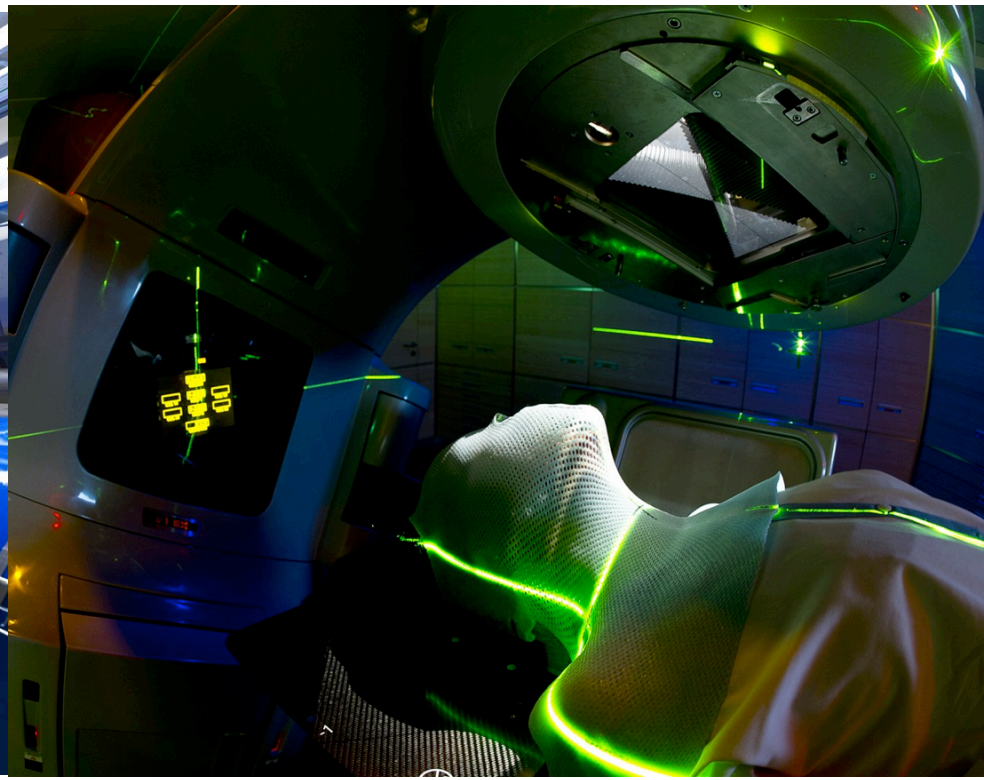
Medical Applications-2

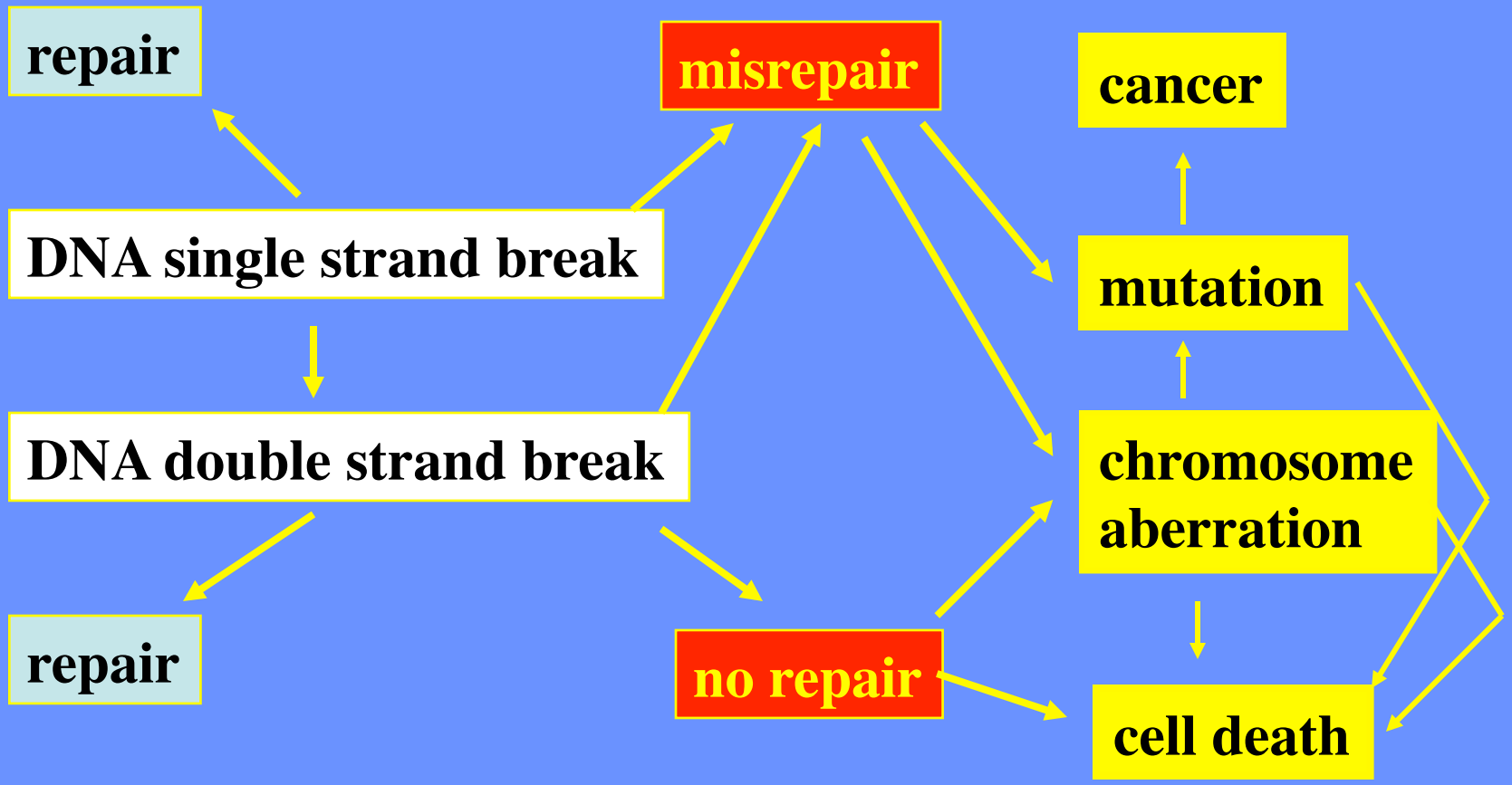


CERN Summer School Student Lectures, 2016

Manjit Dosanjh, CERN
manjit.dosanjh@cern.ch

http://cds.cern.ch/record/1611721

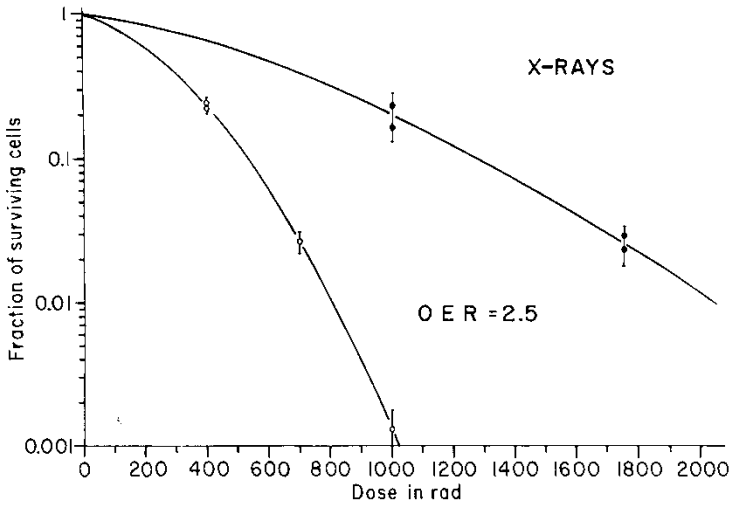
DNA damage and its consequences



Timing of damage effect

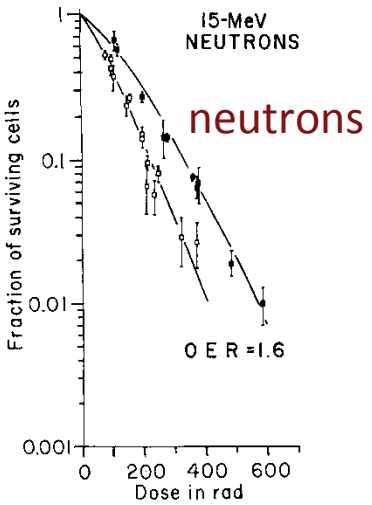
- Immediate/early effects: cell death, animal death
- Short term: minutes, hours, weeks…..
- Delayed effects: cancer induction, genetic effects
- Long term/late effects: years , centuries
- Bystander effect

