Application of Hadron Beams in Cancer Radiotherapy

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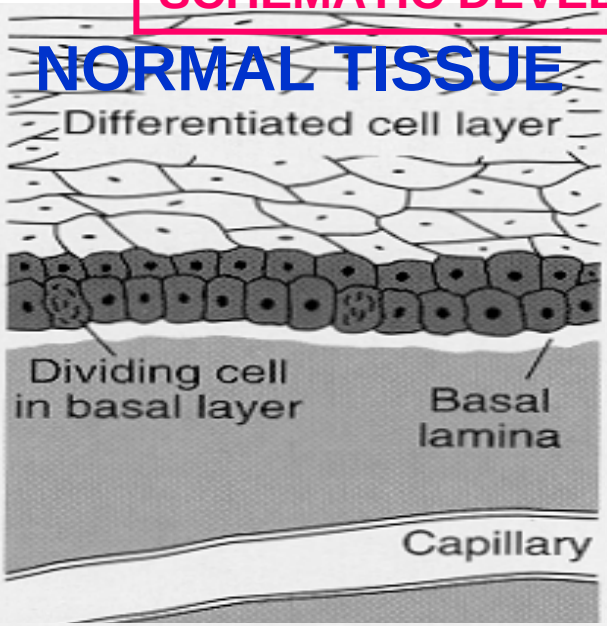
SCHEMATIC DEVELOPMENT OF NEOPLASTIC DISEASE

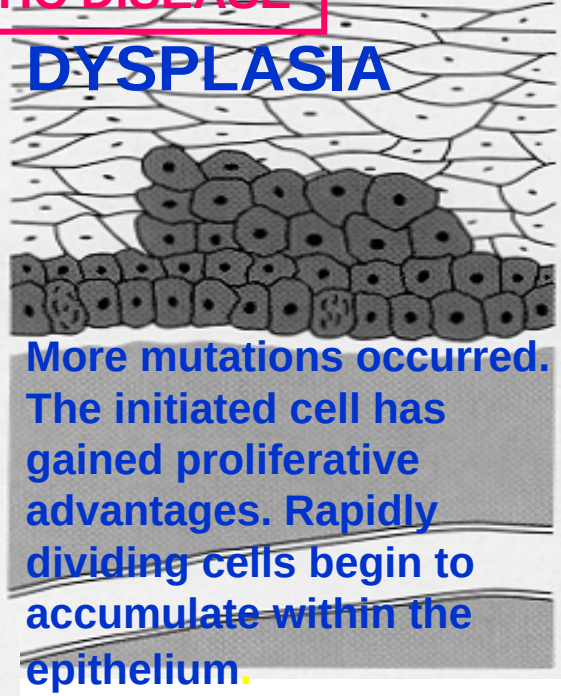
NORMAL TISSUE



CELL INITIATION

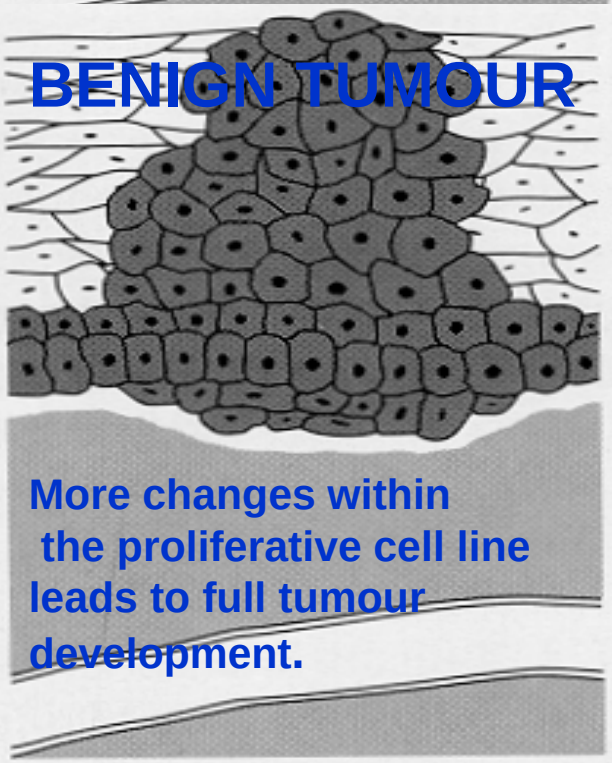
An initiating event creates a mutation in one of the basal cells

DYSPLASIA



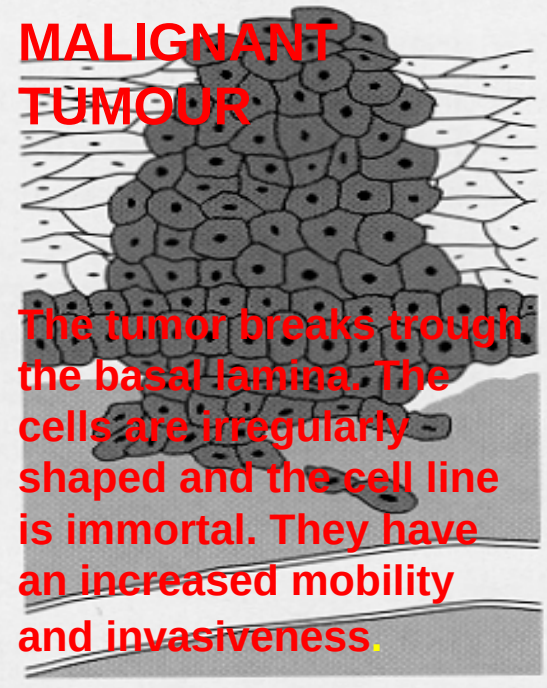
More mutations occurred. The initiated cell has gained proliferative advantages. Rapidly dividing cells begin to accumulate within the epithelium.

BENIGN TUMOUR



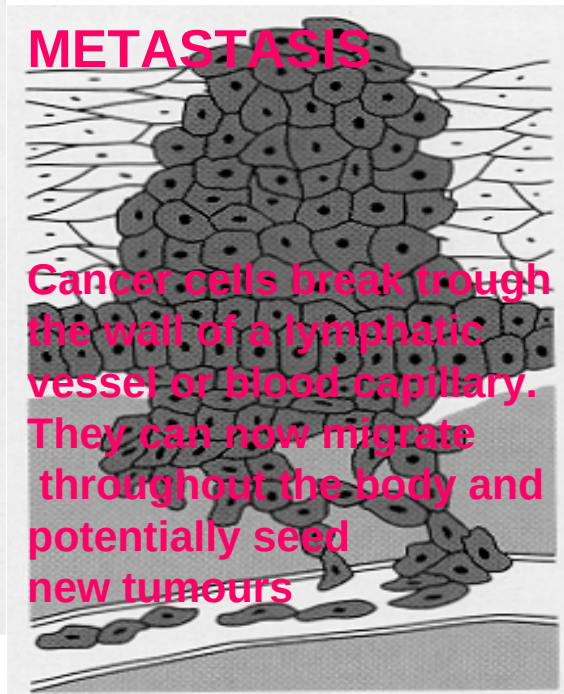
More changes within the proliferative cell line leads to full tumour development.

MALIGNANT TUMOUR



The tumor breaks trough the basal lamina. The cells are irregularly shaped and the cell line is immortal. They have an increased mobility and invasiveness.

METASTASIS



Cancer cells break trough the wall of a lymphatic vessel or blood capillary. They can now migrate throughout the body and potentially seed new tumours

METHODS OF TREATING CANCER

The basic modern approaches to cancer therapy are:

- **surgery,**
- **radiotherapy**,
- **chemotherapy and immunotherapy**.

Radiotherapy, applied alone or in combination with other techniques, **is of basic importance in cancer treatment.**

Over 50% of all cancer patients are nowadays treated with ionising radiation. This results from the major advances in the technology of clinical equipment made in the last decades (medical accelerators, radioactive source technology, diagnostic equipment, imaging techniques, computer technology).

RADIOTHERAPY TECHNIQUES

The basic techniques of modern radiotherapy are:

- **teleradiotherapy,**
- **brachytherapy**,
- **systemic radiotherapy** (radioisotope therapy).

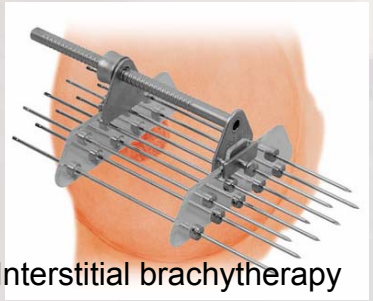
Selectron brachytherapy unit (Cs-137)

Medical accelerator

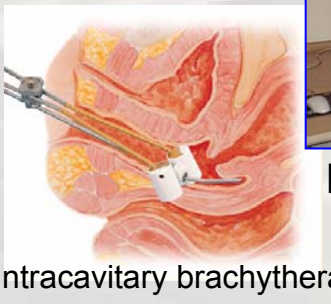
(4-23 MV photons &

4-23 MeV electrons)

Medical Physicist

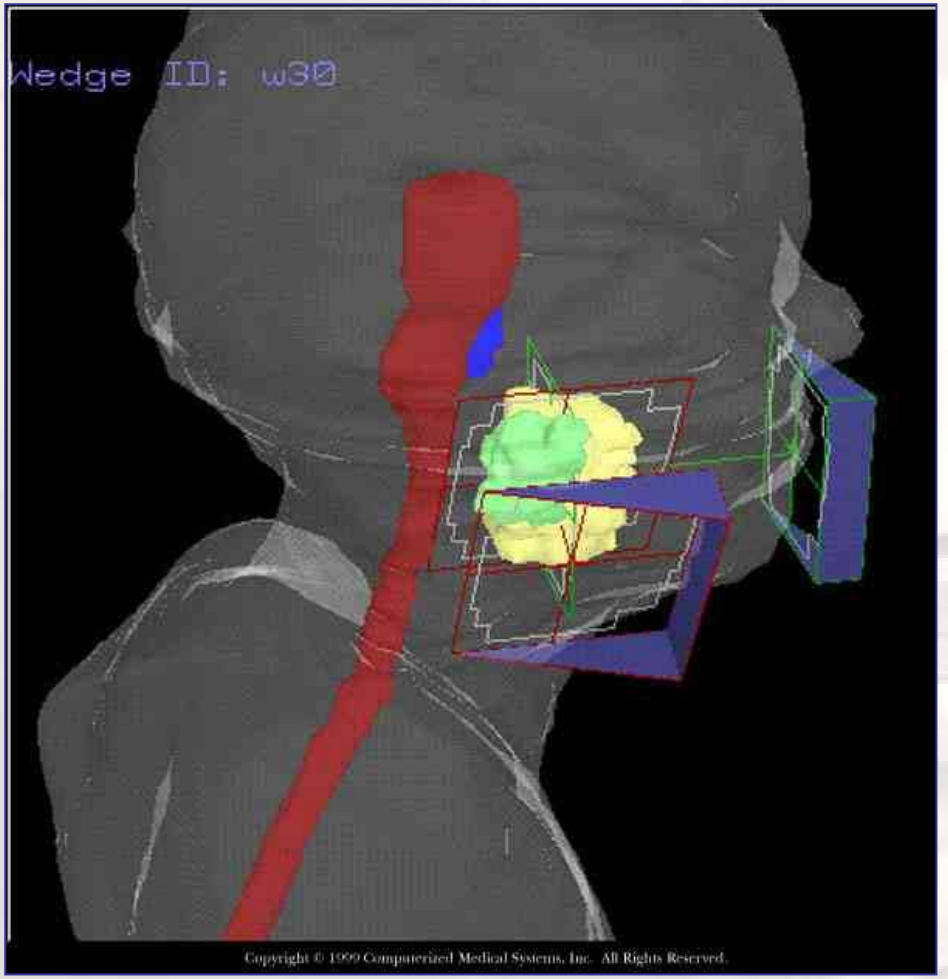


Interstitial brachytherapy



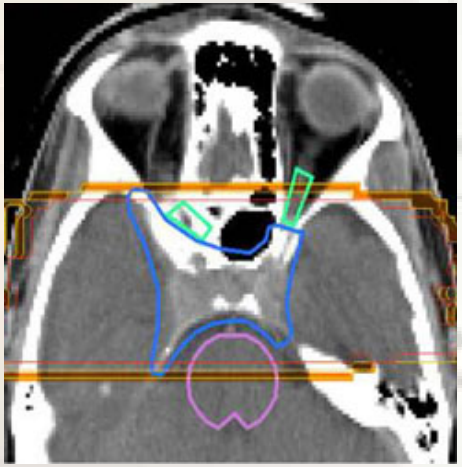
Intracavitary brachytherapy

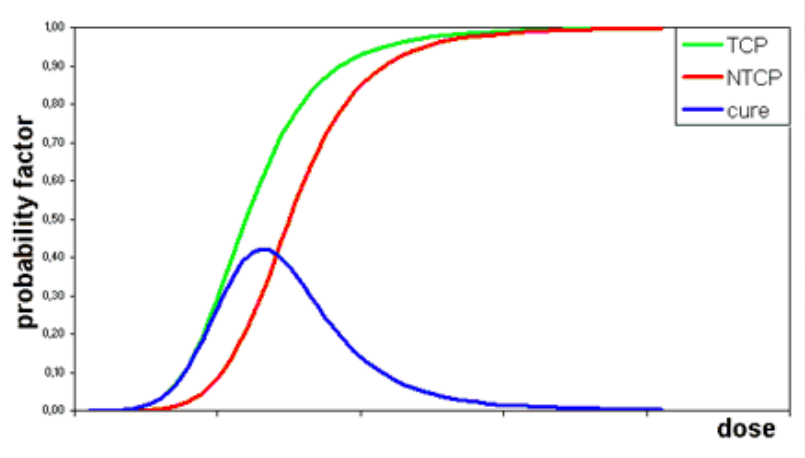
CONFORMAL RADIOTHERAPY WITH PHOTON BEAMS



The aim of radiotherapy is to achieve the best (conformal) distribution of delivered dose over the target volume (tumour volume) independently of its shape, in order to protect the surrounding healthy tissues and critical volumes.

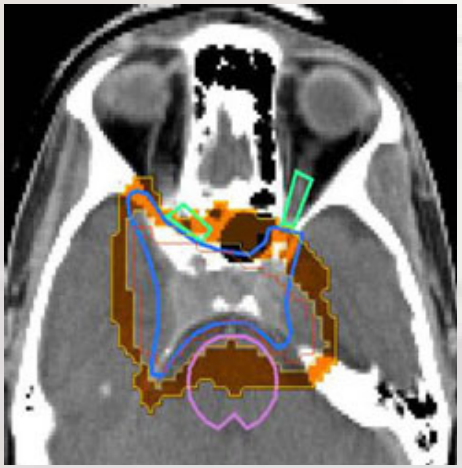
The technique of irradiadion affects the width of the „therapeutic window”

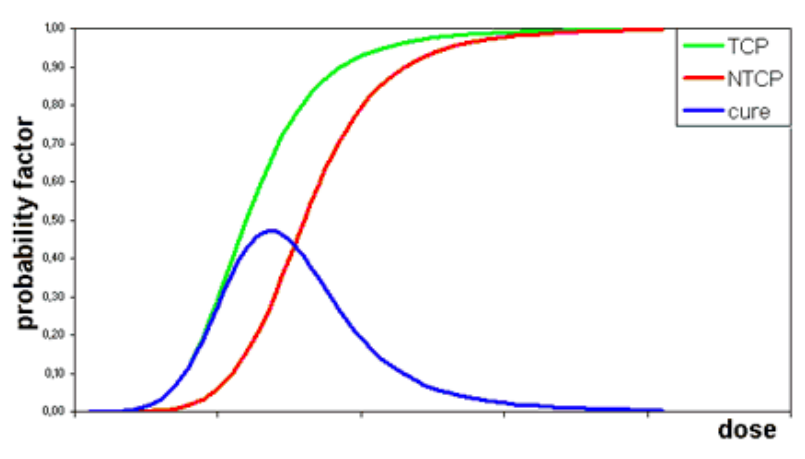




Tumour Control Probability
Normal Tissue Complications
Cure = TCP (1 – NTCP)

Two opposing beams



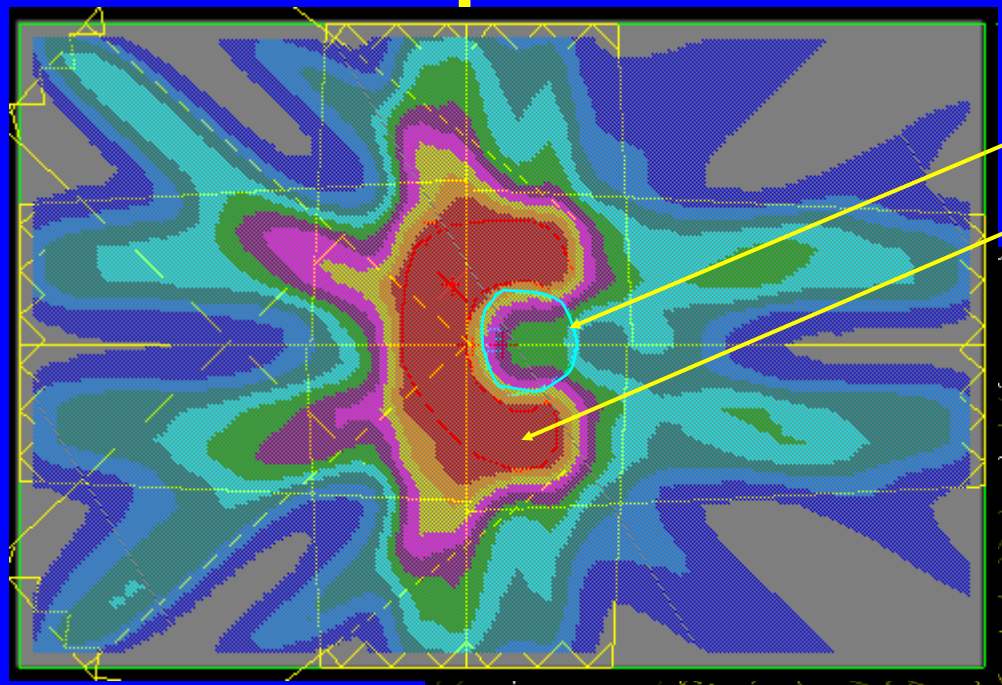


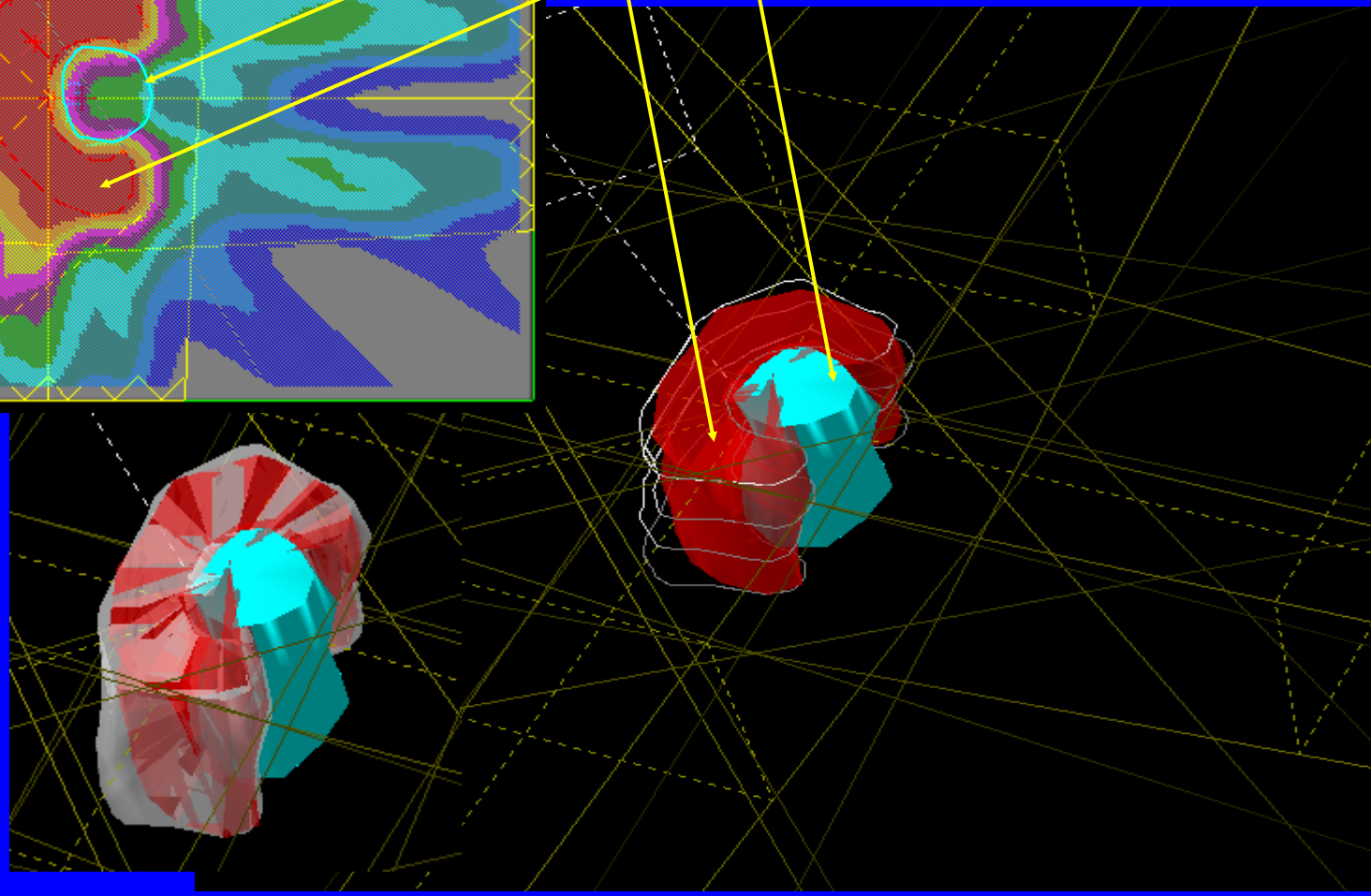
CONFORMAL TECHNIQUE

Four beams

Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de

Intensity Modulated RadioTherapy (IMRT) offers new possibilities of dose conformation





