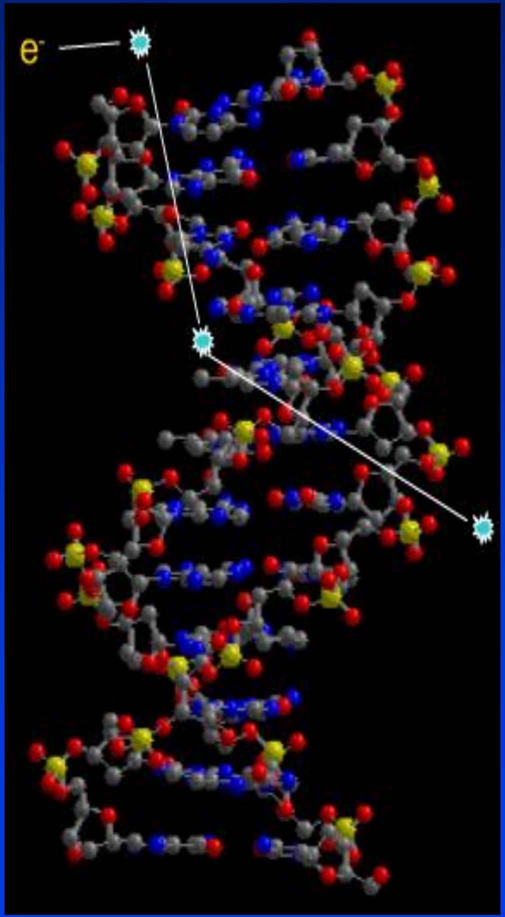
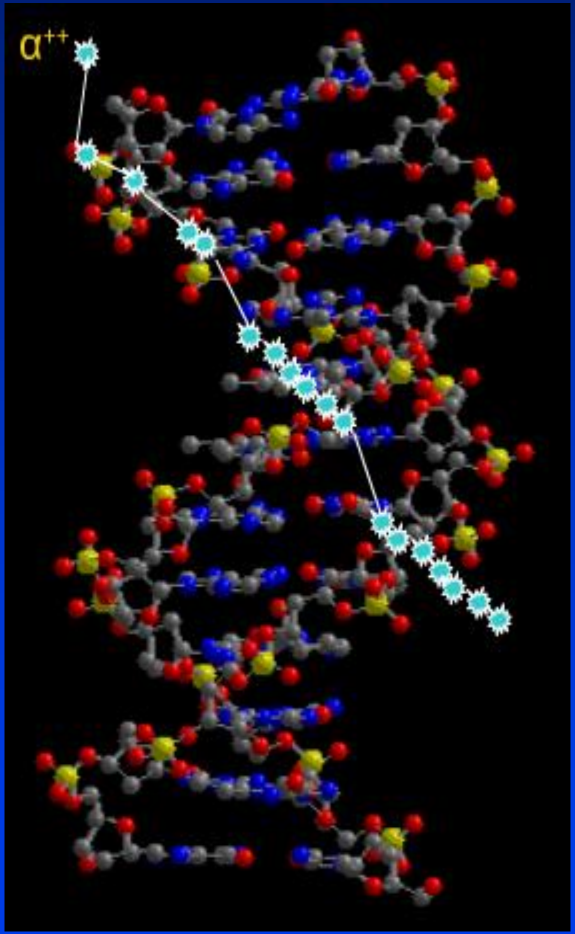
Proton and heavy ion radiotherapy: Effect of LET

As a low LET particle traverses a DNA molecule, ionizations are far apart and double strand breaks are rare



With high LET particles, ionizations are closer together and double strand breaks are more common



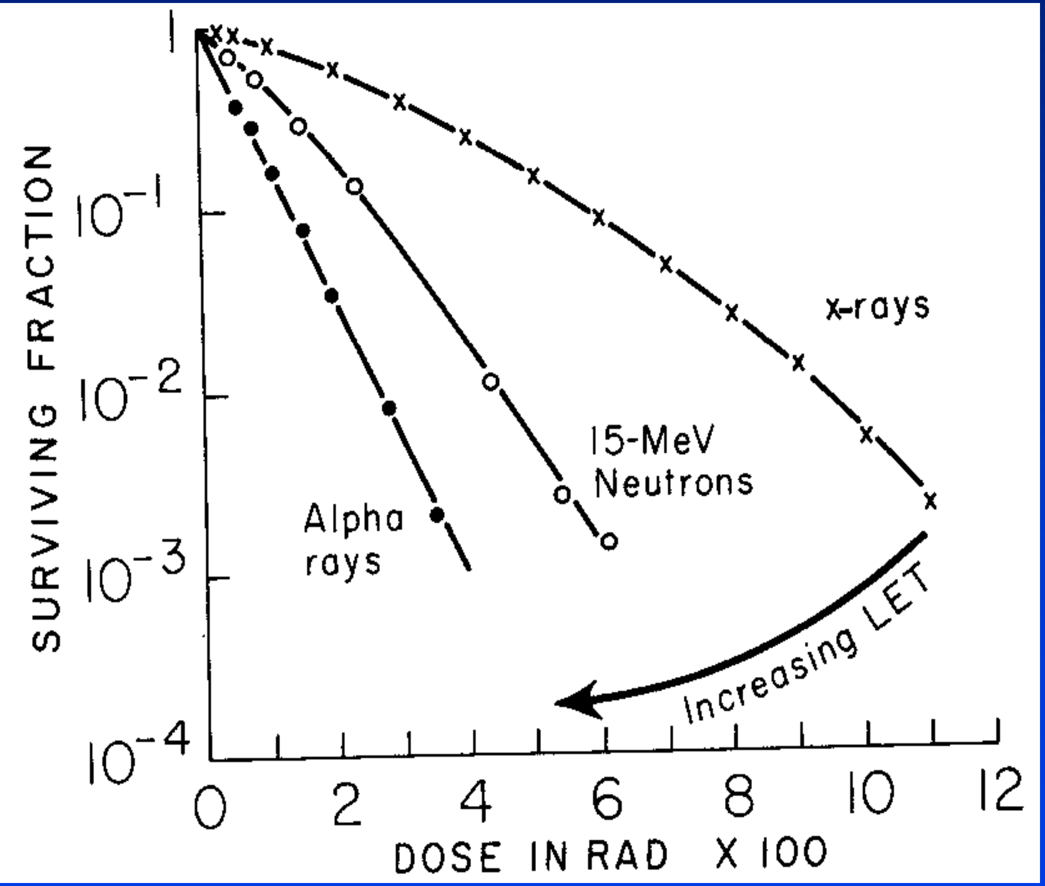
Effect of LET on cell survival curves

Cell sensitivity increases as LET increases

The increase in sensitivity is represented by the RBE

$$RBE = \frac{dose\ of\ ^{60}Co\ radiation}{dose\ of\ \ different\ LET\ radiation}$$

to produce the same biological effect



Factors which influence the RBE

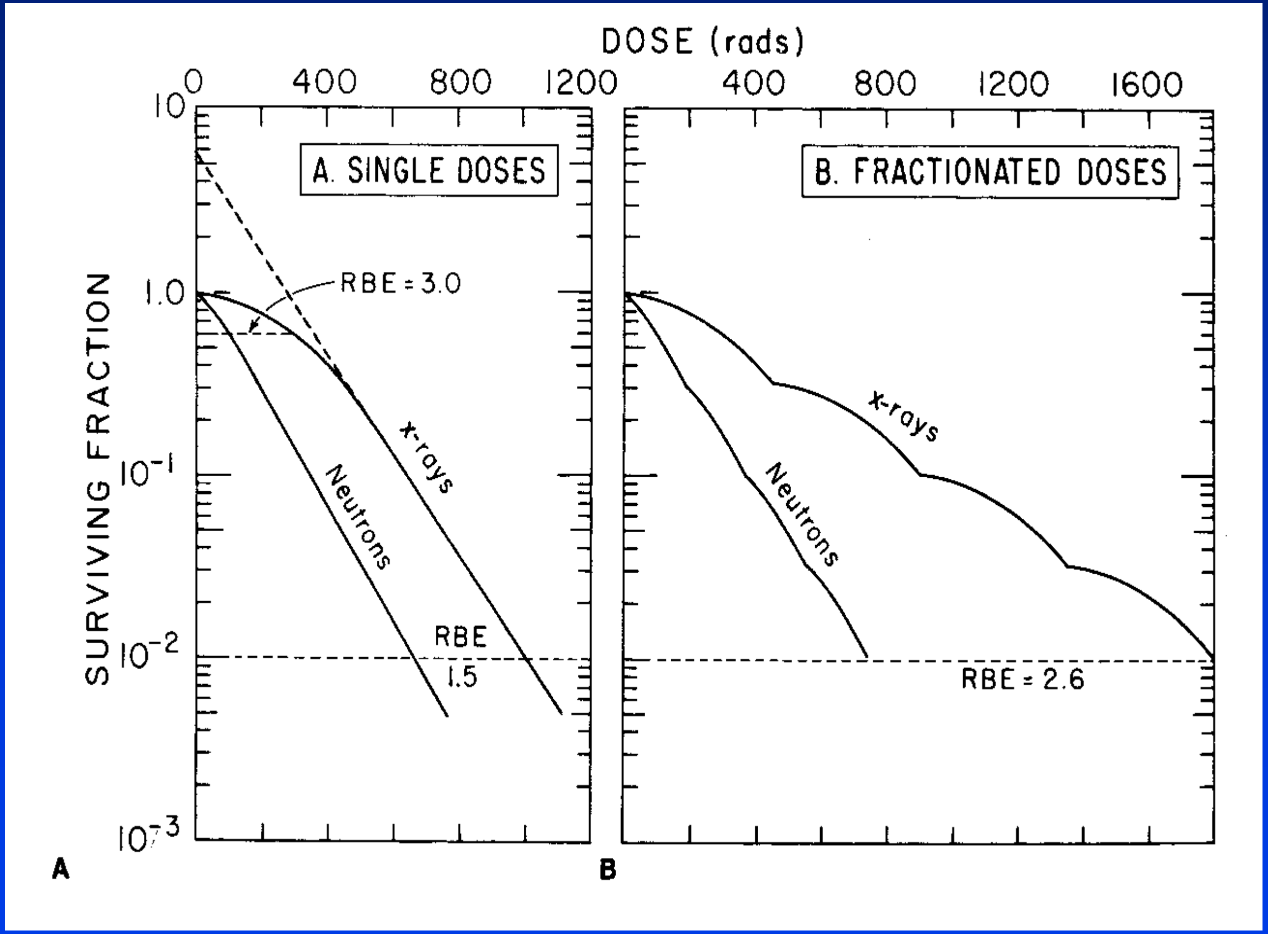
- RBE depends upon:
  - *radiation quality (LET)*
  - *radiation dose*
  - *dose/fraction*
  - *dose rate*
  - *biological system or endpoint*

Effect of dose and dose/fraction on the RBE for neutrons

The RBE is low for high doses (=1.5)

The RBE is high for low doses (=3.0)

The RBE is high for low doses/fraction (=2.6)



Effect of dose and dose/fraction on the RBE

- At low doses (and low doses/fraction), the RBE will be higher since there is more repair at low doses and this favors the standard ^{60}Co radiation
  - *the numerator in the RBE equation increases as dose decreases*
- A similar effect is seen with low dose-rate irradiation

RBE dependence on the type of cell irradiated

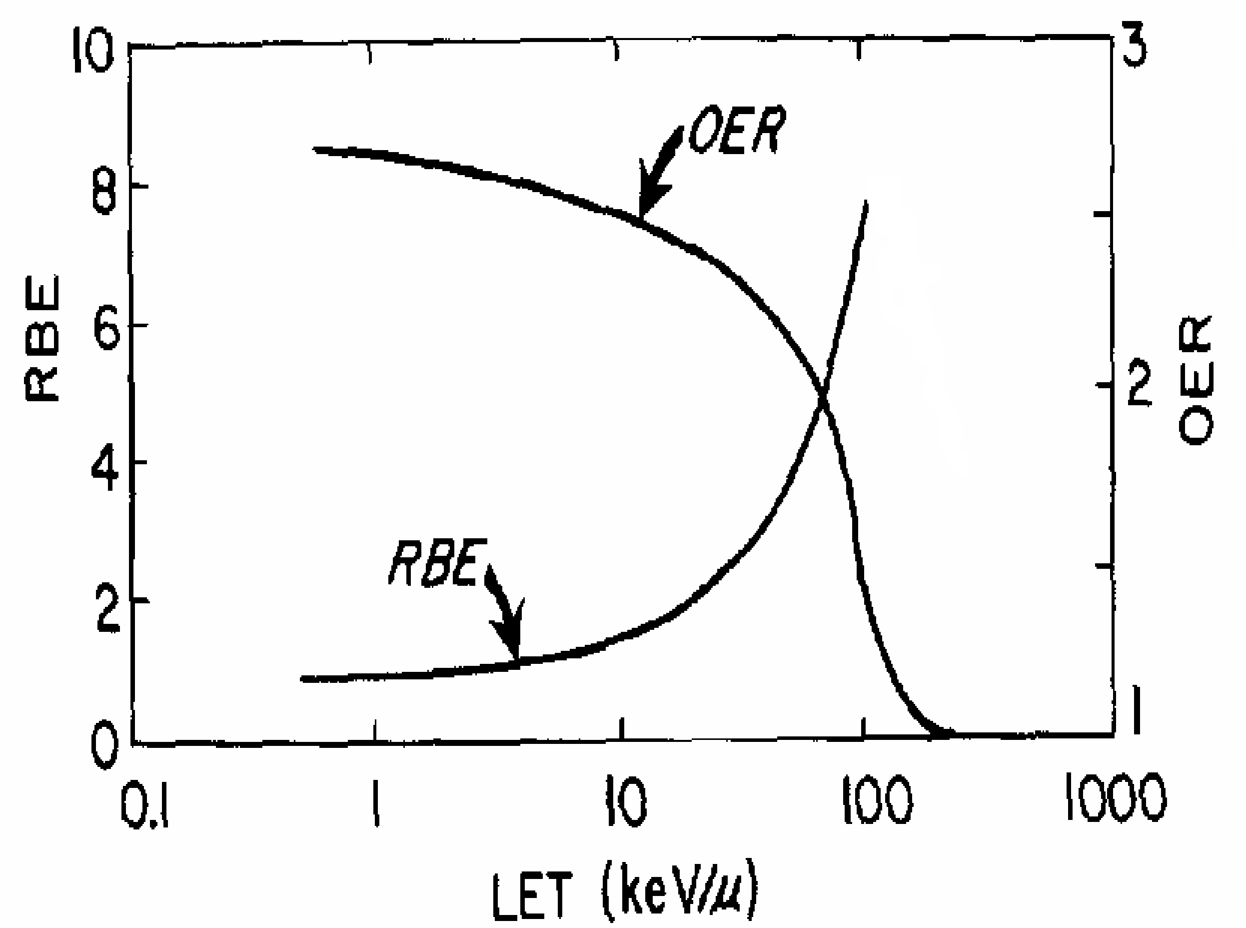
- In general, cells which exhibit large shoulders in their survival curves will have high RBEs
- Conversely, cells with little, if any, shoulder will have low RBEs
- But there are exceptions due to the different interaction mechanisms between low- and high-LET radiations e.g. cell-cycle effect

