Outline

1. Introduction: a historical overview
2. Modern medical diagnostics
3. Particle accelerators for medicine
4. Conventional radiation therapy
    1. Basics of radiation biophysics
    2. Techniques in X-ray therapy
5. Basic principles of hadrontherpy
6. Present and future of hadrontherapy
7. A tour in a hadrontherapy centre
8. Specific topics in hadrontherapy

Dose Unit

***Gray (Gy)*:**

Absorbed energy in *Joule (J)* per *Kg* of tissue.

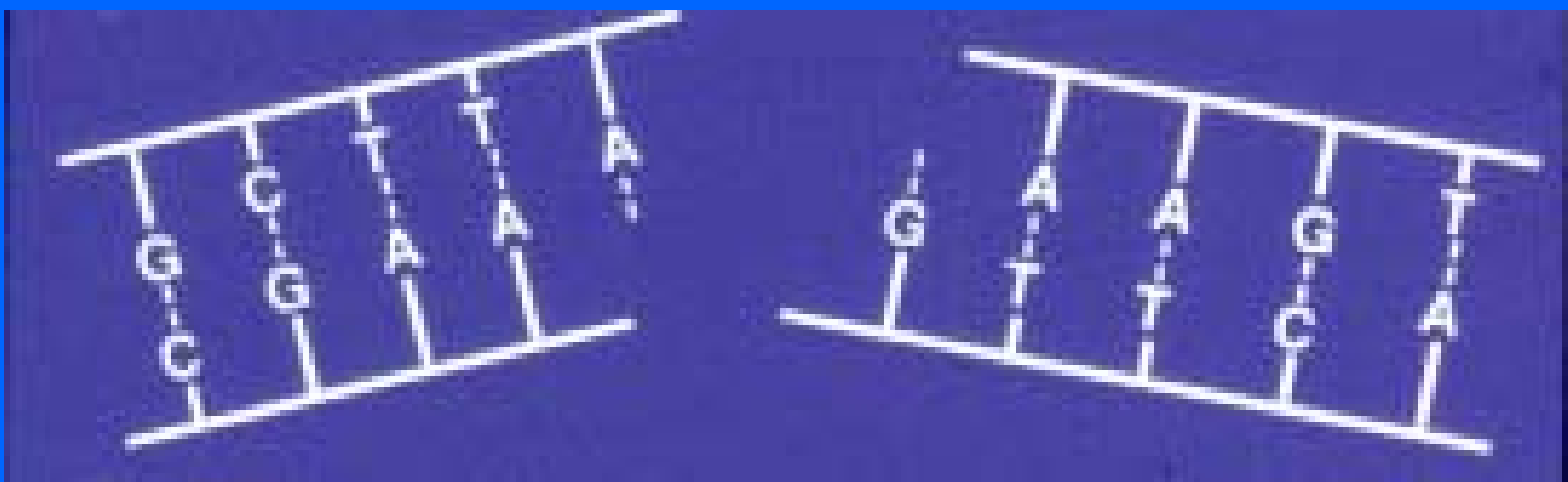
Standard Dose Parameters

- *Standard fractionation:*
  1.8-2 Gy/fraction; 1x day; 5 days/week.

- *Total dose:*

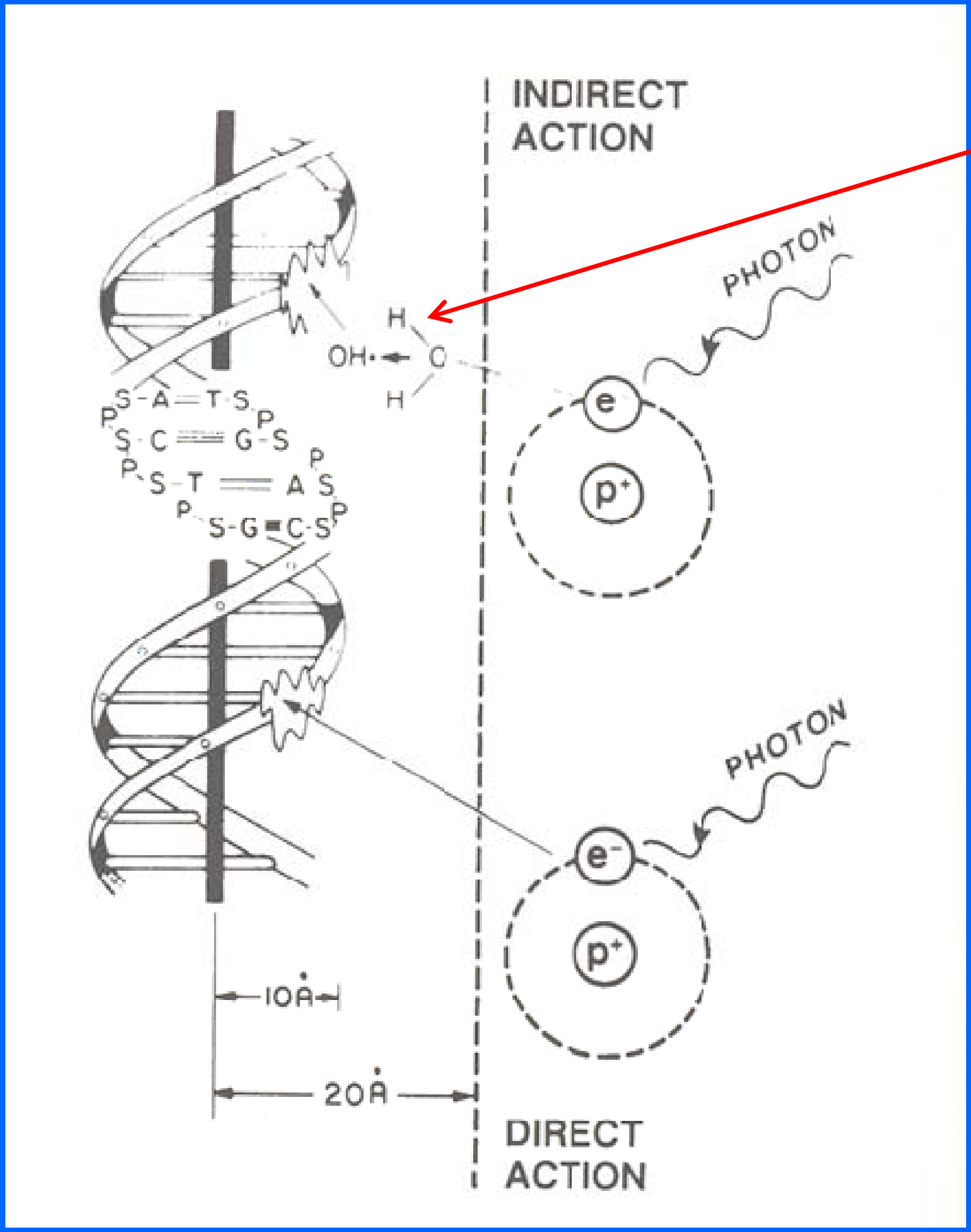
low	(20-30 Gy):	seminoma, lymphoma,...
medium	(45-55 Gy):	subclinical disease,...
high	(65-80 Gy):	prostate, sarcoma,...

Effect of radiation on cells



DNA multiple breaks trigger cell death

Direct and indirect actions of radiation



Free radicals

Effect of radiation on tissues

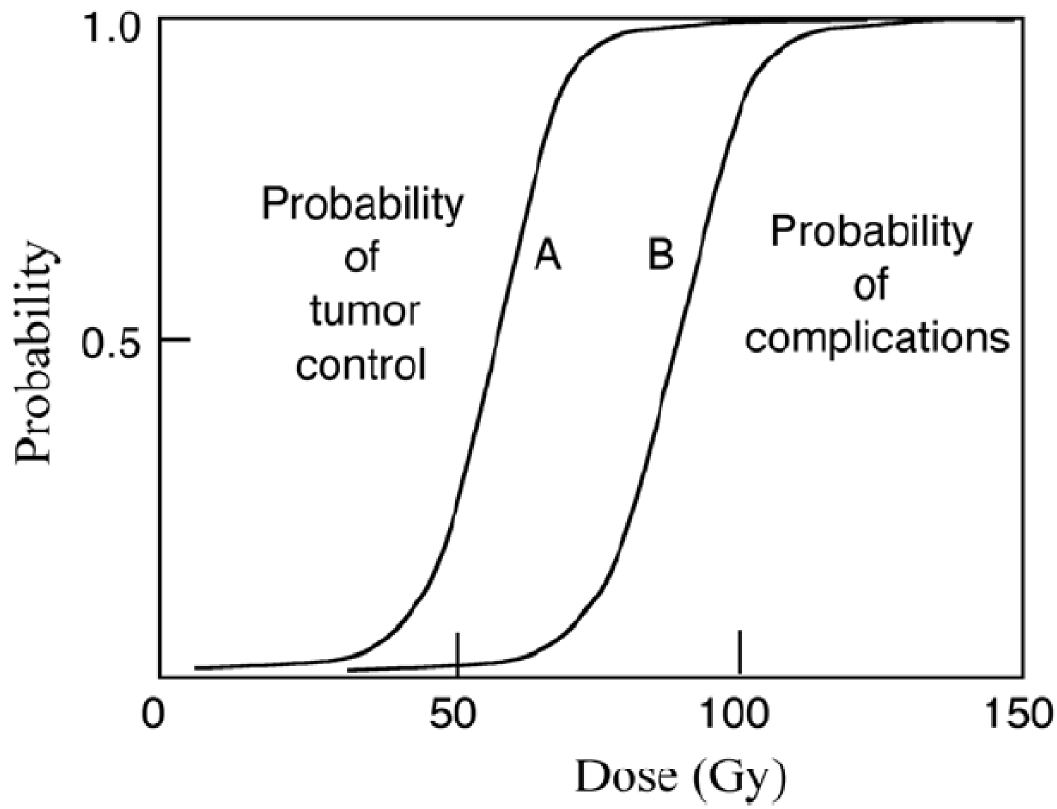


FIG. 14.4. The principle of therapeutic ratio. Curve (A) represents the tumour control probability, curve (B) the probability of complications. The total dose is delivered in 2 Gy fractions.

Sigmoids → small increase of dose may correspond to large increase of control!