FRACTIONATED RADIOTHERAPY

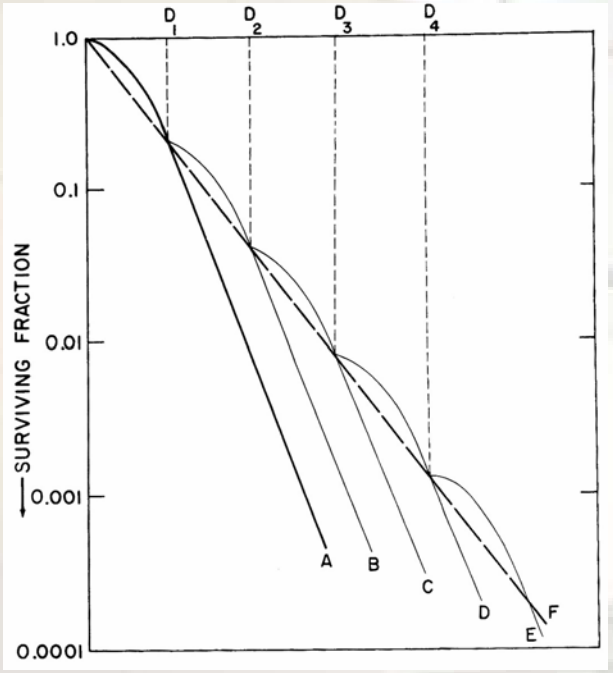


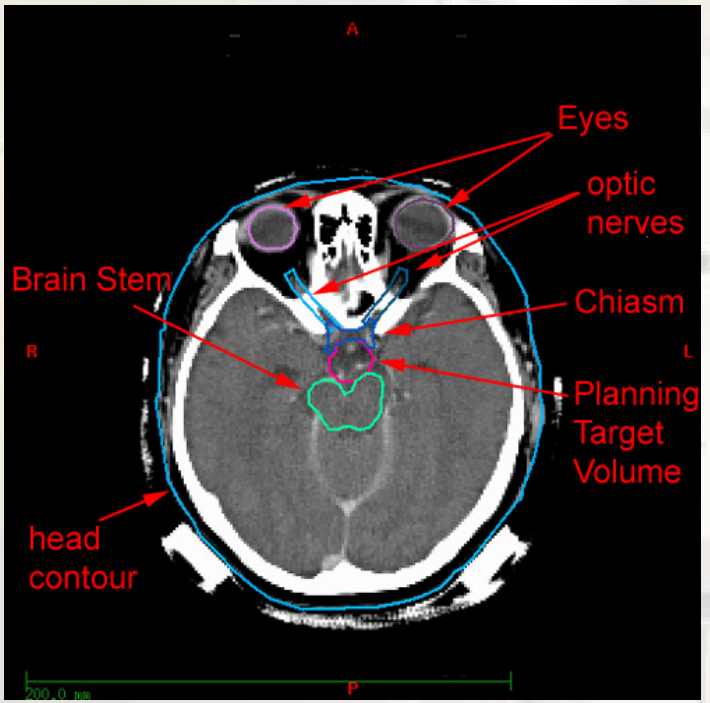
FIGURE 5.11 ● Idealized fractionation experiment. Curve A is the survival curve for single acute exposures of x-rays. Curve F is obtained if each dose is given as a series of small fractions of size D_1 with an interval between fractions sufficient for repair of sublethal damage. Multiple small fractions approximate to a continuous exposure to a low dose rate. (From Elkind MM, Whitmore GF: *Radiobiology of Cultured Mammalian Cells*. New York, Gordon and Breach, 1967, with permission.)

In a typical external radiotherapy beam treatment, a total dose of about 60 Gy is applied to the tumour volume in 30 fractions of 2 Gy given each weekday

Assuming that about ½ of the number of cells exposed to 2 Gy survive, a fraction of about $(½)^{30} \sim 10^{-10}$ survives after a dose of 60 Gy.

There are some 10^{10} cells in 1 cm^3 of tissue.

HOW DOES RADIATION AFFECT CELLS?



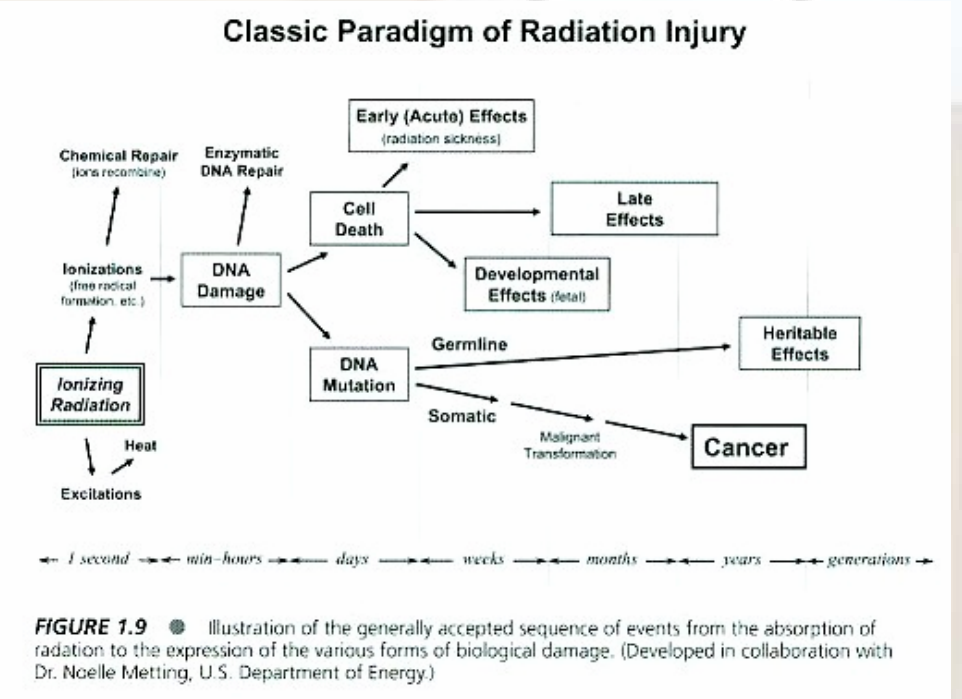


FIGURE 1.9 ● Illustration of the generally accepted sequence of events from the absorption of radiation to the expression of the various forms of biological damage. (Developed in collaboration with Dr. Noelle Metting, U.S. Department of Energy.)

Radiotherapy is designed to cause cell death in the target (tumour) volume while sparing healthy tissues and critical organs

The Cell Survival Curve

(cell cultures *in vitro*)

Note that „high-LET" (i.e. densely ionising radiation, such as neutrons or heavy ions) are more effective cell killers per dose – as given by Relative Biological Effectiveness (RBE)

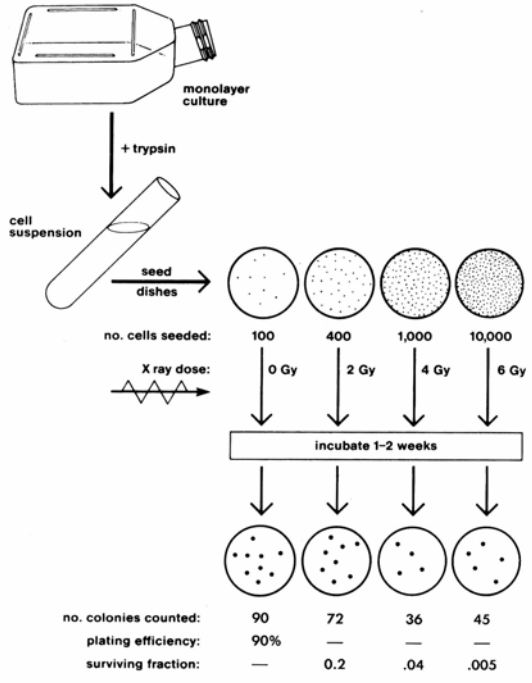


FIGURE 3.2 ● The cell culture technique used to generate a cell survival curve. Cells from a stock culture are prepared into a single-cell suspension by trypsinization, and the cell concentration is counted. Known numbers of cells are inoculated into petri dishes and irradiated. They then are allowed to grow until the surviving cells produce macroscopic colonies that can be counted readily. The number of cells per dish initially inoculated varies with the dose so that the number of colonies surviving is in the range that can be counted conveniently. Surviving fraction is the ratio of colonies produced to cells plated, with a correction necessary for plating efficiency (i.e., for the fact that not all cells plated grow into colonies, even in the absence of radiation).

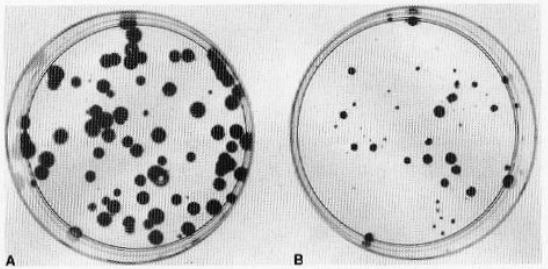


FIGURE 3.1 ● Colonies obtained with Chinese hamster cells cultured *in vitro*. **A:** In this unirradiated control dish, 100 cells were seeded and allowed to grow for 7 days before being stained. There are 70 colonies; therefore, the plating efficiency is 70/100, or 70%. **B:** Two thousand cells were seeded and then exposed to 8 Gy (800 rad) of x-rays. There are 32 colonies on the dish. Thus:

Surviving fraction = Colonies counted/[Cells seeded × (PE/100)]
= 32/(2,000 × 0.7)
= 0.023

Survival curve formulae:

$\alpha D + \beta D^2$

m - target

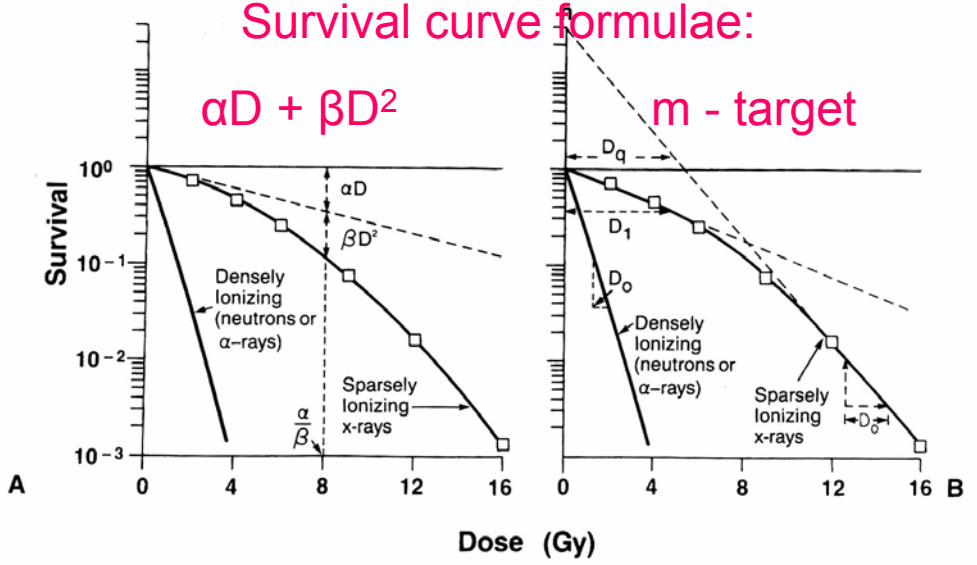


FIGURE 3.3 ● Shape of survival curve for mammalian cells exposed to radiation. The fraction of cells surviving is plotted on a logarithmic scale against dose on a linear scale. For α-particles or low-energy neutrons (said to be densely ionizing), the dose–response curve is a straight line from the origin (i.e., survival is an exponential function of dose). The survival curve can be described by just one parameter, the slope. For x- or γ-rays (said to be sparsely ionizing), the dose–response curve has an initial linear slope, followed by a shoulder; at higher doses, the curve tends to become straight again. **A:** The linear quadratic model. The experimental data are fitted to a linear-quadratic function. There are two components of cell killing: One is proportional to dose (αD); the other is proportional to the square of the dose (βD^2). The dose at which the linear and quadratic components are equal is the ratio α/β. The linear-quadratic curve bends continuously but is a good fit to experimental data for the first few decades of survival. **B:** The multitarget model. The curve is described by the initial slope (D_1), the final slope (D_0), and a parameter that represents the width of the shoulder, either n or D_q.

The Oxygen Effect

Cells deprived of oxygen (anoxic or hypoxic) are generally more resistant to photon radiation than are aerobic (oxygenated) cells. Thus, neighbouring healthy tissues are more likely to be damaged than tumour cells which proliferate rapidly and may lack oxygen supply. From analysis of survival curves the Oxygen Enhancement Ratio (OER) may be found.

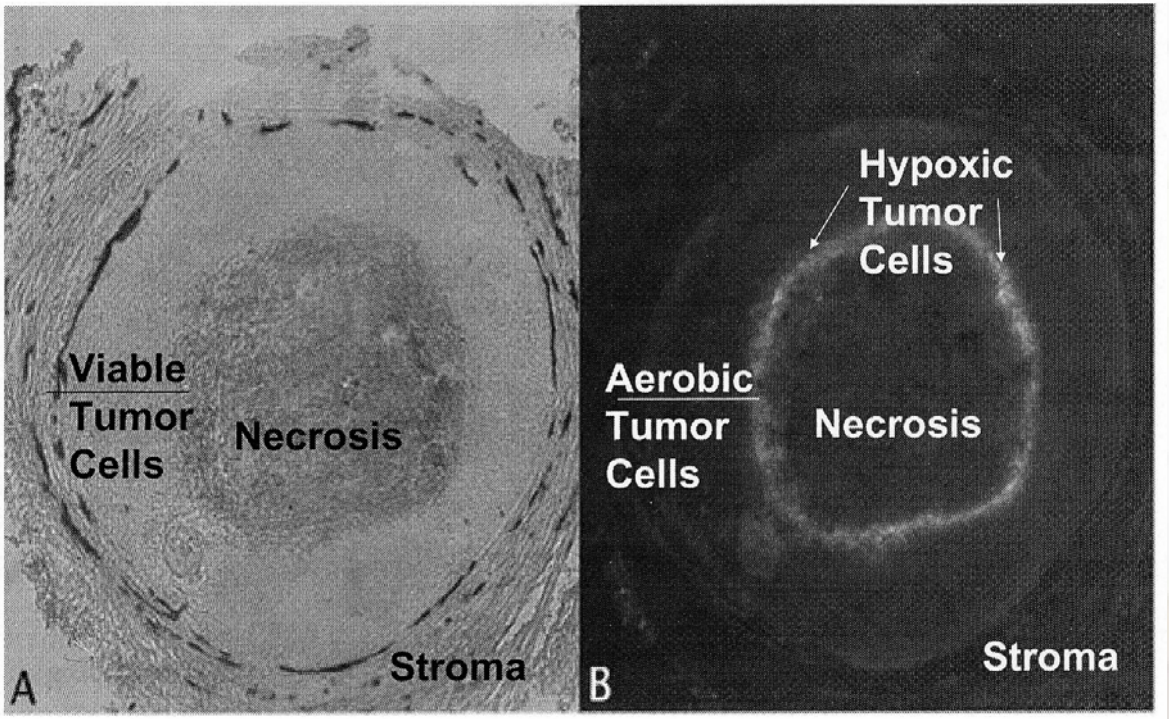


FIGURE 6.12 These images show a section from a rodent tumor illustrating chronic hypoxic cells. The animal was treated with the 2-nitroimidazole hypoxia detection agent EF5 24 hours preceding surgical removal of the tumor. **A:** Photomicrograph of the tumor section illustrating the tumor stroma, viable tumor cells, and necrotic tumor core. **B:** The same tumor section demonstrating the presence of chronically hypoxic tumor cells that stain positive with EF5 (white rim) adjacent to the necrotic core. (Courtesy of Dr. Sydney Evans.)