OER for high and low LET radiations

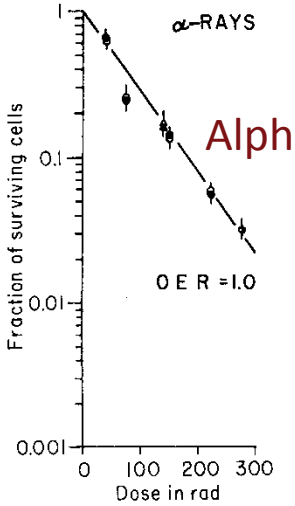


X-rays

OER varies with LET:
X-rays=2.5
Neutrons=1.6
Alpha particles=1.0



neutrons



Alpha particles

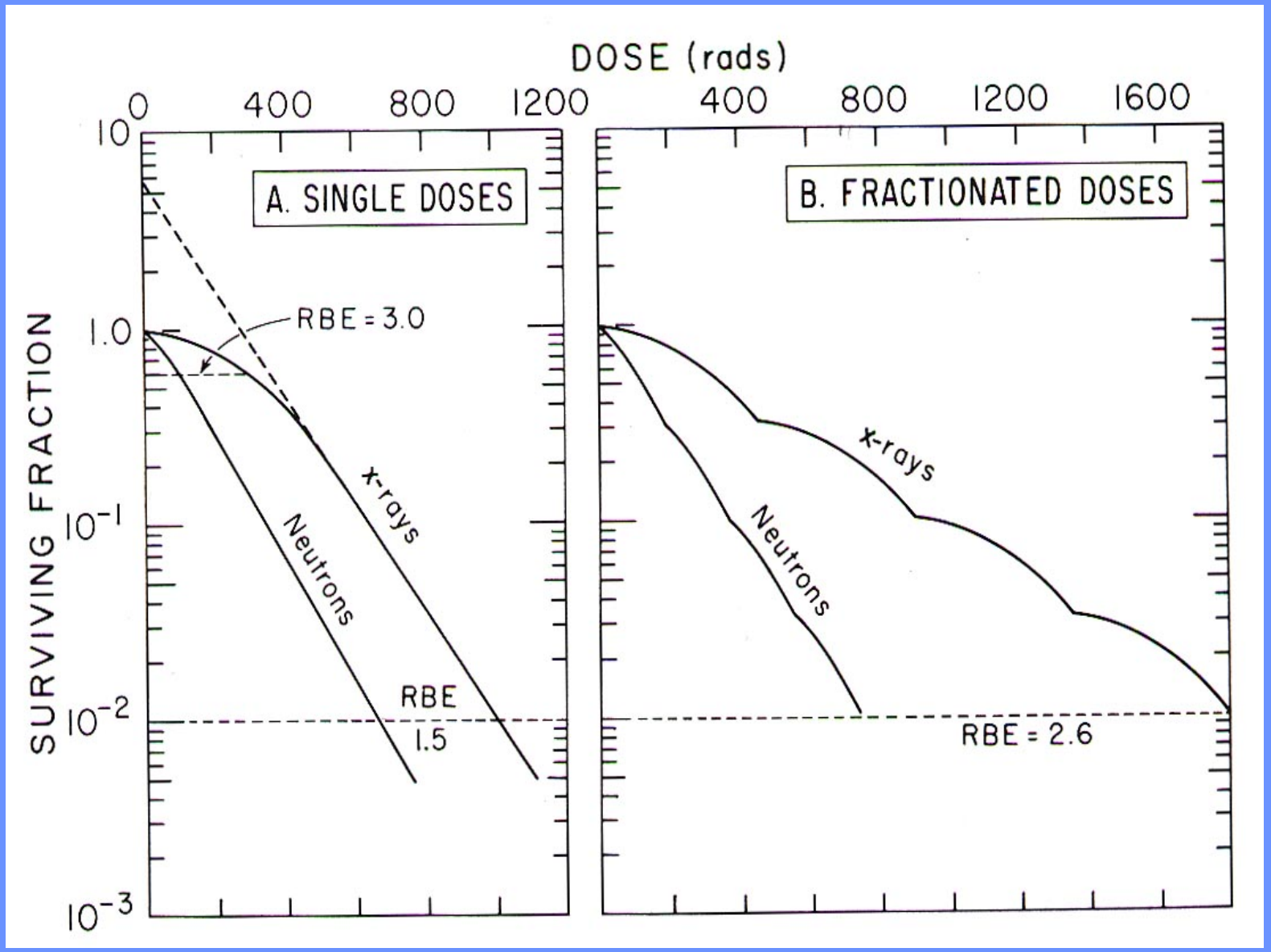
Figure 6.2. The oxygen enhancement ratio (OER) for various types of radiation. The OER for α particles is unity. X-rays exhibit a larger OER of 2.5. Neutrons (15-MeV $d^+ \rightarrow T$) are between these extremes, with an OER of 1.6. (Adapted from Barendsen GW, Koot CJ, van Kersen GR, Bewley DK, Field SW, Parnell CJ: Int J Radiat Biol 10:317, 1966; and Broerse JJ, Barendsen GW, van Kersen GR: Int J Radiat Biol 13:559, 1967, with permission.)

Re-oxygenation in Radiotherapy

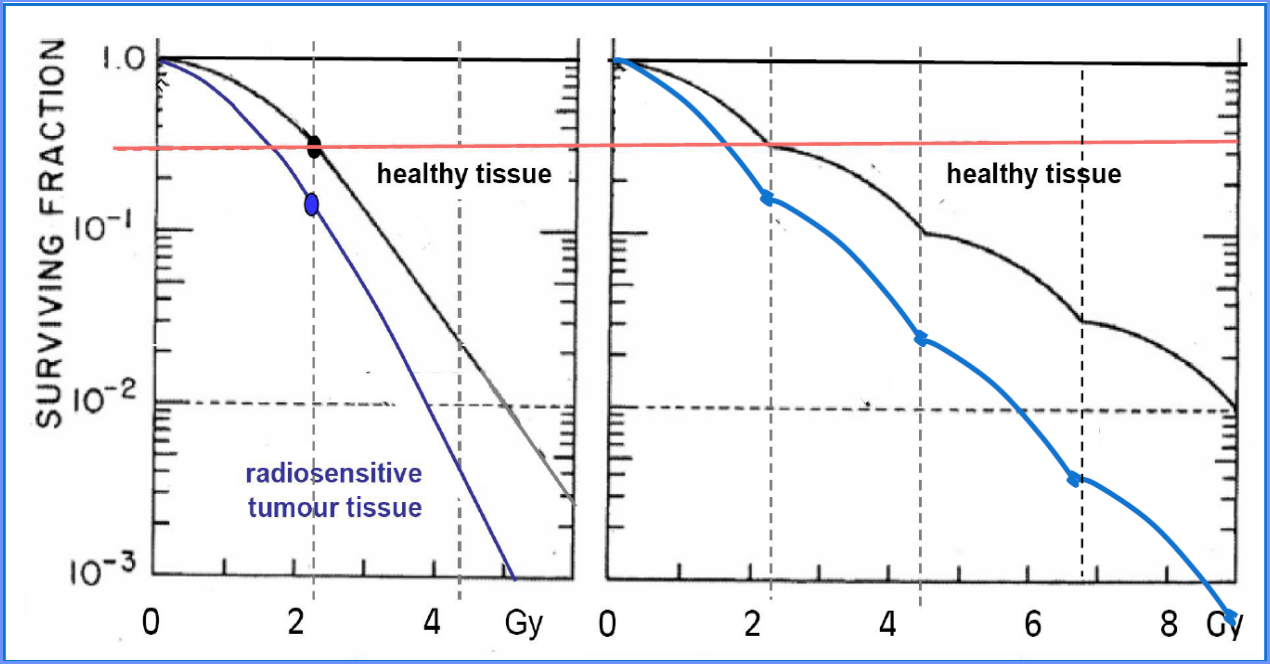
- Hypoxia confers resistance to X-rays/ gamma rays – also to chemotherapeutic drugs
- Human tumours that do not respond to radiotherapy may not re-oxygenate
- Optimal fractionation regimen depends on reoxygenation

