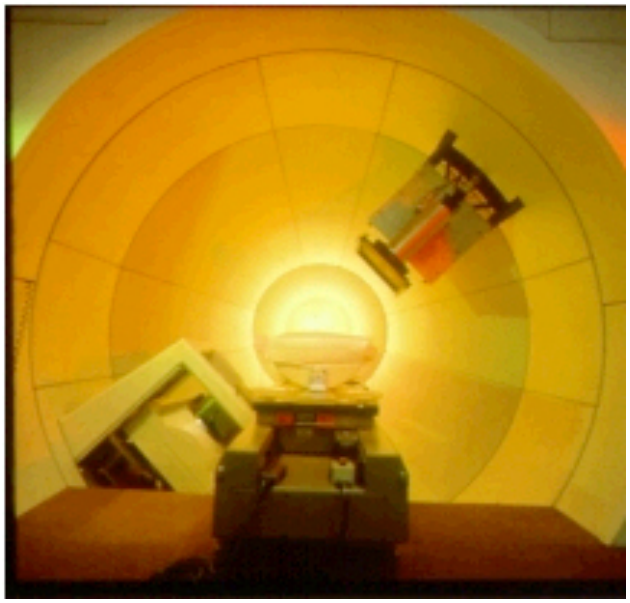
1Gy = 1Joule/Kg, a 250 MeV proton has 5 x 10^{-11}Joules, so 1 Gy is deposited by 2 x 10^{10} protons, if the protons stop inside 1 Kg. Typically 1/2 to 2/3 the energy is deposited outside the tumor.)

Physician want 2 to 10 Gy.

For spot scanning, consider a voxel as 4x4x4 mm^3 (multiple scattering precludes a smaller voxel). 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 control to 1 %.)

4. Various Hadron Facility

(You will hear about these, in detail as the Conference proceeds.)