The standard procedures of radiotherapy

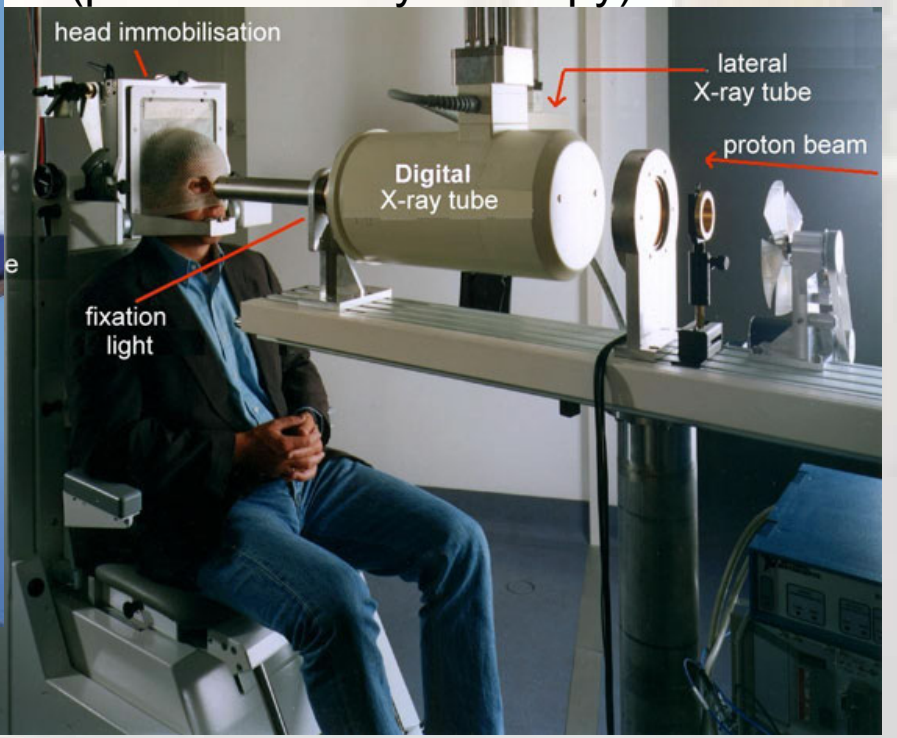
- Clinical workout, therapy decision
- Choice of patient immobilisation technique
- Diagnostic & topographic imaging
- Tumour localisation
- Computer Therapy Planning
- Patient setup
- Patient irradiation
- Treatment verification & Evidence

Patient Immobilisation

Since the patient has to be repeatedly irradiated (typically 30 times when 2-Gy fractions are delivered), his/her body should not move during irradiation and his/her positioning should be repeatable with an accuracy of 0.5-3 mm, depending on site irradiated.

Individual vacuum couch with positioning frame (for prostate treatment)

Immobilisation of patient's head with respect to treatment chair (proton beam eye therapy)



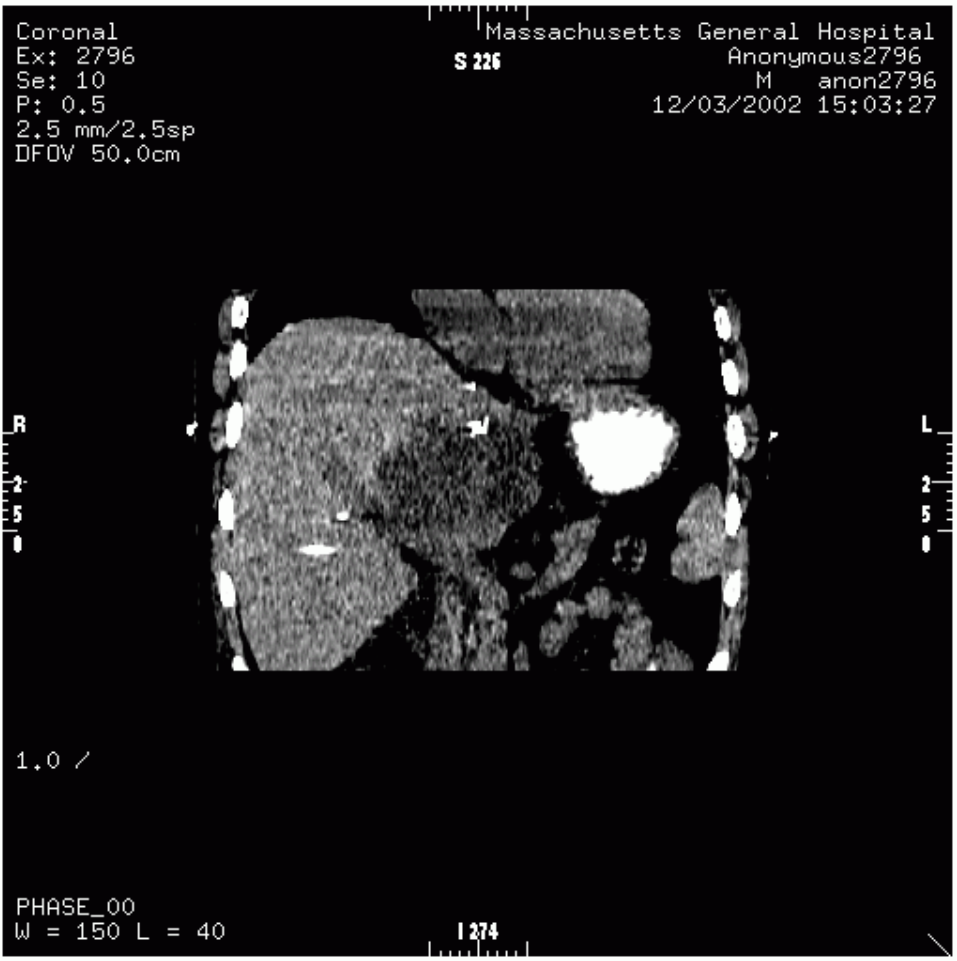
Optical system for verifying patient positioning

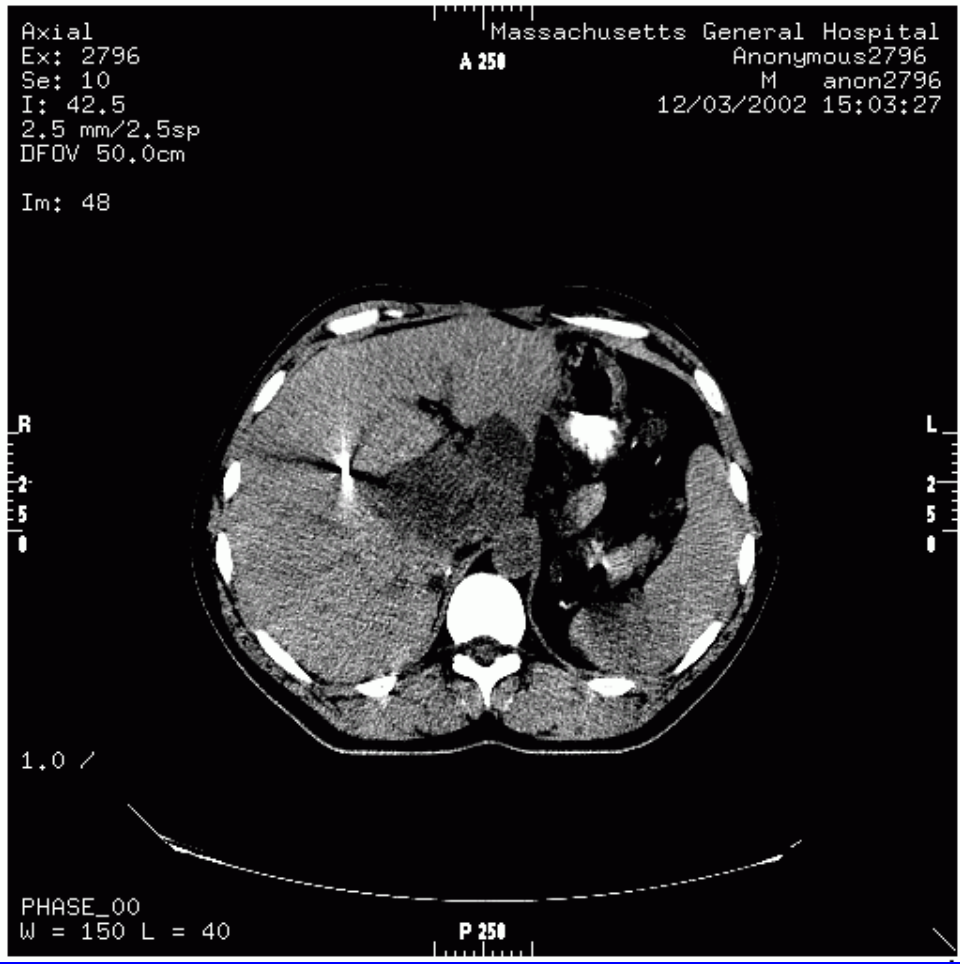
3D surface scanning (*Laser-based, LCD based*)

Advantage: Anatomical information

Challenge: Not yet real-time (1-2 seconds / image)

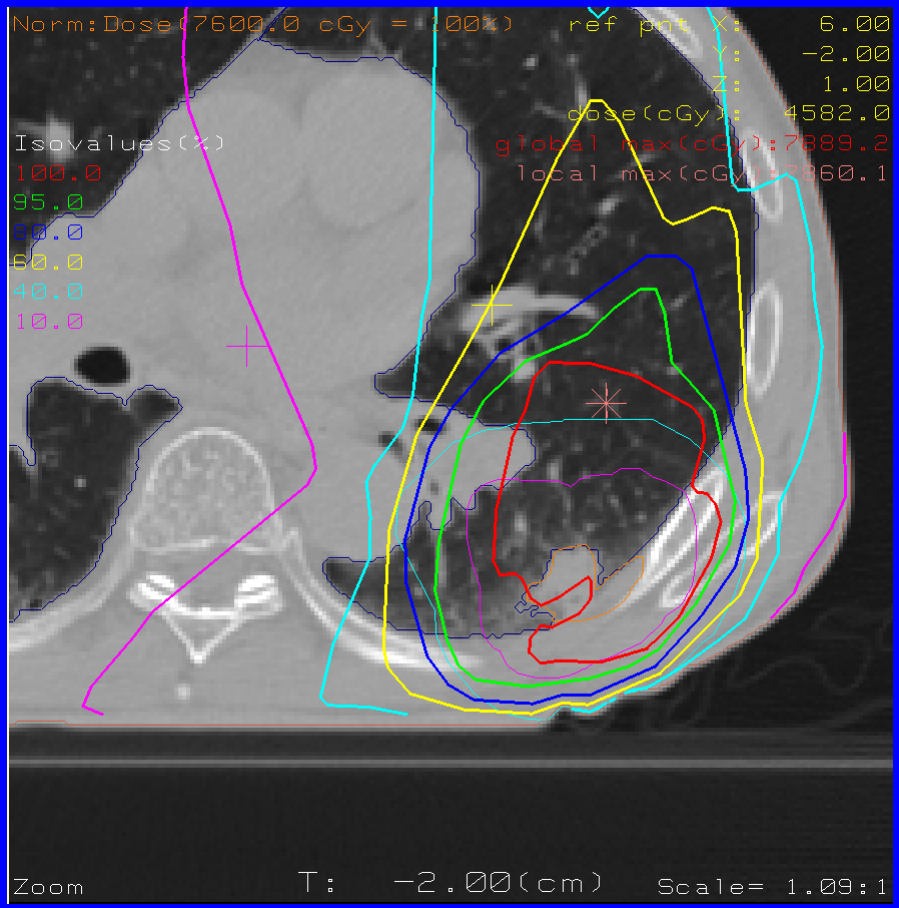
Problem – movement of target volume

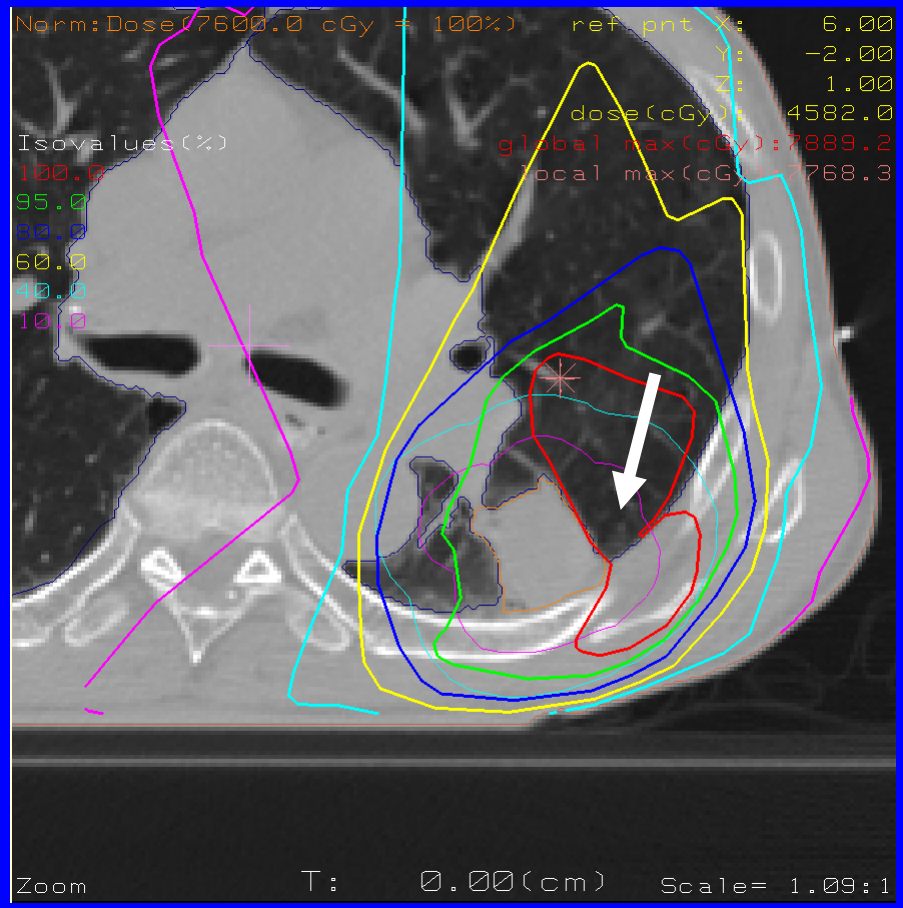




E Rietzel

Respiratory movement of the target volume in the lung - (a study of 3D Carbon RT)





Approximation: All fields delivered simultaneously

E Rietzel

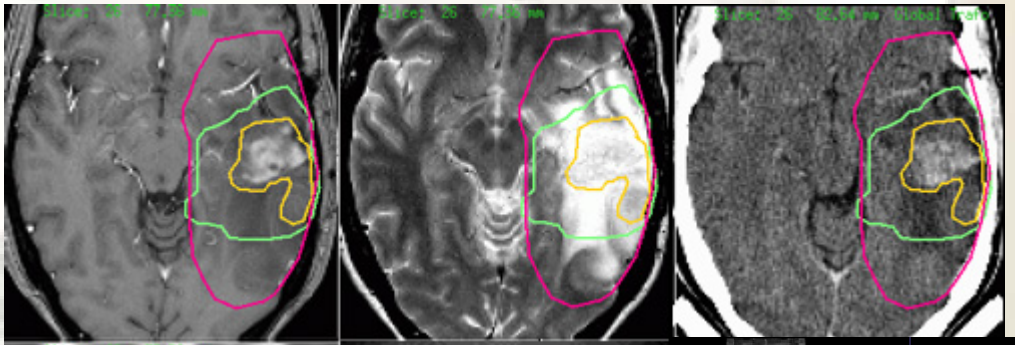
Imaging

Application of different imaging techniques (CT, MRI, PET) provides the diagnosis and enables the target volume to be determined.

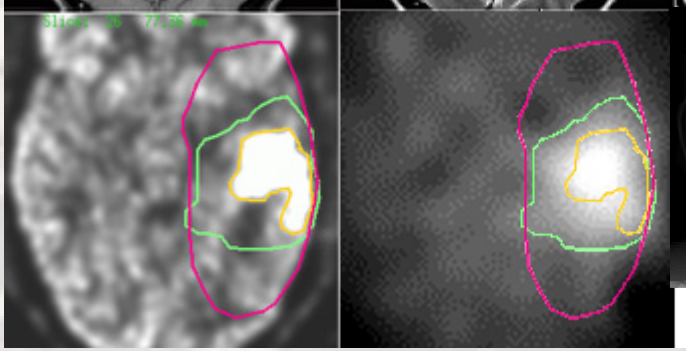
MRI (T1)

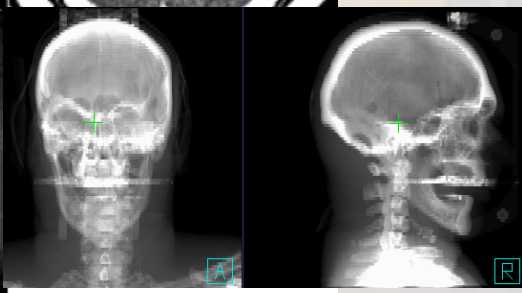
CT

MRI (T2)



PET





DIGITAL RADIOGRAPHY RECONSTRUCTION (DRR)

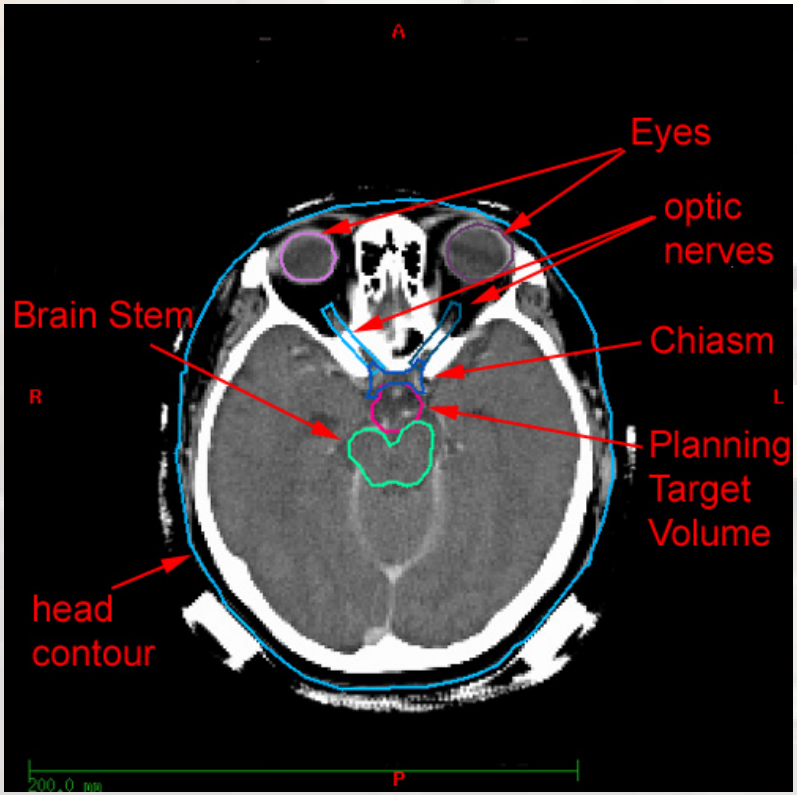
18F-FDG PET

123I-IMT SPECT

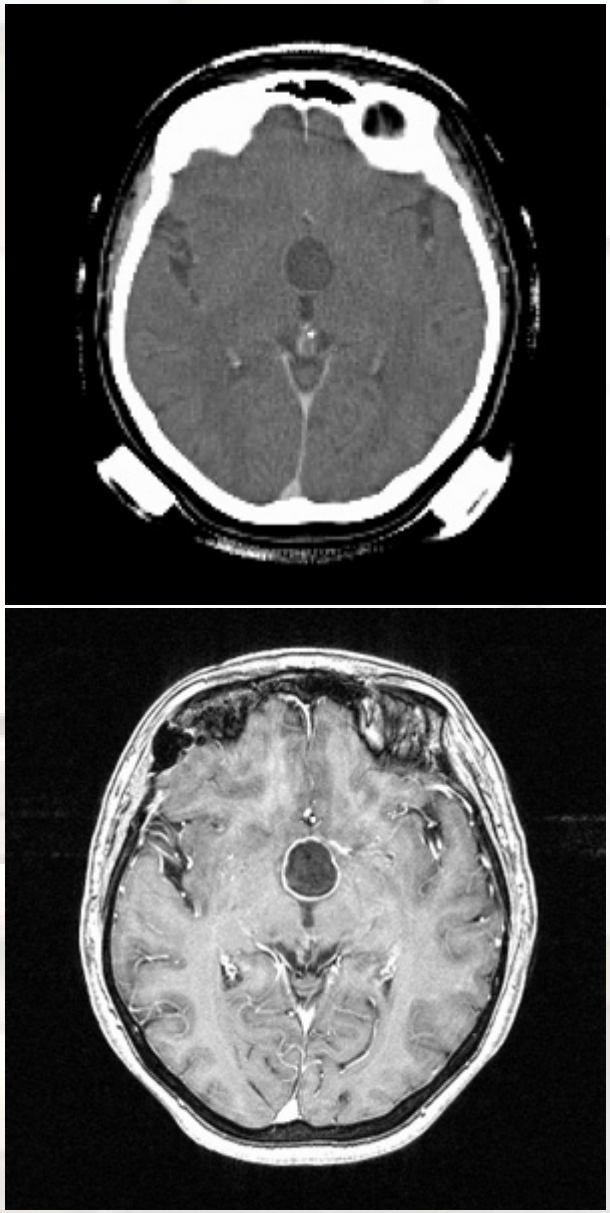
(recurrent astrocytoma in the left temporal lobe)

Determination of tumour volume

From a sequence of tomography scans (CT +MRI) it is possible to determine the target volumes, critical volumes and patient topography for therapy planning purposes.