Variation of RBE and OER with LET

As LET increases:

RBE increases

and OER decreases



Influence of LET on cell-cycle effect

- For high-LET radiations the cell-cycle effect is less than with low LET radiations
  - *cancer cells or late reacting normal tissue cells trapped in resistant phases of the cell cycle will be less protected when treated with high-LET radiations*

Why high-LET radiotherapy?

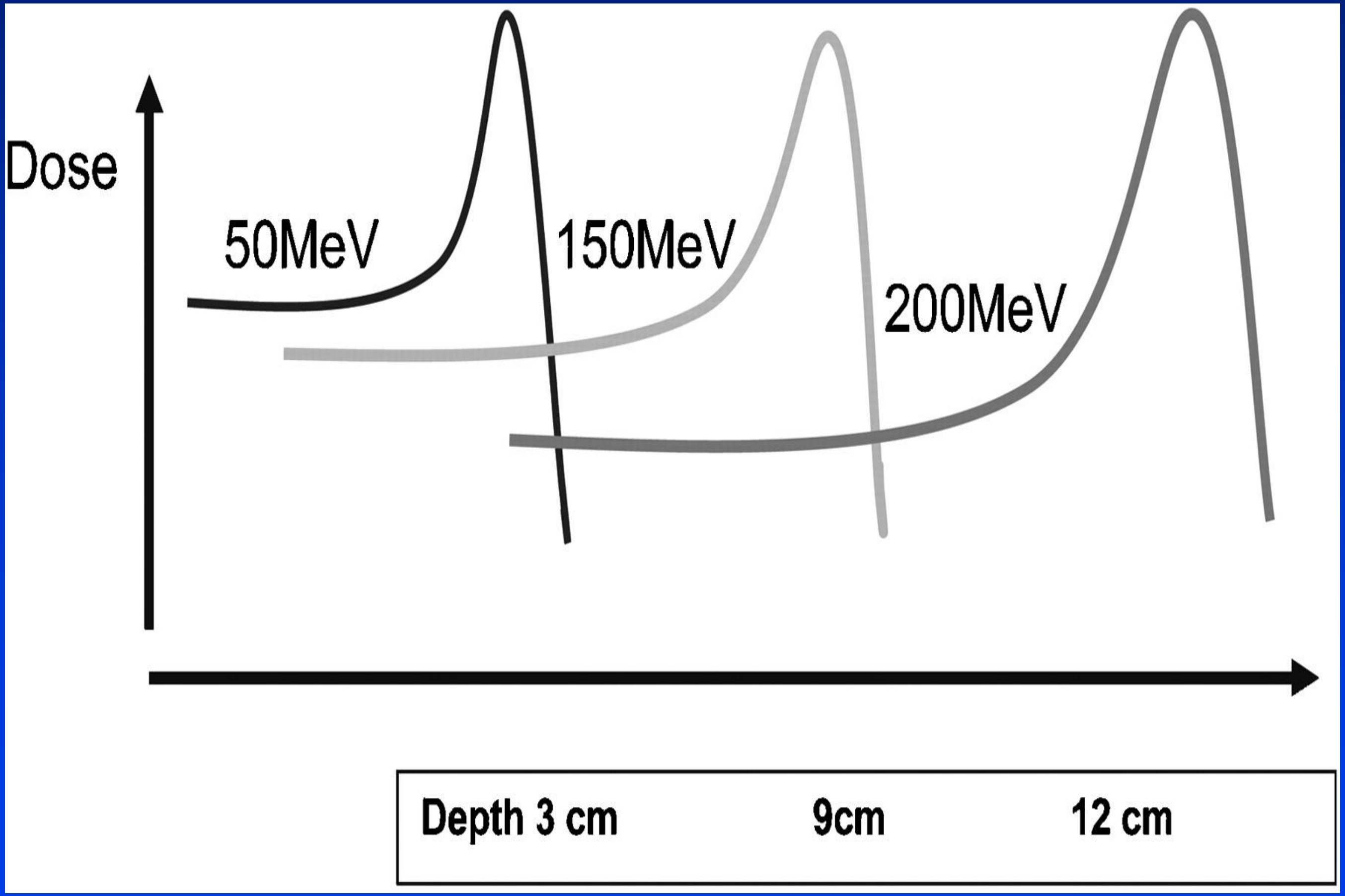
- Physical benefits
  - *the Bragg peak*
  - *reduced penumbra*
- Radiobiological benefits
  - *reduced effect of hypoxia*
  - *reduced cell cycle effect*

Why protons?

- The major reason is physical
  - *the Bragg peak*

Depth-dose characteristics of high-energy protons

The depth of the Bragg peak can be adjusted by changing beam energy



(Jones, 2006)

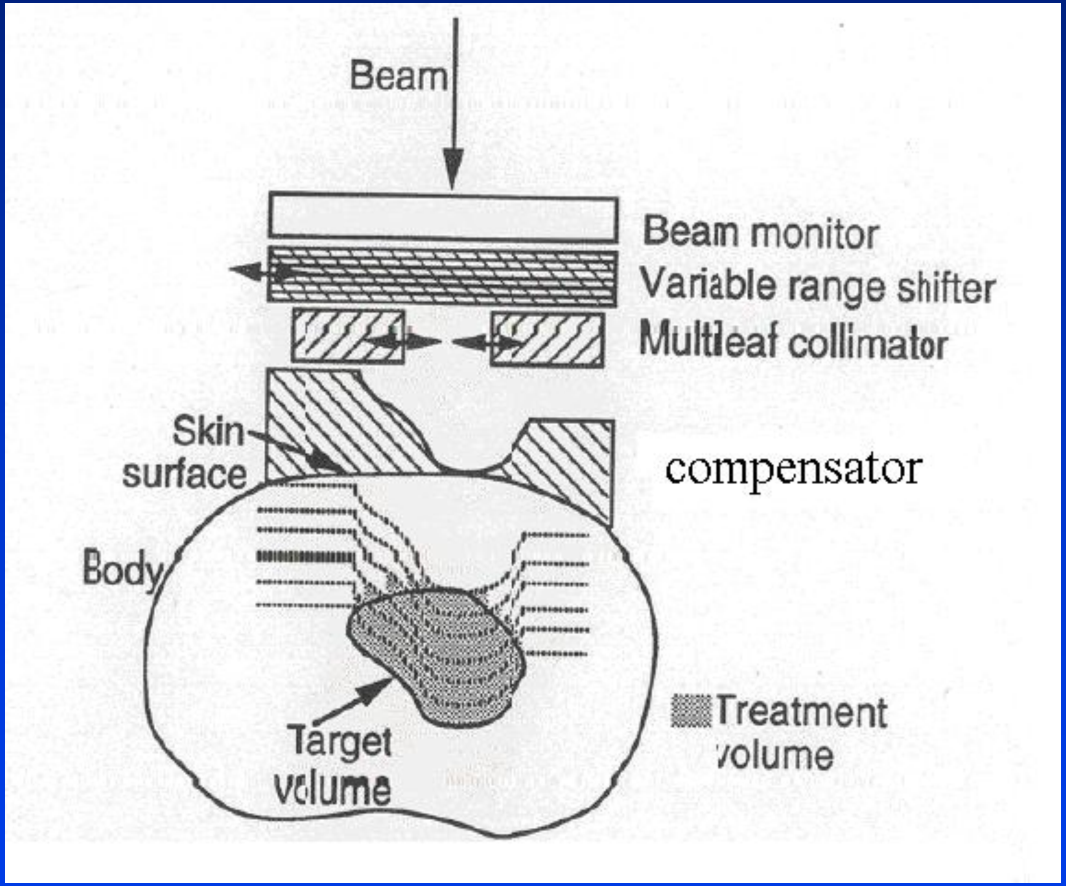
The Bragg peak

- Depth can be changed by varying the energy
- Too narrow for all but very small lesions
- Can be widened by mixing beams of several energies using a range filter (diluted Bragg peak)

Variable range shifter

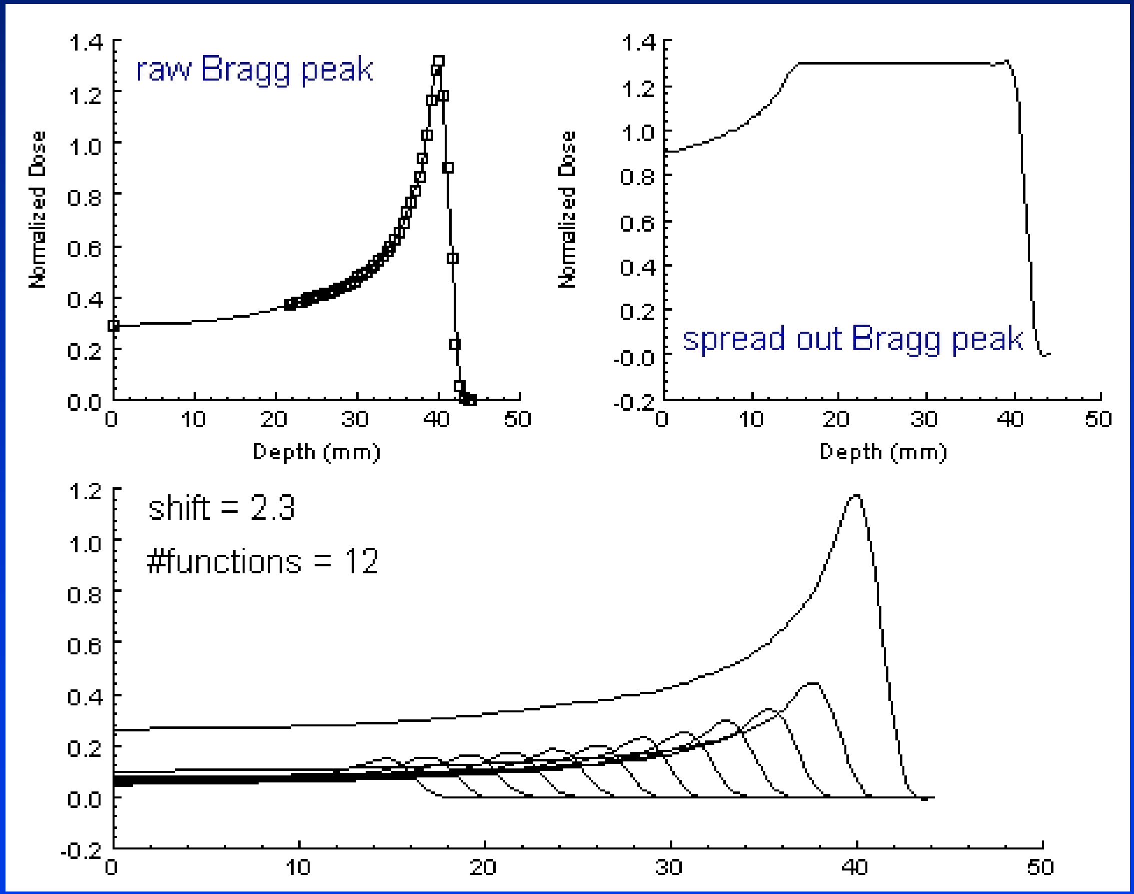
The number of slabs of the range shifter are varied to modulate the energy of the beam reaching the patient in order to produce the spread out Bragg peak

The patient specific compensator is designed to shape the distal extent of the high dose region



Spreading out the proton Bragg peak

By using 12 slabs of range shifter in this example it is possible to produce a spread out Bragg peak of uniform intensity from 15 to 40 mm in depth