The facility at PSI

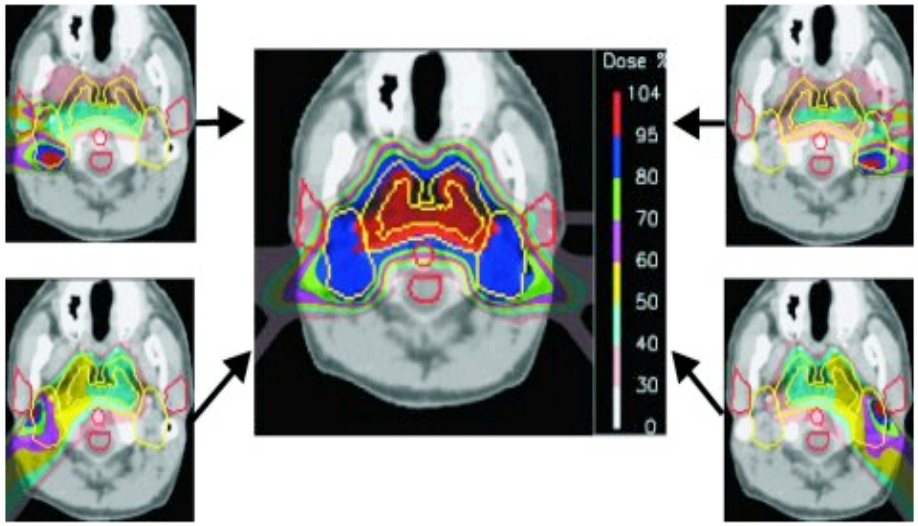