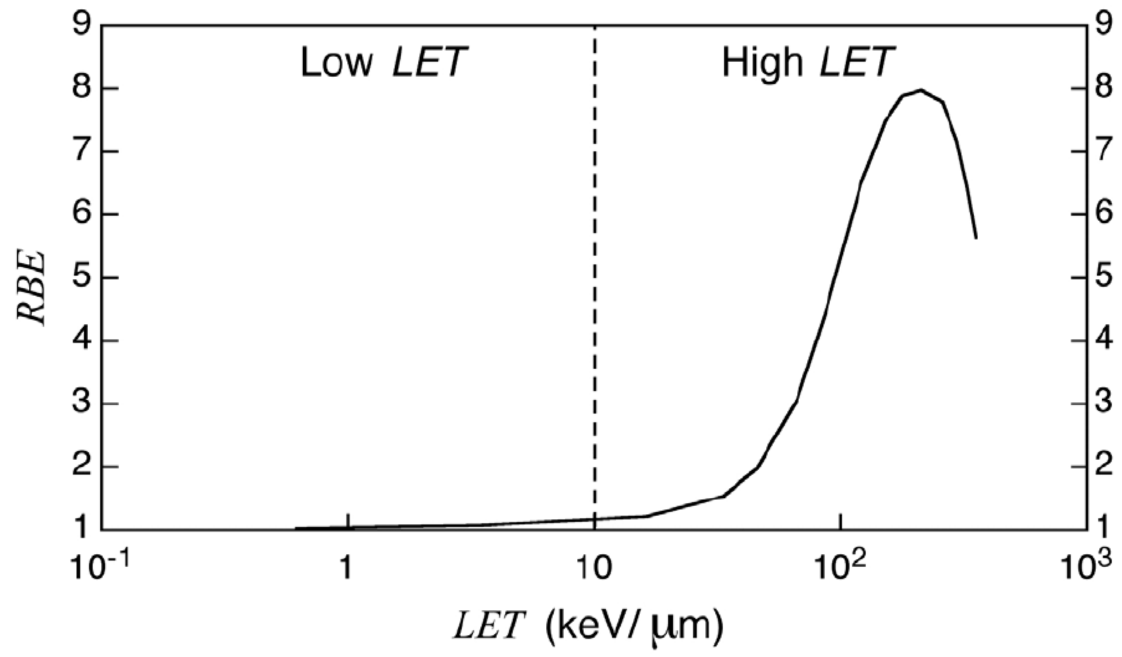
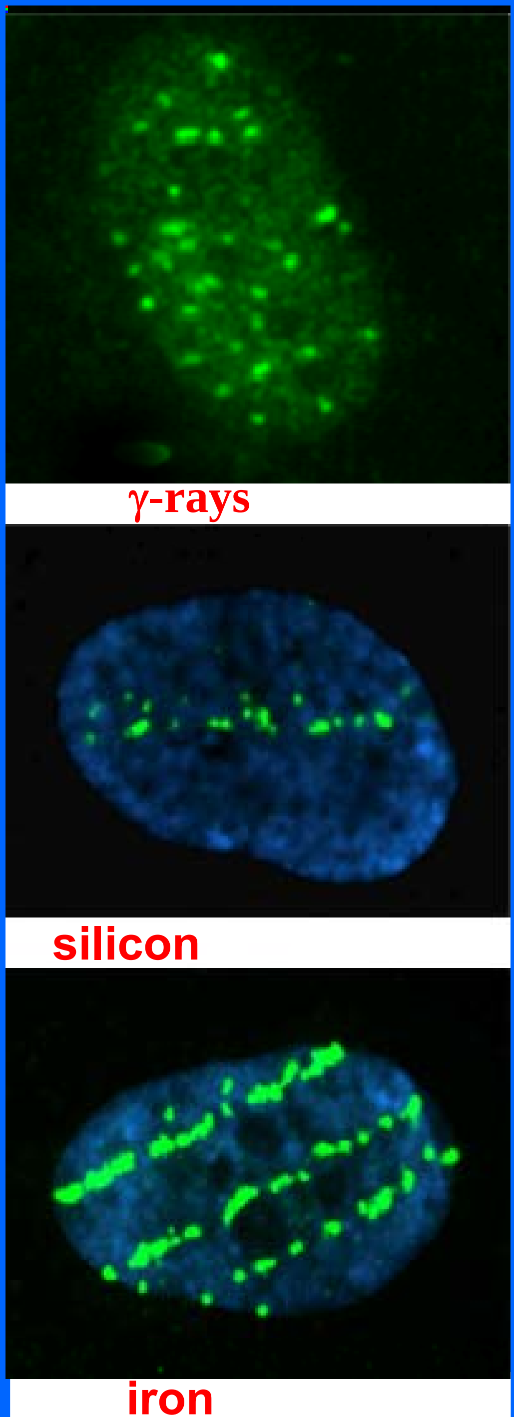


FIG. 14.7. Relative biological effectiveness (RBE) against LET. The vertical dashed line separates the low LET region where RBE ≈ 1 from the high LET region where RBE first rises with LET, reaches a peak of about 8 for LET ≈ 200 keV/µm and then drops with a further increase in LET.

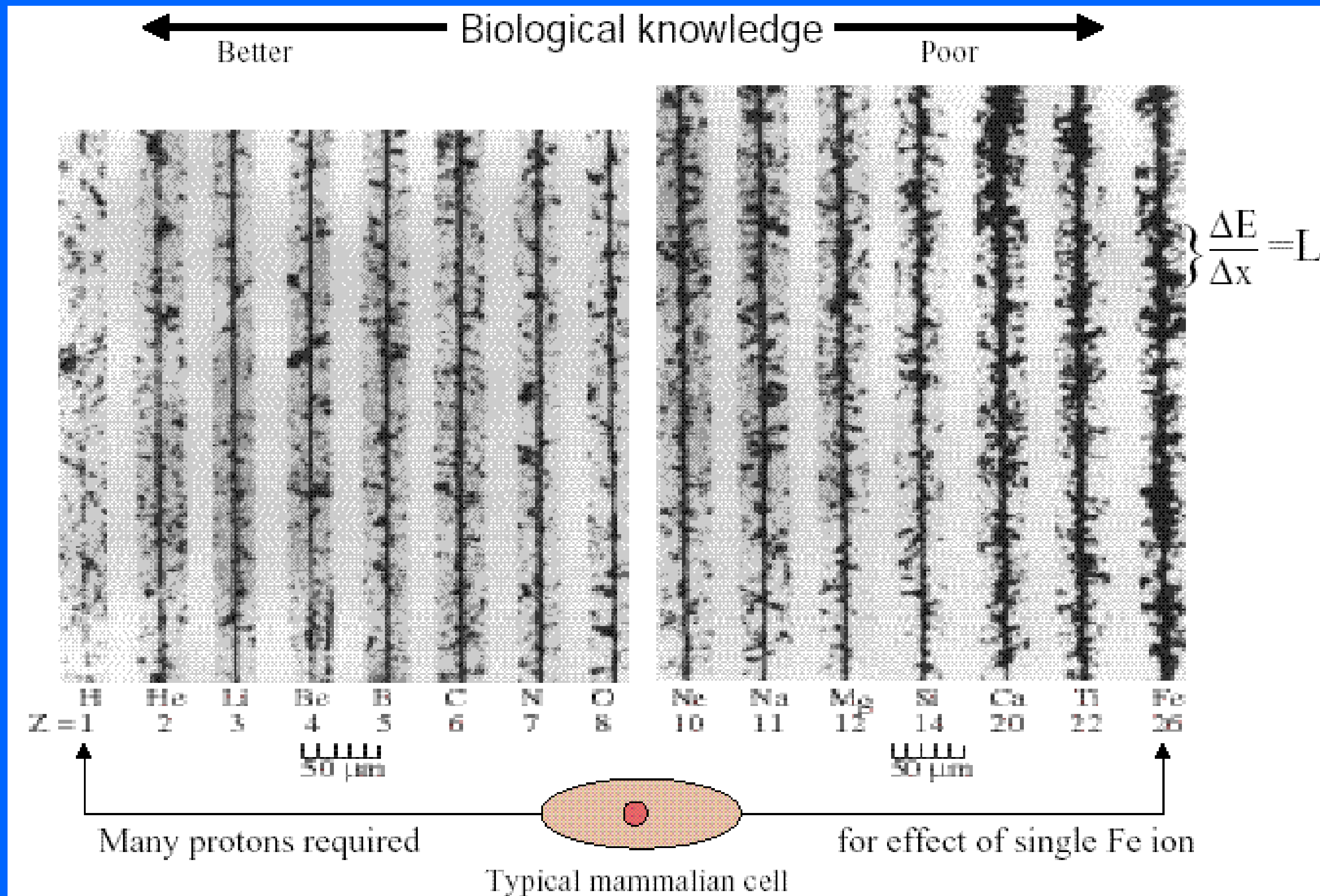
- **LET – Linear energy transfer measured in keV/µm or eV/nm**

- **DNA ~ 3 nm**
- **Ionization W ~ 10-20 eV**
- **High LET = ionizations inside DNA → Direct action**

- **RBE – Relative Biological Effectivness with respect to X-rays (RBE =1 by definition)**



DNA visualized by immuno - fluorescence of γ-H2AX histone in human skin fibroblasts exposed to 2 Gy of ionizing radiation



Cucinotta and Durante, Lancet Oncol. 2006

Nuclear emulsions

The oxigen effect and OER

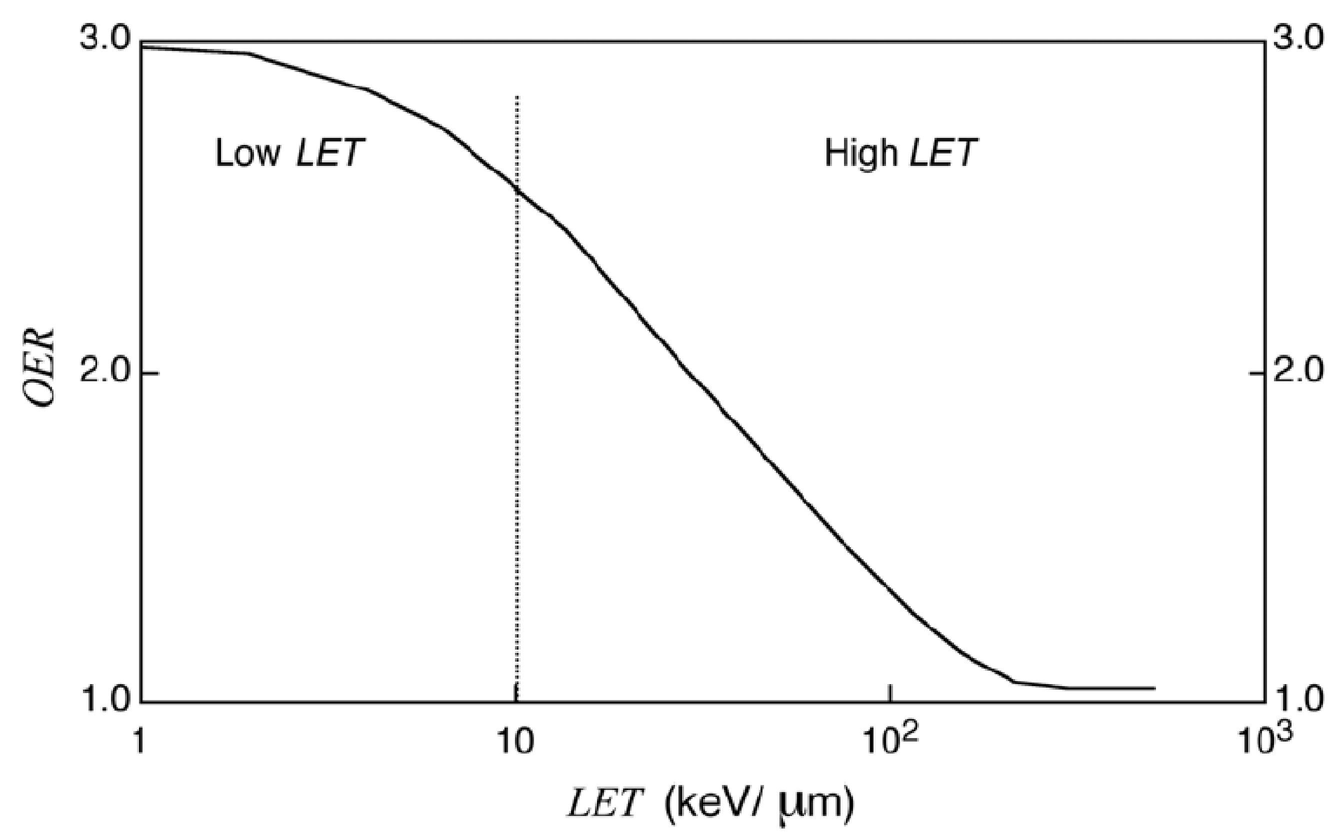
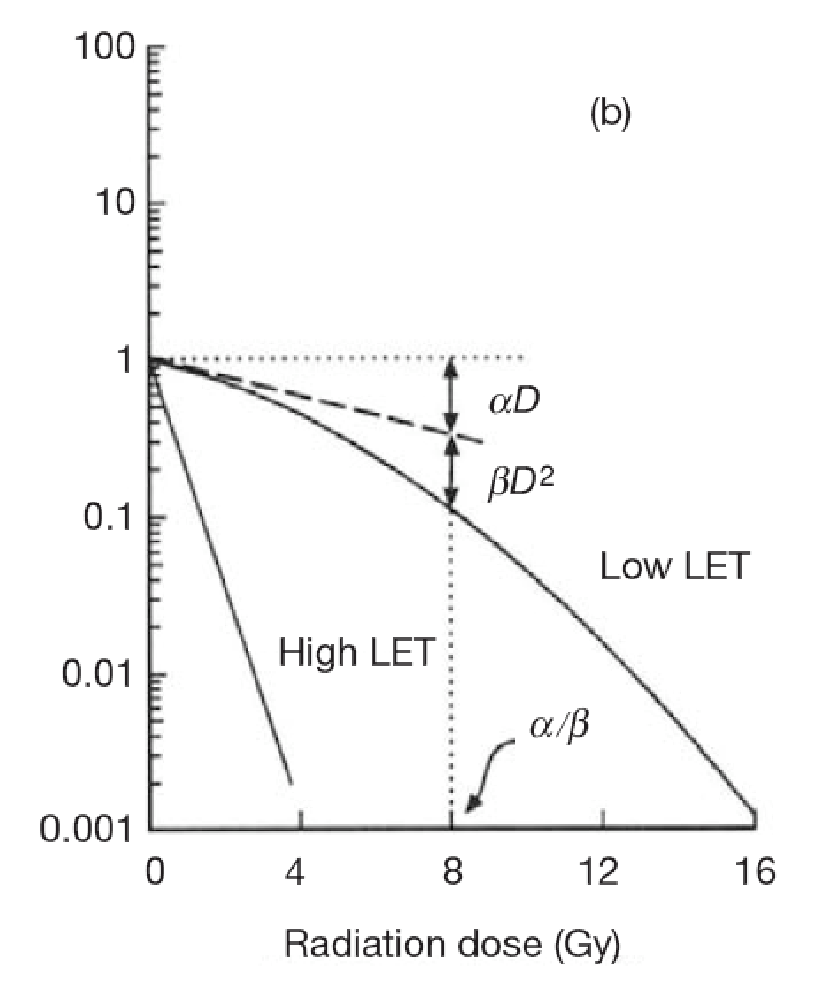