Scans

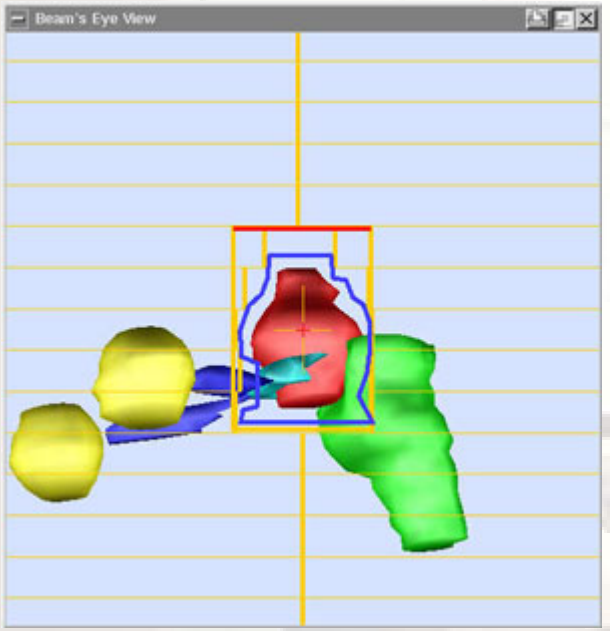


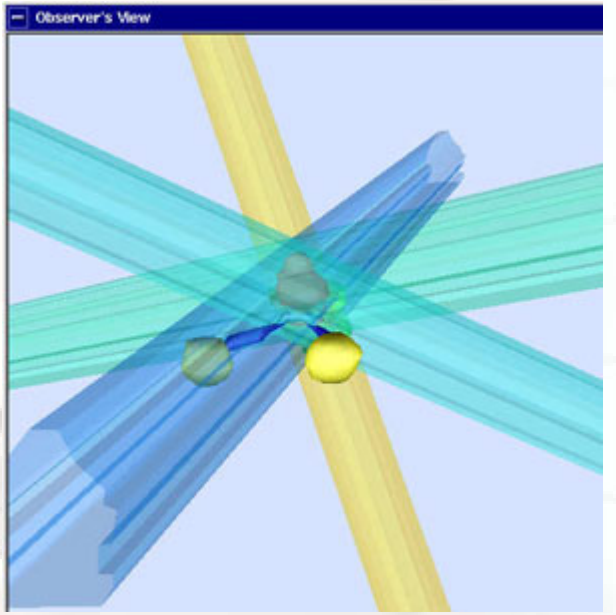
CT

MRI

Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy A multimedia introduction to methods and techniques, Springer Electronic Media http://www.springer.de

Computer radiotherapy planning – optimising the placement of photon beams required to model the spatial distribution of dose





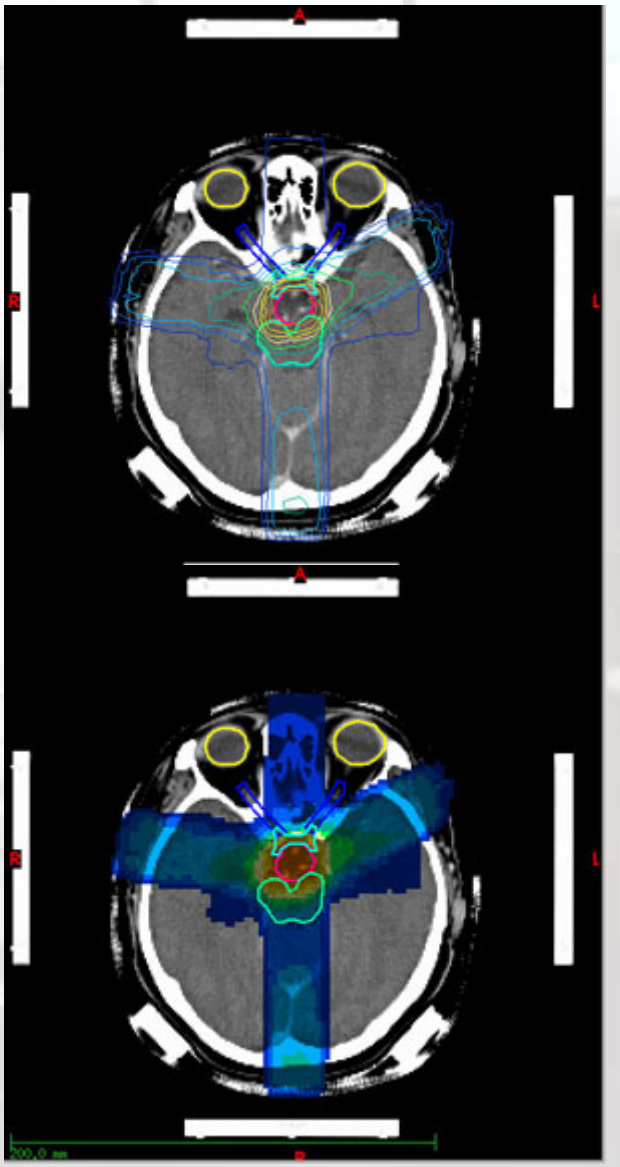
projections:

„beam's eye view" (BEV) **geometrical projection**

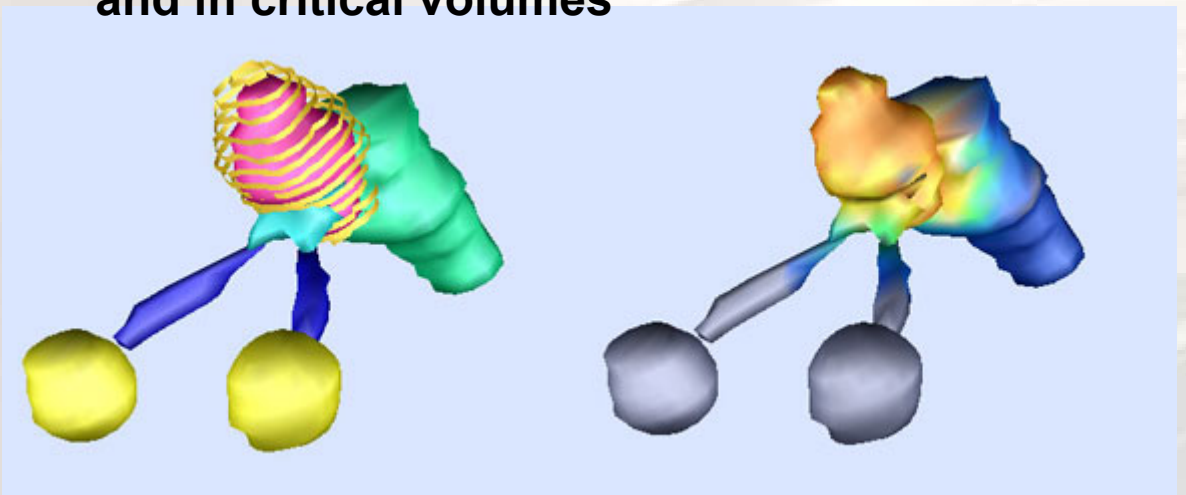
Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de

Computer radiotherapy planning – viewing and optimising the 3D dose distribution

Izodoses

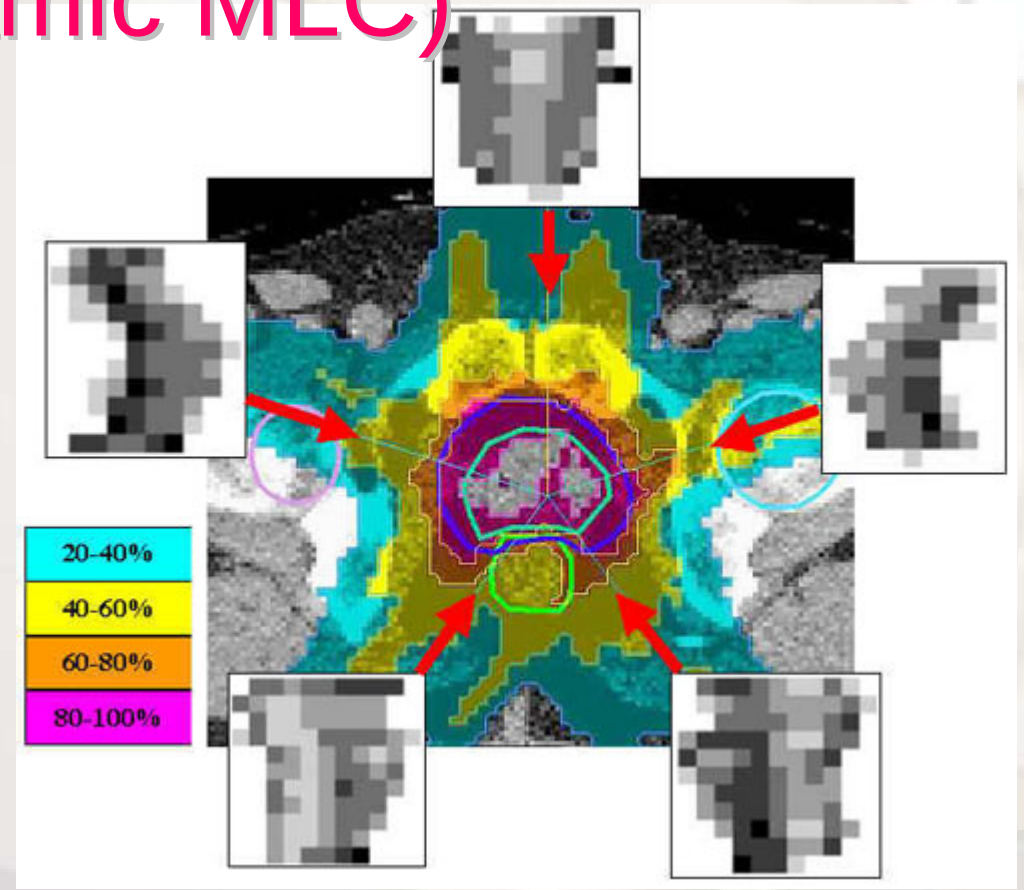


Dose distribution in the target volume and in critical volumes



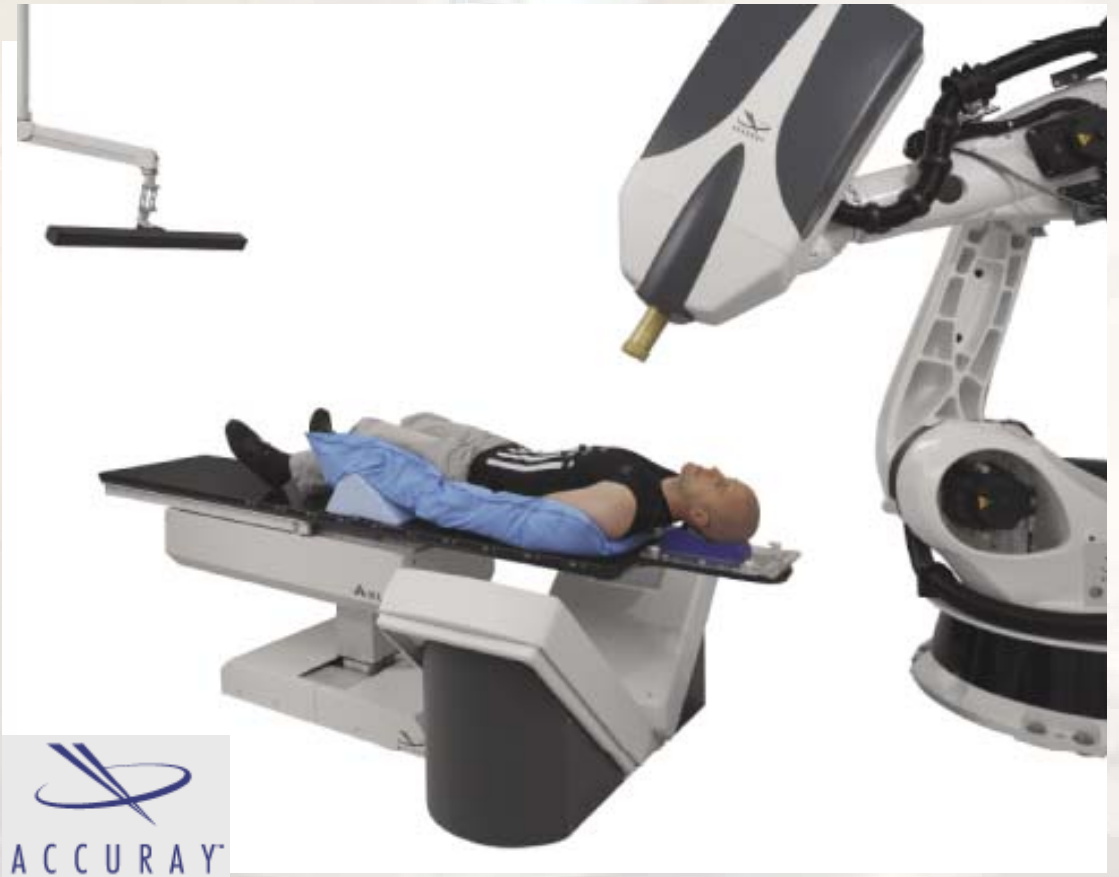
Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de

Verification of the irradiation fields (dynamic MLC)



A sequence of fluence maps is shown for five photon beams providing the optimum individual treatment plan for the prostate.

The future medical linear accelerator ?



Is this the standard against which Hadron RT should compete?

Key features:

+„true” 3D mobility,

+ Pencil beam (6MV) conformality

+ DRR patient positioning

+ On-line organ tracking

? Dose delivery algorithm

? „true” IMRT

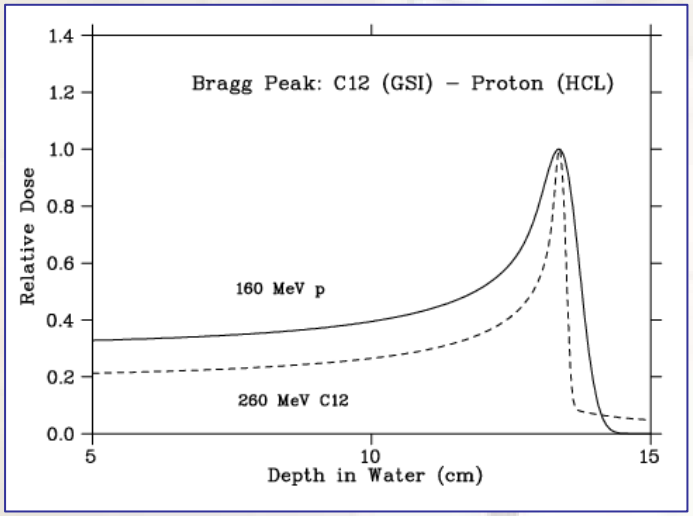
? „true” 3D Radiotherapy planning….

What new elements are introduced by Hadron Radiotherapy?

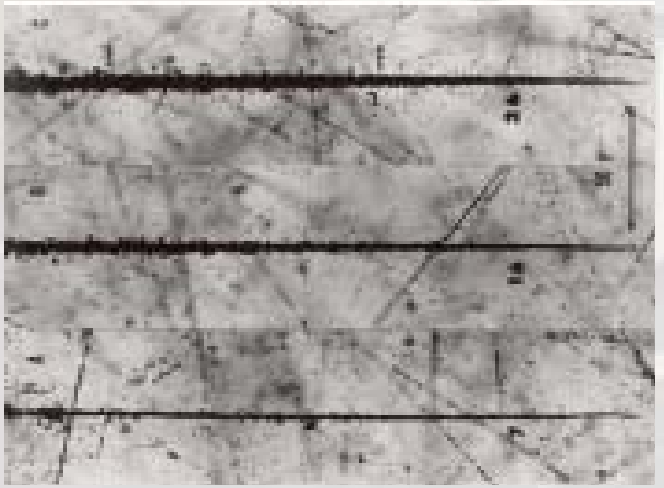
- conformity of dose (well-defined range, charged particles)
- Bragg Peak at distal end of ion range
- RBE (Relative Bological Effectiveness) > 1
- OER (Oxygen Enhancement Ratio) ~ 1

Conformity of dose (well-defined range, charged particles)

Ion Beams („high-LET")



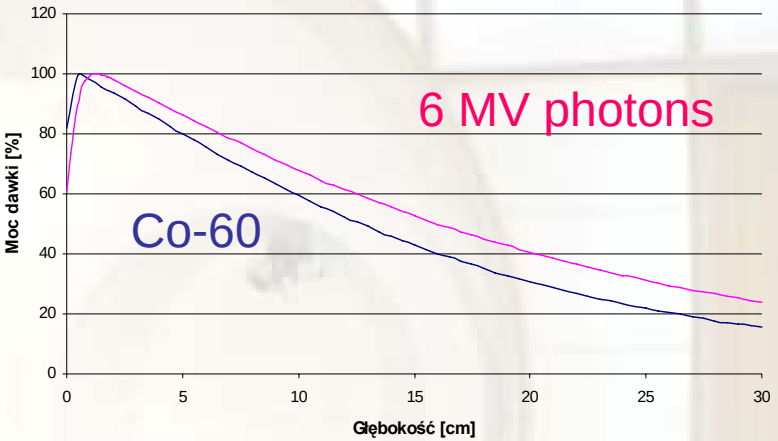
Note: no effect of Bragg peak in ion tracks!

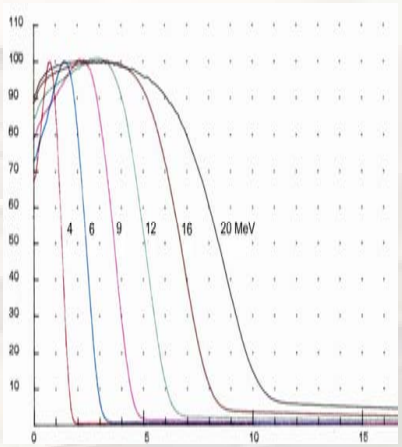


Ion tracks in nuclear emulsion

RBE?