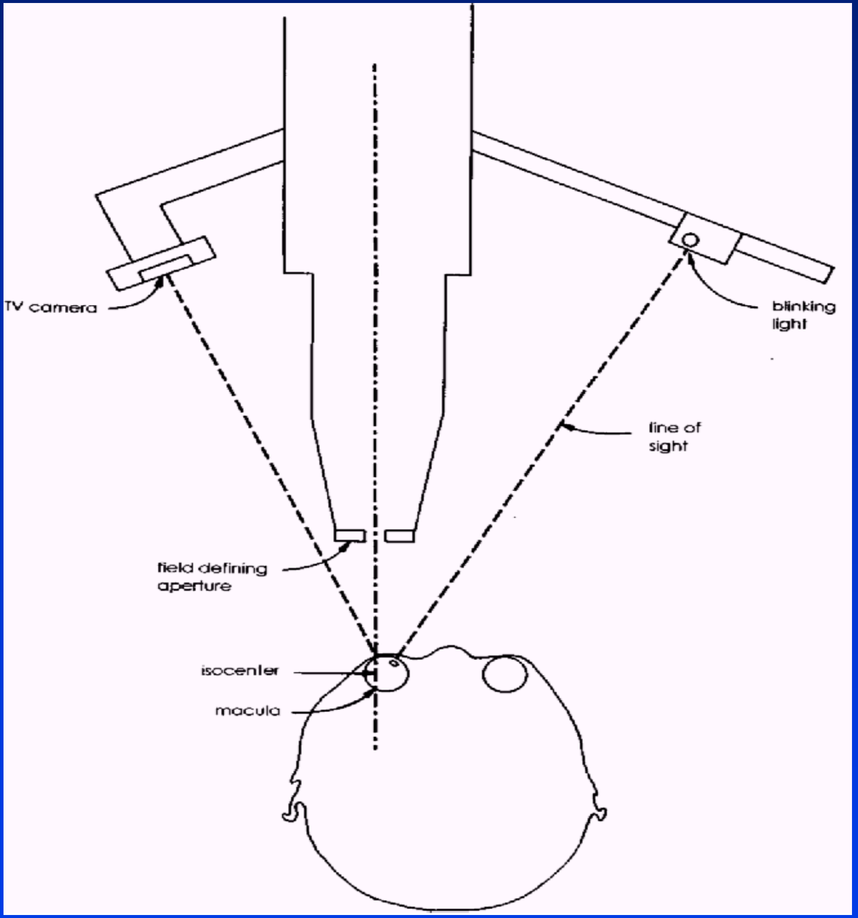
Biological benefits within the spread out Bragg peak

- Because the spread out Bragg peak contains protons from the low-LET plateau region, the average LET is not very high
  - *biological benefits such as reduced effects of oxygen and the cell cycle will be greatly reduced*

Proton treatment for macular degeneration using the Bragg peak

For beams that do not need to be spread out, the LET of the protons remains high

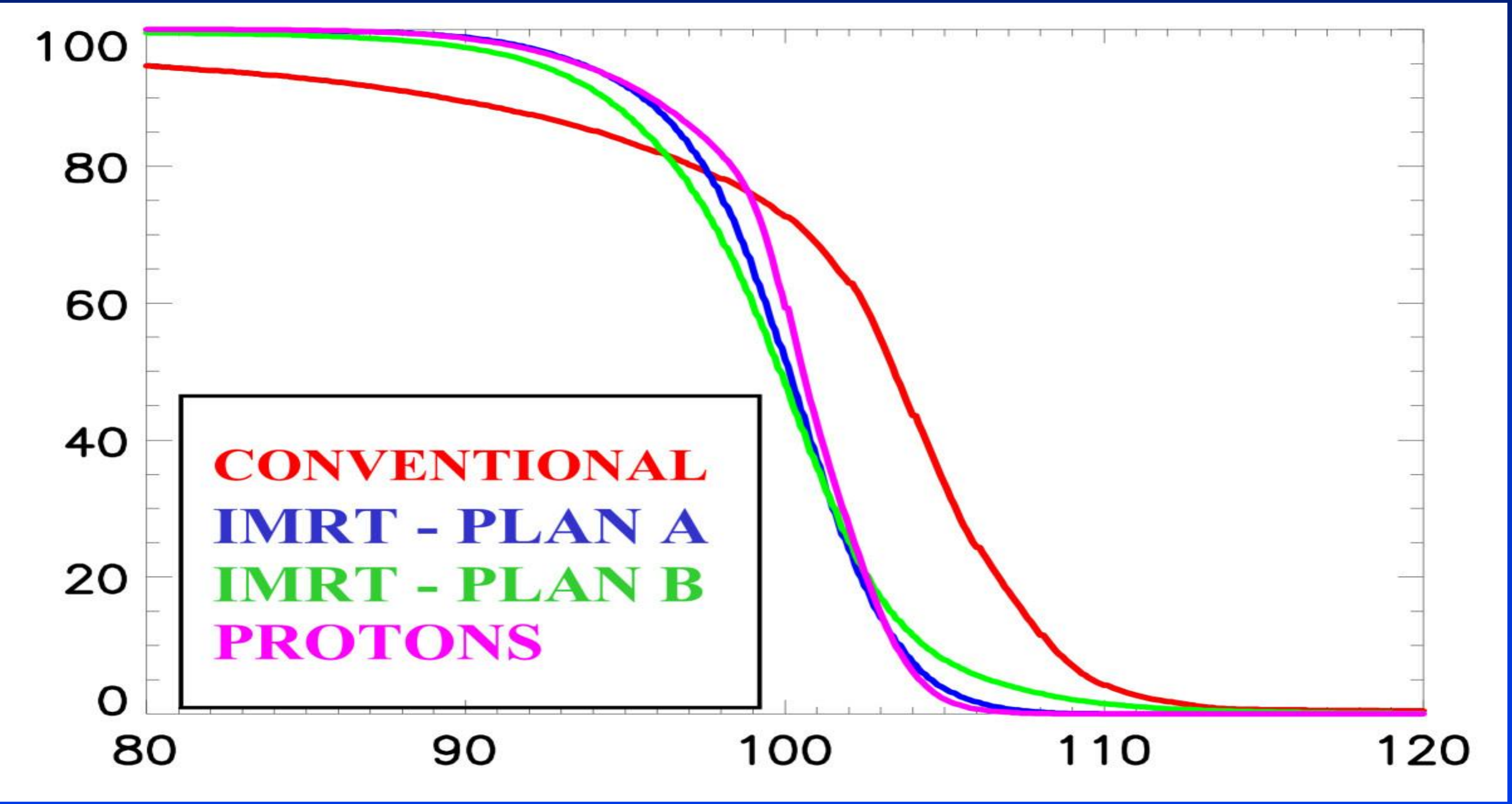
Biological benefits of high LET radiations are maintained



Moyes et al, Medical Physics 26, 777, 1999

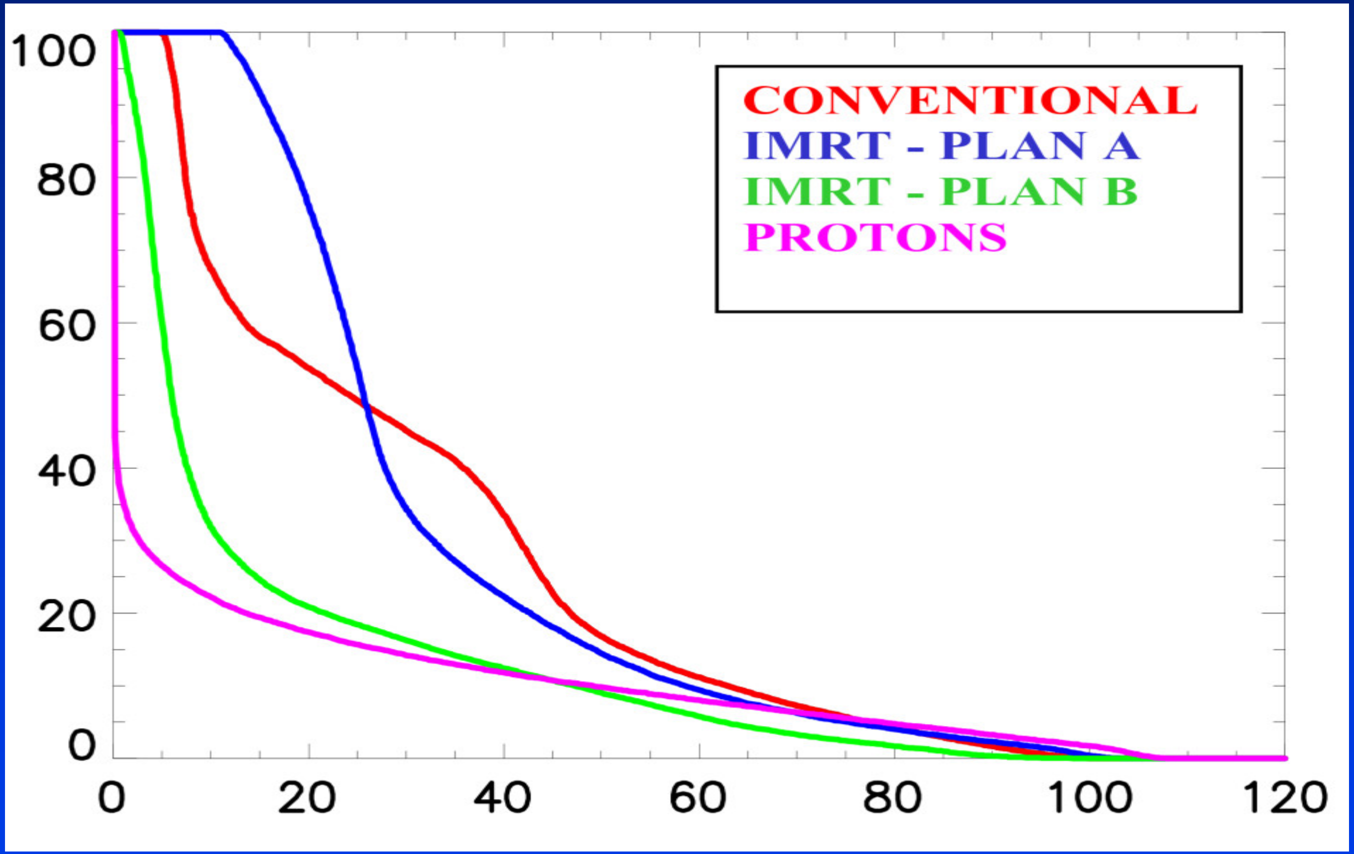
Partial breast irradiation using the spread-out Bragg peak