Fractionation

- Increased survival when a dose is split into two or more fractions separated by a time interval
- There is a point at which an increase in the number of fractions will no longer increase survival - plateau in the response


DOSE (rads)
0
400
800
1200
400
800
1200
1600
SURVIVING FRACTION
10
1.0
10^{-1}
10^{-2}
10^{-3}
A. SINGLE DOSES
B. FRACTIONATED DOSES
RBE = 3.0
x-rays
Neutrons
RBE
1.5
x-rays
Neutrons
RBE = 2.6

Cell survival and fractionation



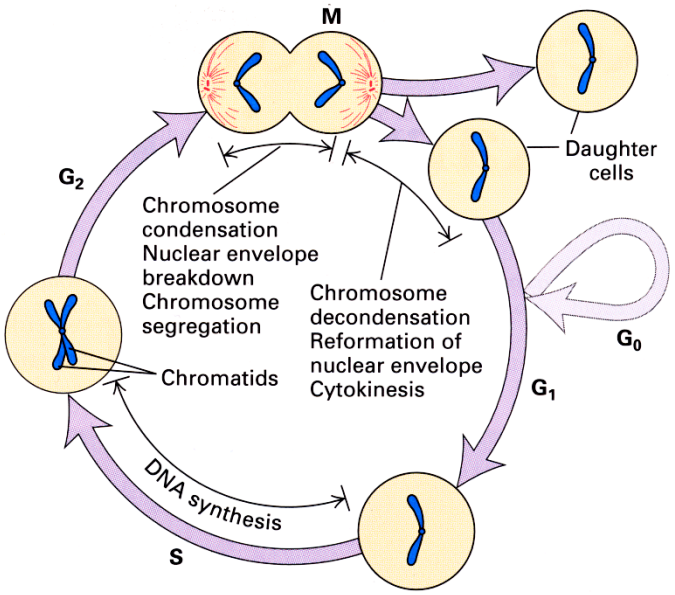
60-75 Gy are typically given in around 30 fractions over 6 weeks

The tumour dose is limited by the close-by healthy tissues which cannot receive more than 25-35 Gy

Cells spend most time in G0 phase—out of the cell cycle

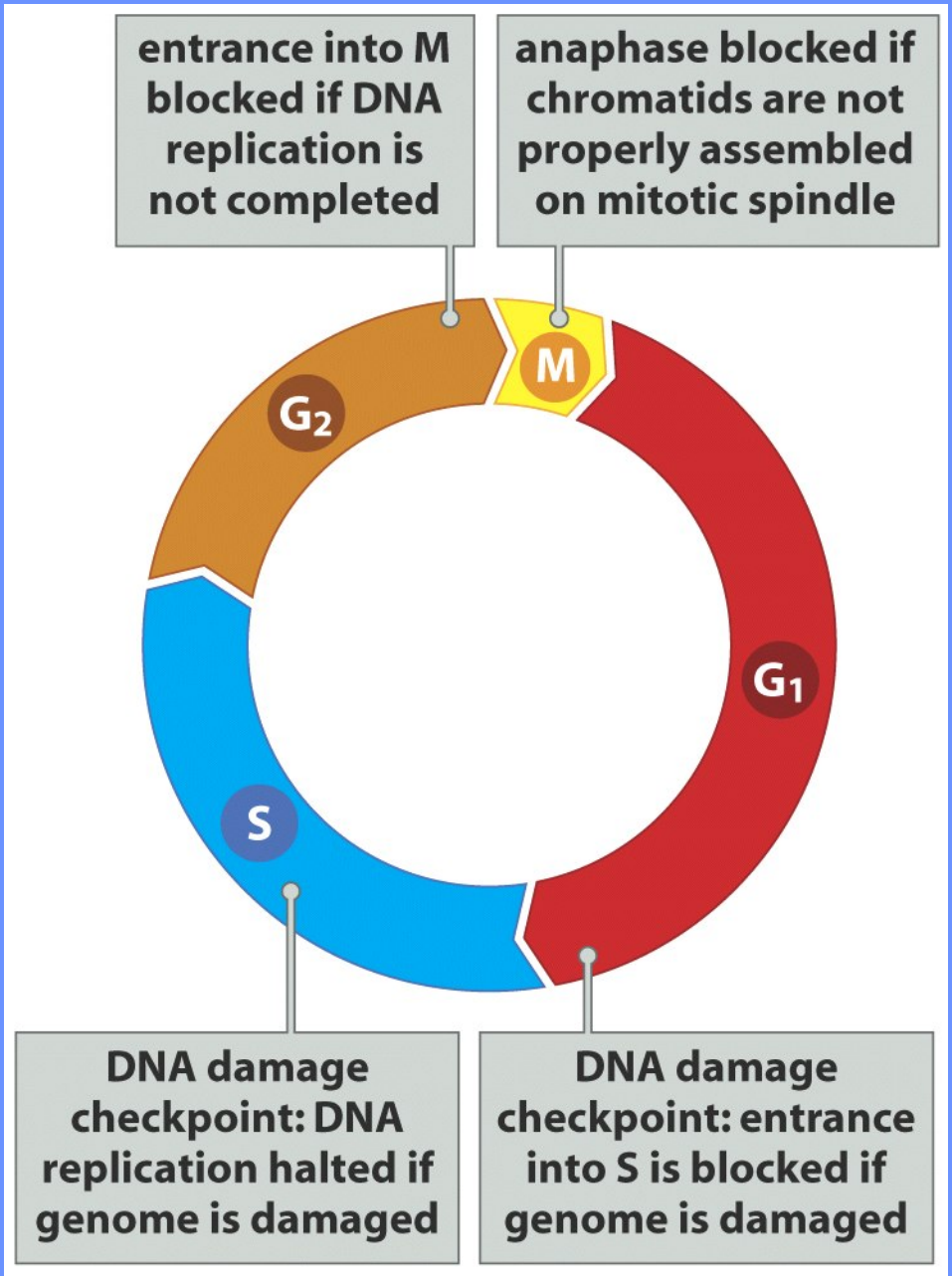
Go= growth arrest
G1= Gap 1
G2 + Gap 2
S = synthesis
M = mitosis