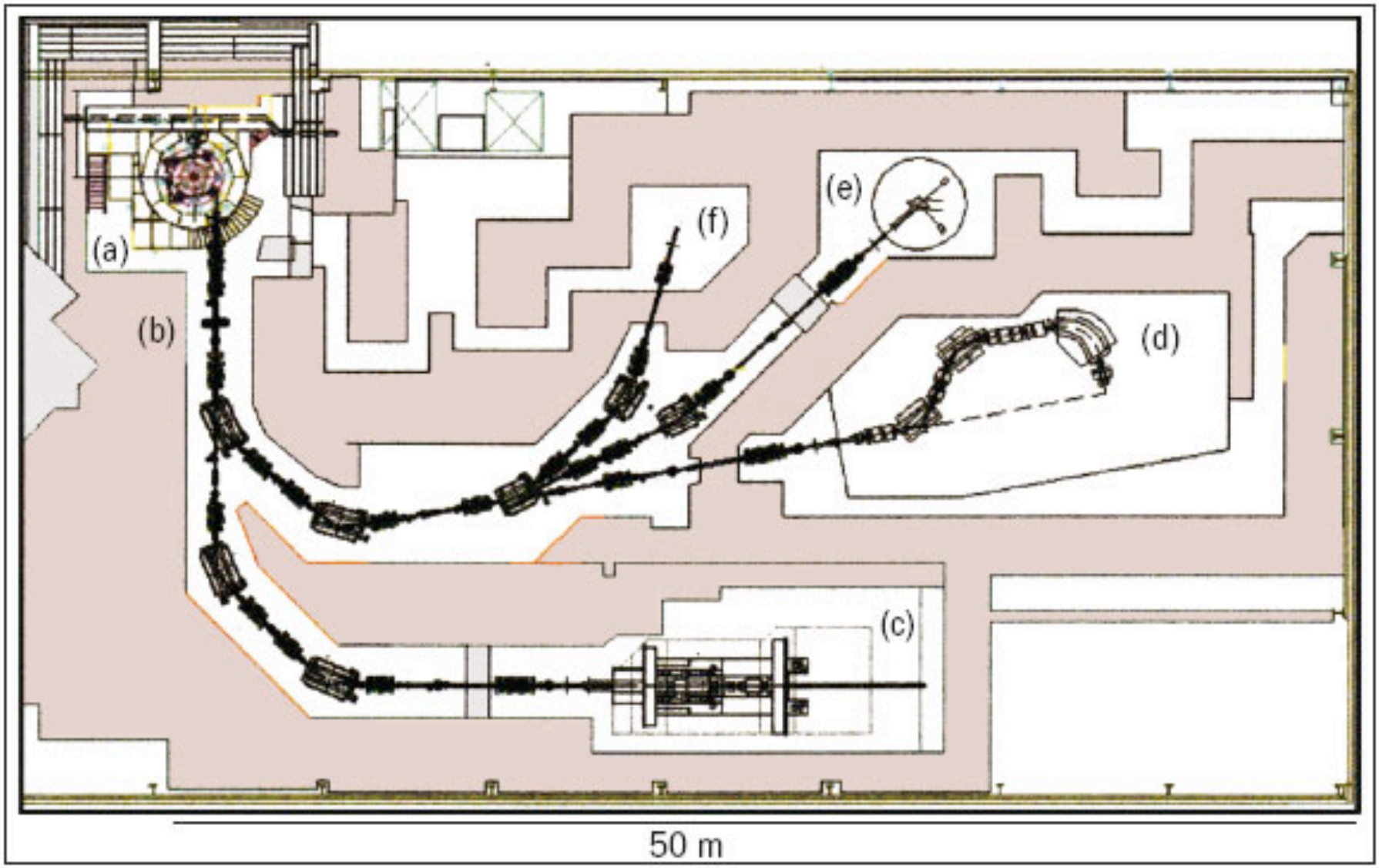
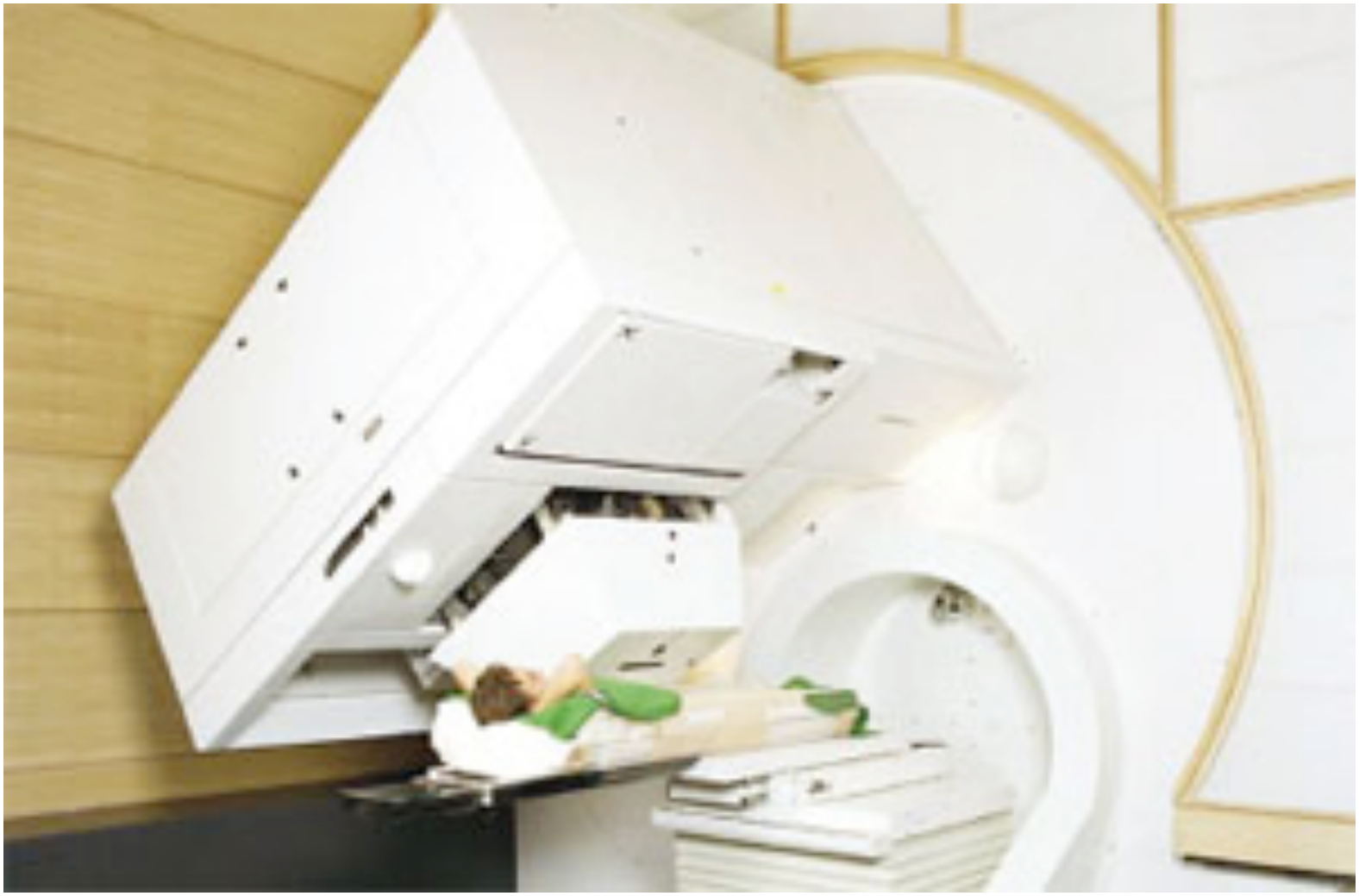