Target volume DVHs for this breast treatment by different modalities



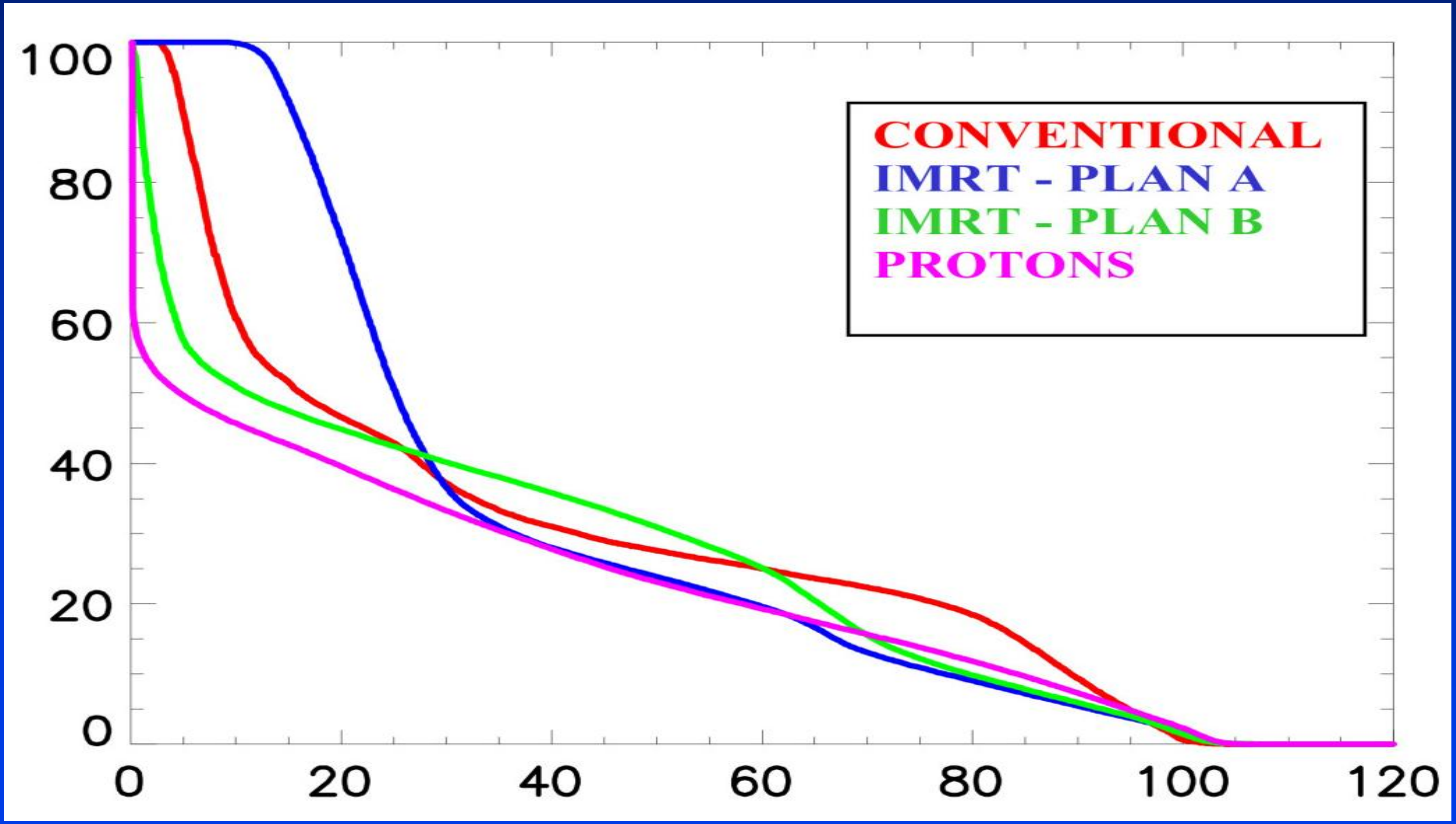
Weber, 2006

Heart DVHs for this patient



Weber, 2006

Ipsilateral lung DVHs for this patient

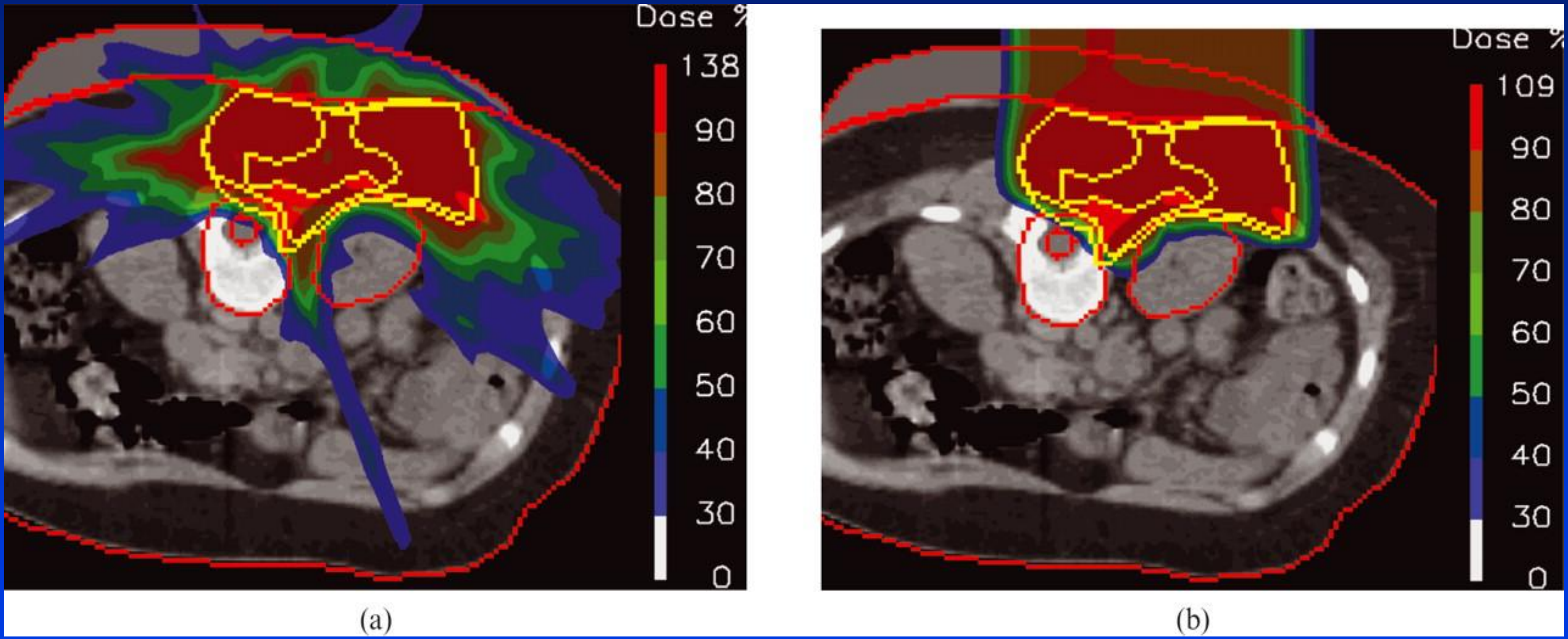


Weber, 2006

Comparisons of protons, IMRT, and conventional photons for breast treatments

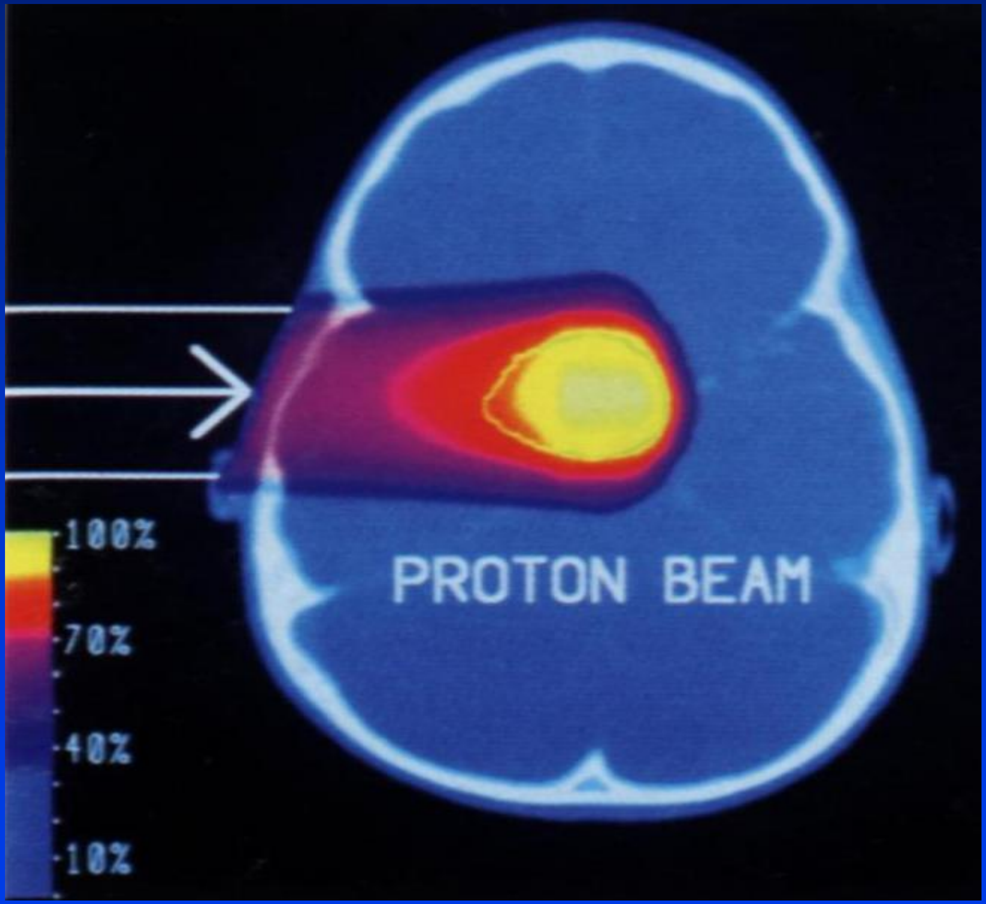
PTV/OARs Series (ref. no.)	$V_{95\%}$ Protons (mean)	$V_{95\%}$ IMRT (mean)	$V_{95\%}$ Photons (mean)	Mean Dose (%) Protons	Mean Dose (%) IMRT	Mean Dose (%) Photons
PTV (breast only)						
Lomax *et al*. [33]	97.1	92.2	86.6			
Johansson *et al*. [34]	94.0	85.9	88.8			
Fogliata *et al*. [38]	99.8	95.5	92.2			
Heart						
Lomax *et al*. [33]				11.6	24.0	29.3
Johansson *et al*. [34]				21.0*	41.0*	61.0*
Fogliata *et al*. [38]				4.4	5.6	5.0
Lung (ipsilateral)						
Lomax *et al*. [33]				25.0	33.0	33.3
Johansson *et al*. [34]				1.0*	18.0*	29.0*
Fogliata *et al*. [38]				7.0	17.1	22.5

IMRT vs. protons



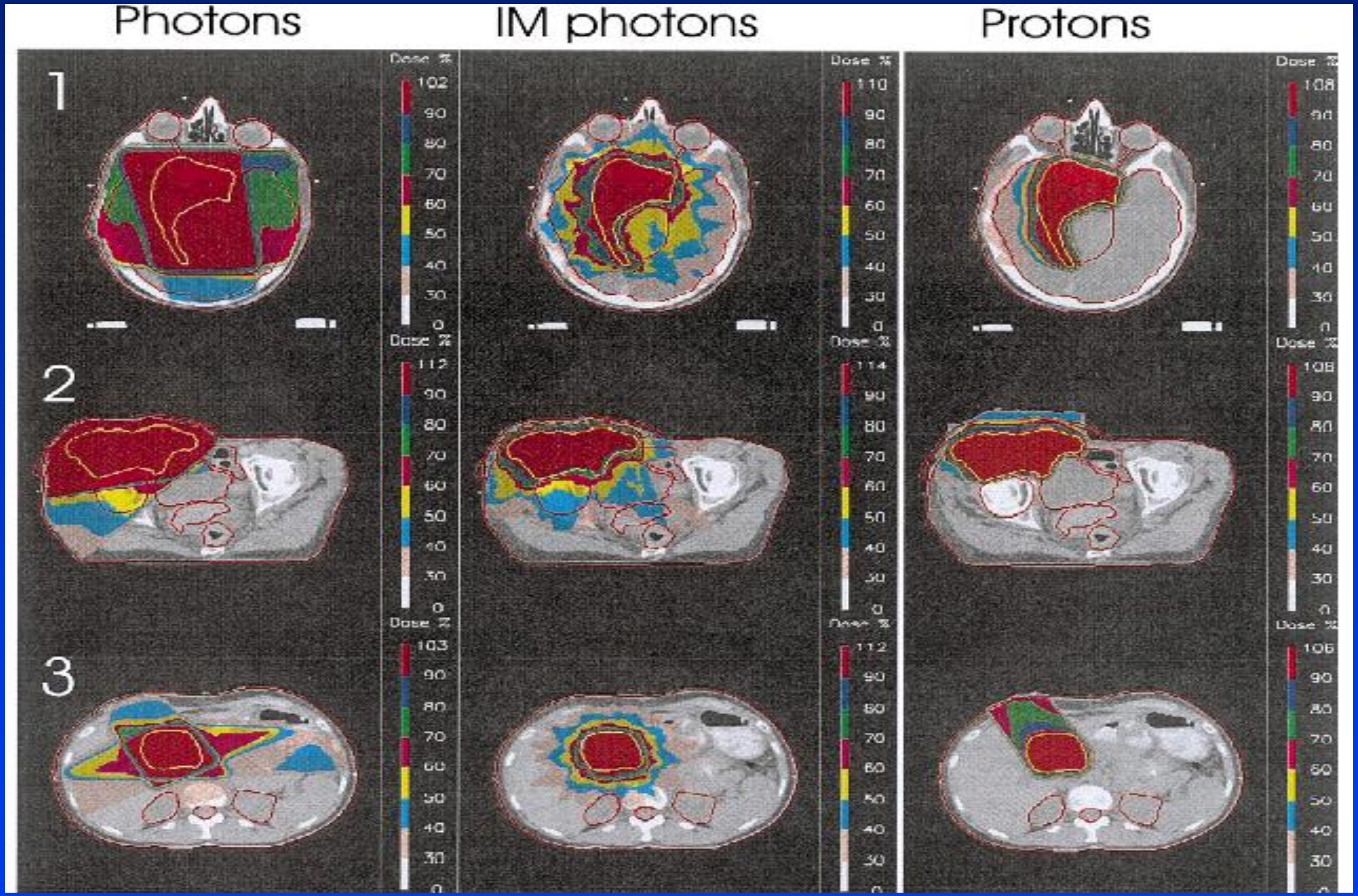
Comparative dose distributions for (a) IMRT and (b) protons for a recurrent sarcoma in a 12-year-old boy (Jones, 2006)

Proton beam treating an intracranial lesion



Comparison of protons and IMRT

Lomax, et al, Radiotherapy and Oncology 51, 257, 1999



Intensity Modulated Proton Therapy (IMPT)

In intensity modulated proton therapy, a narrow proton pencil beam is scanned magnetically over the target volume, while both the energy and the intensity of the beam are modulated

Intensity Modulated Proton Therapy (IMPT)