Fate of different Chromosomes in each Phase of the cell cycle

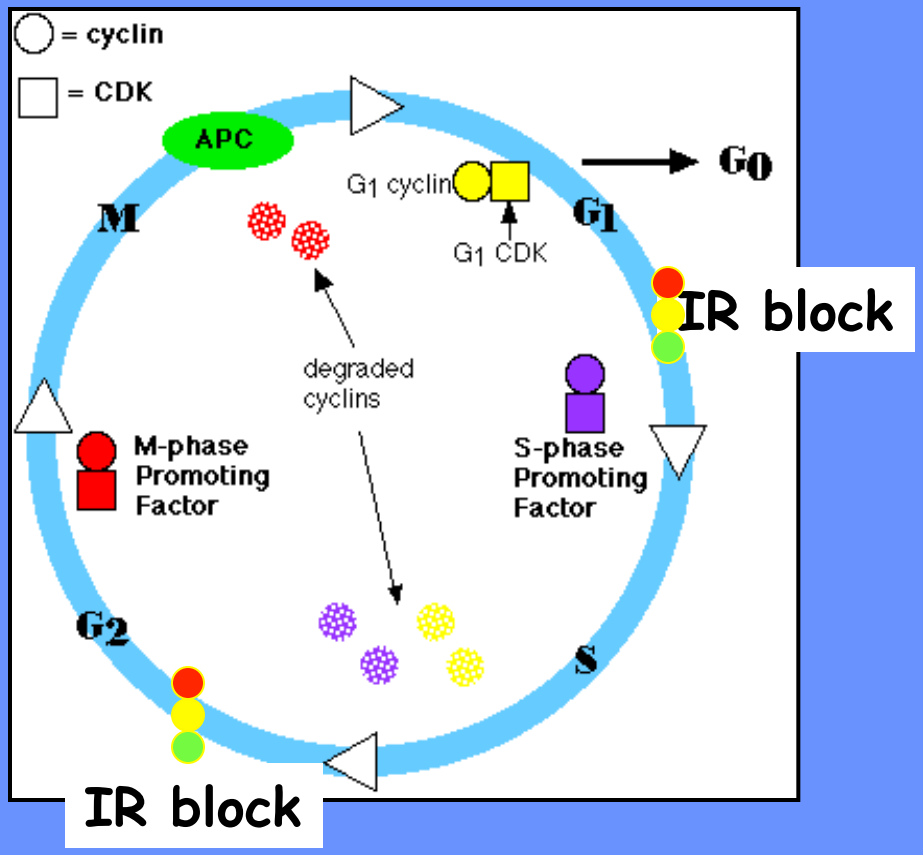


▲ **FIGURE 13-1 The fate of a single parental chromosome throughout the eukaryotic cell cycle.** Although chromosomes condense only during mitosis, they are shown in condensed form to emphasize the number of chromosomes at different cell-cycle stages. The nuclear envelope is not depicted. Following mitosis (M), daughter cells contain 2*n* chromosomes in diploid organisms and 1*n* chromosomes in haploid organisms including yeasts maintained in the haploid state. In proliferating cells, G_1 is the period between "birth" of a cell following mitosis and the initiation of DNA synthesis, which marks the beginning of the S phase. At the end of the S phase, cells enter G_2 containing twice the number of chromosomes as G_1 cells (4*n* in diploid organisms). The end of G_2 is marked by the onset of mitosis, during which numerous events leading to cell division occur. The G_1, S, and G_2 phases are collectively referred to as interphase, the period between one mitosis and the next. Most nonproliferating cells in vertebrates leave the cell cycle in G_1, entering the G_0 state. See also Figure 1-10.

Figure 8.4 *The Biology of Cancer* (© Garland Science 2007)