Fig 4 Example of intensity modulated therapy with protons. A high degree of conformity is achieved using a low number of dose fields. The advantage compared with photons is the general reduction of dose burden outside of the target volume (courtesy of T.Lomax, PSI)



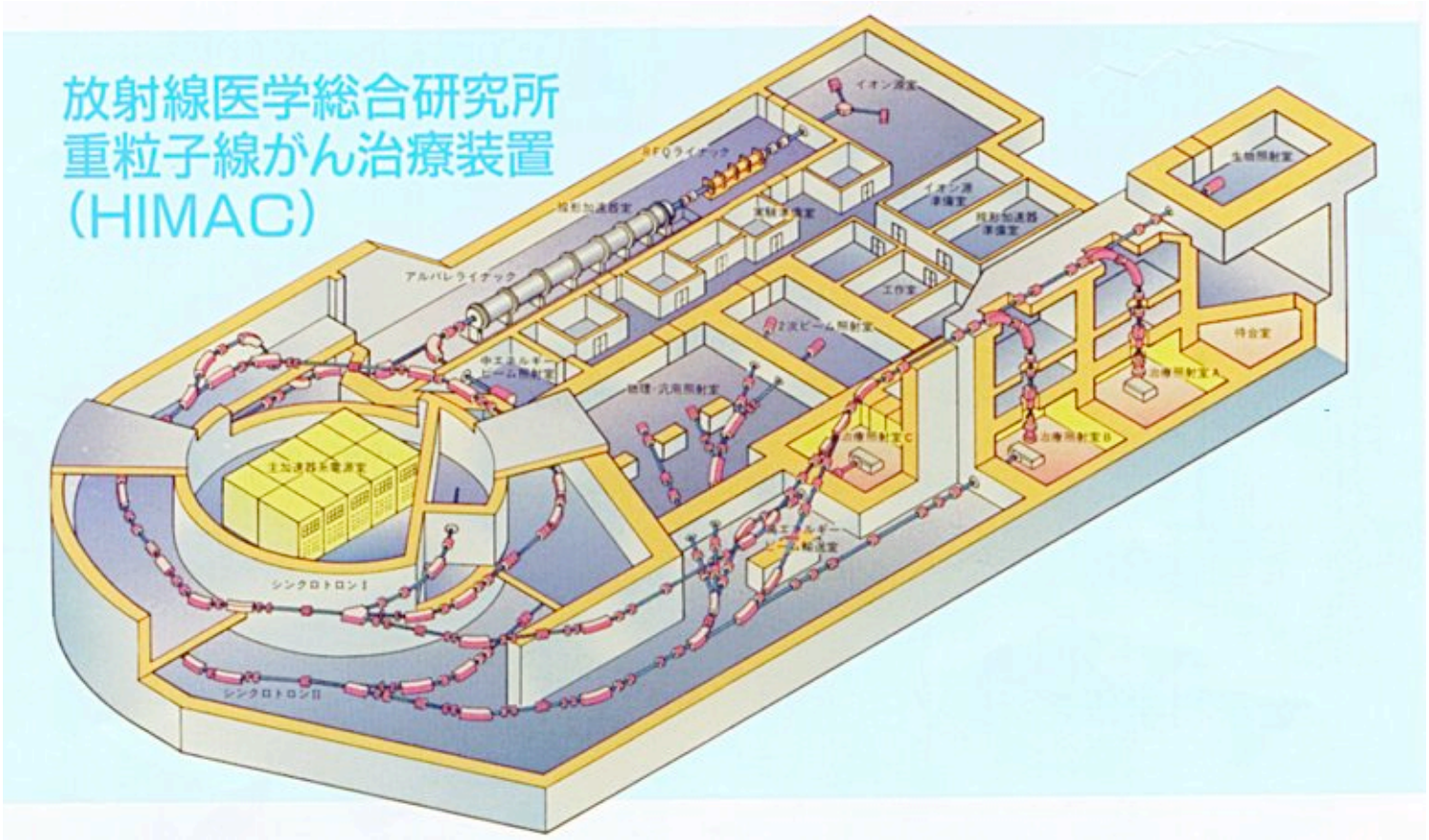
The PSI PROSCAN Facility (a) sc accelerator, (c and d) gantries, (e) Eye treatment room

The PSI sc accelerator. Diameter 3.25 m, 250 MeV protons
Built by ACCEL (based on design by Hank Blosser)
ACCEL bought out by Varian on Jan 4, 2007.