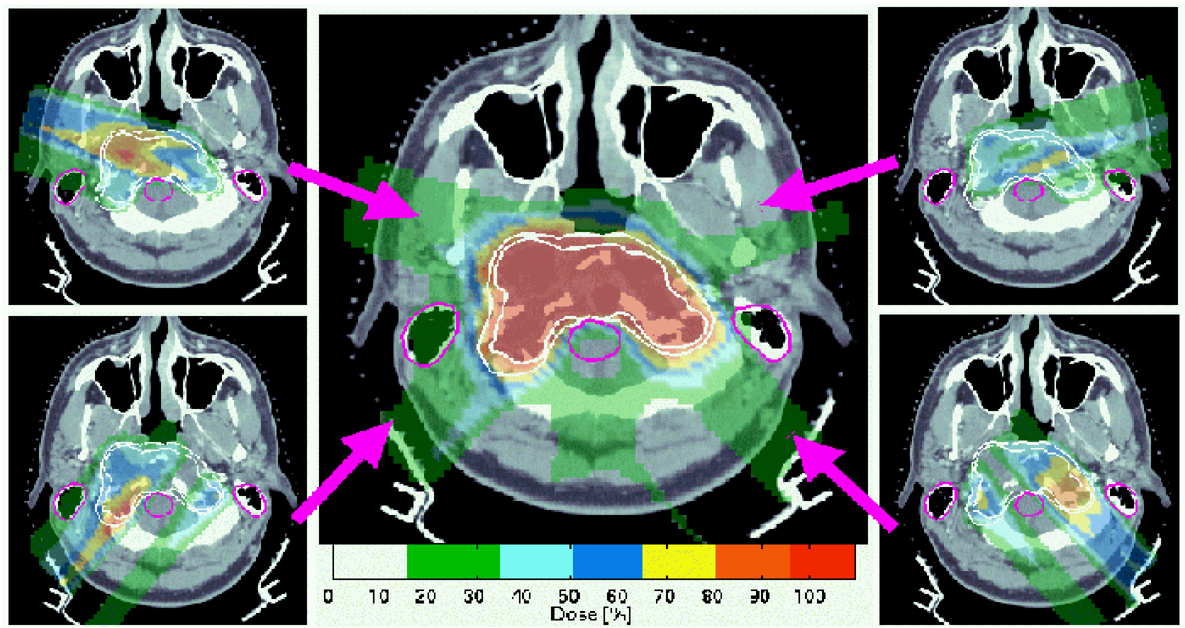
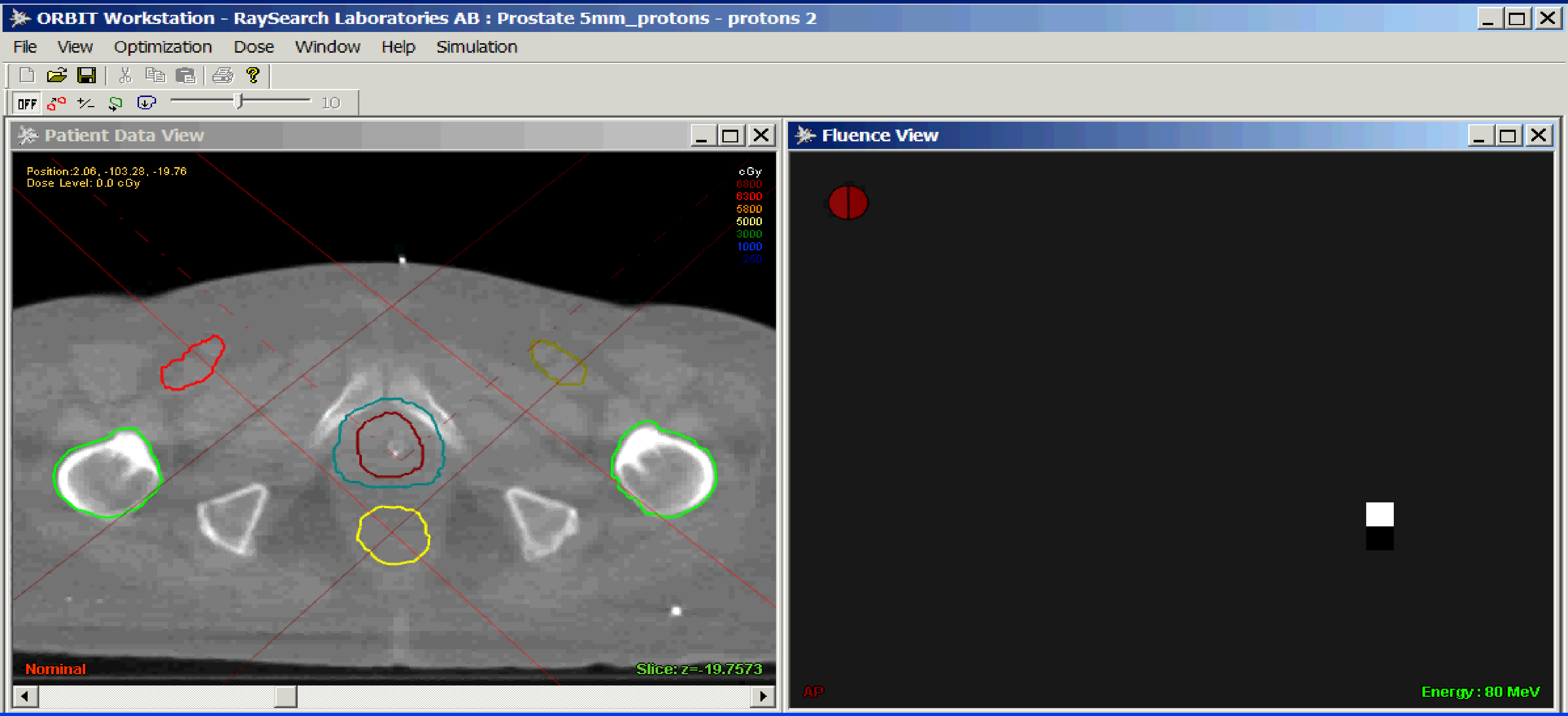


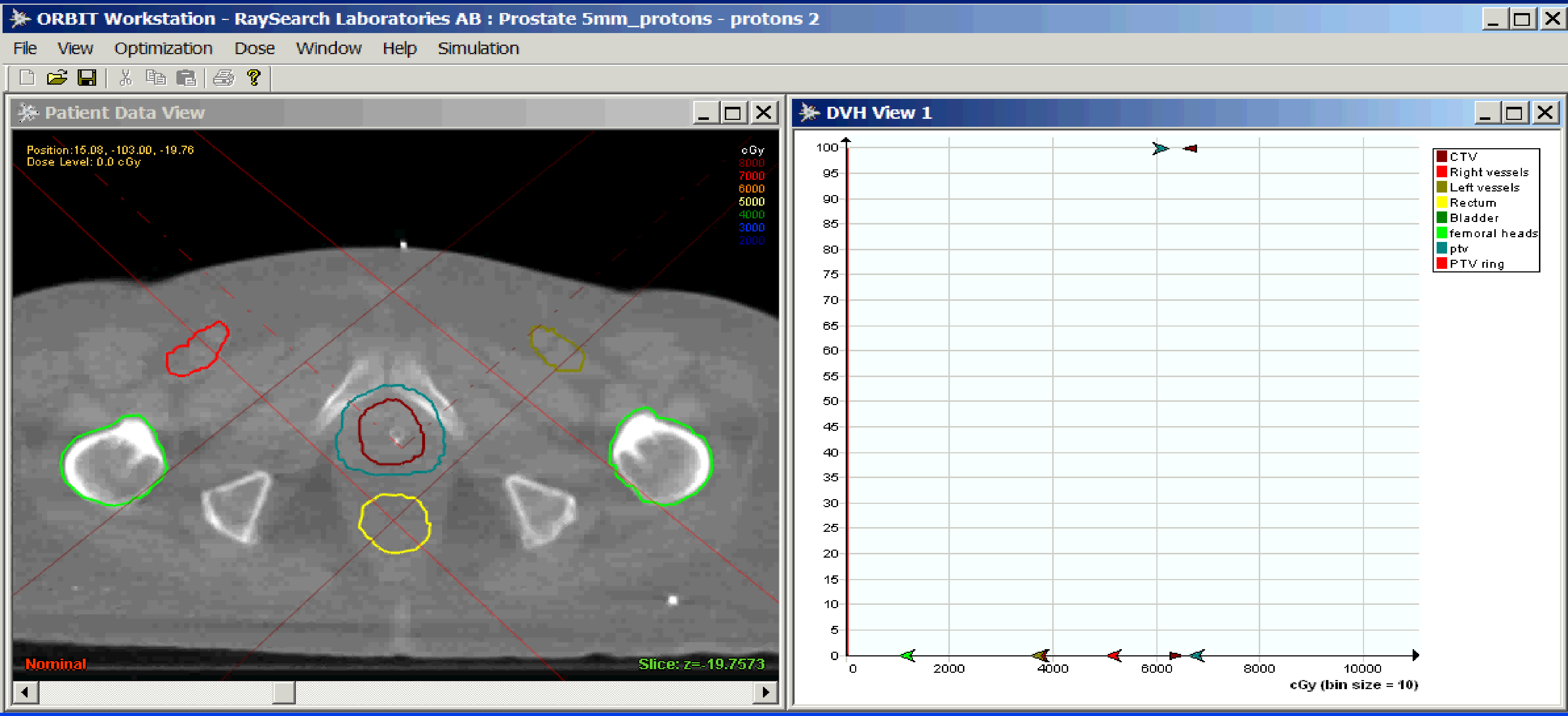
Figure 1: IMPT treatment plan for a head & neck case: uniform dose distribution on the target is achieved by superposition of inhomogeneous distribution delivered by proton beams from different directions.

(From the German Cancer Research Centre)

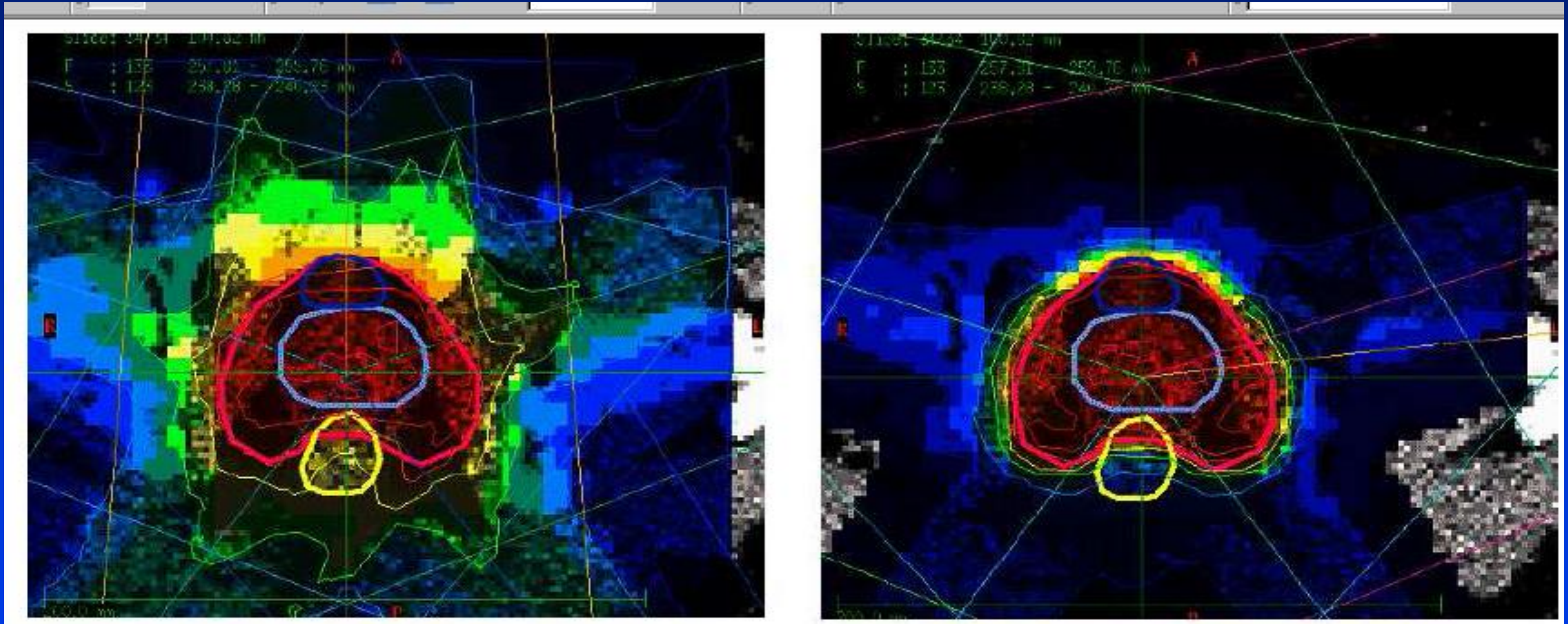
Intensity and energy modulation with protons



Iterative DVH modification for this patient



Proton IMPT vs. photon IMRT for prostate cancer

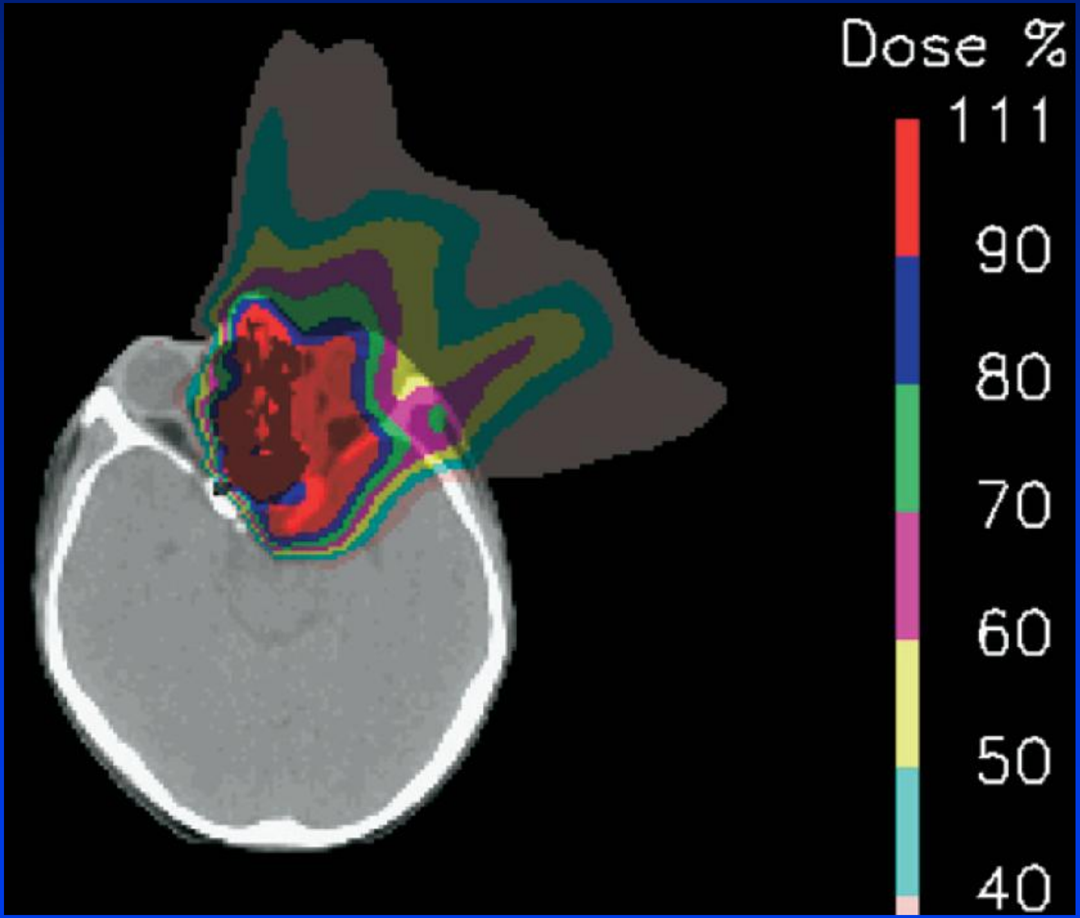


Photons Protons

Oelfke, (2003)