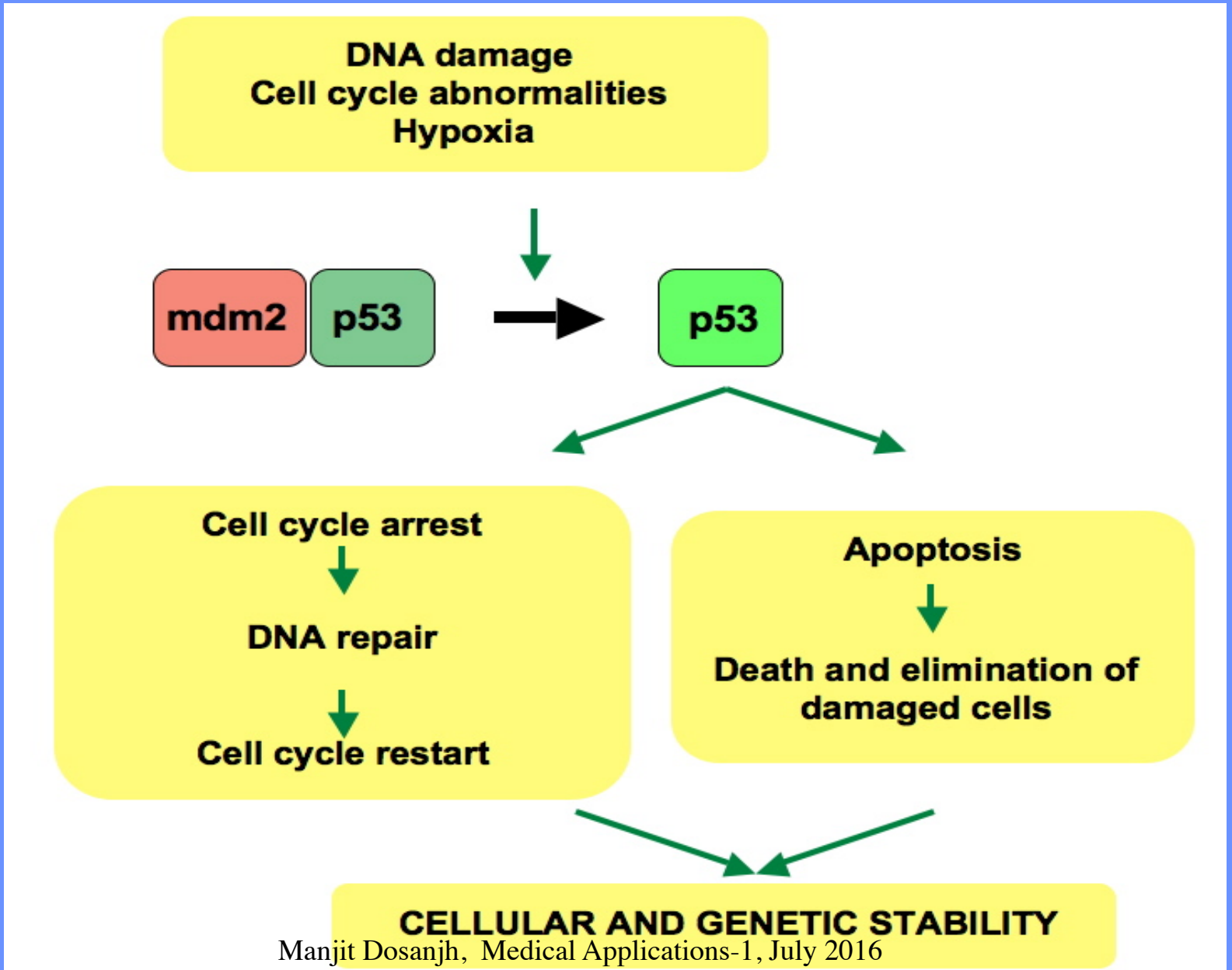


Regulation of the cell cycle

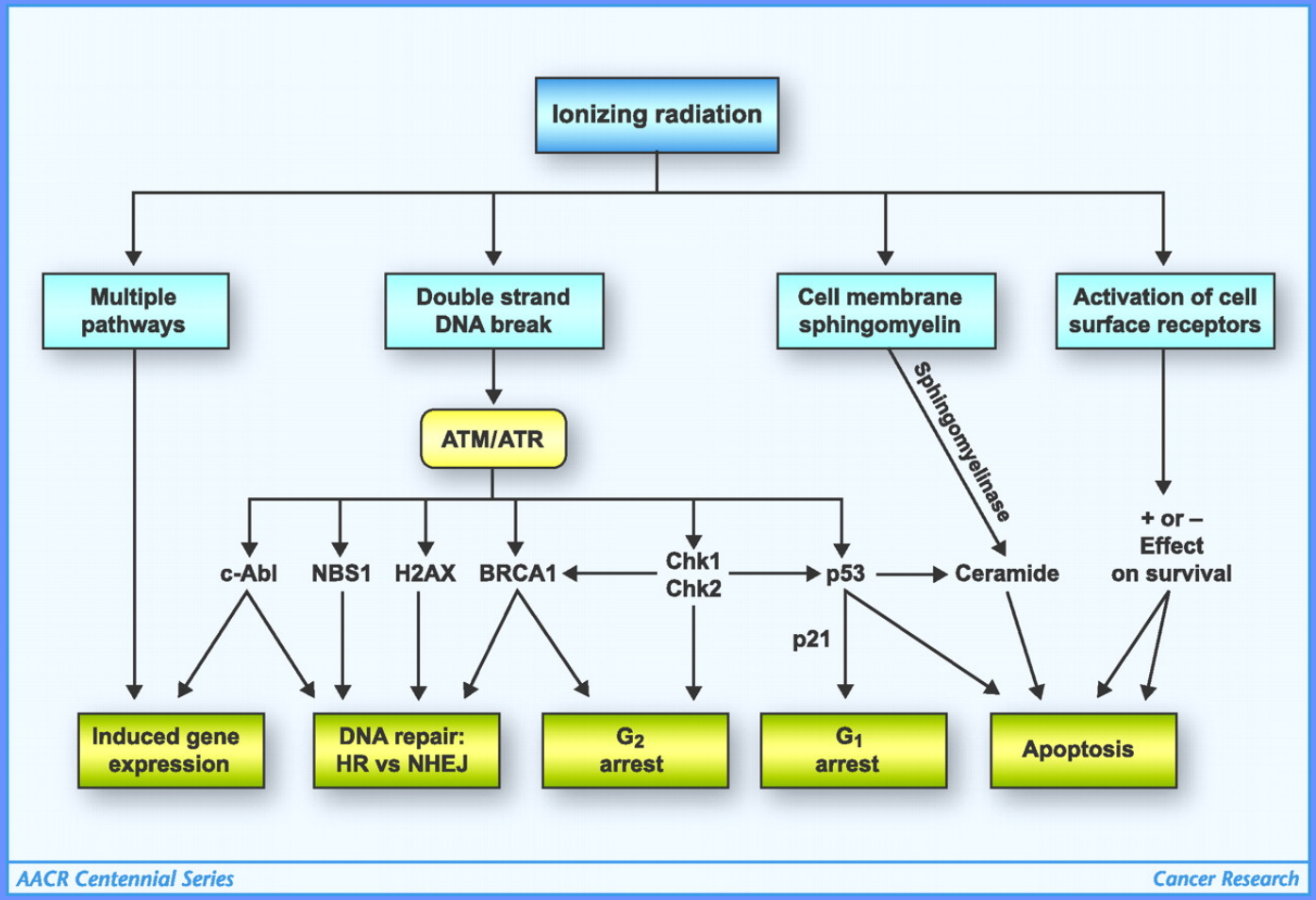


Cell cycle arrest can occur in response to DNA damage (e.g. IR) in order to allow for DNA repair.

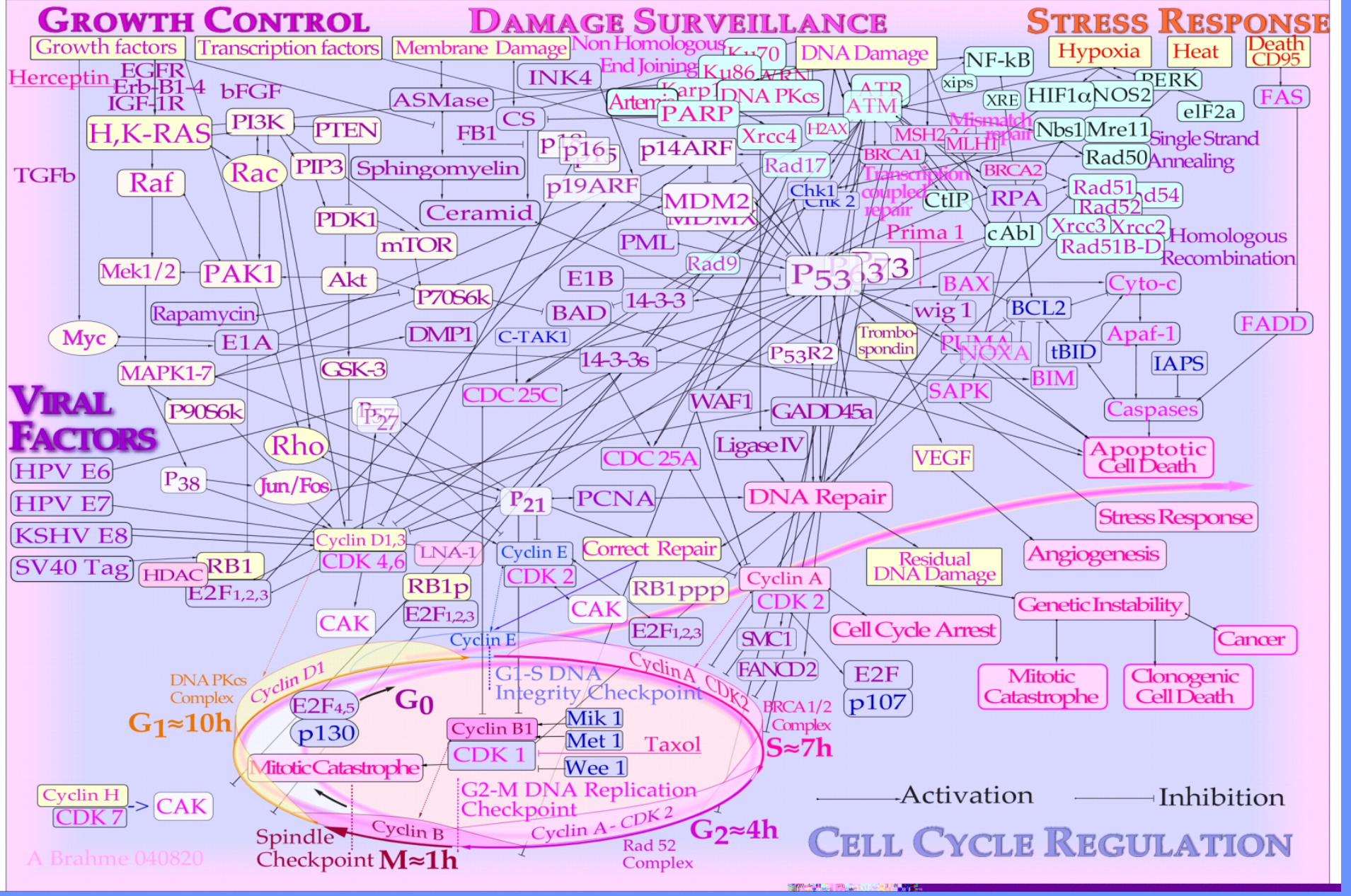
P53-guardian of the genome…..Lane,92



Simplified view of some of the cellular pathways involved in response IR



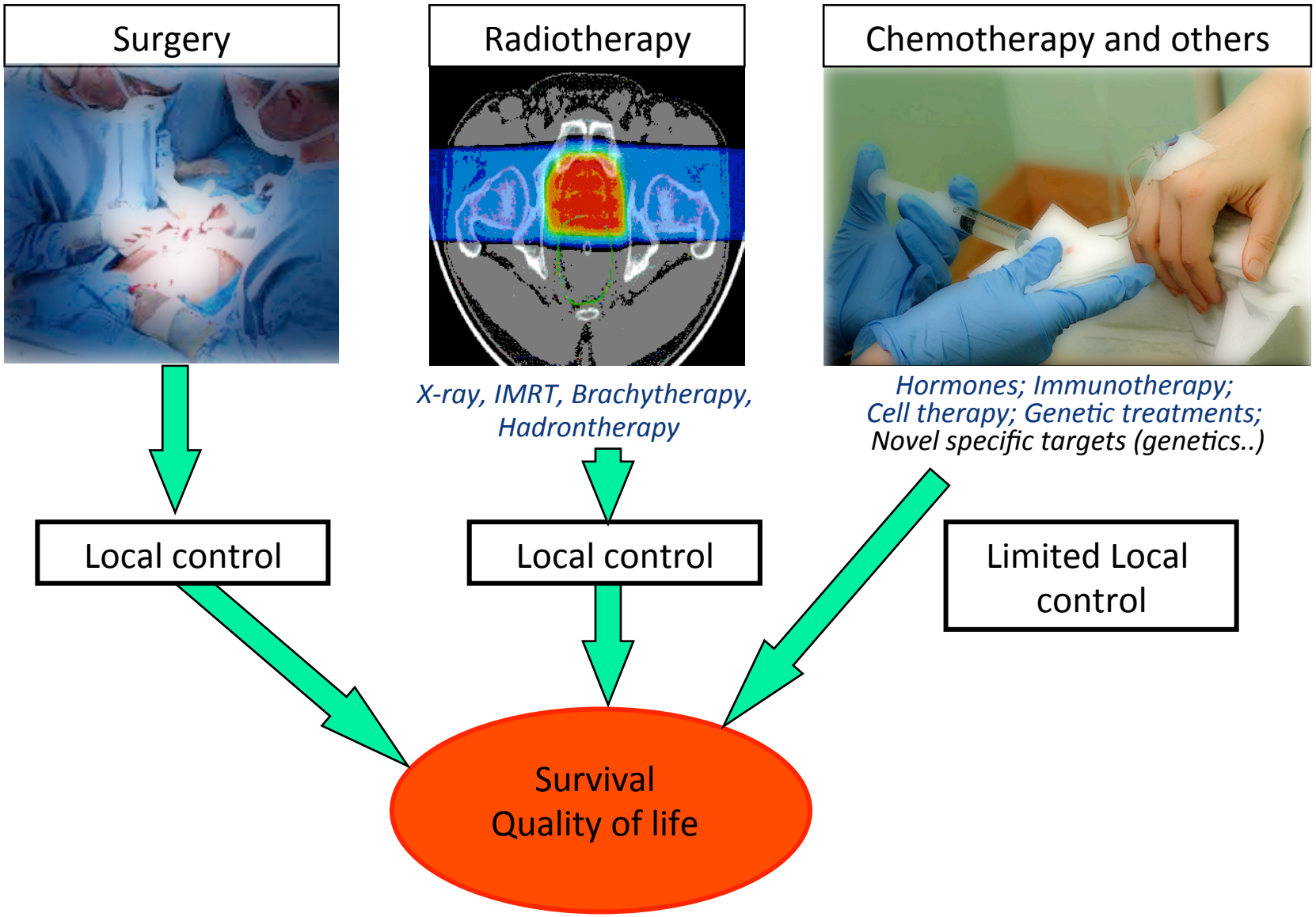
Connell, P. P. et al. Cancer Res 2009;69:383-392