FIG. 14.6. Oxygen enhancement ratio (OER) against LET. The vertical dashed line separates the low LET region where LET <10 µm from the high LET region where LET > 10 µm.

- **OER – Oxygen Enhancement Ratio – Low LET radiations are sensitive to oxygen (formation of free radicals)**

Survival curves



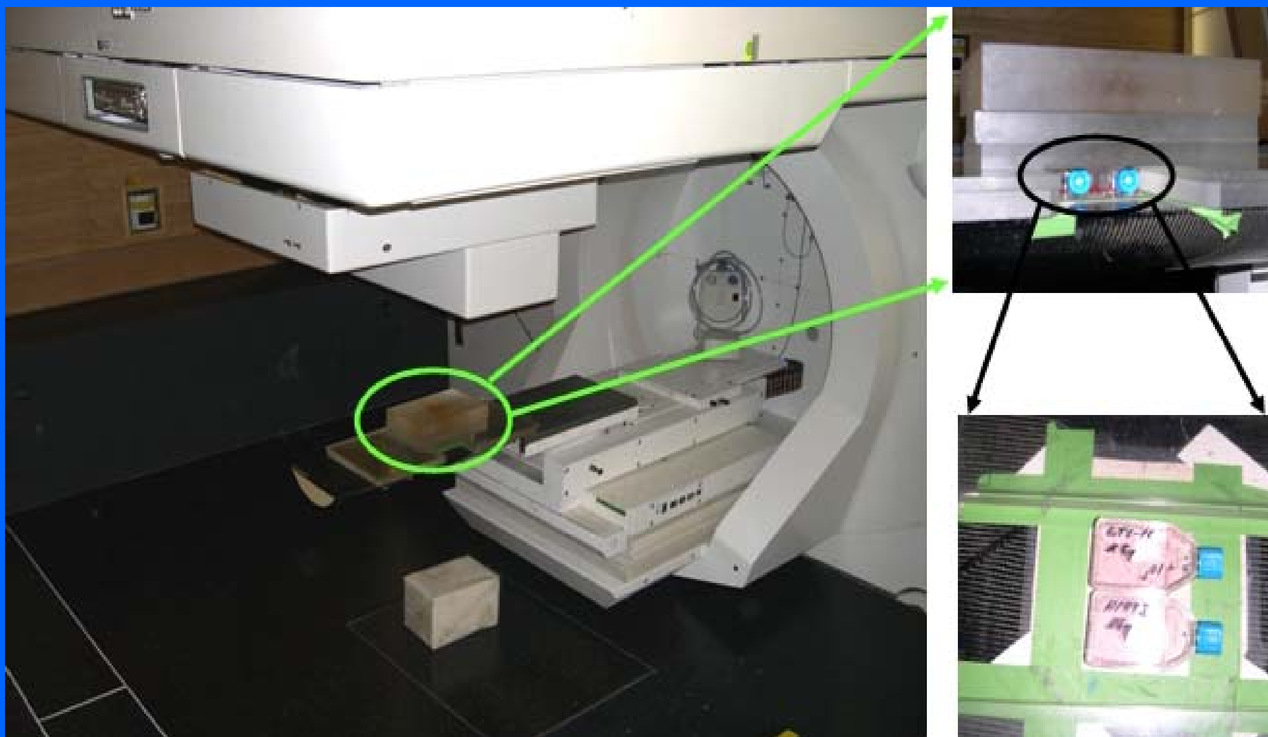
$$S(D) = e^{-\alpha D - \beta D^2}$$

$S(D)$ is the fraction of cells surviving a dose D;
α is a constant describing the initial slope of the cell survival curve;
β is a smaller constant describing the quadratic component of cell killing.

- **Example: α=0.25; $\beta \approx 0$ for a certain radiation. Which is the dose that gives a survival probability of 10^{-9} ? Answer: 80 Gy**

Survival curves

• **The survival curves are obtained through very delicate counting experiments**



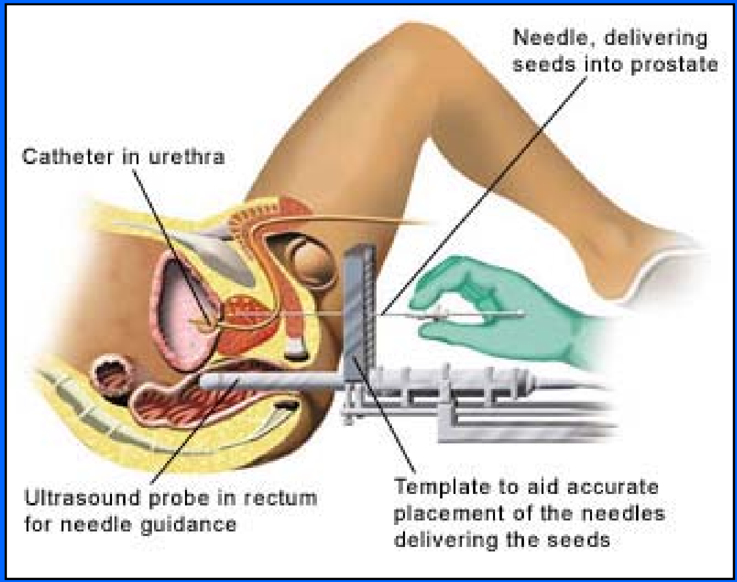
Irradiation of tumoural cells with protons at PSI by the Bern Group

After irradiation the survived cells form colonies which are fixed, colored and counted!

Fractionation

- The dose in radiation therapy is not given all at once but in several fractions mainly to
  - spare normal tissues through a repair of sub-lethal damage between dose fractions and repopulation of cells.
  - increase tumour damage through reoxygenation and redistribution of tumour cells.
- The current standard fractionation is based on 5 daily treatments per week and the total treatment time of several weeks. This regimen reflects practical aspects of dose delivery to a patient, successful outcome to patient treatments, and convenience to staff delivering the treatment.

Methods in conventional radiation therapy

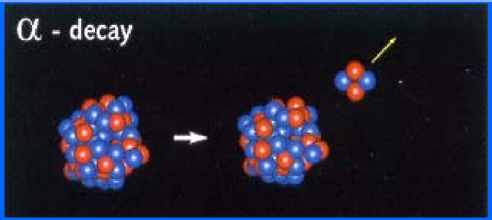


- Brachitherapy
  - Insertion of radiation sources in the body
- Teletherapy
  - Bombardment of the tumour tissues with radiation coming from outside the body of the patient
- Radio immunotherapy
  - The radiation is brought by a radioisotope attached to a specifically selective vector

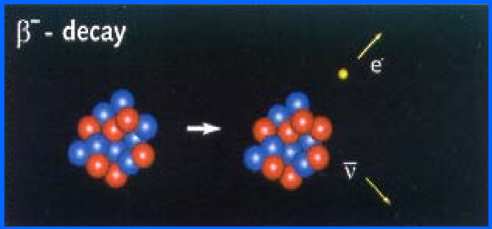
Radioactivity in cancer therapy

targeted radioimmunotherapy

α particles from Bismuth-213 for leukaemia

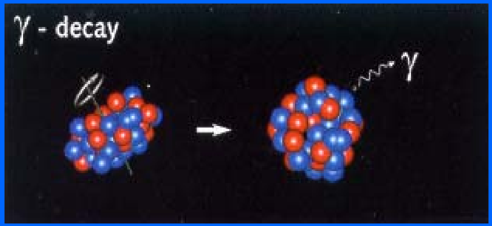


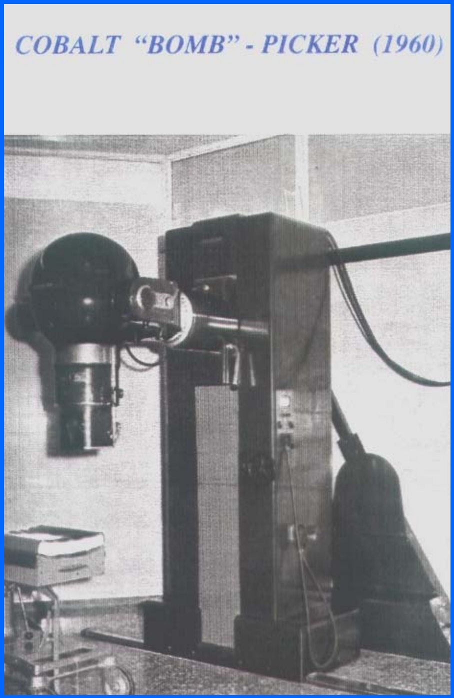
β particles from Yttrium-90 for glioblastoma