Proton IMRT for a rhabdomyosarcoma

Example of an intensity-modulated proton therapy plan with sparing of the lacrimal gland for a 12-year-old boy with an orbital rhabdomyosarcoma initially infiltrating the surrounding soft tissue

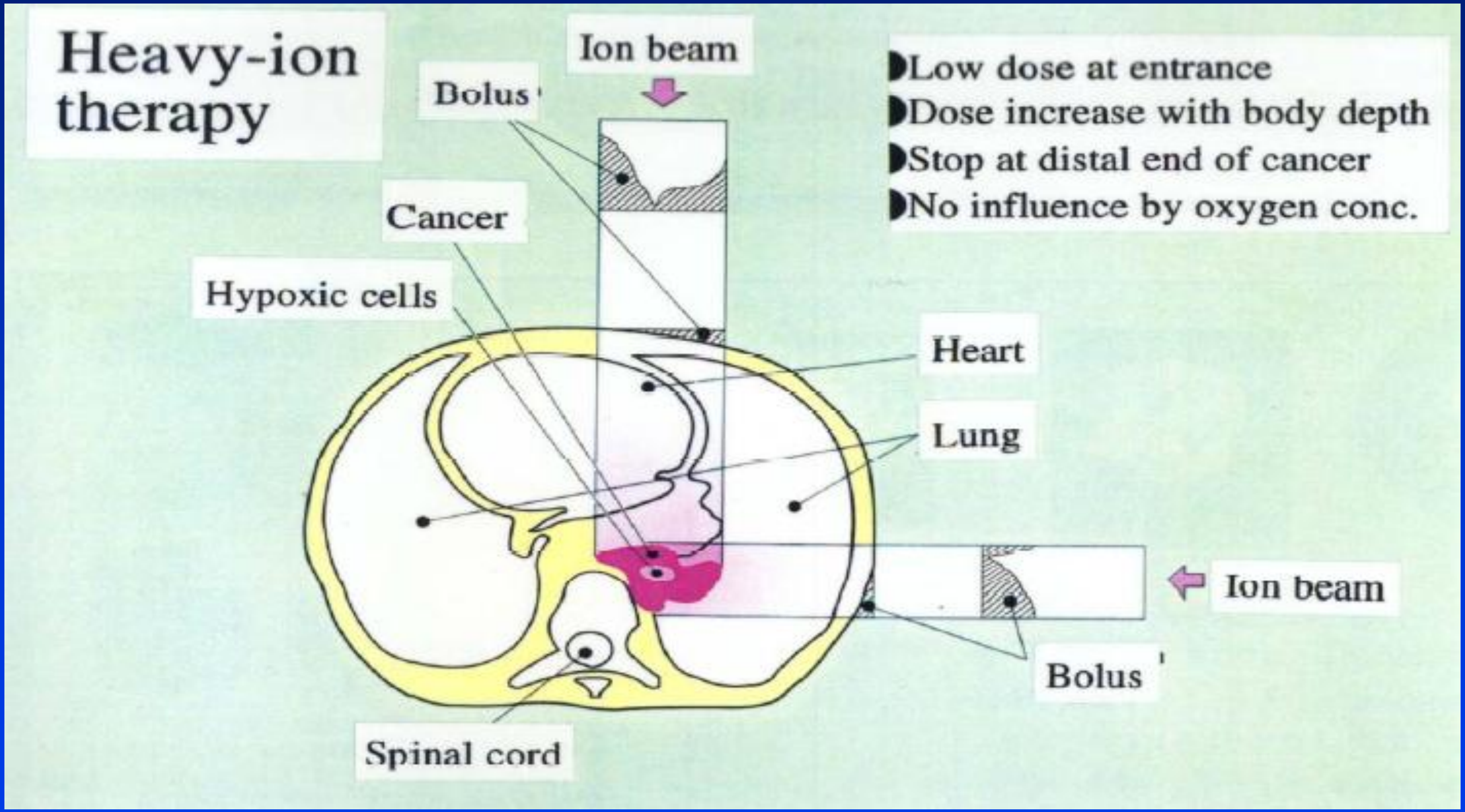


Timmermann, 2006

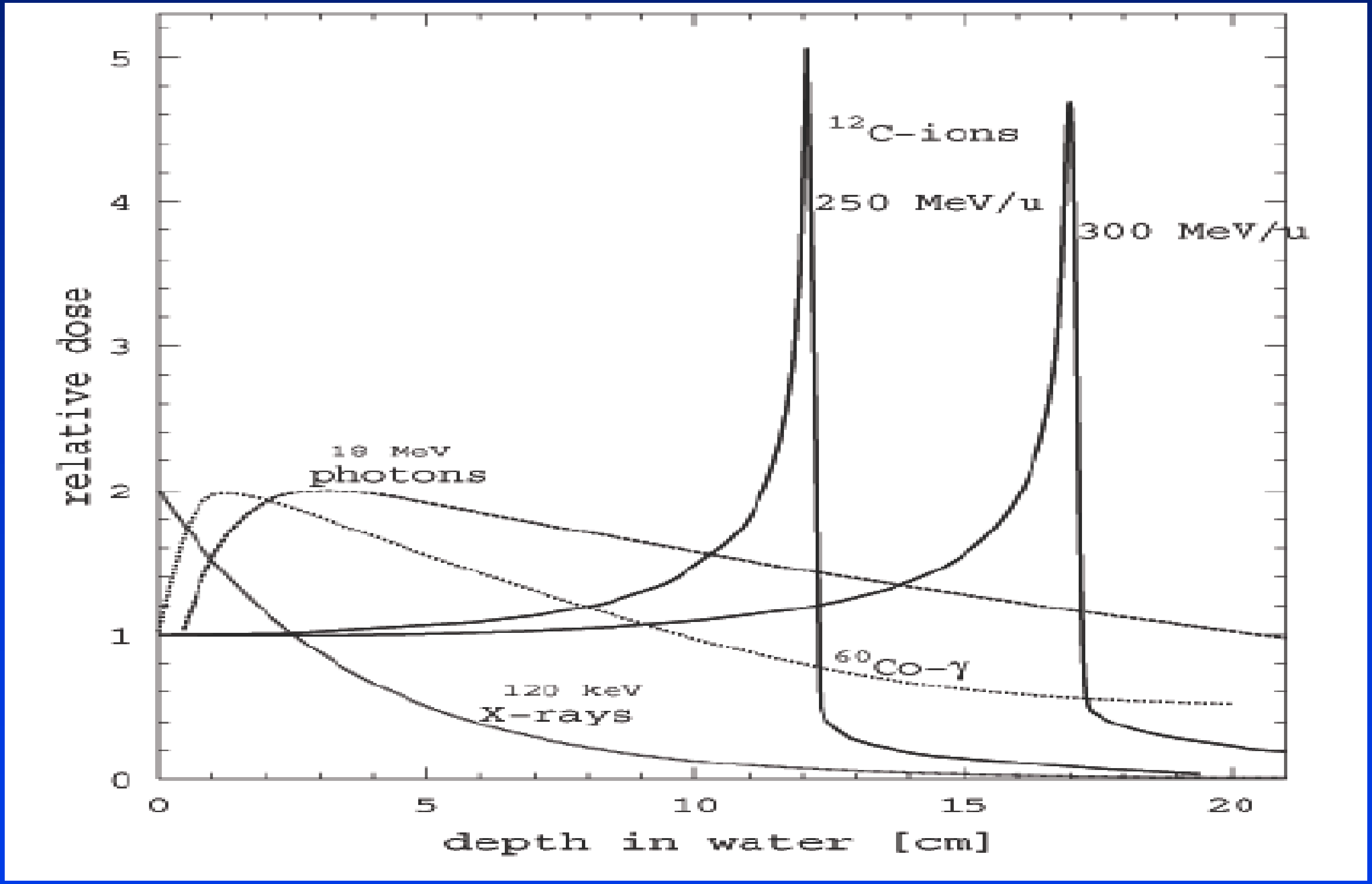
Why heavy ions?

- Physical advantages:
  - *Bragg peak*
  - *adjustable Bragg peak depth*
  - *sharp beam edges (small penumbra)*
- Biological advantages:
  - *potentially low OER, reduced cell-cycle effect*

Why heavy ions work



Carbon ion Bragg peaks



Carbon ions vs. protons

Bragg peaks with heavy ions are much narrower than those for protons and the dose in the plateau region is lower

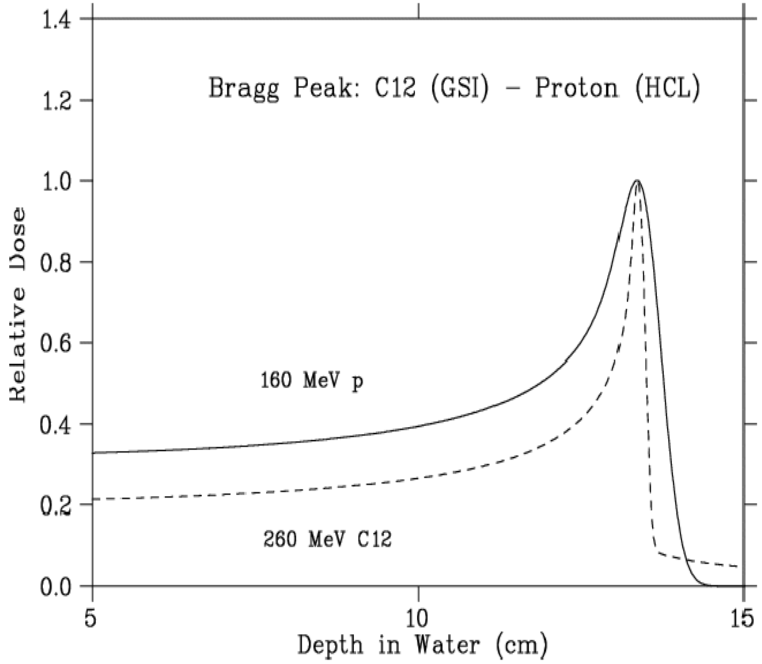


Figure 5. Depth dose curves for proton and carbon beams. The solid curve represent a Bragg peak of 160 MeV protons characteristic for the Harvard Cyclotron (HCL)i Boston. The dashed curve shows the much narrower Bragg peak of a 260 MeV/u carbo ion beam measured at GSI (Courtesy of O. Jäkel).

Biological effectiveness within the spread out Bragg peak

- Compared with protons, the Bragg peak for heavy ions is much higher and the radiation within the Bragg peak has a much higher LET
- Consequently, when the Bragg peak is spread out, much of the biological benefit is retained

Changes of RBE with depth for spread-out Bragg peaks

Within the spread out Bragg peak, LET (and RBE) will be highest at the distal end of the beam where there is less plateau region contamination

To get a uniform biologically effective dose throughout the target volume, the physical dose must be higher at the proximal side of the beam