Conventional Radiotherapy ('low-LET"





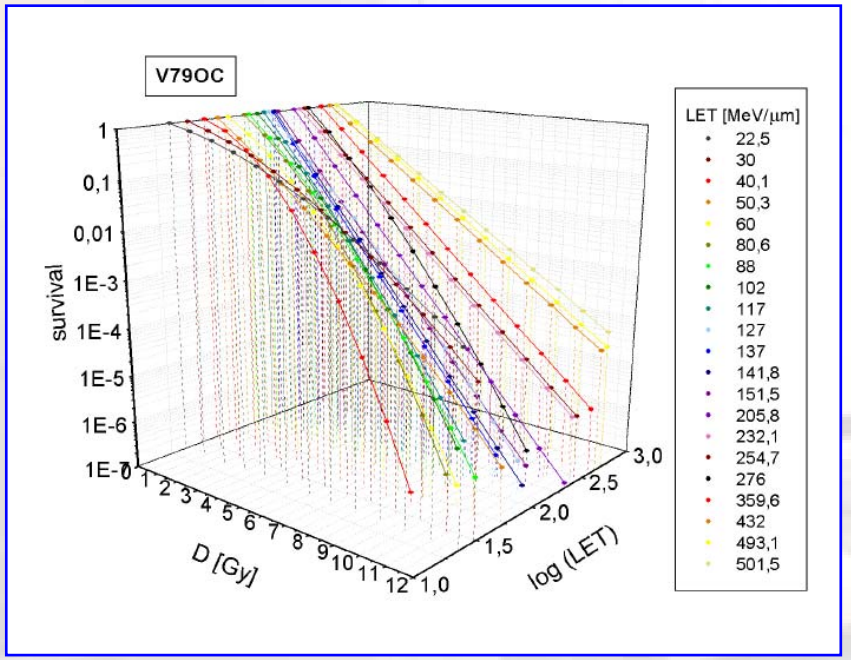
Electron Beams

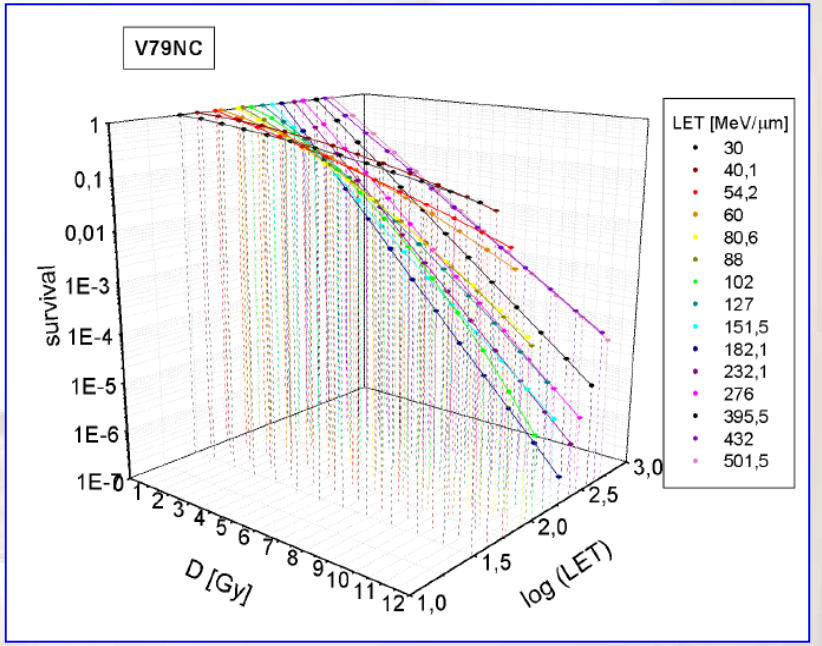
(4-20 MeV)

Percent dose-depth distributions

RBE (Relative Bological Effectiveness) > 1
OER (Oxygen Enhancement Ratio) ~ 1

How does cell survival depend on ion LET (-dE/dX)?





Survival of V79 cells *in vitro* vs. LET of a Carbon-12 beam:

Aerated cells

Anoxic cells

Data: Furusawa *et al. Radiat. Res*. **154**, 485-496 (2000)

RBE (Relative Biological Effectiveness) > 1

Fractionation is less effective for high-LET RT, but RBE may then be higher

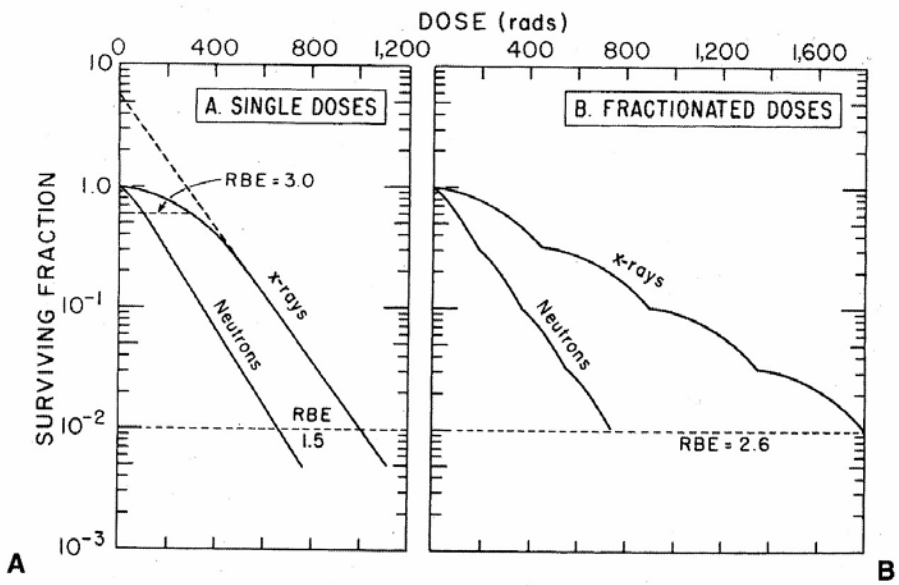
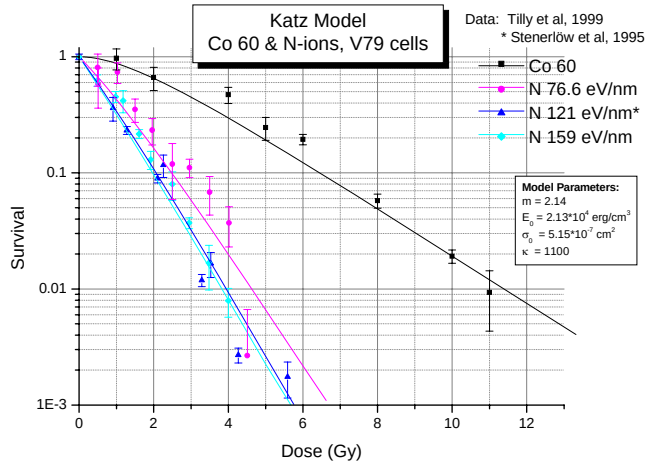
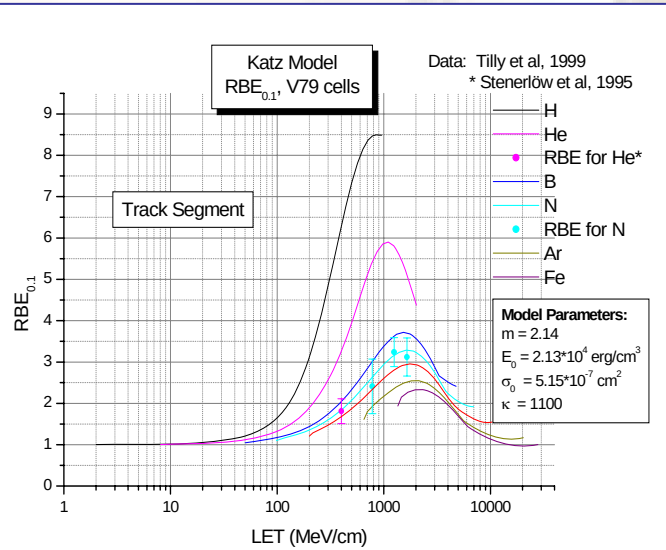


FIGURE 7.3 Typical survival curves for mammalian cells exposed to x-rays and fast neutrons. **A:** Single doses. The survival curve for x-rays has a large initial shoulder; for fast neutrons, the initial shoulder is smaller and the final slope steeper. Because the survival curves have different shapes, the relative biologic effectiveness (RBE) does not have a unique value but varies with dose, getting larger as the size of the dose is reduced. **B:** Fractionated doses. The effect of giving doses of x-rays or fast neutrons in four equal fractions to produce the same level of survival as in **A**. The shoulder of the survival curves is reexpressed after each dose fraction; the fact that the shoulder is larger for x-rays than for neutrons results in an enlarged RBE for fractionated treatments.

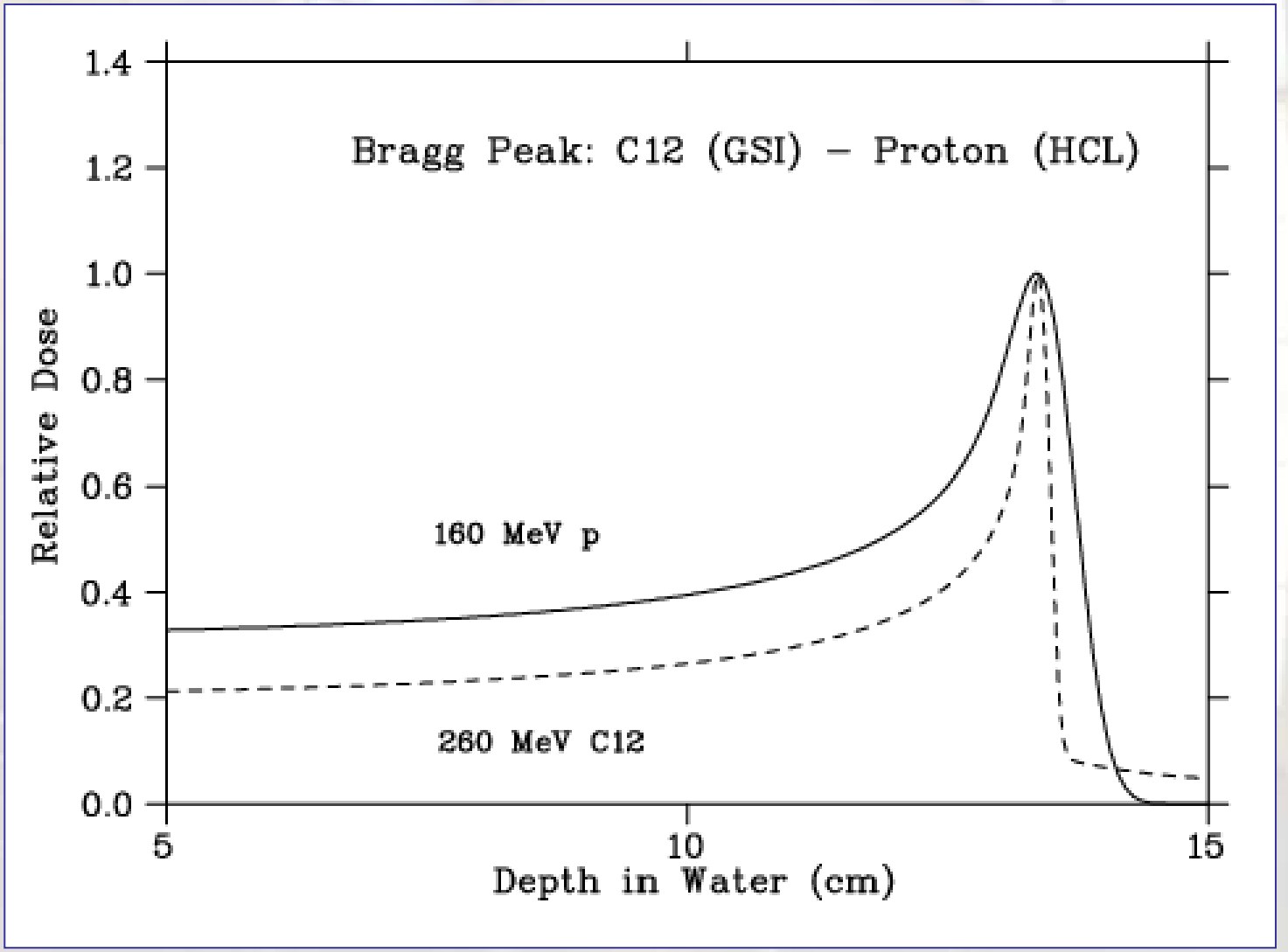




Conclusion: Fewer fractions needed in heavy-ion radiotherapy…..

High-LET survival & RBE can be modelled

Entrance dose **Bragg Peak dose**



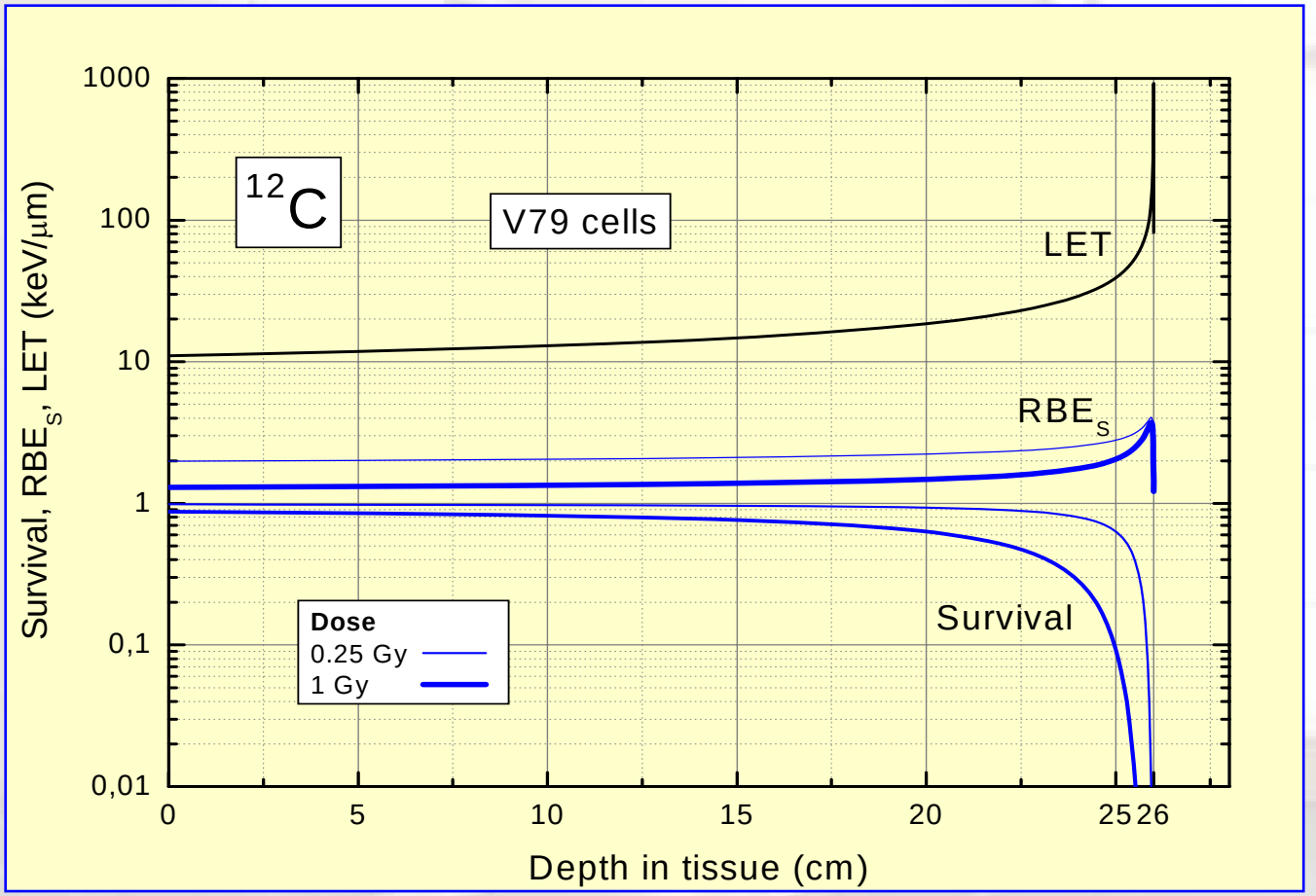
ION PARAMETERS (BEAM DATA)

The CSDA range of all ion beams is R = 26.0 cm, in water

Ion	Z	A	E_{in} MeV/A	β_{in}	LET(Z, β_{in}) keV/μ	Fluence/1Gy 10^7 ions cm^{-2}	σ_Z mm
p	1	1	199.2	0.5669	0.4469	139.87	2.78
He	2	4	199.2	0.5669	1.7874	34.97	1.38
Li	3	7	230.9	0.5982	3.666	17.05	1.05
B	5	11	324.8	0.6710	8.3644	7.472	0.82
C	6	12	385.2	0.7067	11.027	5.668	0.78
N	7	14	424.0	0.7265	14.328	4.362	0.72
O	8	16	461.3	0.7434	18.006	3.471	0.67
Ne	10	20	532.2	0.7713	24.476	2.307	0.59

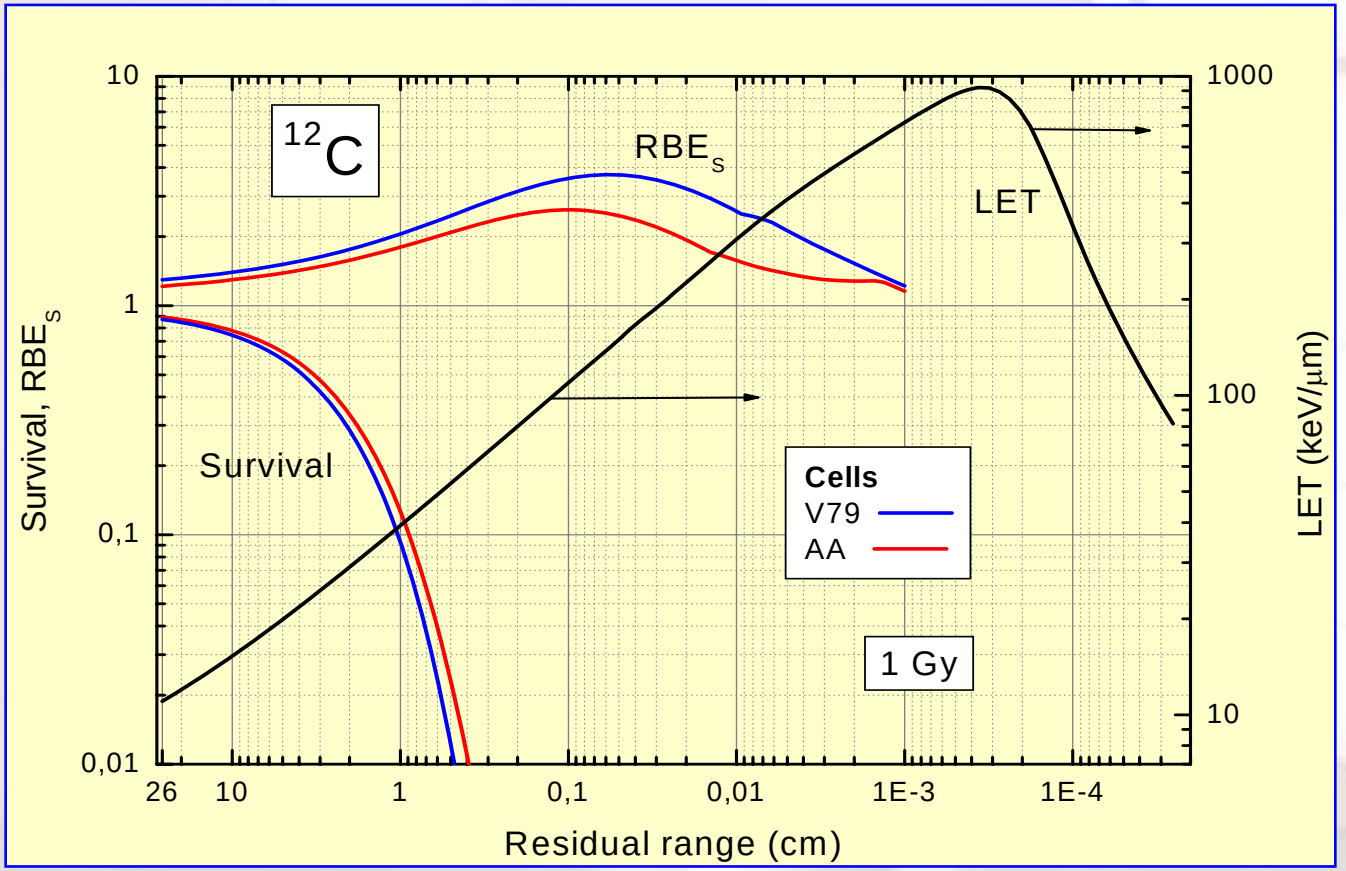
Values at Beam Entrance (range straggling)