teletherapy

gammas from Cobalt-60 for deep tumours





Cobalt source 2000

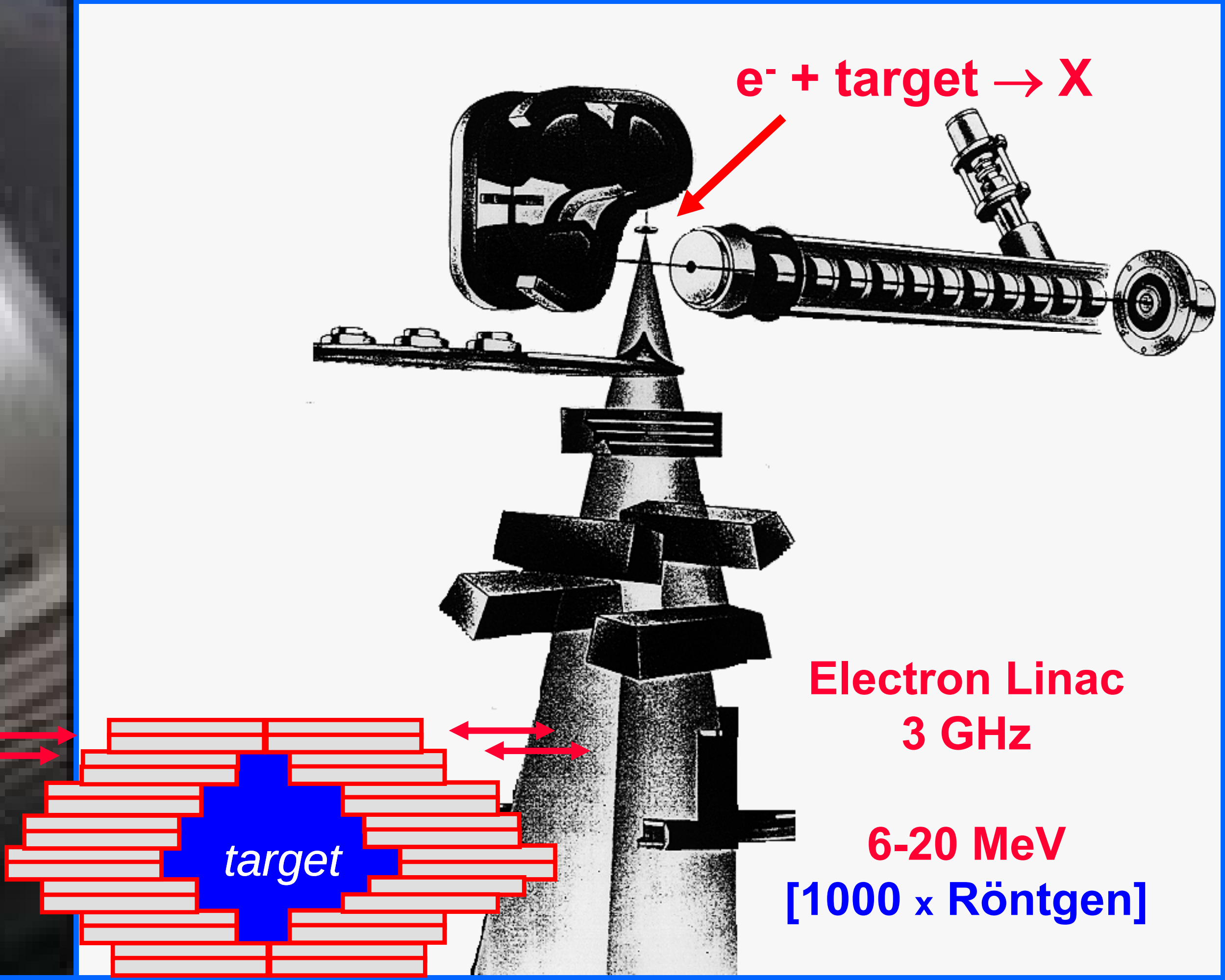
Cobalt-60

(1 MeV gammas)

is produced in reactors

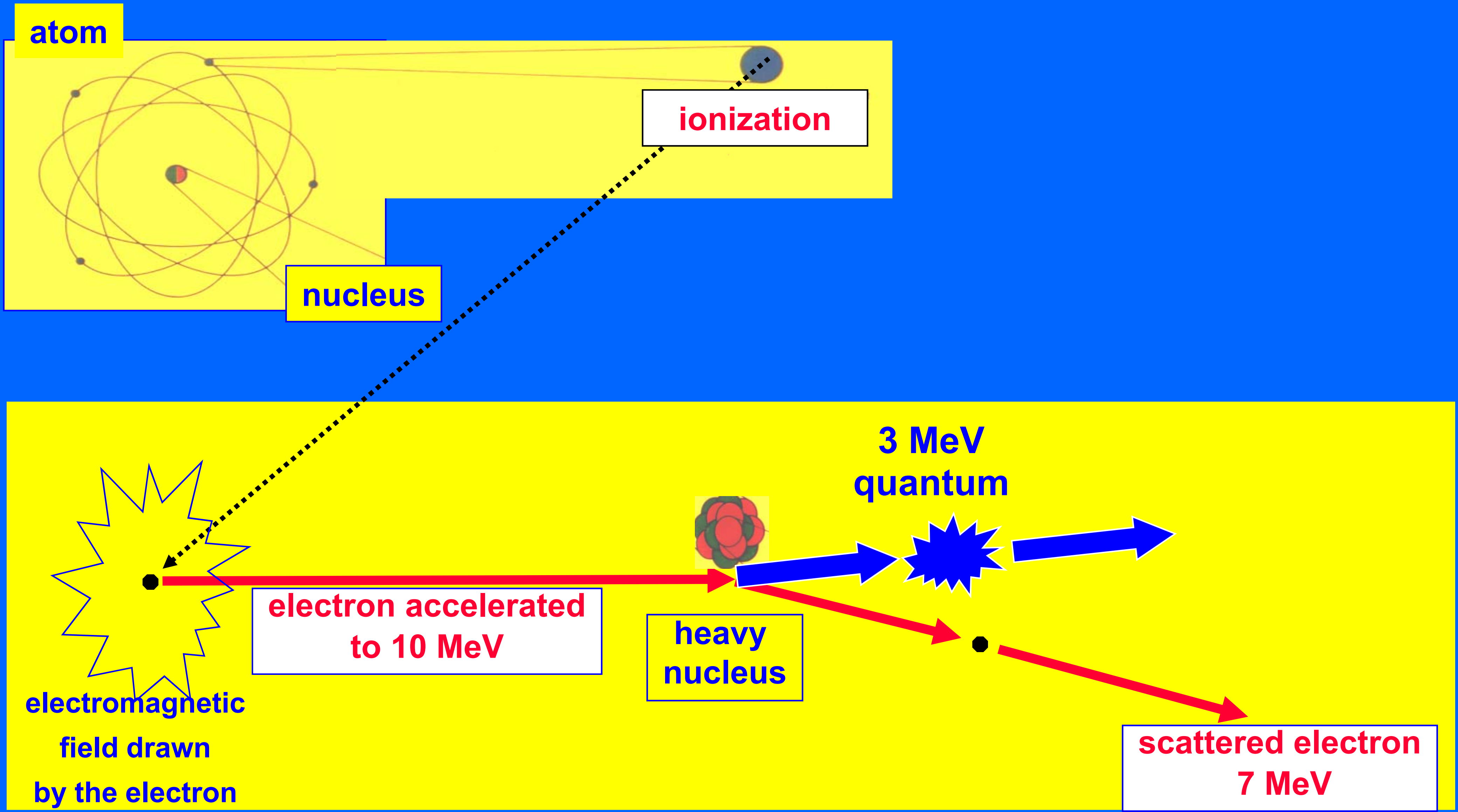
by slow neutrons

Teletherapy with X-rays

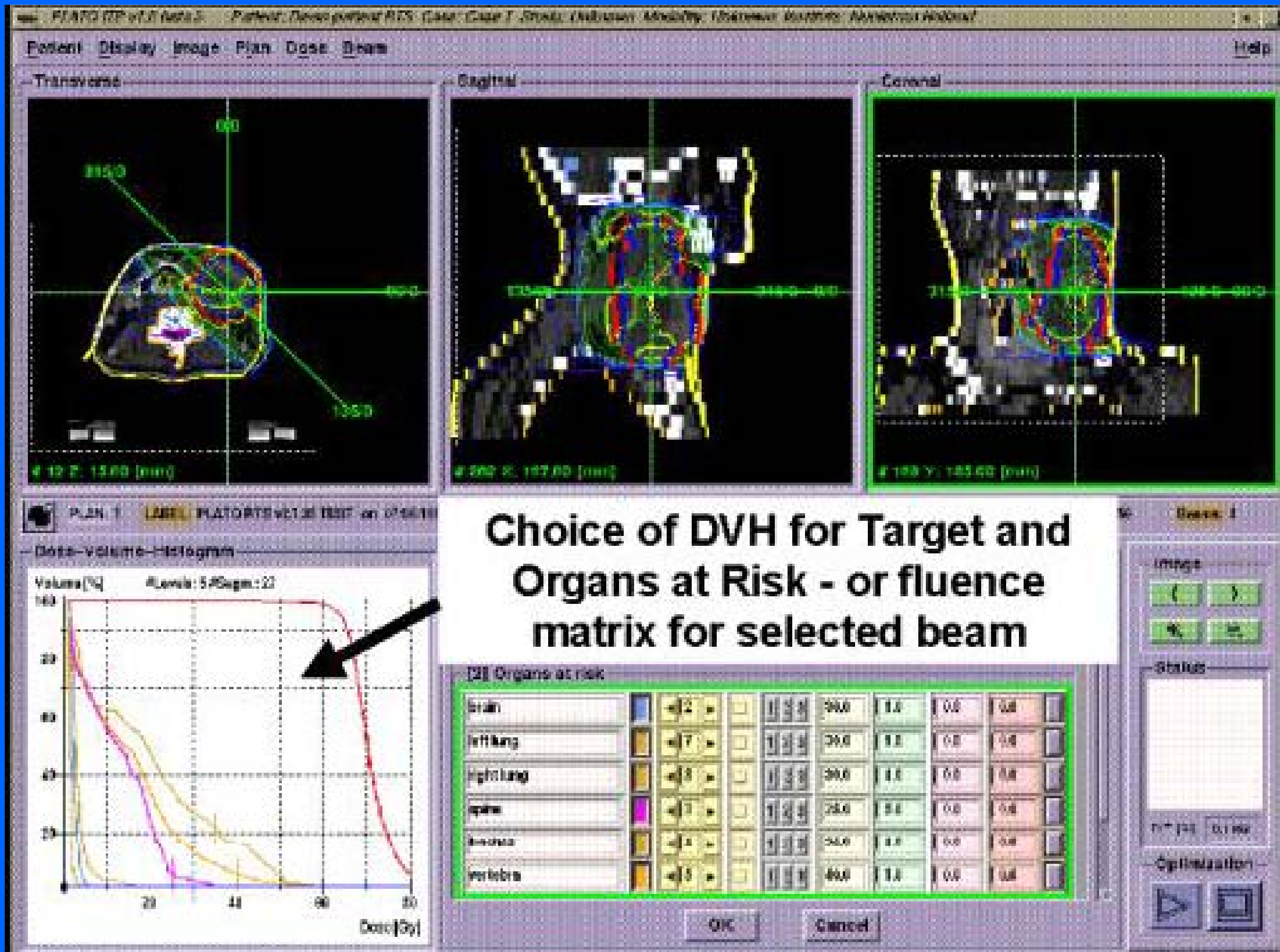


- Electron linacs to produce gamma rays (called X-rays by medical doctors)
- 20'000 patients/year every 10 million inhabitants