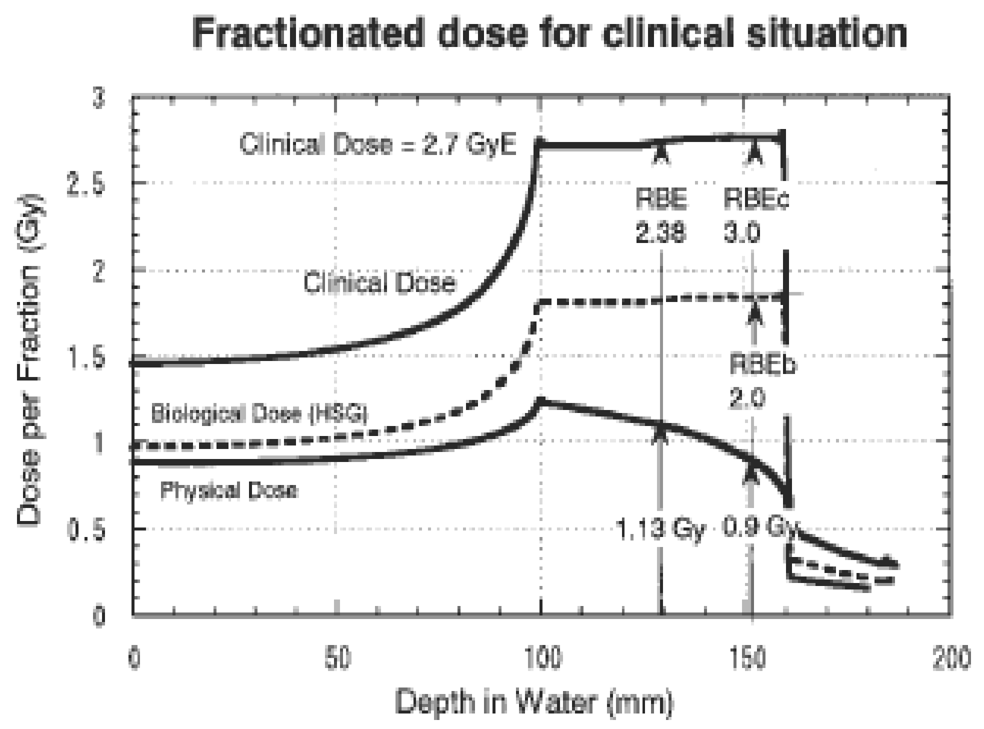
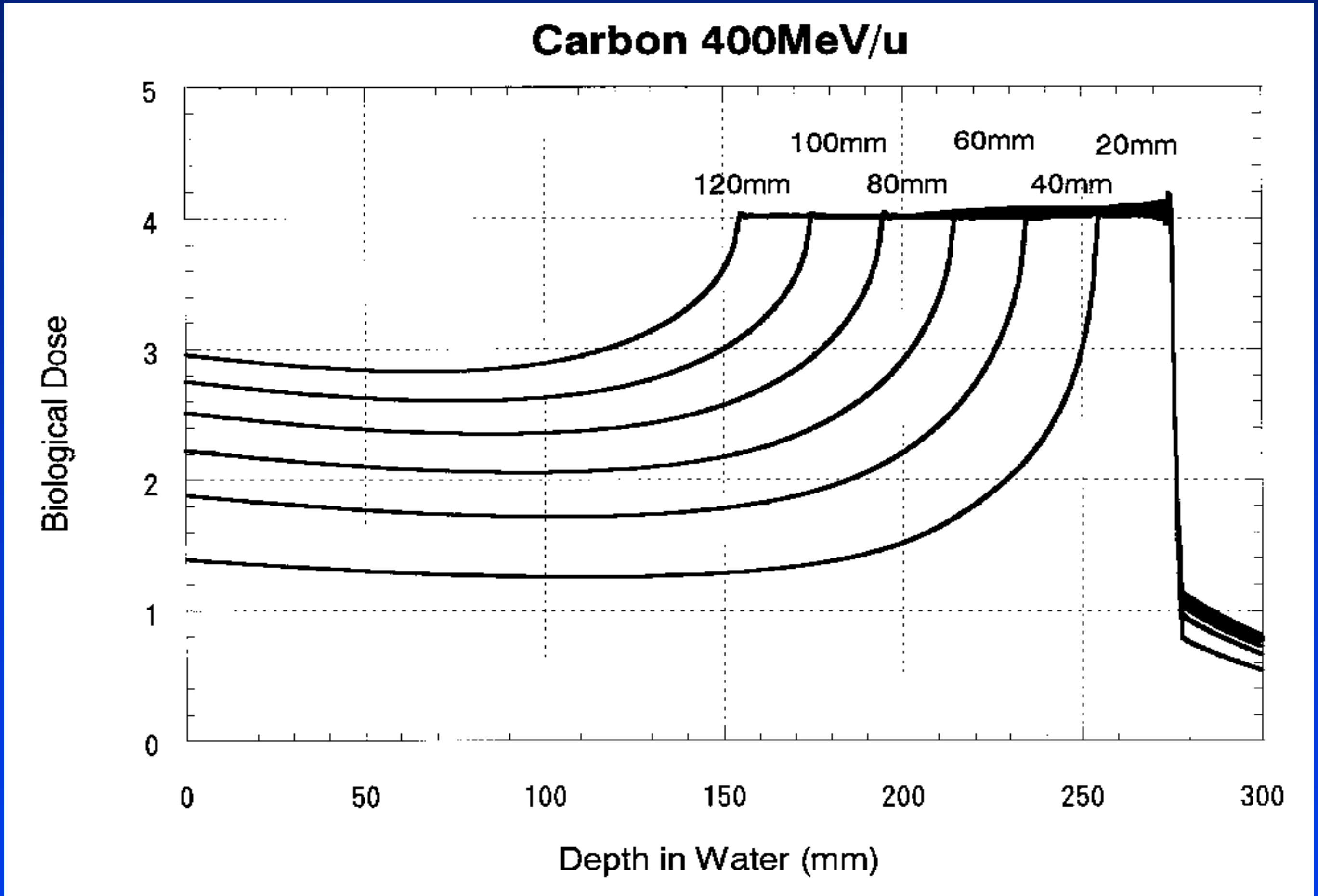


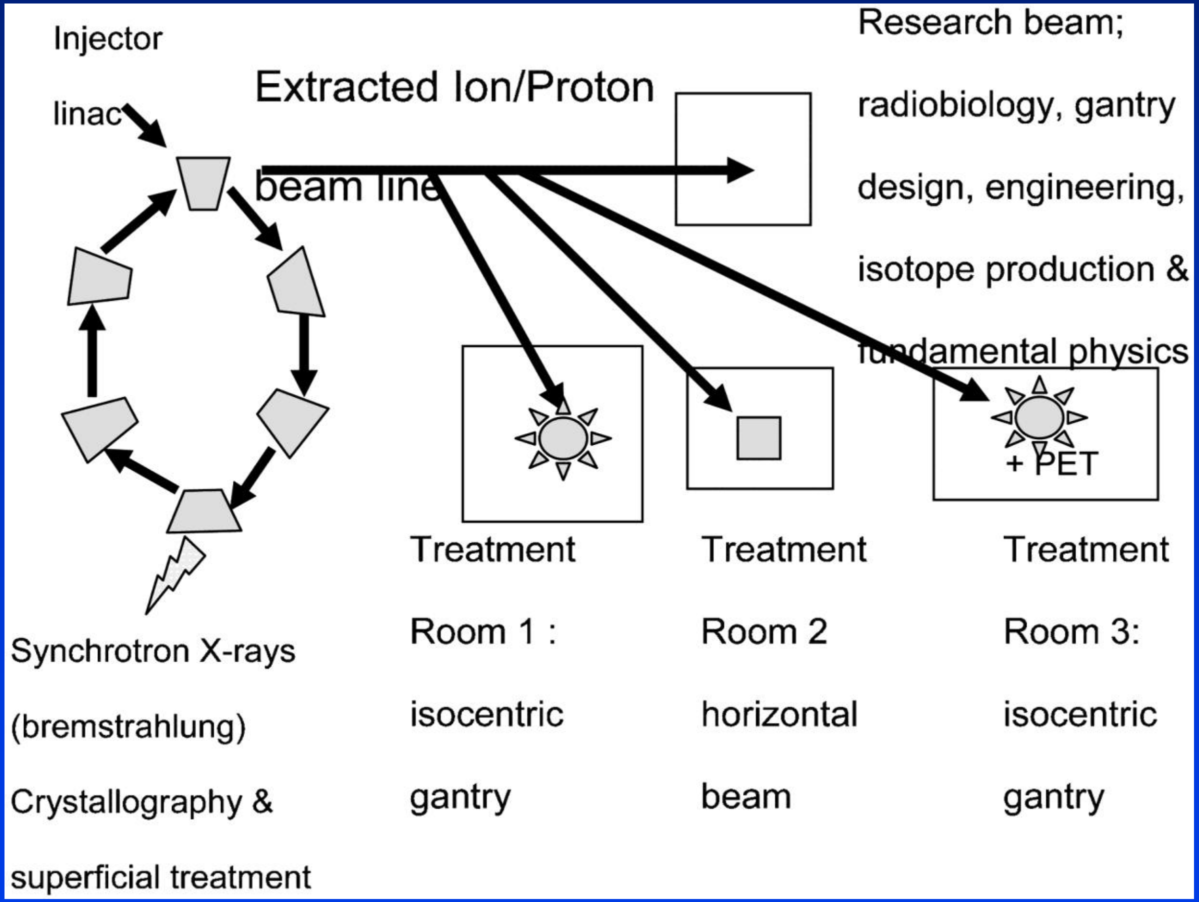
Fig. 5. Schematic method used to determine the RBE at the center of the SOBP for the clinical situation.

400 MeV C-ion Bragg peak diluted using 6-step Lucite range shifter



Heavy ion therapy

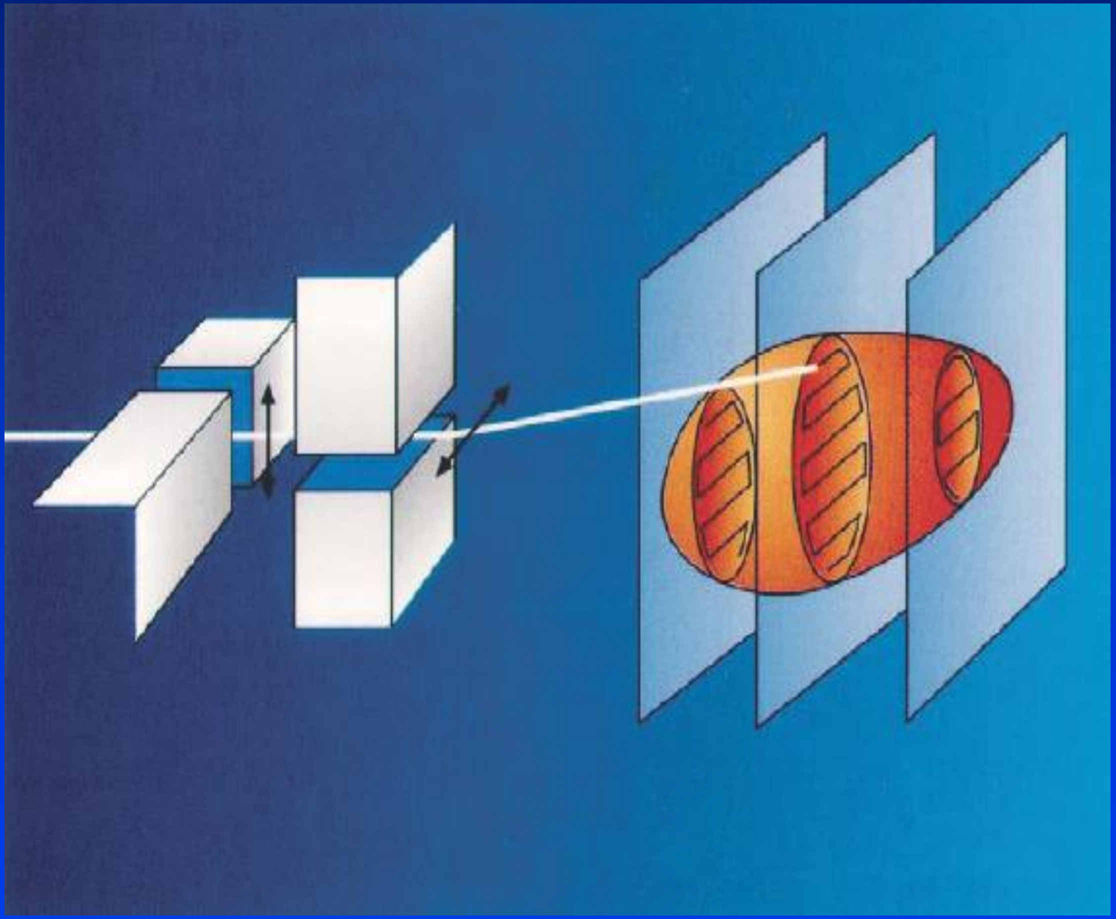
A schematic diagram of a synchrotron treatment center (Jones, 2006)



Active raster scan system for C ions at GSI, Darmstadt, Germany

Instead of a shaped collimator beams can be shaped by active raster scanning

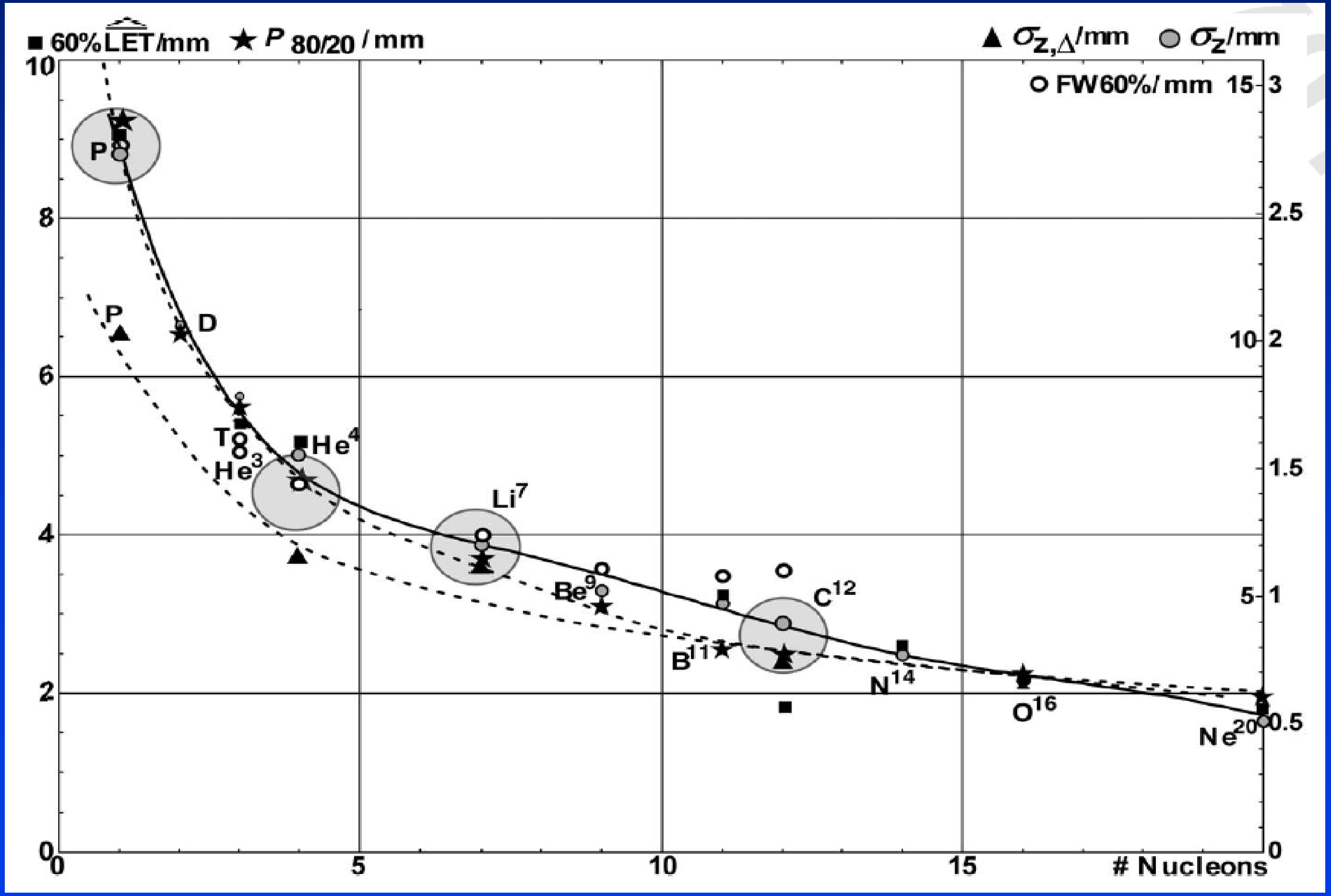
The energy of the beam can be continuously adjusted, thus avoiding the need for a physical range shifter