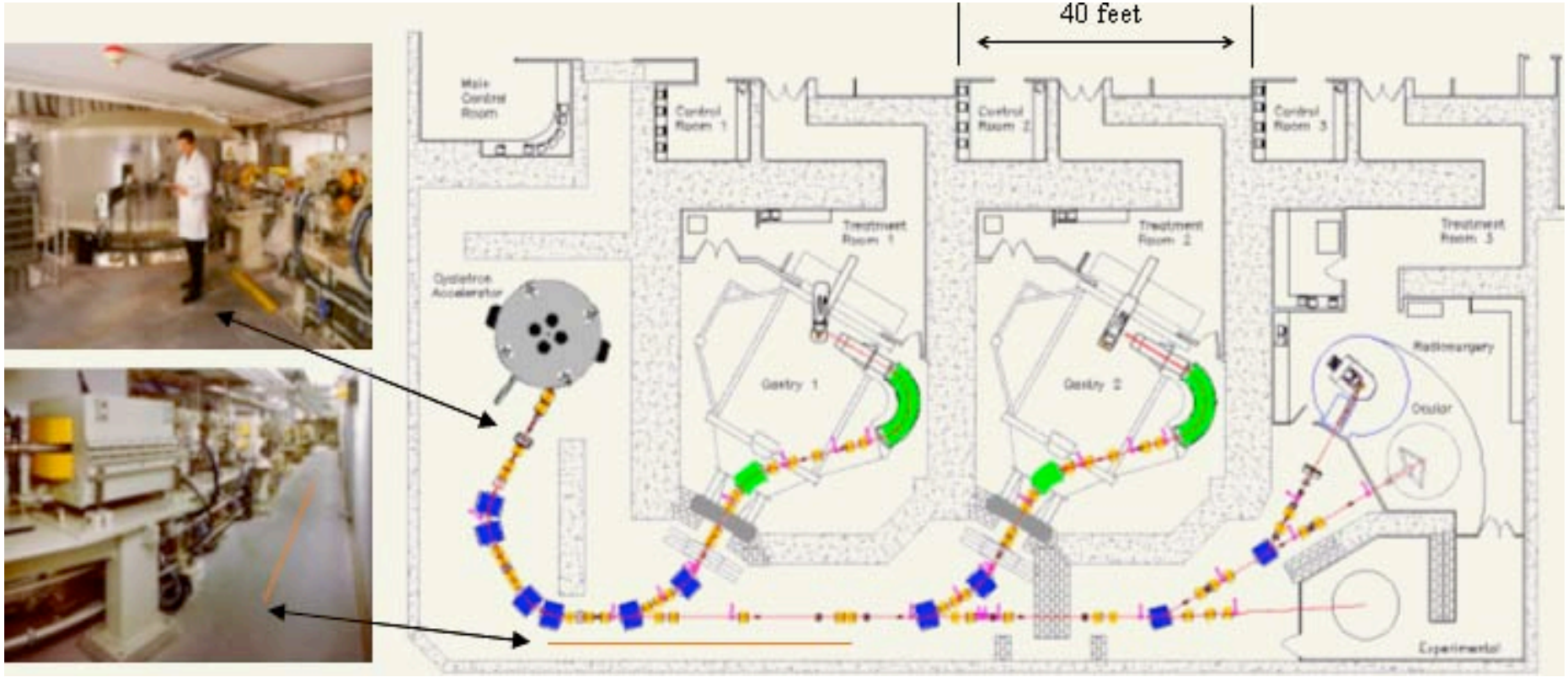
The PSI PROSCAN Gantry (100 tons)

Himac (Japan)