DEPTH DISTRIBUTIONS OF LET, SURVIVAL AND RBE_S



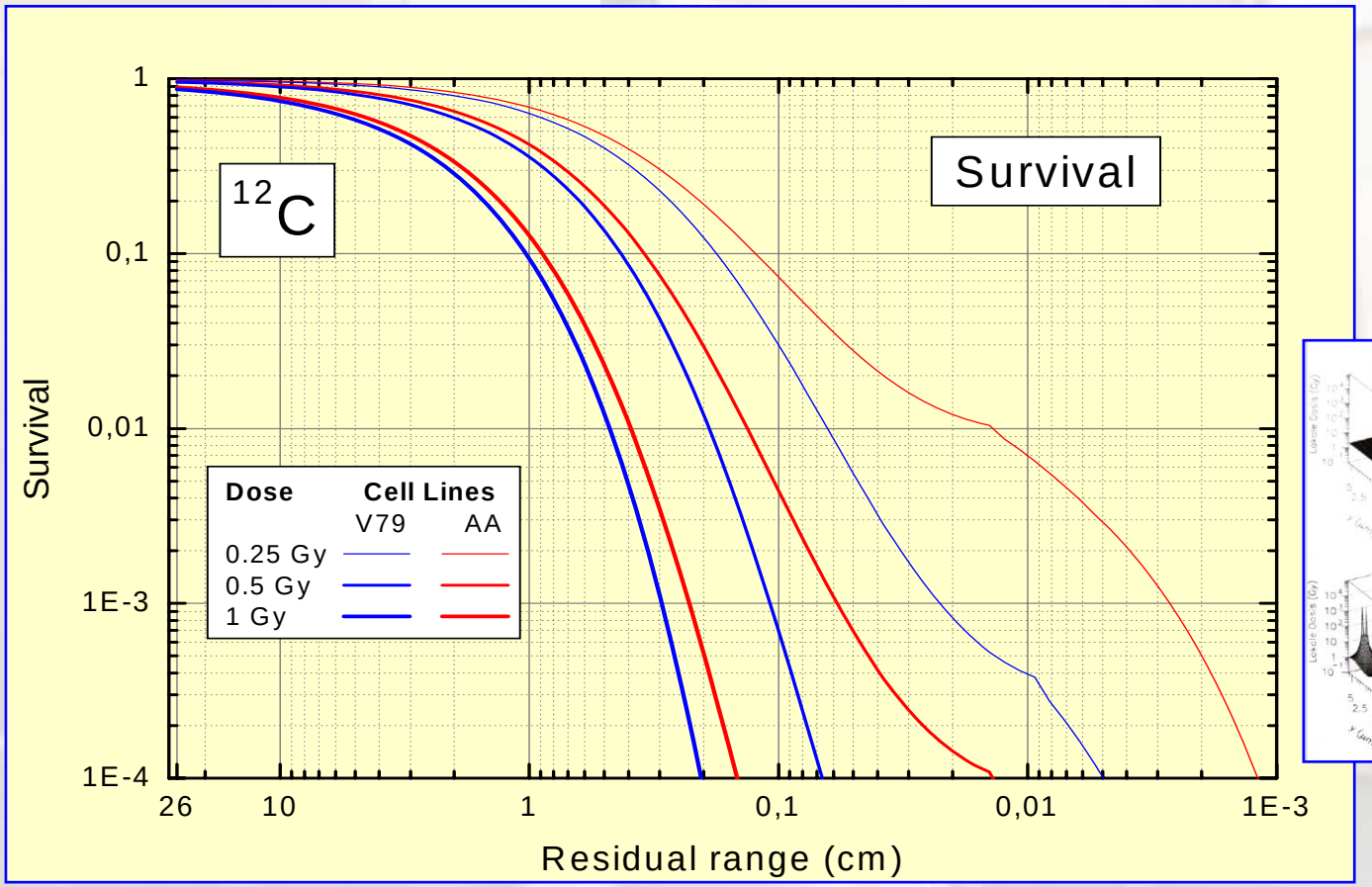
Depth distributions of ion LET, cell survival and RBE_S for V79 and AA cells in a beam of ^{12}C ions of initial energy 385.2 MeV/amu, delivering an entrance dose of 1.0 Gy.

DEPTH DISTRIBUTIONS OF LET, SURVIVAL AND RBE_S

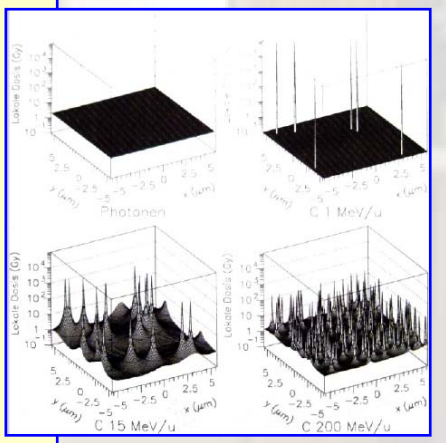


Depth distributions of ion LET, cell survival and RBE_S for V79 and AA cells in a beam of ^{12}C ions of initial energy 385.2 MeV/amu, delivering an entrance dose of 1.0 Gy.

DEPTH DISTRIBUTIONS OF LET, SURVIVAL AND RBE_S



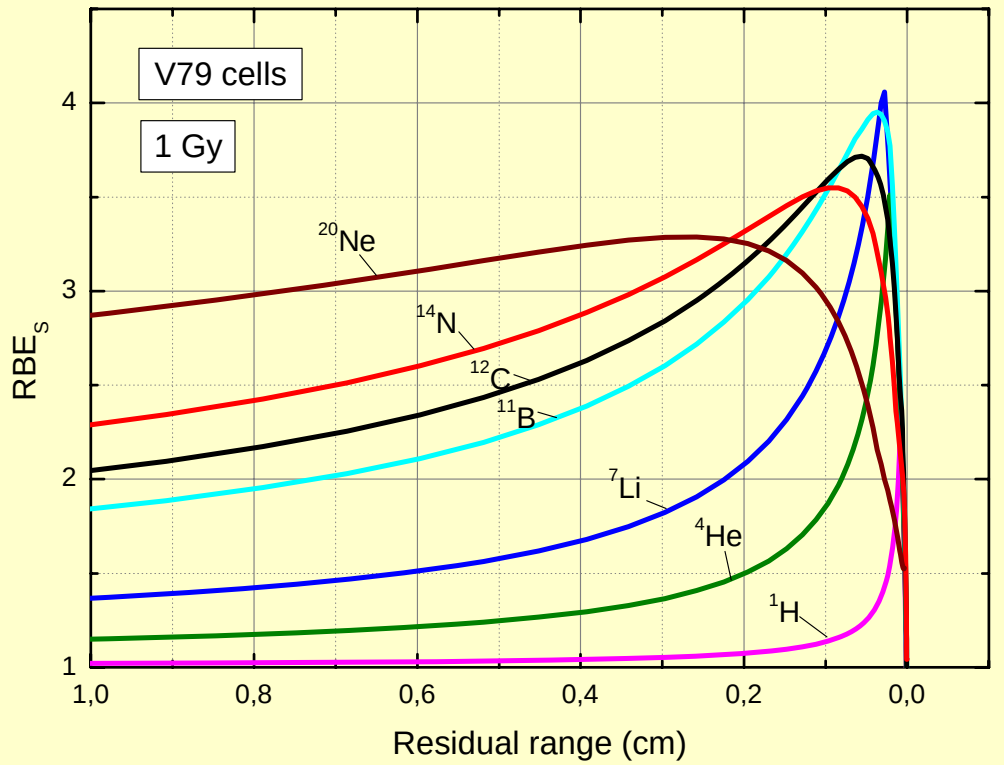
The Fluence Problem



Depth distributions of ion LET, cell survival and RBES for V79 and AA cells in a beam of ^{12}C ions of initial energy 385.2 MeV/amu, delivering entrance dose 0.25, 0.5 and 1.0 Gy.

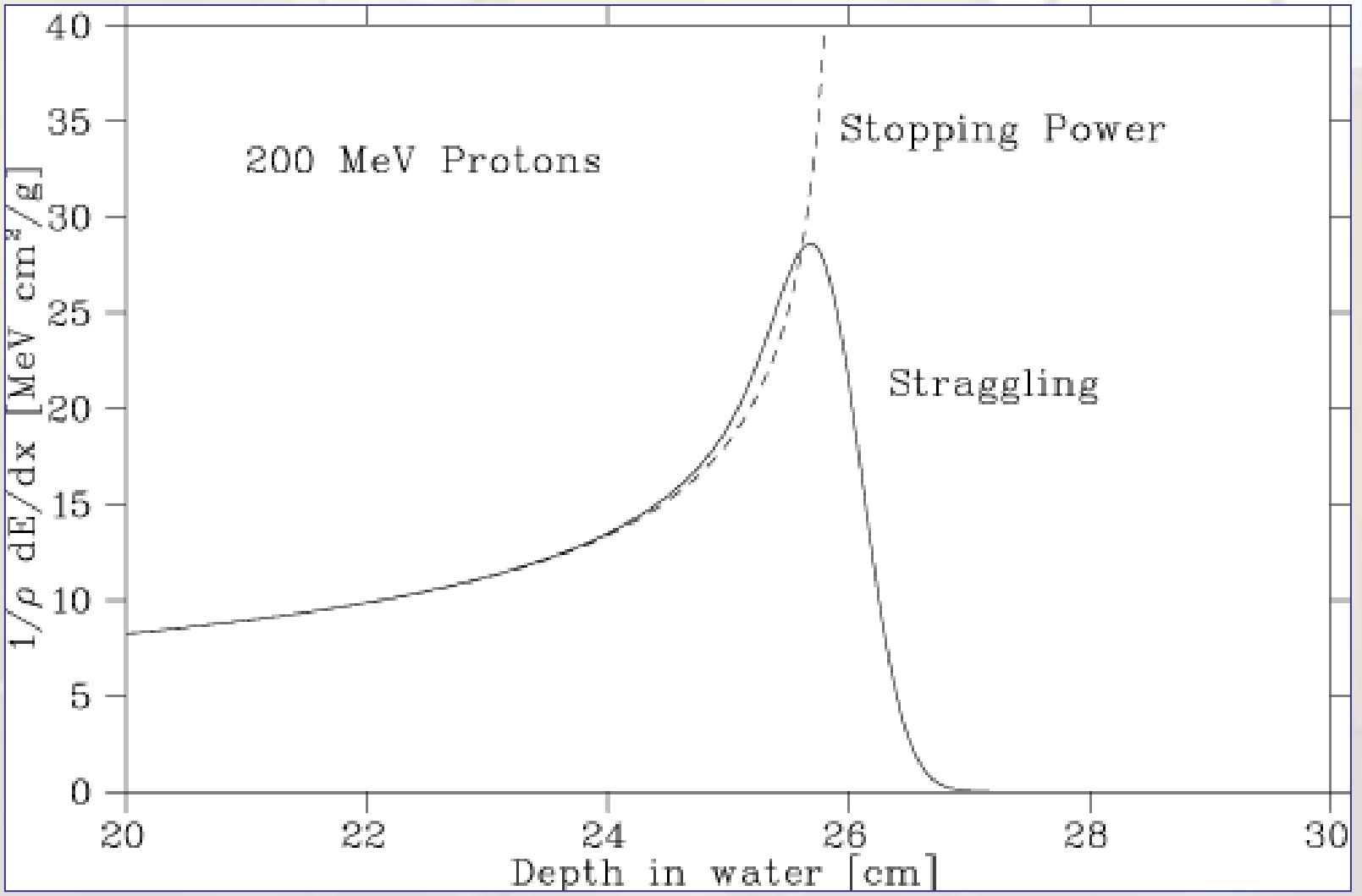
DEPTH DISTRIBUTIONS OF RBE_S (V79 CELLS) FOR LIGHT ION BEAMS

(is Carbon-12 the best ion for hadron radiotherapy?)



RBE_S- depth dependences of V79 cells over the last 1 cm of residual ion ranges, for ligh ion beams of range 26 cm, delivering an entrance dose of 1 Gy. Aerobic V79 cells are represented by parameters fitted to the data of Furusawa *et al.* (2000)

Protons – Bragg peak or Straggling ?

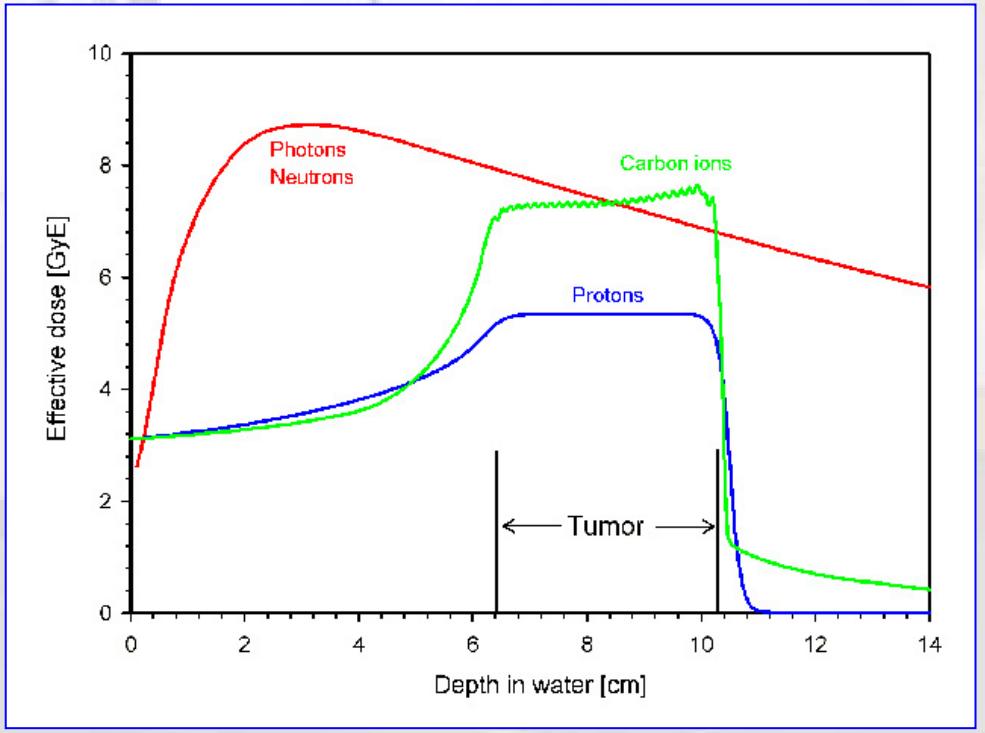


Elements of a Hadron Radiotherapy Installation

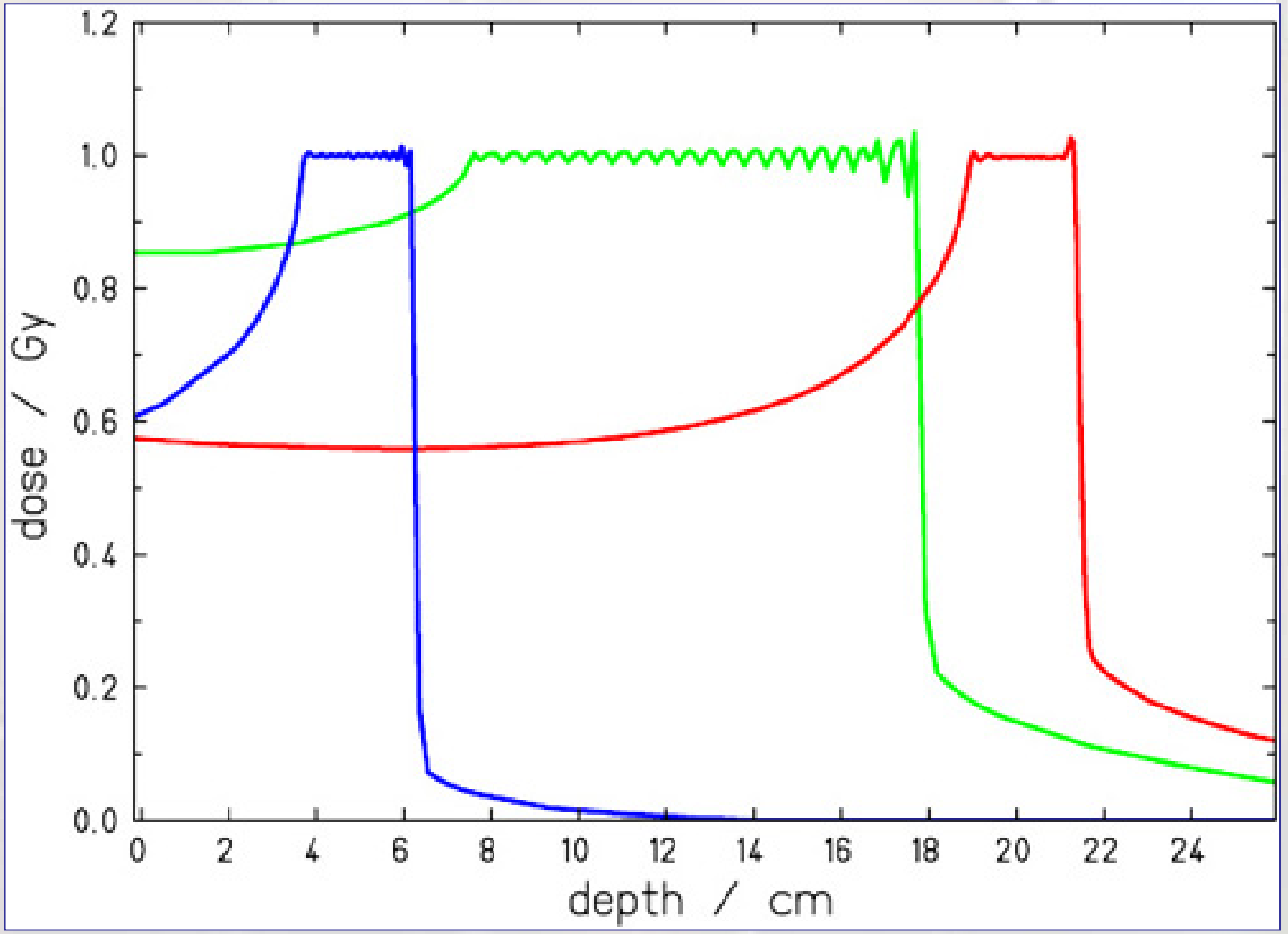
- accelerator (H, C, 250 MeV/u, variable energy, beam sweeping?)
- beam transport system
- Gantry (isocentric patient irradiation)
- PET imaging

Spread-out Bragg peak (SOBP)