Production of X "quanta"

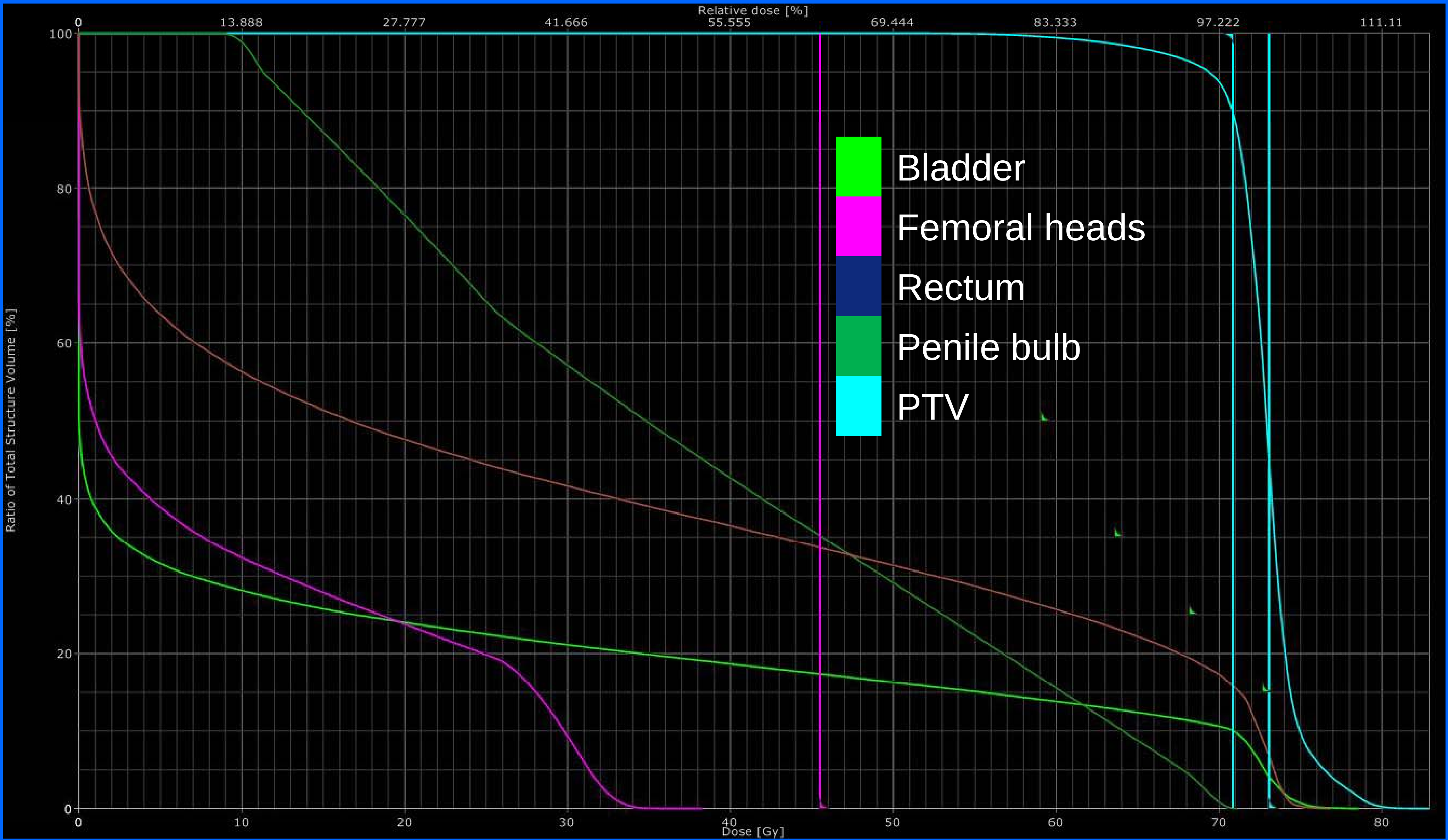


Computerized Treatment Planning System (TPS)

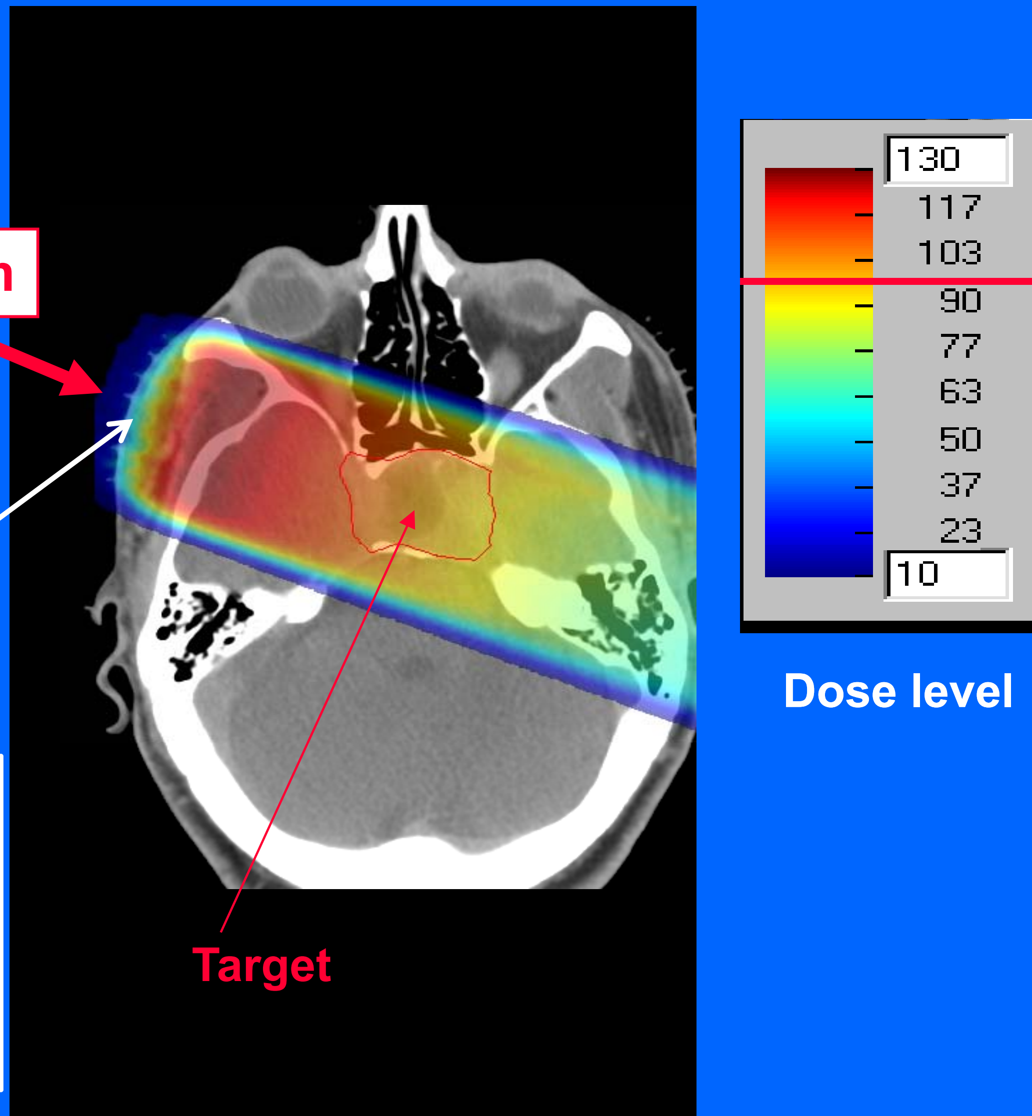


- **TC scan data are used to**
  - **design the volume to be irradiated**
  - **choose the radiation fields**
  - **calculate the doses to the target and to healthy tissues**
- **The dose is given in about 30-40 fractions of about 2 Gray**

Dose Volume Histograms (DVH)



The problem of X ray therapy



Physicists:

Build up effect

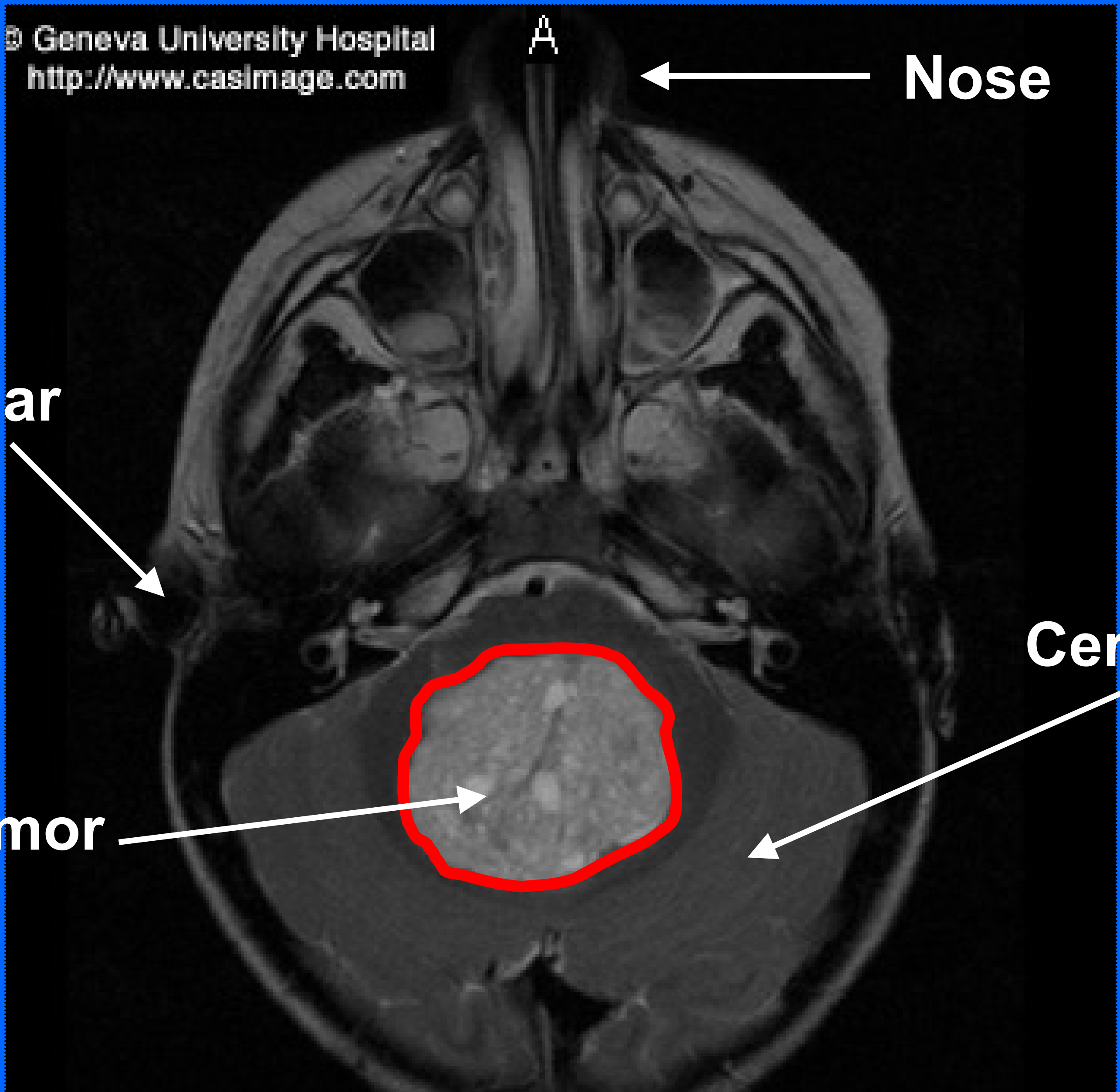
Medical doctors:

Skin sparing effect

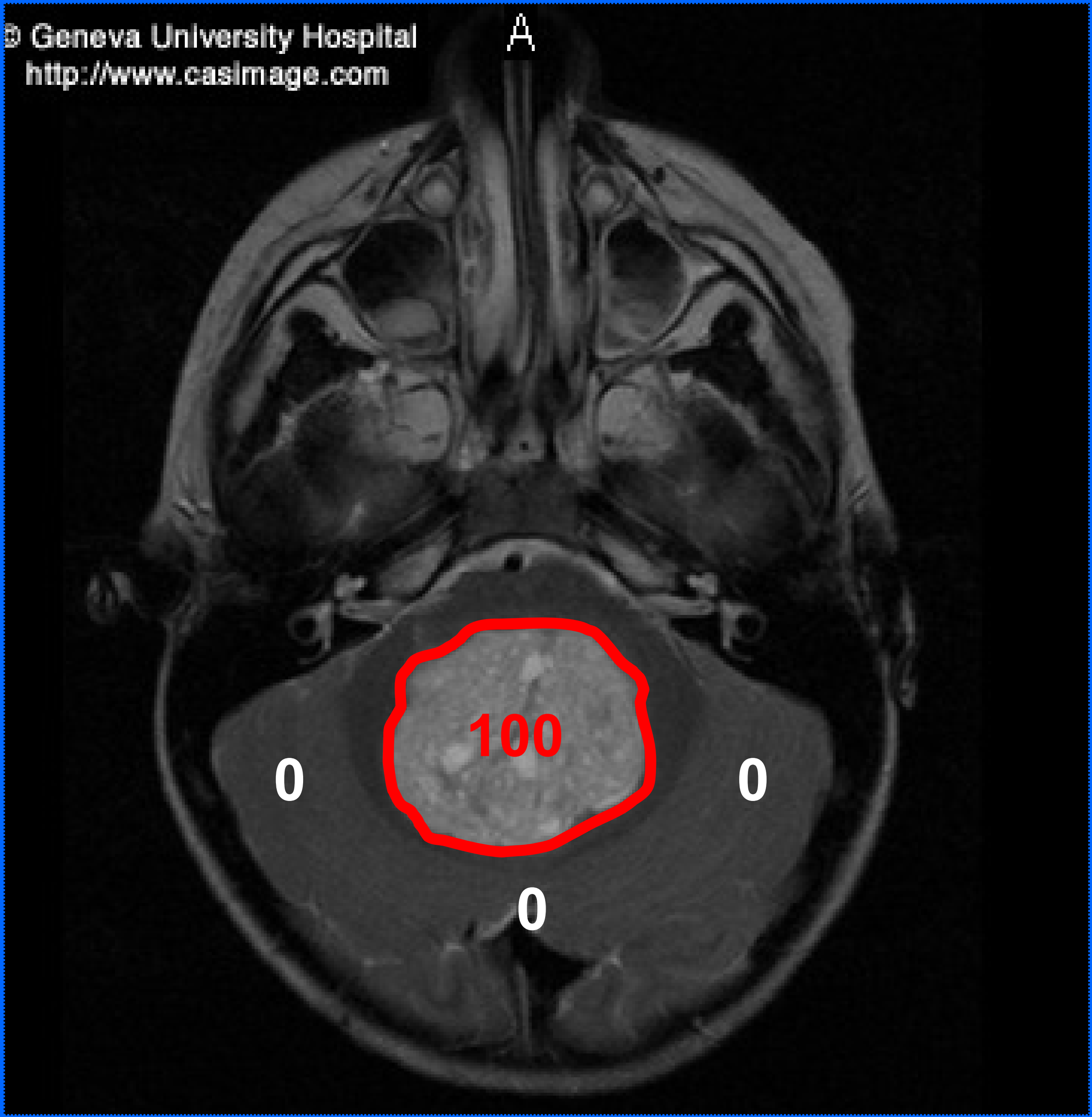
Courtesy

Prof. R. Miralbell,

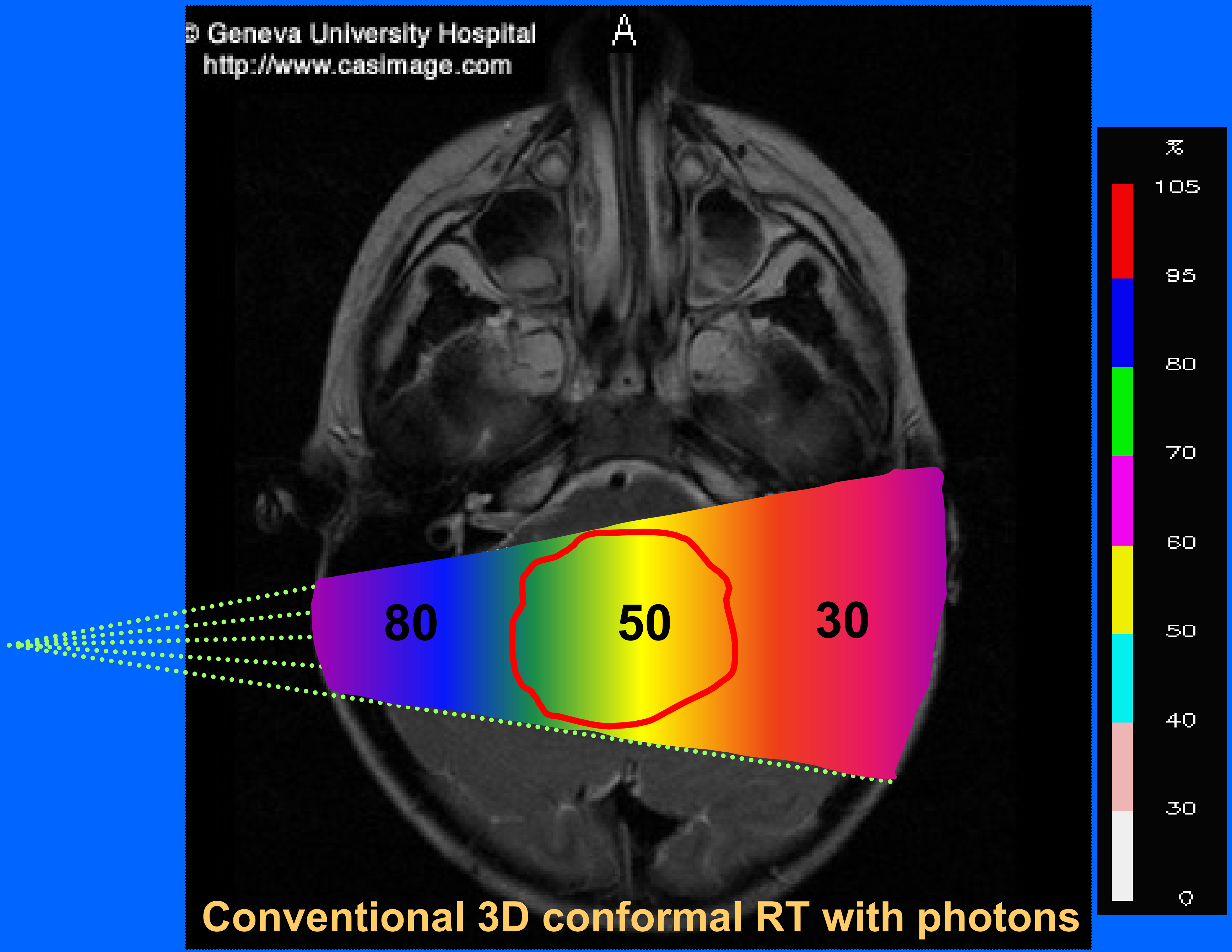
HUG, Geneva



MRI: tumor of the Central Nervous System



The ideal case… with ideal radiation !!!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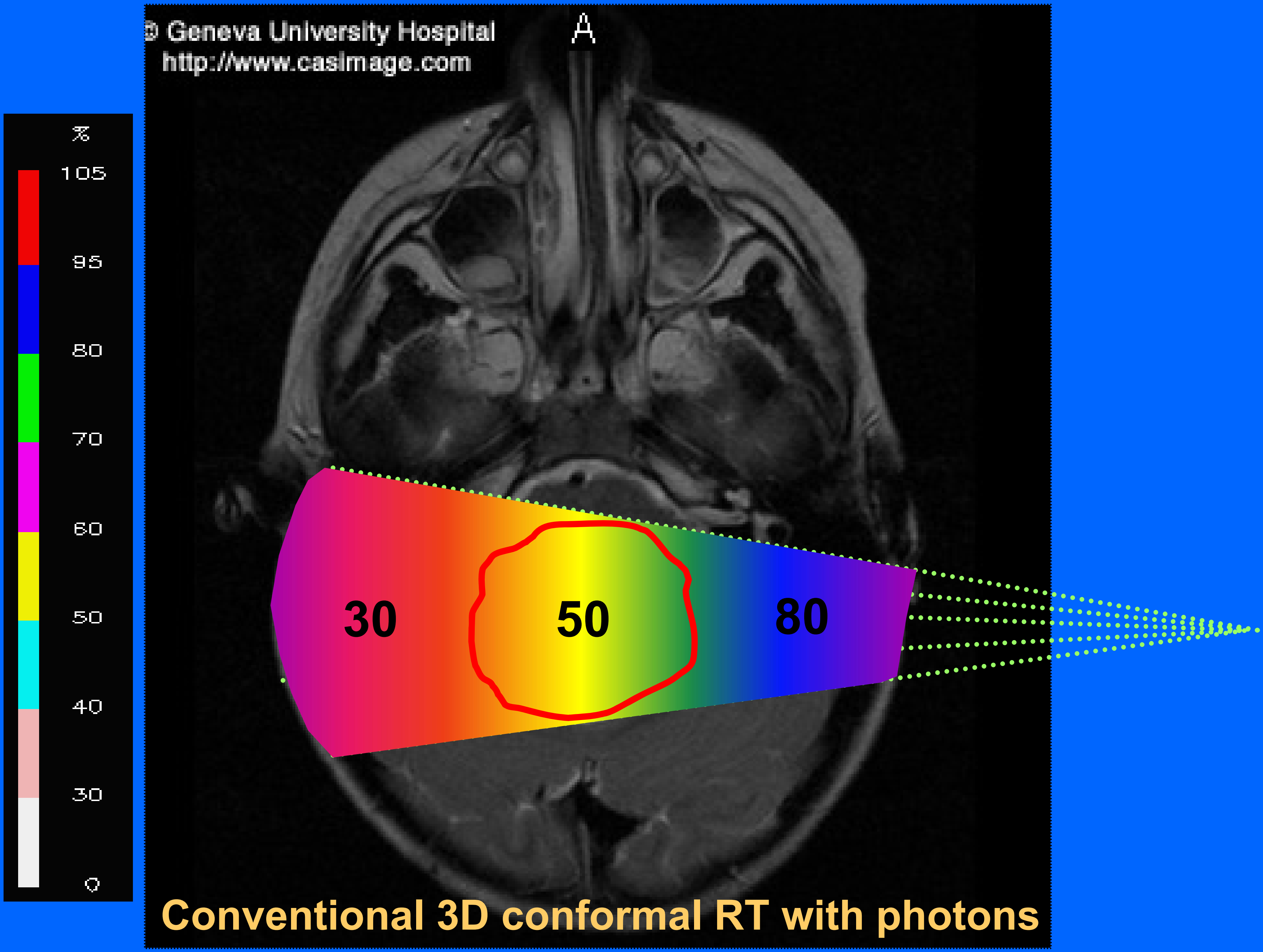
Conventional 3D conformal RT with photons