Brahme 2004
Int J Radiat Oncol Biol Phys, V 58, pp 603-616

Radiation Therapy

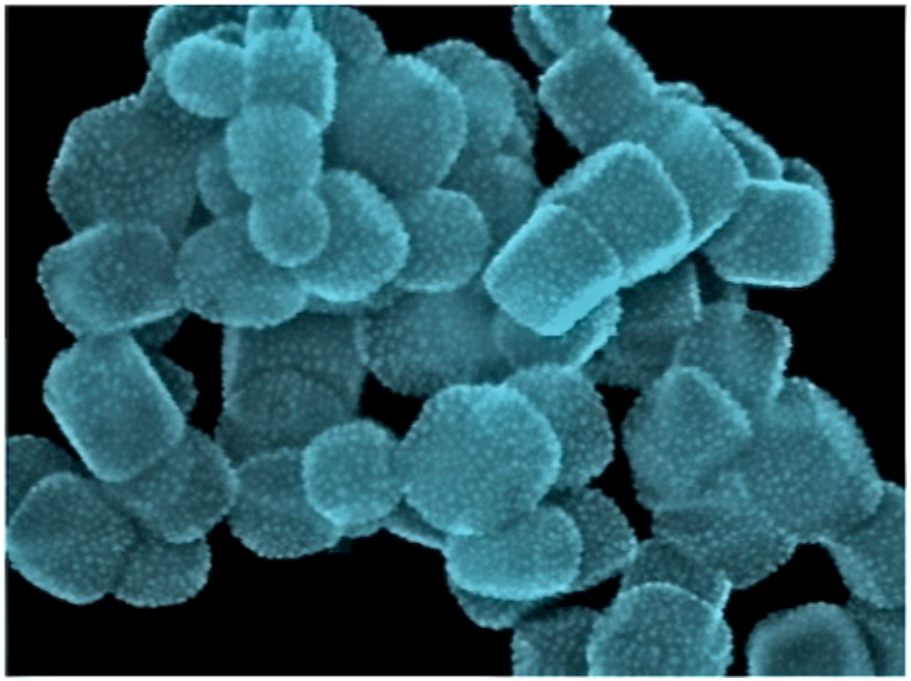
Cancer Treatment Options…



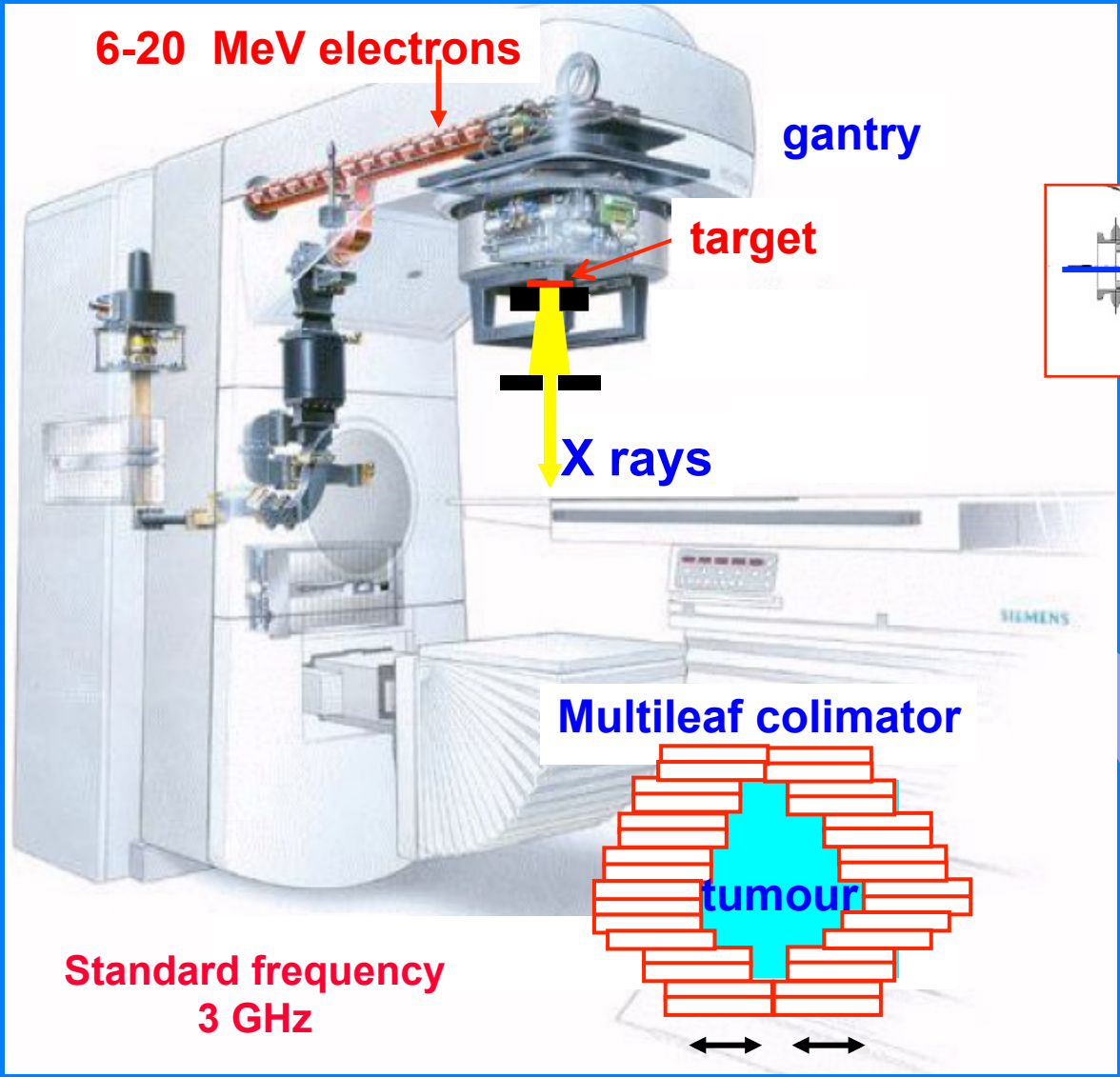
The ideal treatment

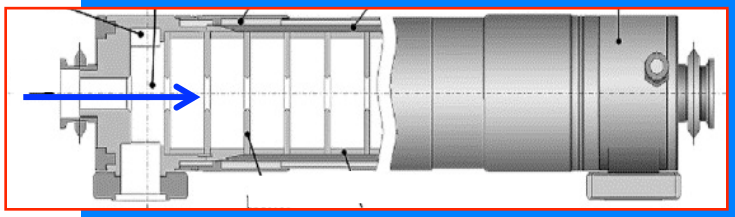
eliminate all tumour cells without affecting normal cells