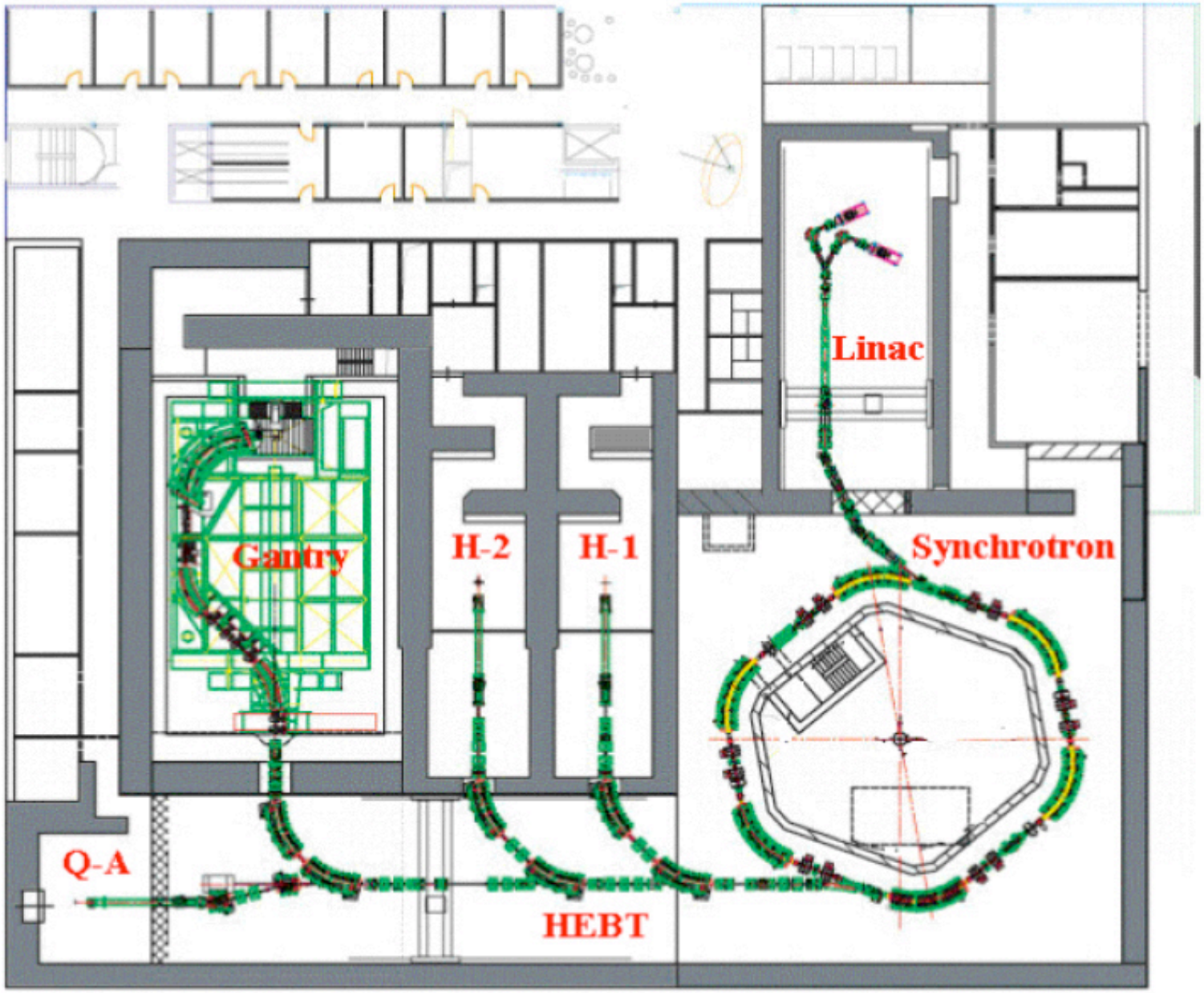


The Japanese two proton ion synchrotrons at HIMAC. The pulse of ions is synchronized with the respiration of the patient so as to minimize the effect of organ movement. The facility is being re-conditioned. A new one could be 1/3 as large.

Massachusetts General Hospital



The Heidelberg Facility



5. Experience at the HIMAC

(Again,you will hear much more as the Conference proceeds. Based on a visit.)

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.

5. Experience at the HIMAC (Cont)

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. There are three treatment rooms, two with horizontal beams and one with a vertical beam. There is no gantry and the patients are turned (But don't always hold perfectly still in an awkward position.) There is talk of building a gantry in a few years, but it is not obvious it will actually be built. For therapy 2 x 10^9 carbon ions per second are used.

5. Experience at the HIMAC (Cont)

The therapy is of many different types of cancers (with some very noticeable omissions). A break down is (out of 1,500 patients), 276 head, 329 lung, 222 prostate, 170 bone, and 170 liver.

A new facility in Hyogo (near Kobe) will have both carbon and proton capability and therefore will be able to compare the two modalities. At the moment there are no clinical comparisons.

6. Alternatives

A good number of different approaches have been developed for hadron therapy. Perhaps, some of this -- at least in the past -- was due to the availability of some machine (previously used for nuclear physics).

At this time, specially built machines are cyclotrons and synchrotrons.

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.

6. Alternatives (Cont)

Cyclotrons are sc spiral ridge scaling FFAGs.

Perhaps the most compact is the Accel machine, which will provide 250 MeV carbon from a machine of 3.25 m diameter.

Five companies supply turn-key proton therapy machines.

No one has considered non-scaling FFAGs and thinking these would be interesting alternatives, we (Eberhard Keil and Dejan Trbojevic) have been working on this possibility for the last few years. I will tell you about our current design in a talk later in the Conference.

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 RBE is perhaps the most important aspect.) The Americans are going only for protons.
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 they may not be needed.
6. All present facilities are synchrotrons or spiral ridge cyclotrons, but a linac is under construction in Italy.

Thank you for your attention.