… in practice !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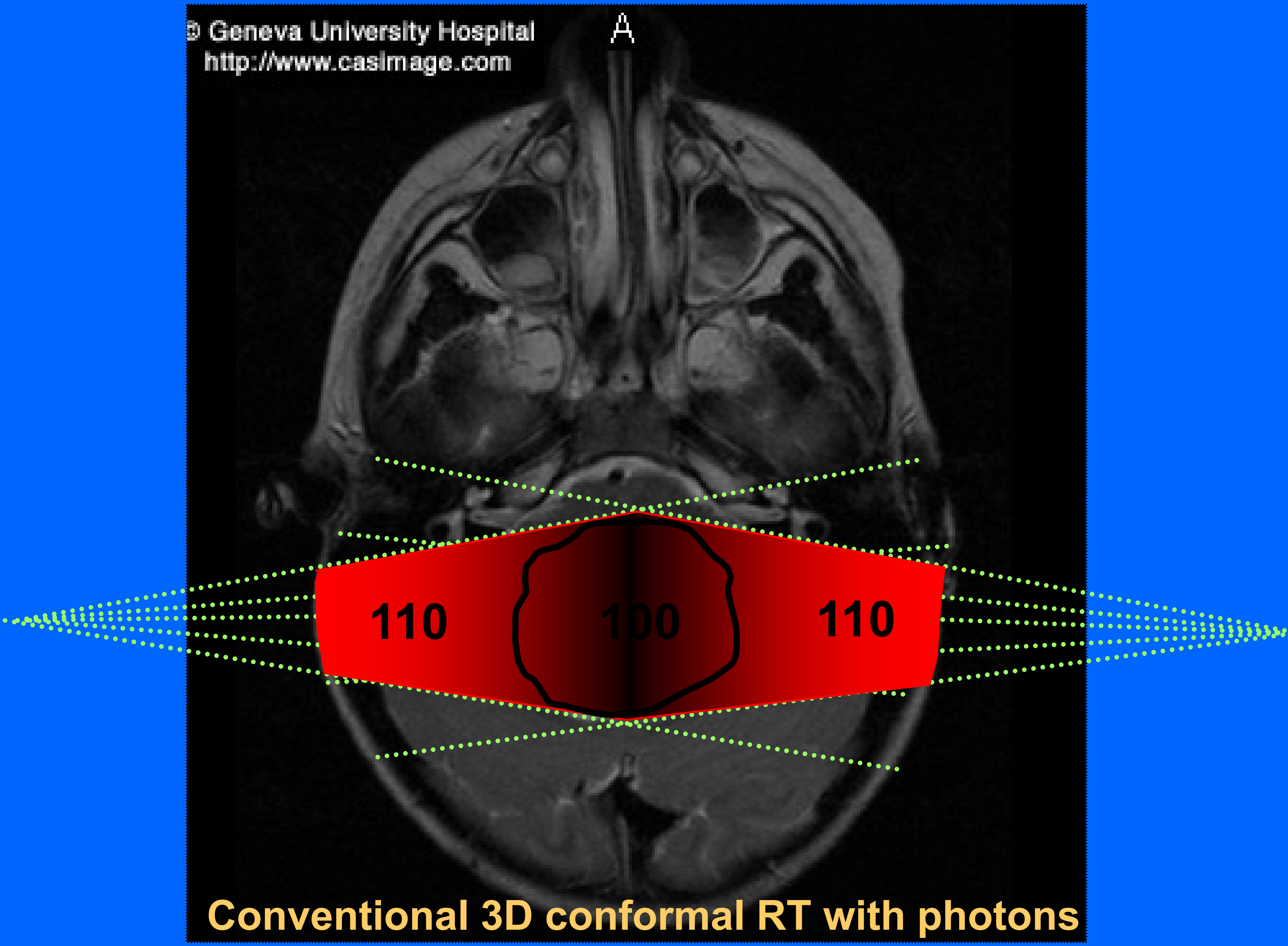
Conventional 3D conformal RT with photons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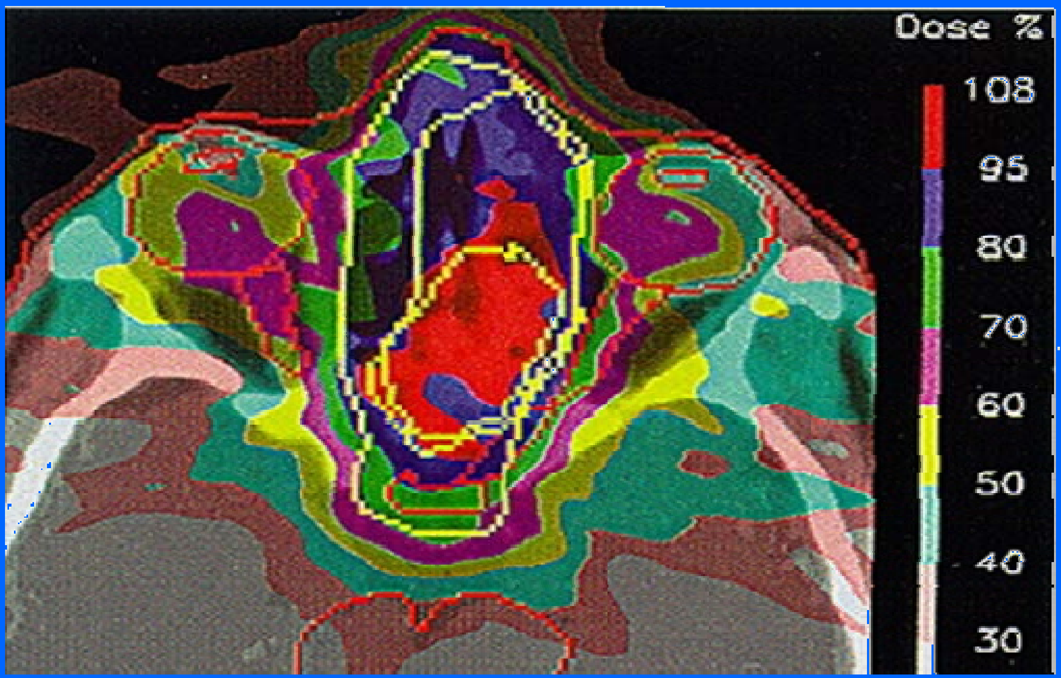
Conventional 3D conformal RT with photons

The problem of X ray therapy

Solution:

- **Use of many crossed beams**
- **Intensity Modulation Radiation Therapy (IMRT)**

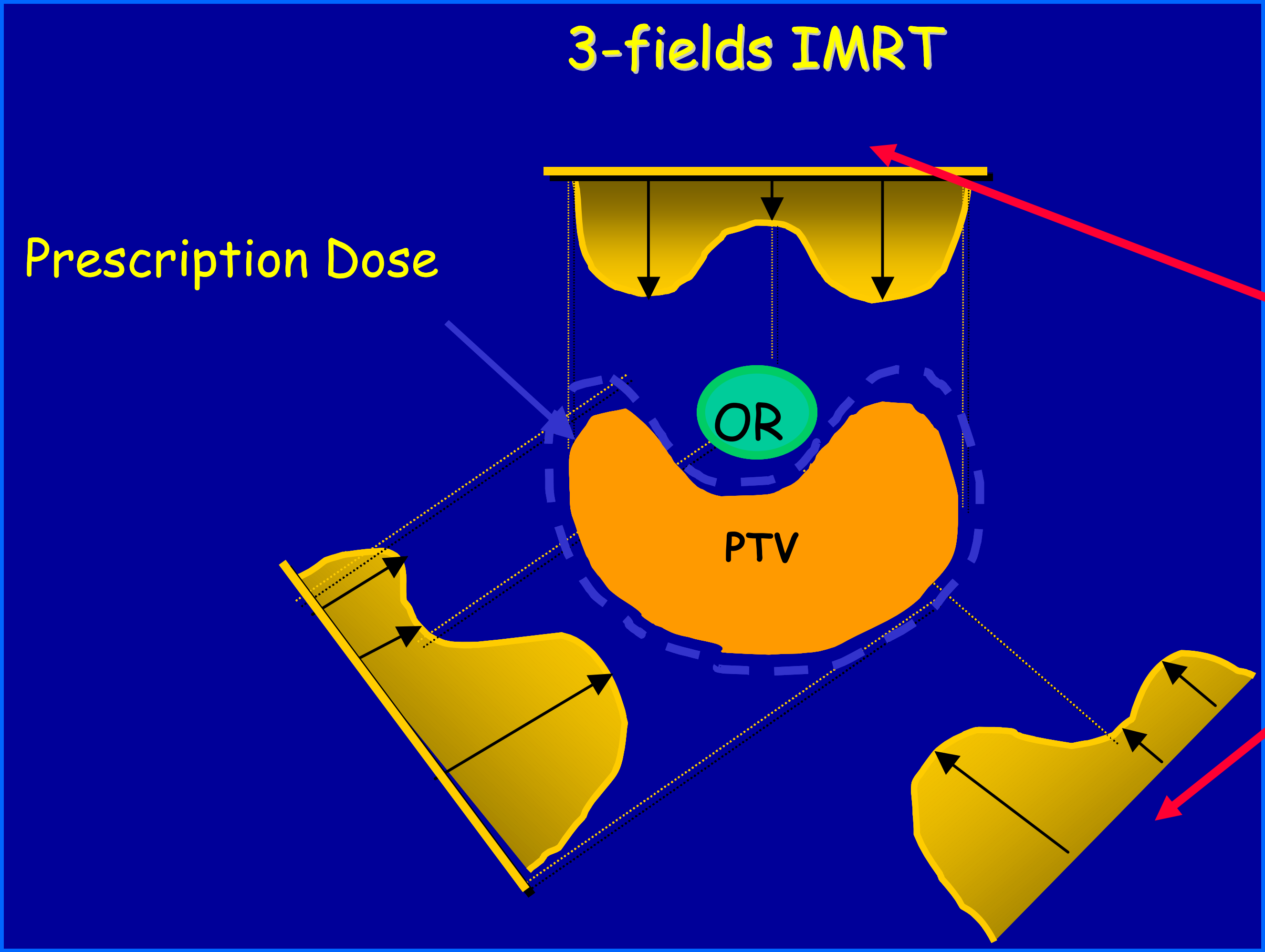


9 different photon beams

The limit is due to the dose given to the healthy tissues!