- „passive” method
- „active” method



Spreading out the Bragg peak using absorption filters



Spreading out the Bragg peak using absorption filters

Figure 3-2 Ridge Filter

Figure 3-3 Bolus

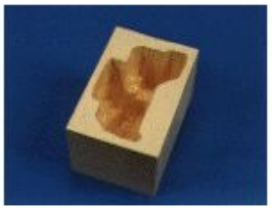
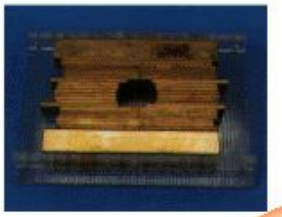
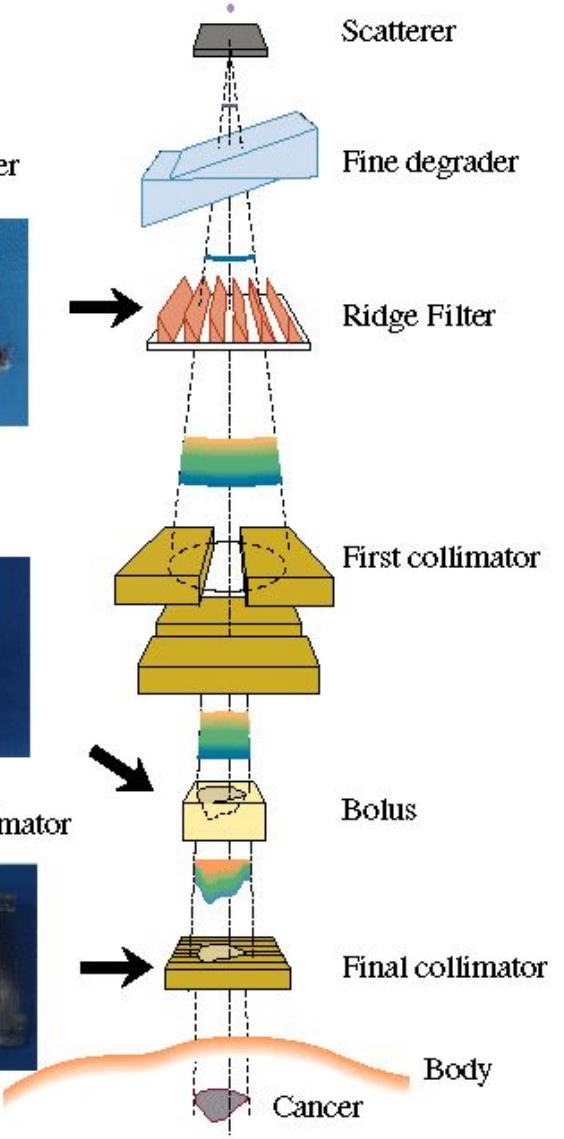
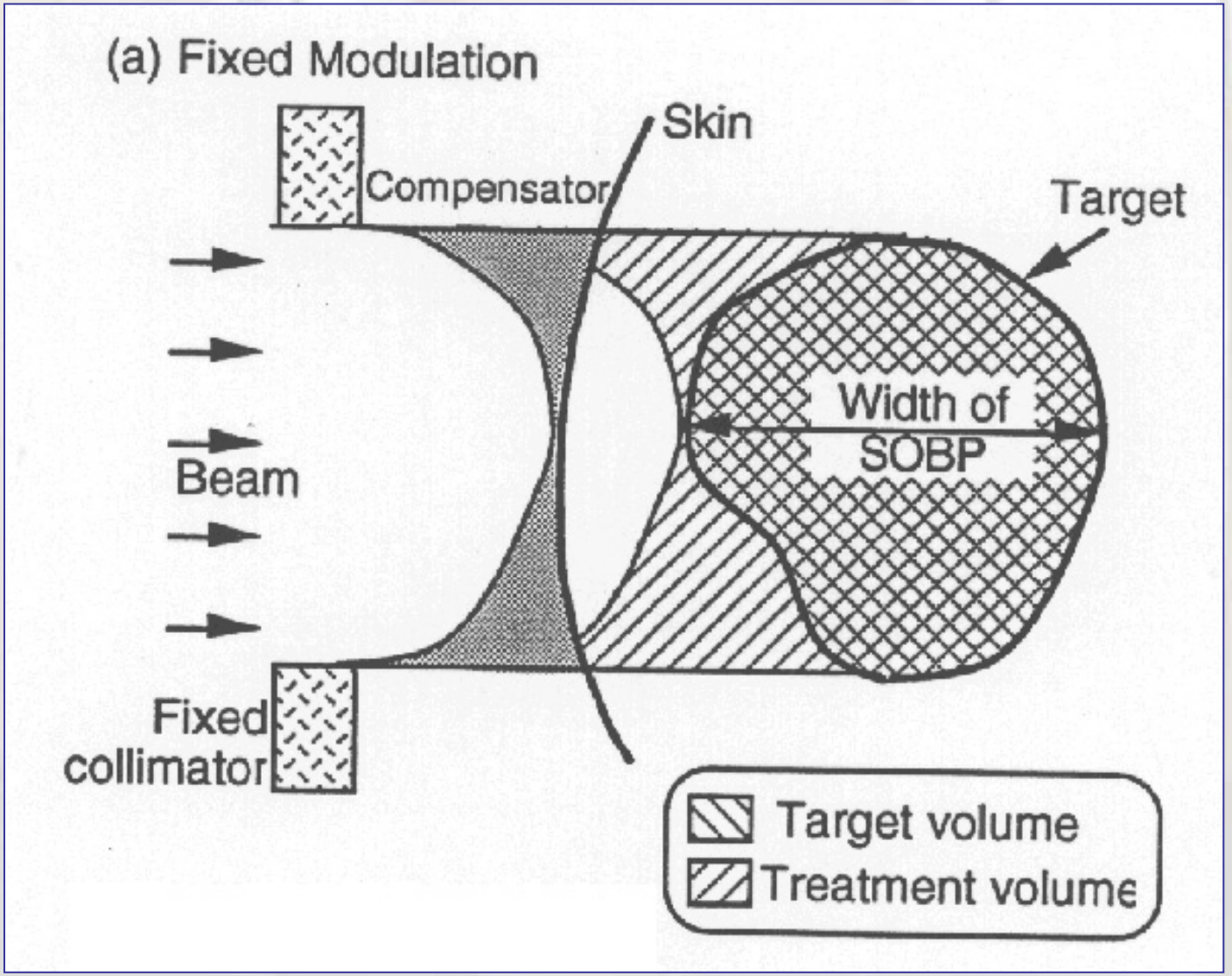


Figure 3-4 Final collimator

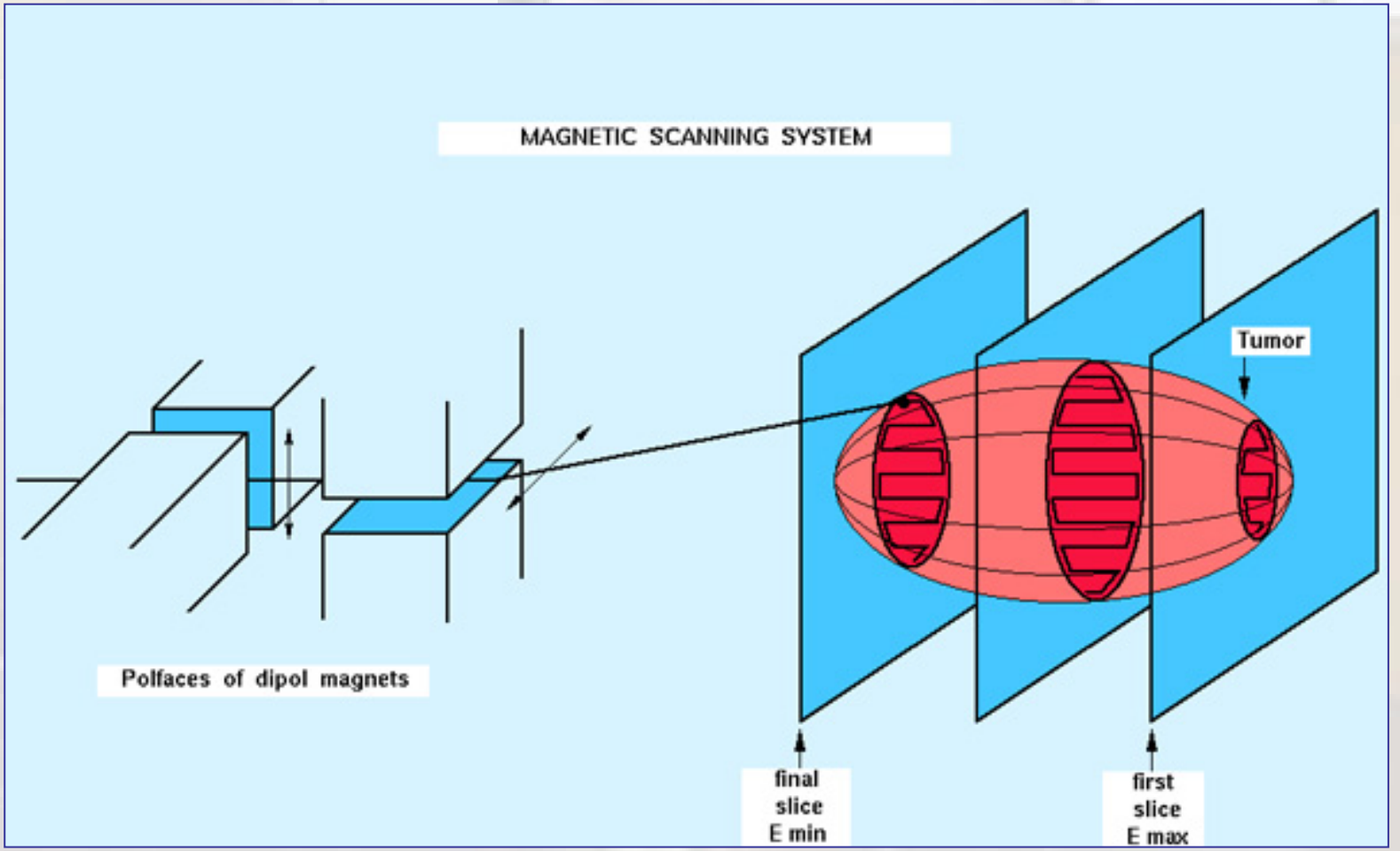




Compensation Filters (detail)

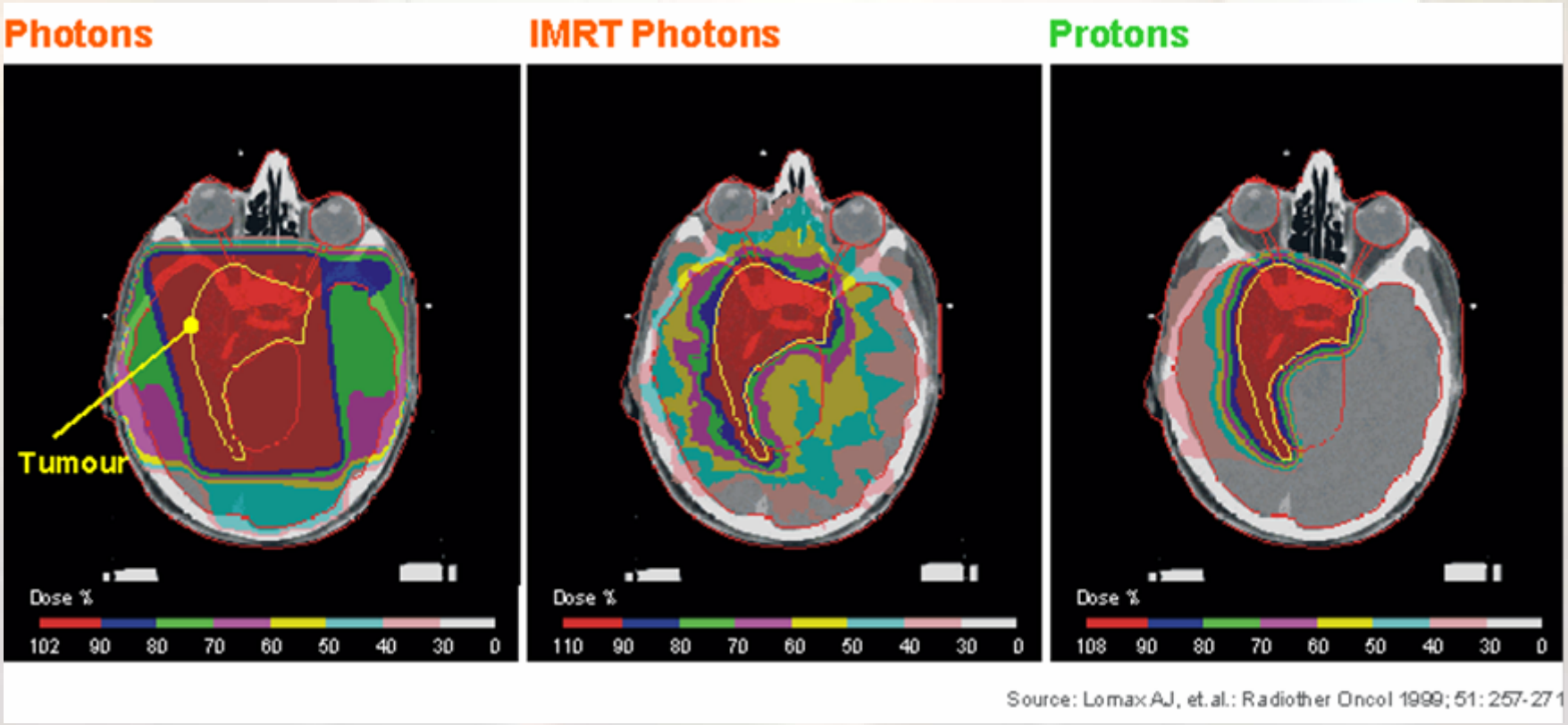


Principle of the Active Beam (GSI Darmstadt)



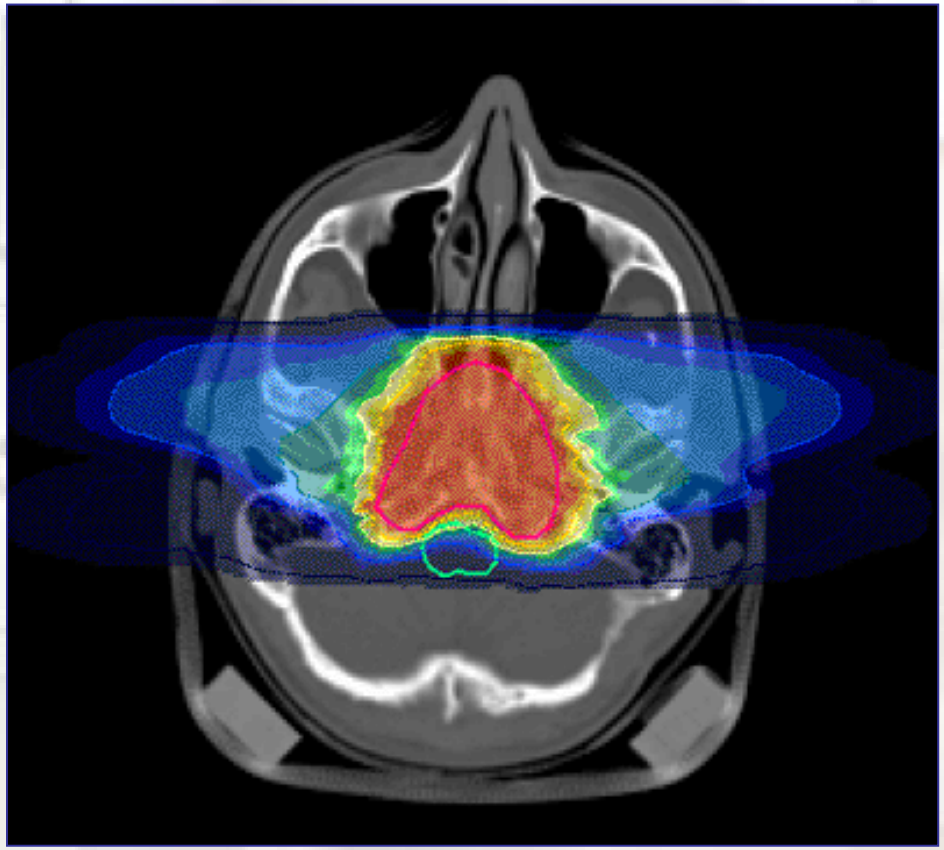
Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy
A multimedia introduction to methods and techniques,
Springer Electronic Media http://www.springer.de

Comparison of treatment techniques



Source: Lomax AJ, et.al.: Radiother Oncol 1999; 51: 257-271

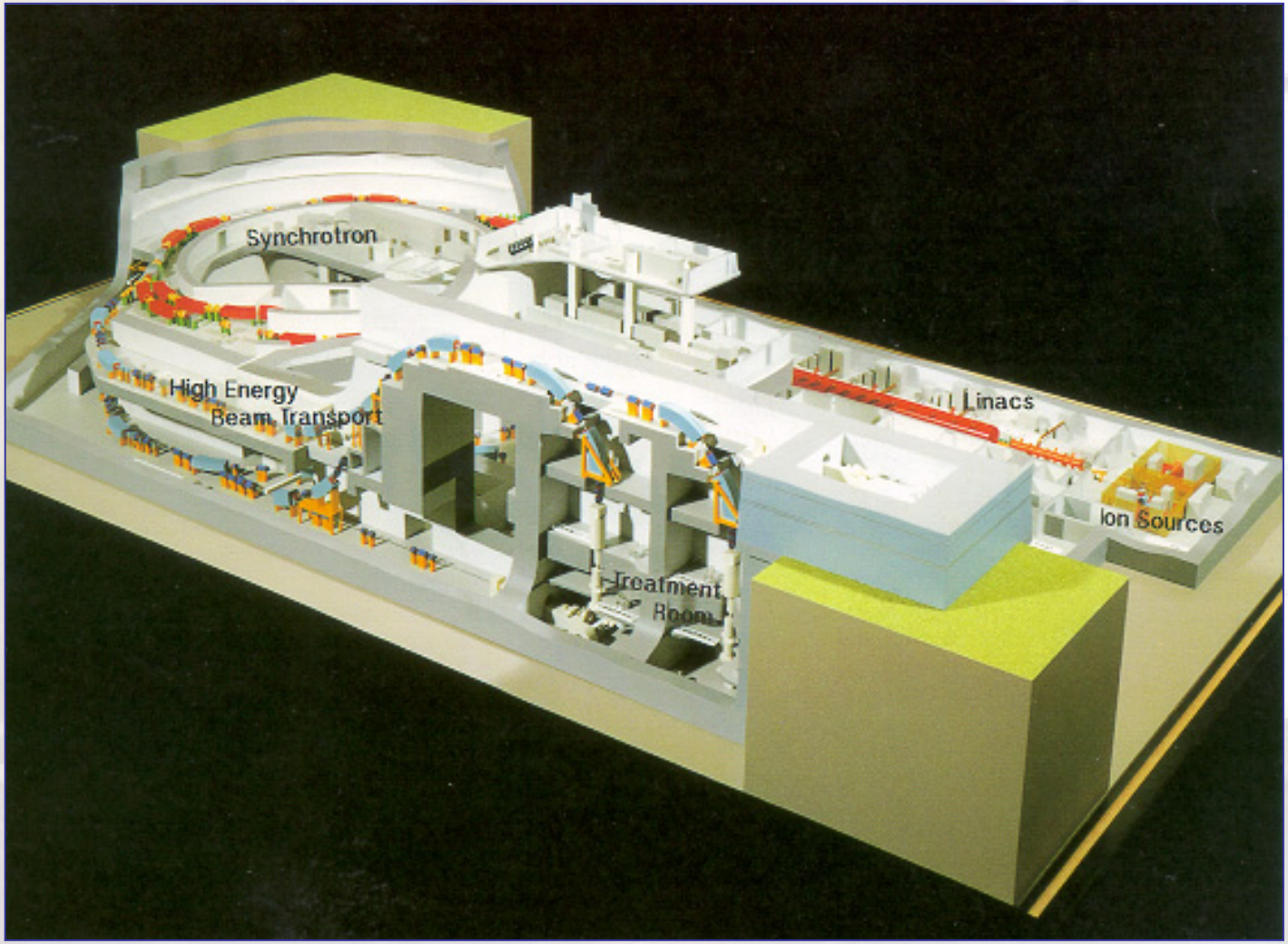
Distribution of „biological dose”or distribution of survival?