Scattering of heavy ions

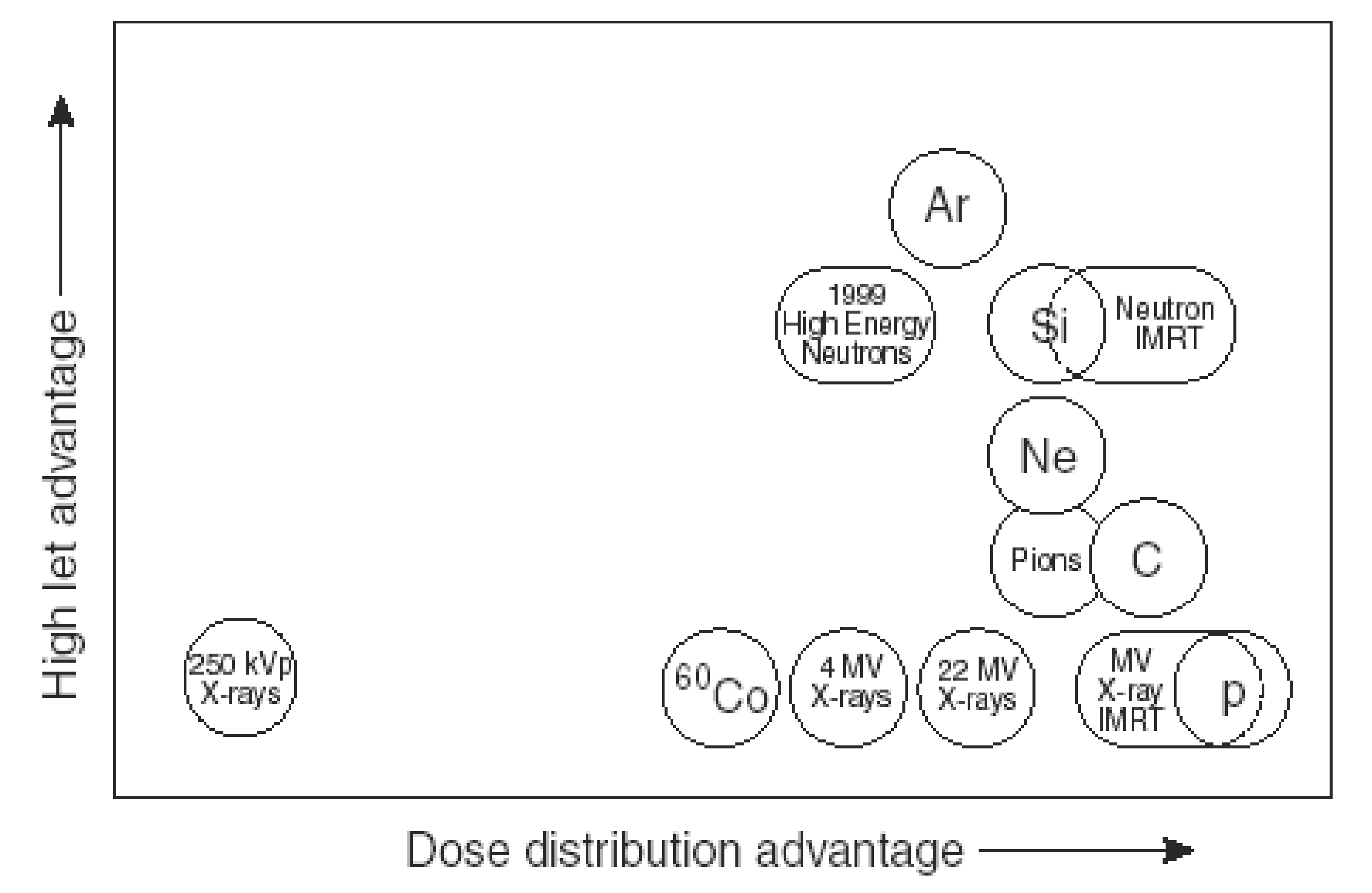
- Multiple scattering is reduced considerably as the size of the particle increases
  - *this reduces the penumbra*

Penumbra decreases as atomic number increases



Kempe, 2007

Physical and biological advantages of different types of radiotherapy



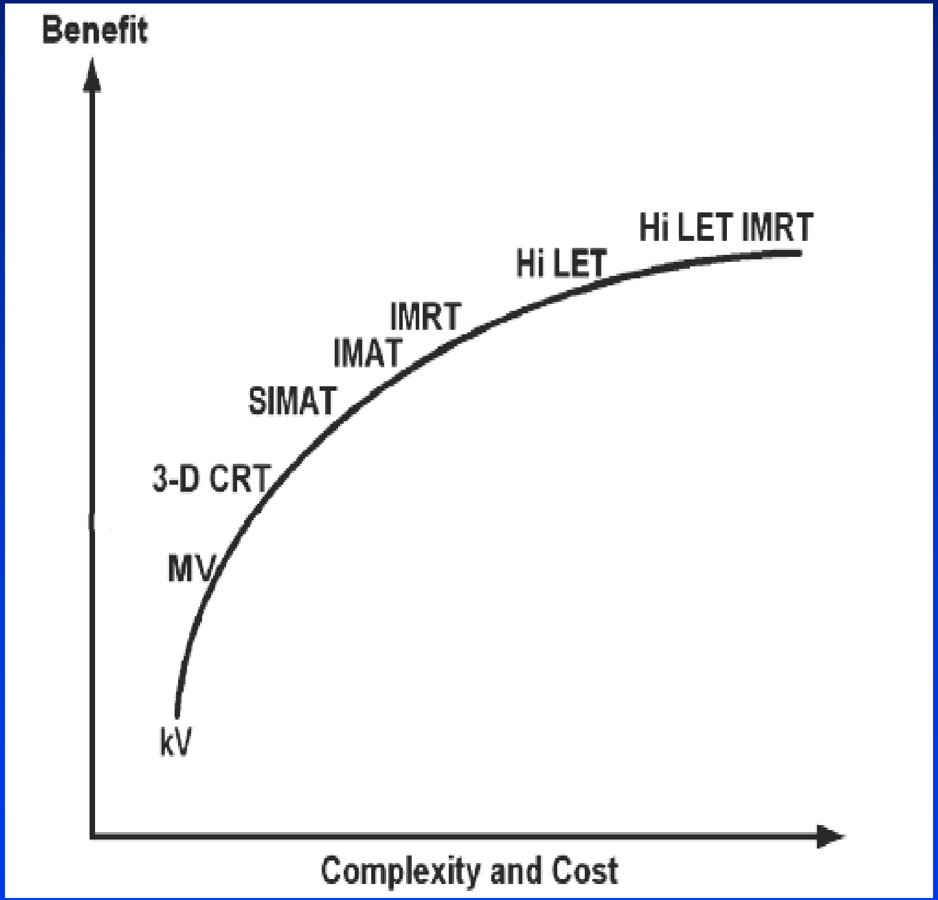
Heavy ions

Disadvantages:

- Very large
- Very expensive

Benefit vs. Cost

Schematic of benefit versus cost achieved with technical advances in radiation therapy. kV, kilovoltage x-rays; MV, megavoltage x-rays; 3-D CRT, 3-D conformal radiation therapy; SIMAT, simplified intensity-modulated arc therapy (forward planned); IMAT, intensity-modulated arc therapy (inverse planned); IMRT, intensity-modulated radiation therapy; Hi LET, High LET charged particle radiation therapy; Hi LET IMRT, High LET charged particle intensity-modulated radiation therapy.



From van Dyk, Vol. 2

Summary: applications and relative costs of different modalities

Table 2. Summary of Present External Beam Radiotherapy Options for Malignant Tumors[a]

Particle	Tumor Characteristics	Energy deposition	Bragg peak	Radiation source	Accelerator cost[b]
Photons	Rapidly growing, oxygenated	Low LET	No	Cobalt 60; electron linac;microtron	1
Electrons	Superficial	Low LET	No	Electron Linac; microtron	1–2
Protons	Early stage, near-critical structures	Low LET	Yes	Synchroton; cyclotron	10–15
Fast neutrons	Slow growing, hypoxic	High LET	No	Proton linac; cyclotron;	8–10
Heavy ions	Same as fast neutrons	High LET	Yes	Synchrotron	40
Pions	Same as fast neutrons	High LET	Yes	Proton linac; cyclotron	35–40
Slow neutrons	Glioblastoma; Some melanomas	Very high LET with BNCT	No	Low energy accelerator; nuclear reactor	1–2

Particle therapy facilities worldwide

WHO, WHERE	COUNTRY	PARTICLE	MAX. CLINICAL ENERGY (MeV)	BEAM DIRECTION	START OF TREATMENT	TOTAL PATIENTS TREATED	DATE OF TOTAL
ITEP, Moscow	Russia	p	250	horiz.	1969	4024	Dec-07
St.Petersburg	Russia	p	1000	horiz.	1975	1327	Dec-07
PSI, Villigen	Switzerland	p	72	horiz.	1984	5076	Dec-08
Dubna	Russia	p	200****	horiz.	1999	489	Dec-08
Uppsala	Sweden	p	200	horiz.	1989	929	Dec-08
Clatterbridge	England	p	62	horiz.	1989	1803	Dec-08
Loma Linda	CA.,USA	p	250	gantry,horiz.	1990	13500	Dec-08
Nice	France	p	65	horiz.	1991	3690	Dec-08
Orsay	France	p	200	horiz.	1991	4497	Dec-08
iThemba Labs	South Africa	p	200	horiz.	1993	503	Dec-08
MPRI(2)	IN.,USA	p	200	horiz.	2004	632	Dec-08
UCSF	CA.,USA	p	60	horiz.	1994	1113	Dec-08
HIMAC, Chiba	Japan	ion	800/u	horiz.,vertical	1994	4504	Feb-09
TRIUMF, Vancouver	Canada	p	72	horiz.	1995	137	Dec-08
PSI, Villigen	Switzerland	p**	250*	gantry	1996	426	Dec-08
G.S.I. Darmstadt	Germany	ion**	430/u	horiz.	1997	384	Dec-07
HZB (HMI), Berlin	Germany	p	72	horiz.	1998	1227	Dec-08

Over 60,000 proton and 5,000 carbon ion patients treated

WHO, WHERE	COUNTRY	PARTICLE	MAX. CLINICAL ENERGY (MeV)	BEAM DIRECTION	START OF TREATMENT	TOTAL PATIENTS TREATED	DATE OF TOTAL
NCC, Kashiwa	Japan	p	235	gantry	1998	607	Dec-08
HIBMC,Hyogo	Japan	p	230	gantry	2001	2033	Dec-08
HIBMC,Hyogo	Japan	ion	320	horiz.,vertical	2002	454	Dec-08
PMRC(2), Tsukuba	Japan	p	250	gantry	2001	1367	Dec-08
NPTC, MGH Boston	USA	p	235	gantry,horiz.	2001	3515	Oct-08
INFN-LNS, Catania	Italy	p	60	horiz.	2002	174	Mar-09
Shizuoka	Japan	p	235	gantry, horiz.	2003	692	Dec-08
WERC,Tsuruga	Japan	p	200	horiz.,vertical	2002	56	Dec-08
WPTC, Zibo	China	p	230	gantry, horiz.	2004	767	Dec-08
MD Anderson Cancer Center, Houston, TX	USA	p***	250	gantry, horiz.	2006	1000	Dec-08
FPTI, Jacksonville, FL	USA	p	230	gantry, horiz.	2006	988	Dec-08
NCC, Ilsan	South Korea	p	230	gantry, horiz.	2007	330	Dec-08
RPTC, Munich	Germany	p**	250	gantry, horiz.	2009	treatment started	Mar-09
Oklahoma City, OK	USA	p	230	gantry, horiz.	2009	treatment started	Jul-09

Proton and heavy ion radiotherapy: Summary

- The Bragg peak provides significant dose distribution advantages
- Because the Bragg peak is so narrow it needs to be spread out
- The average LET in the proton spread out Bragg peak is too low for any biological benefit
- With heavy ions the biological benefit is retained
- Heavy ion radiotherapy machines are very expensive