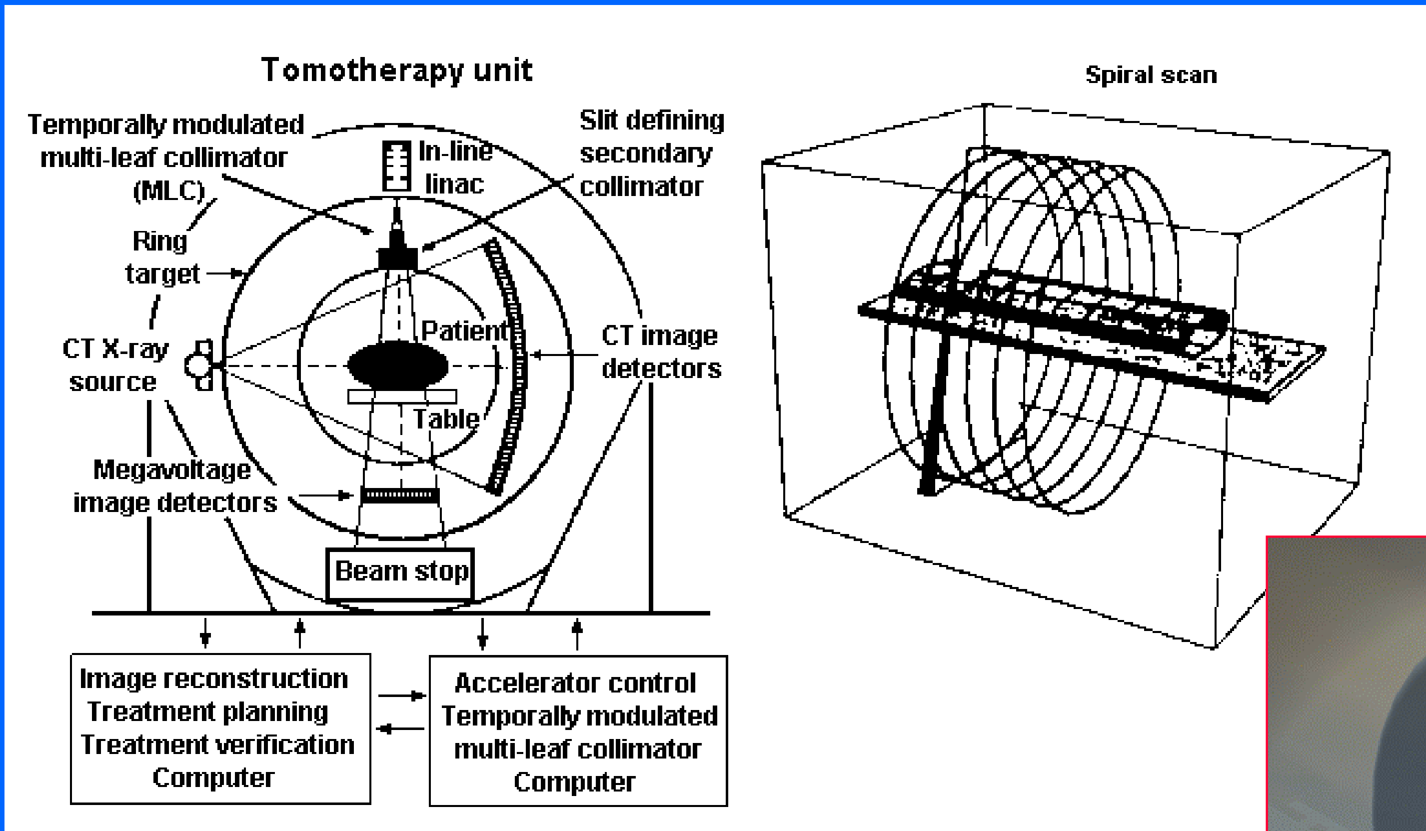
Especially near organs at risk (OAR)

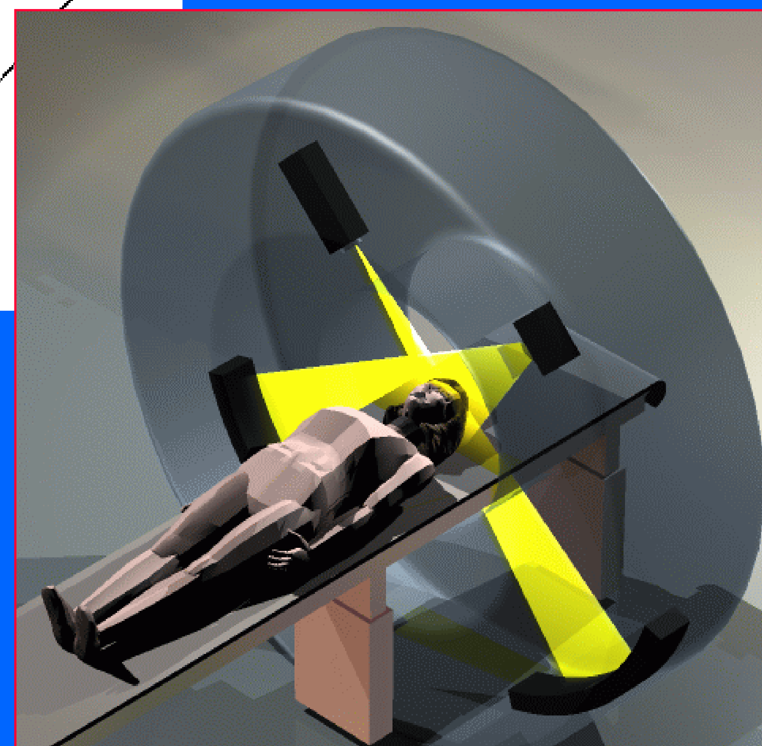
Multi leaf collimators and IMRT



Multi leaf collimator which moves during irradiation

- **It is possible to obtain concave dose volumes**
- **Time consuming (used for selected cases)**

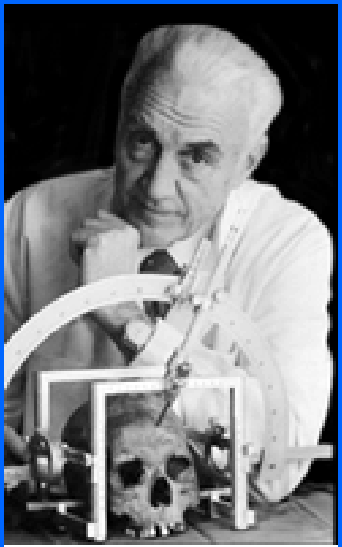




- The tumour is irradiated as the accelerator rotates and the patient is moved (spiral pattern)
- The intensity is modulated through the use of a multi-leaf collimator
- CT imaging integrated within the device itself

The "gamma knife"

- Proposed in 1967 by Lars Leksell (neurosurgeon) and Borje Larsson (physicist) at Karolinska Institutet, Stockholm
- Treatment of selected brain tumors, arteriovenous malformations and brain dysfunctions
- Small volume diseases (located in the head) treated in one session only ("stereo-tactic radio-surgery")
- Today, more than 30000 patients every year



Lars Leksell poses with his Gamma Knife head frame

The original 1967 Leksell Gamma Knife

Today's Leksell Gamma Knife

201 ^{60}Co radiation sources

- Lightweight 6 MV linear accelerator to produce X-rays mounted on a robotic arm
- Use of X-rays taken during treatment to establish the position of the lesion and monitor the treatment
- Possibility of multiple fractions
- Used to treat small volume tumours (ex . Brain, head & neck, lung, spine, abdomen and pelvis) and lesions throughout the spine

Intra Operative Radiation Therapy (IORT)

Irradiation with an electron beam during surgery

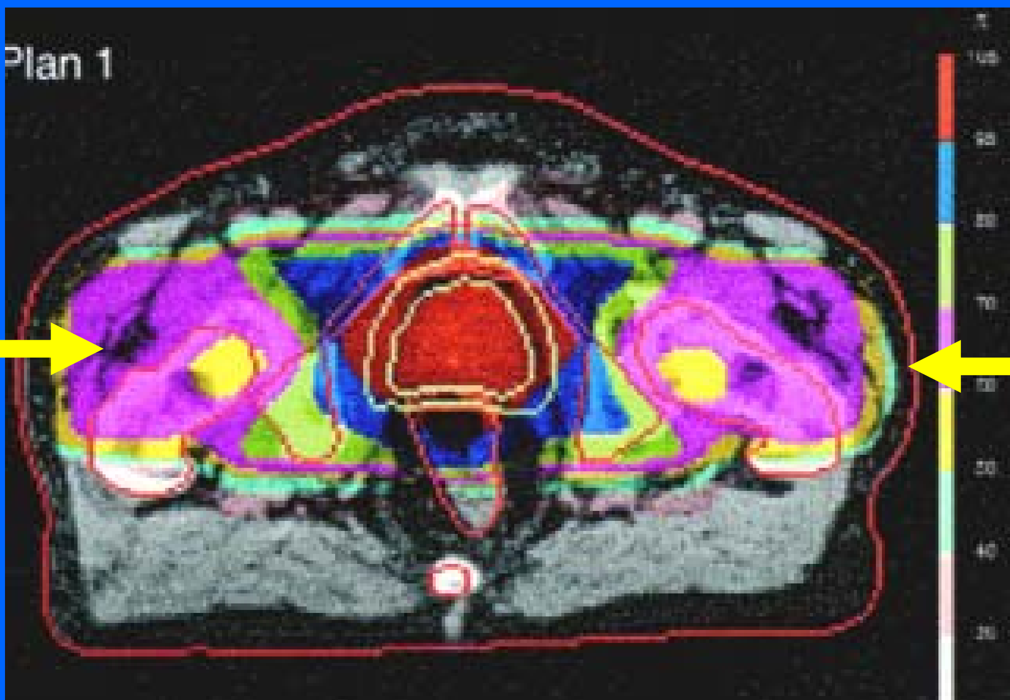
Electron energies: 3 – 9 MeV

Mean dose rate: 6 – 30 Gy/min

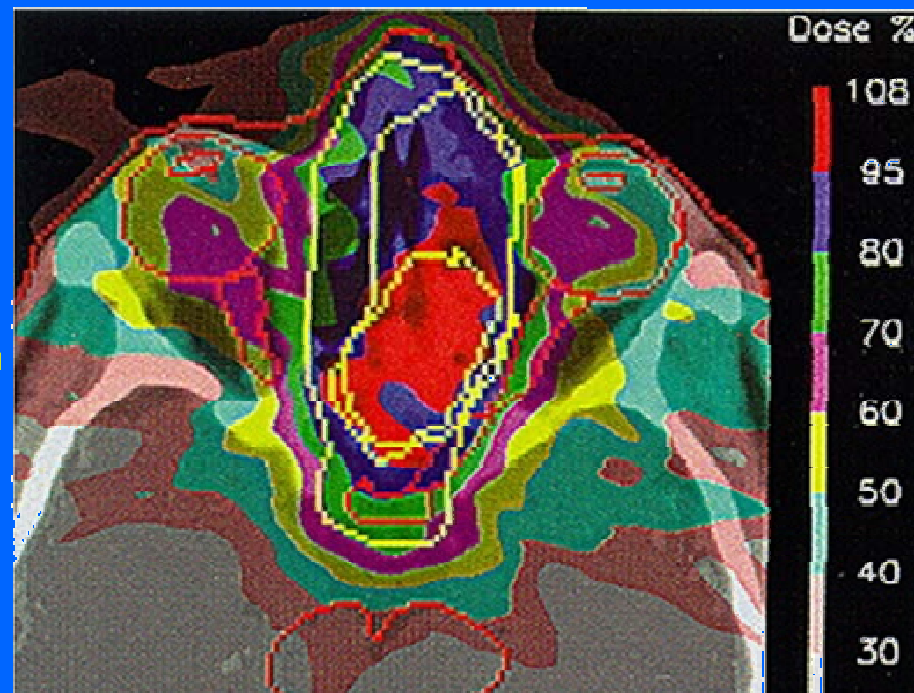
Irradiation time (21 Gy): 0.7 – 3.5 min

Can we do better ?

2 X ray beams



9 X ray beams (IMRT)



A question for a particle physicist

Are there better radiations to attack the tumour and spare at best the healthy tissues?

Answer : BEAMS OF CHARGED HADRONS

End of part IV