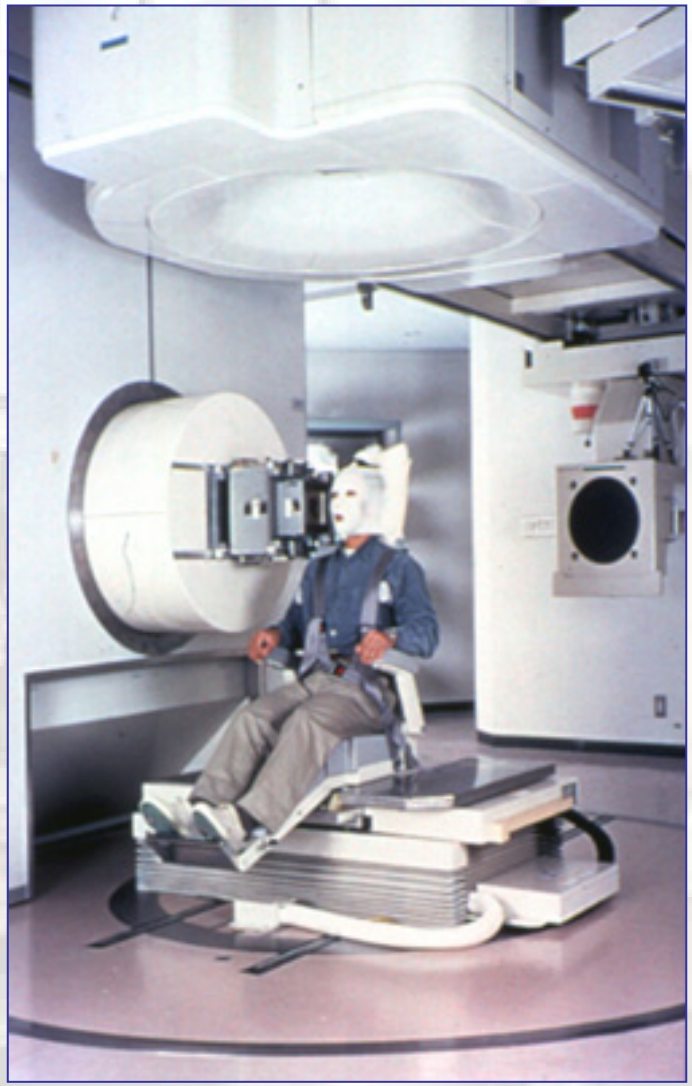


Source: W. Schlegel & A. Mahr, Eds. 3D Conformal Radiation Therapy A multimedia introduction to methods and techniques, Springer Electronic Media http://www.springer.de

Transversal cuts through the biologically effective dose distribution planned for a medial tumor of the base of the skull using two nearly opposing fields. Dose values in this color-wash presentations are: dark gray > 0.1% to < 10%; blue < 50%, green < 60%, yellow < 80%, dark yellow < 90%, red >= 90%. The PTV is indicated by red contours, the OARs by yellow (optical chiasm) and green (brain stem, myelon) contours (GSI Darmstadt).

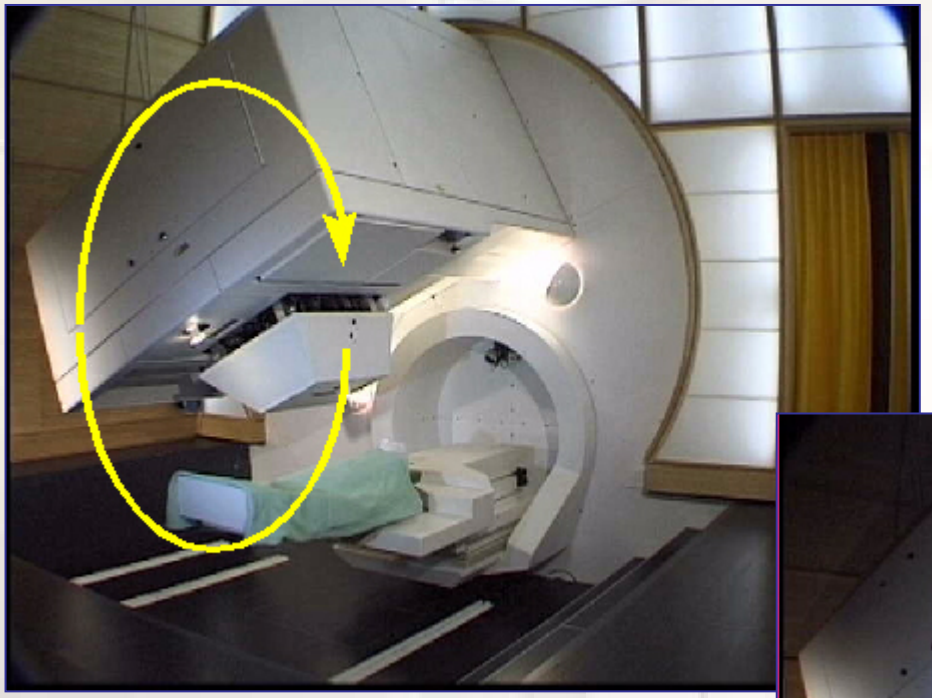
HIMAC – NIRS, Japan

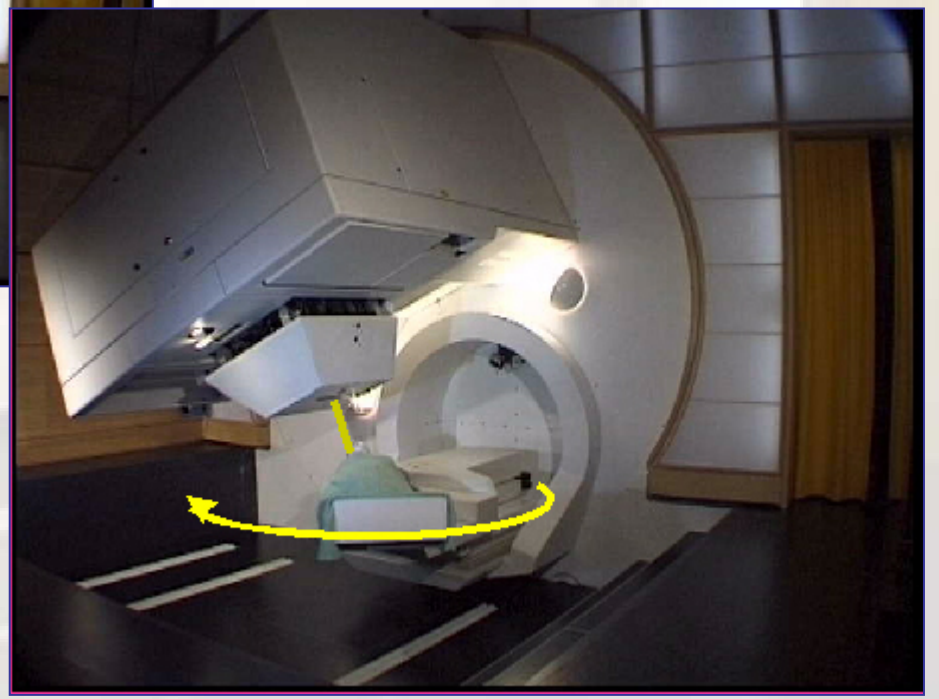




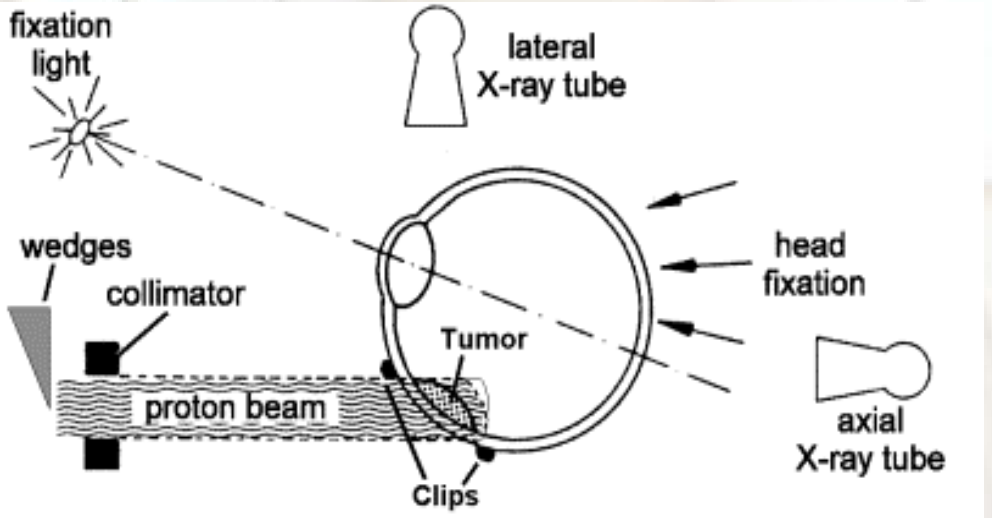
Patient chair and X-ray computer tomograph for CTs in seated position at HIMAC

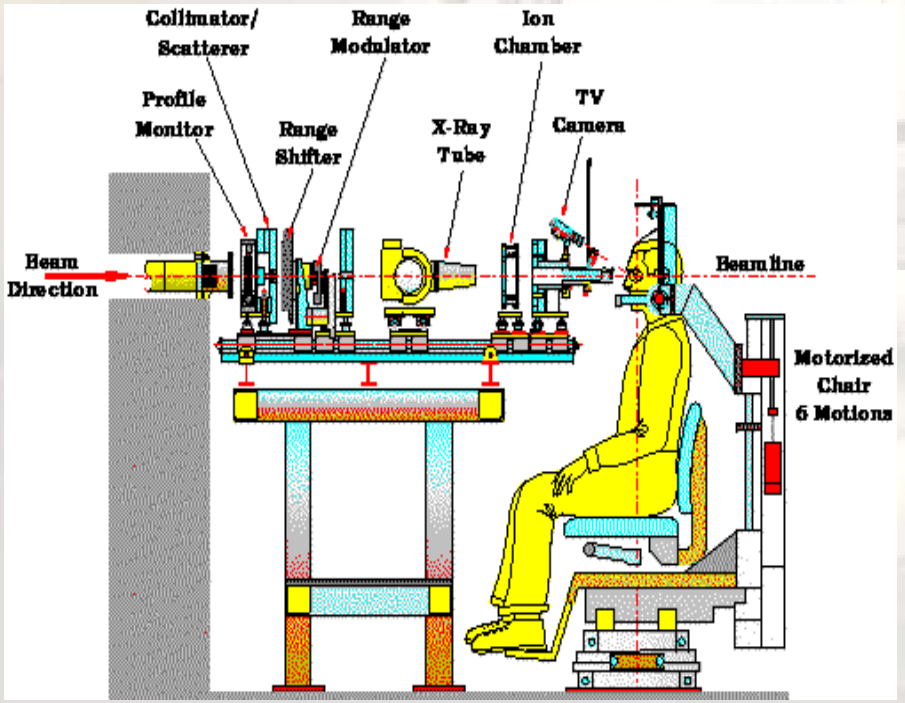
Gantry (PSI Villigen)



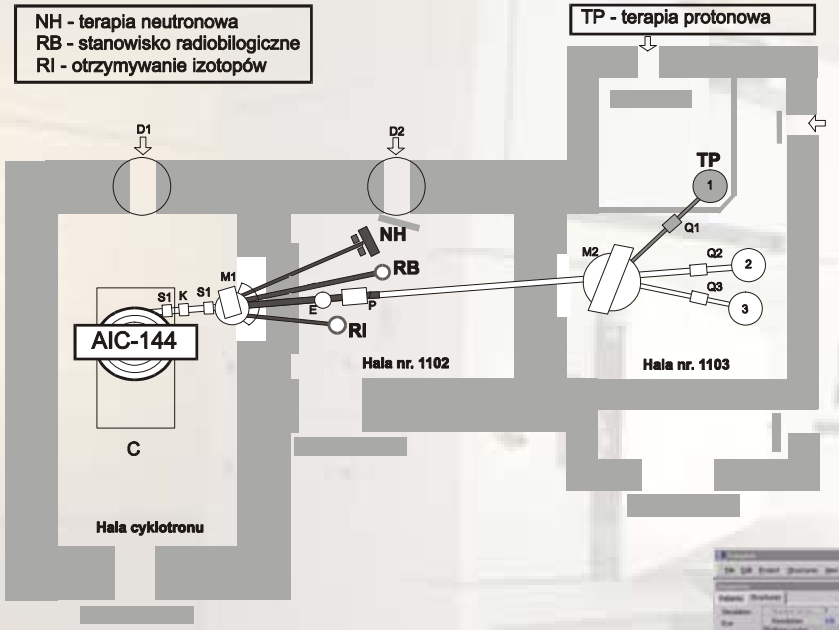


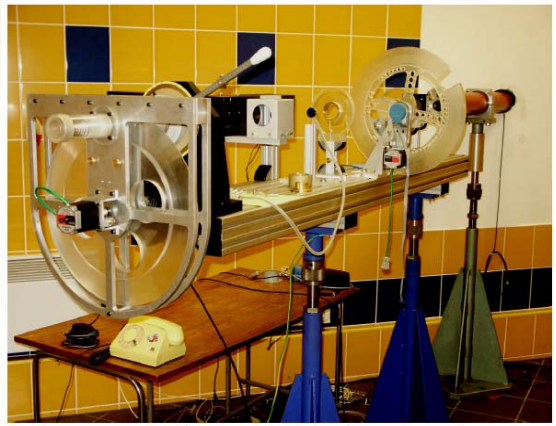
Proton radiotherapy of eye melanoma





THE PROTON RADIOTHERAPY OF EYE MELANOMA PROJECT
at the Institute of Nuclear Physics (IFJ PAN) in Krakow

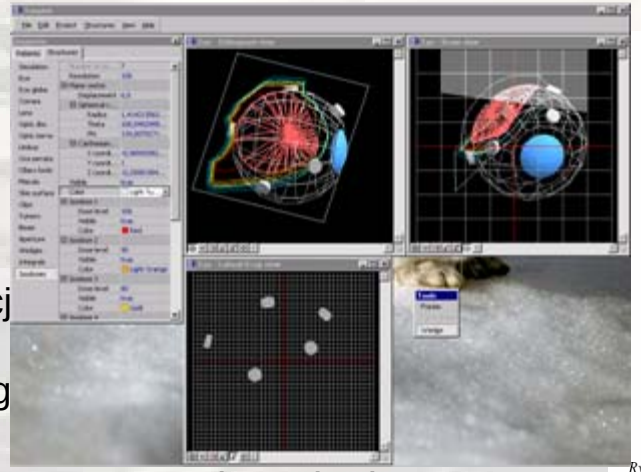




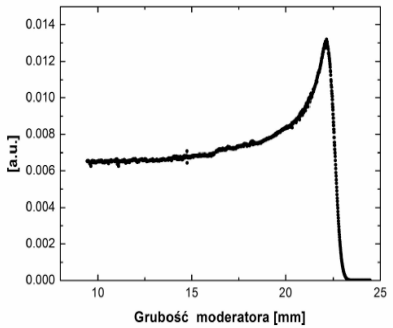
Rys.3 Oprzyrządowana ława optyczna zainstalowana w pomieszczeniu radioterapii protonowej w IFJ PAN Kraków. Widoczne są elementy układu formowania i monitorowania wiązki protonowej, układu podglądu położenia oka, układu pozycjonowania oka oraz układu do pomiaru rozkładu dawki w obszarze piku Bragga.

Milestones (June 2006):

- 55 MeV beam extracted
- decision to fund project positive inwestycj
- beam measurements (Bragg peak)
- initial measurements of spread-out Bragg peak (SOBP)
- beam control electronics assembled



EYEPLAN-PC thrapy planning program (AGH+IFJ) (VARIAN-Eclipse)



Bragg peak at IFJ

Rys.4 Rozkład dawki wiązki protonów o energii nominalnej 55 MeV na różnych głębokościach w pleksiglasie (PMMA) zarejestrowany na stanowisku pomiarowym w pomieszczeniu radioterapii IFJ PAN Kraków. Widoczny jest charakterystyczny kształt tzw. krzywej Bragga dla niemodulowanej wiązki protonów.

THE ENLIGHT PROJECT

European **N**etwork for Research in **Light**-Ion Radiotherapy

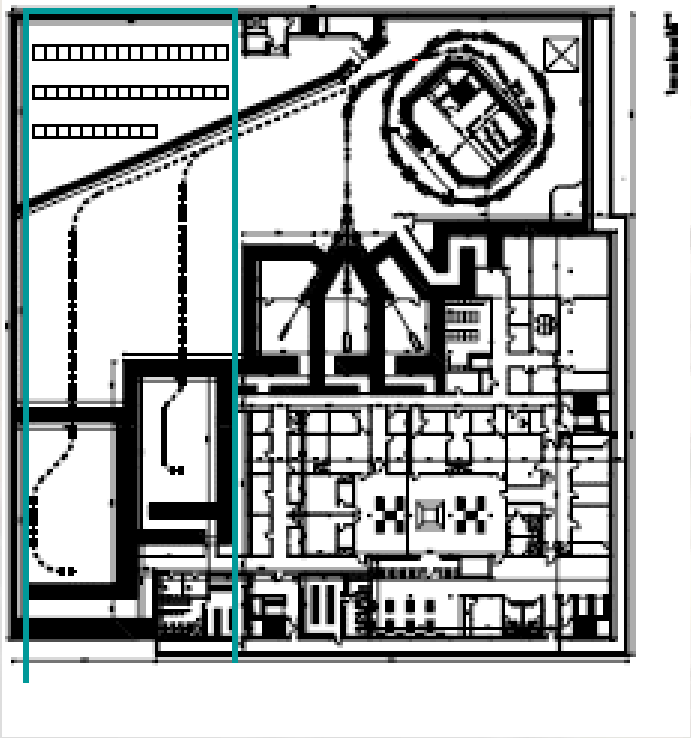
Network began within the 5th EU Framework Programme, with the following members:

ESTRO (**E**uropean **S**ociety for **T**herapeutic **R**adiology and **O**ncology)
EORTC (**E**uropean **O**rganisation for **R**esearch in the **T**reatment of **C**ancer)
ETOILE (**E**space de **T**raitement **O**ncologique par **i**ons **L**egers – **Lyon** (France)
Karolinska Institutet – **Stockholm** (Sweden)
GHIP (**G**erman **H**eavy-**I**on **P**roject) GSI-Darmstadt & **Heidelberg University** (Germany)
Virgen Hospital – Macarena (Spain)
MED-AUSTRON – Wiener Neustadt (Austria)
TERA Foundation – **Milan** (Italy)
CERN – Geneve (Switzerland)

WILL WE HAVE A HADRON RADIOTHERAPY FACILITY IN POLAND?

ENLIGHT and the European projects

- GSI project for the University of Heidelberg Clinics
- TERA project for CNAO in Pavia
- Med-Austron for Wiener Neustadt (partner of PIMMS since 1996)
- ETOILE in Lyon
- Nordic Centre in Stockholm



Modular PIMMS accelerator (CERN) for European ENLIGHT hadron RT installations