- Physics :
  - 100% of the dose on target
  - 0% dose in surrounding healthy tissues or critical organs
- Biology :
  - differential effect
  - kill 100% of cancer cells
  - "protect" normal cells



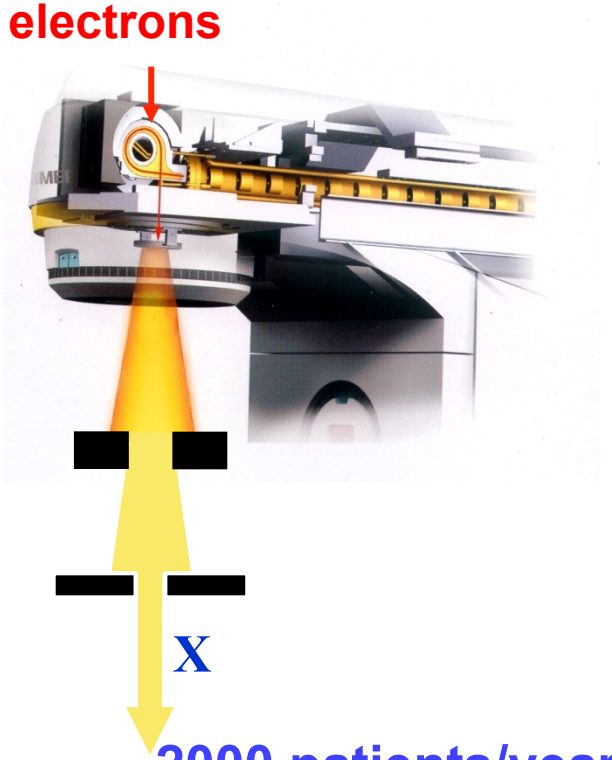
‘Conventional’ radiotherapy: linear accelerators dominate





TERA

‘Conventional’ radiotherapy: linear accelerators dominate



2000 patients/year every 1 million inhabitants have a 30-35 session treatment of about 2 grays (Gy) (*)

(*) dose = energy / mass - measured in gray = joule / kg

TERA

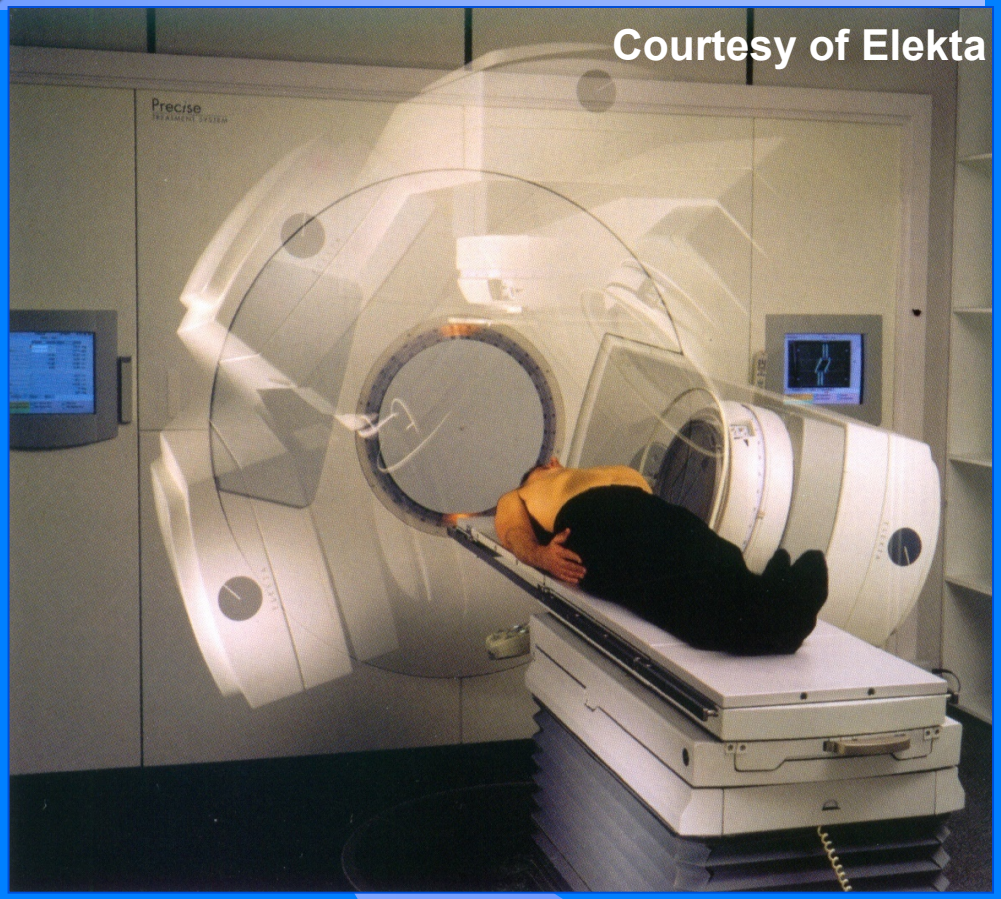
'Conventional' radiotherapy: linear accelerators dominate

In 1 treatment room:

4 sessions/h
10 h/day
40 sessions/d
250 d/year

Maximum: 10 000 sessions/year
≤10,000/30 = 330 patients/year

6-7 X-ray treatment rooms per million inhabitants



Courtesy of Elekta

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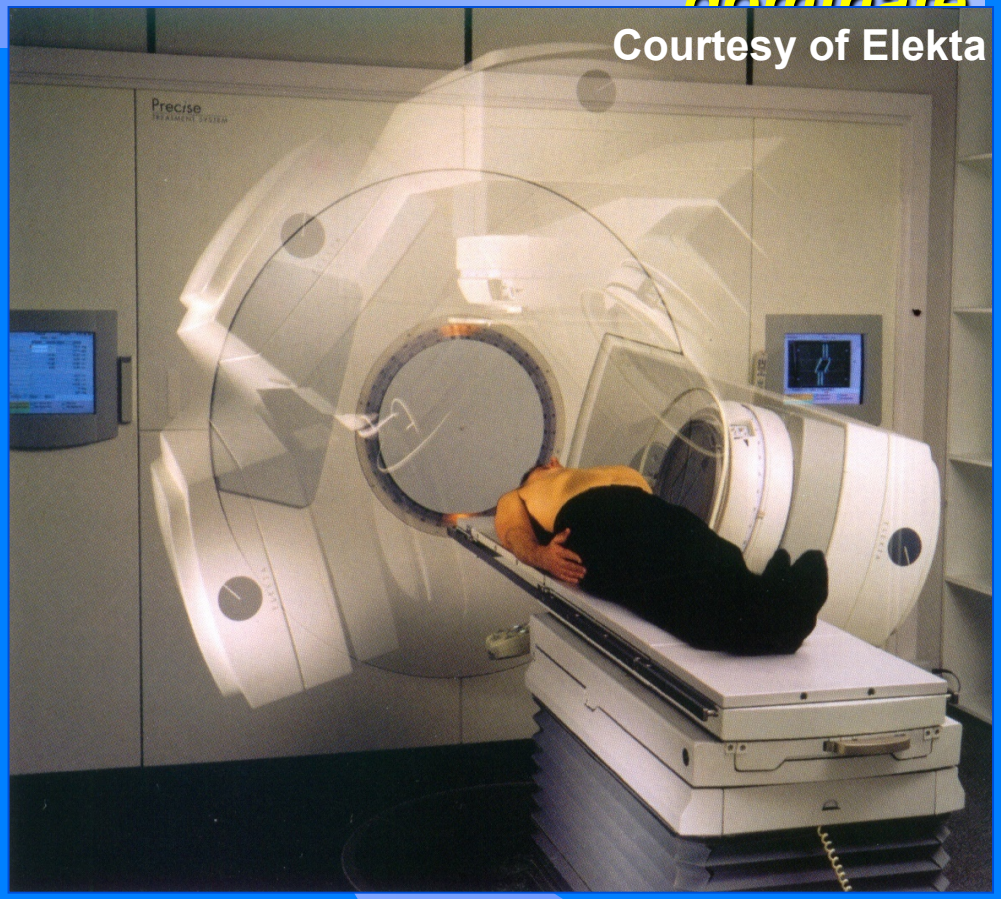
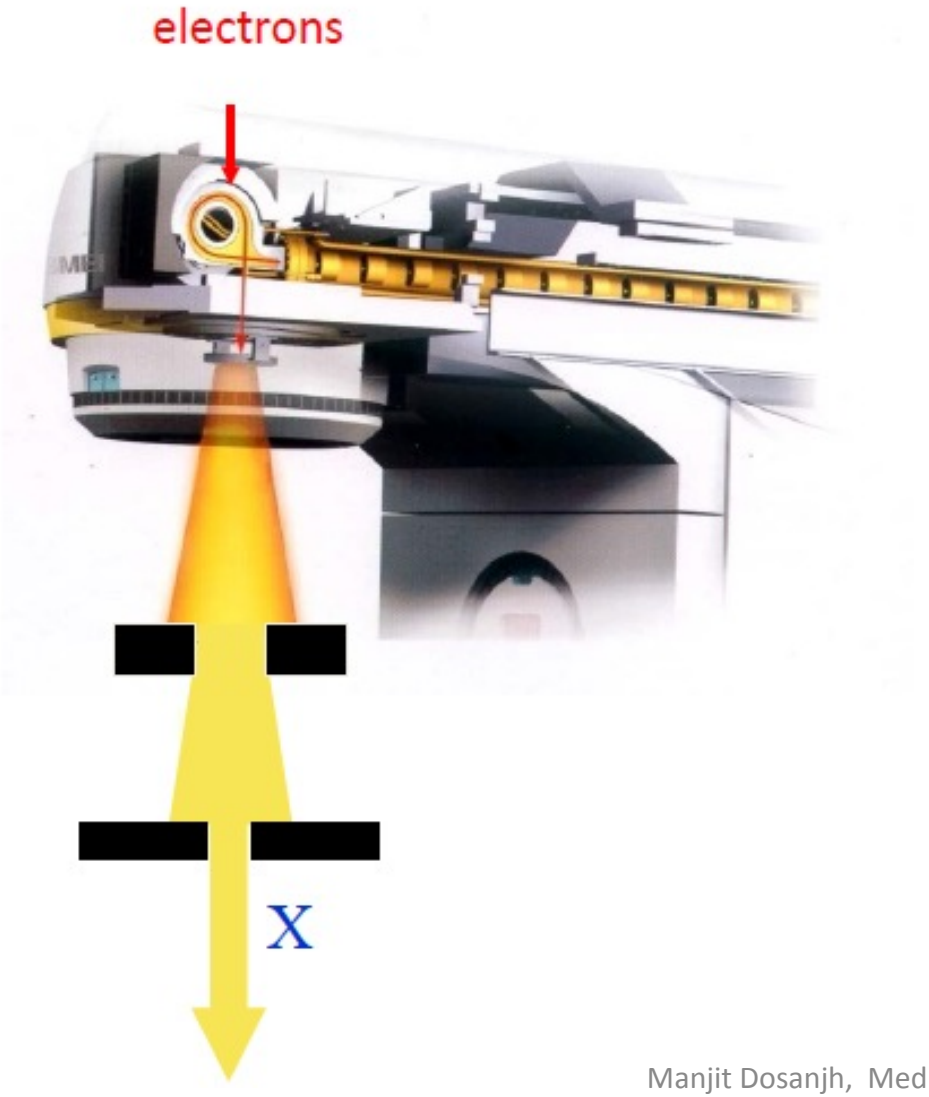


Courtesy of Elekta

In the world around 10,000 electron linacs

50% of all the existing accelerators above 1 MeV

Linacs for radiation therapy



The most used accelerator in hospitals worldwide is a linear accelerator (linac)

Around 10, 000 electron linacs are used daily for radiotherapy

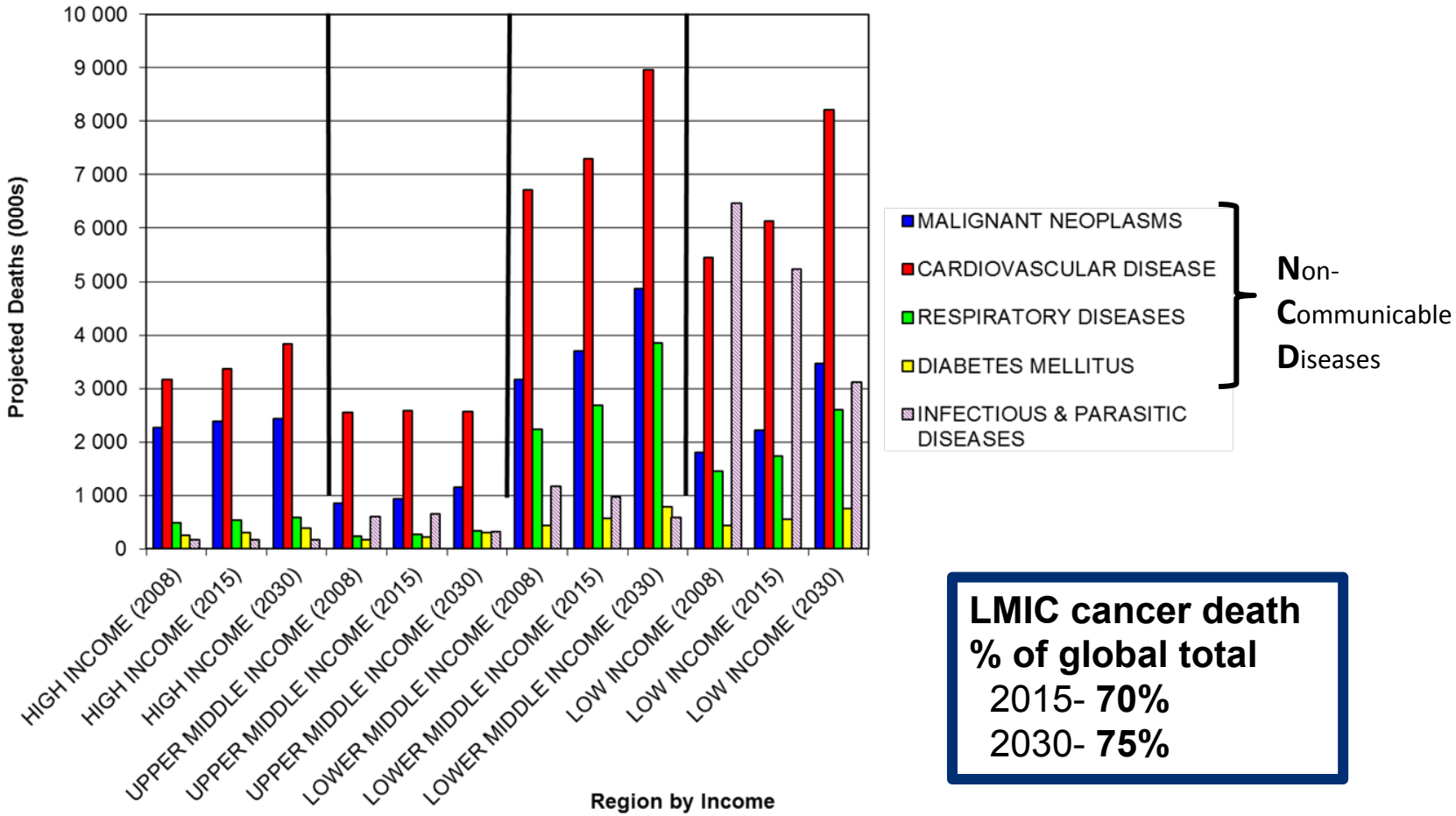
1 linac for every 250,000 inhabitants is considered optimal, you can see how many are needed globally in order to have access conventional RT

Defining the Problem:

International Cancer Expert Corps
Partnering to transform global cancer care

WHO Global Burden of Disease

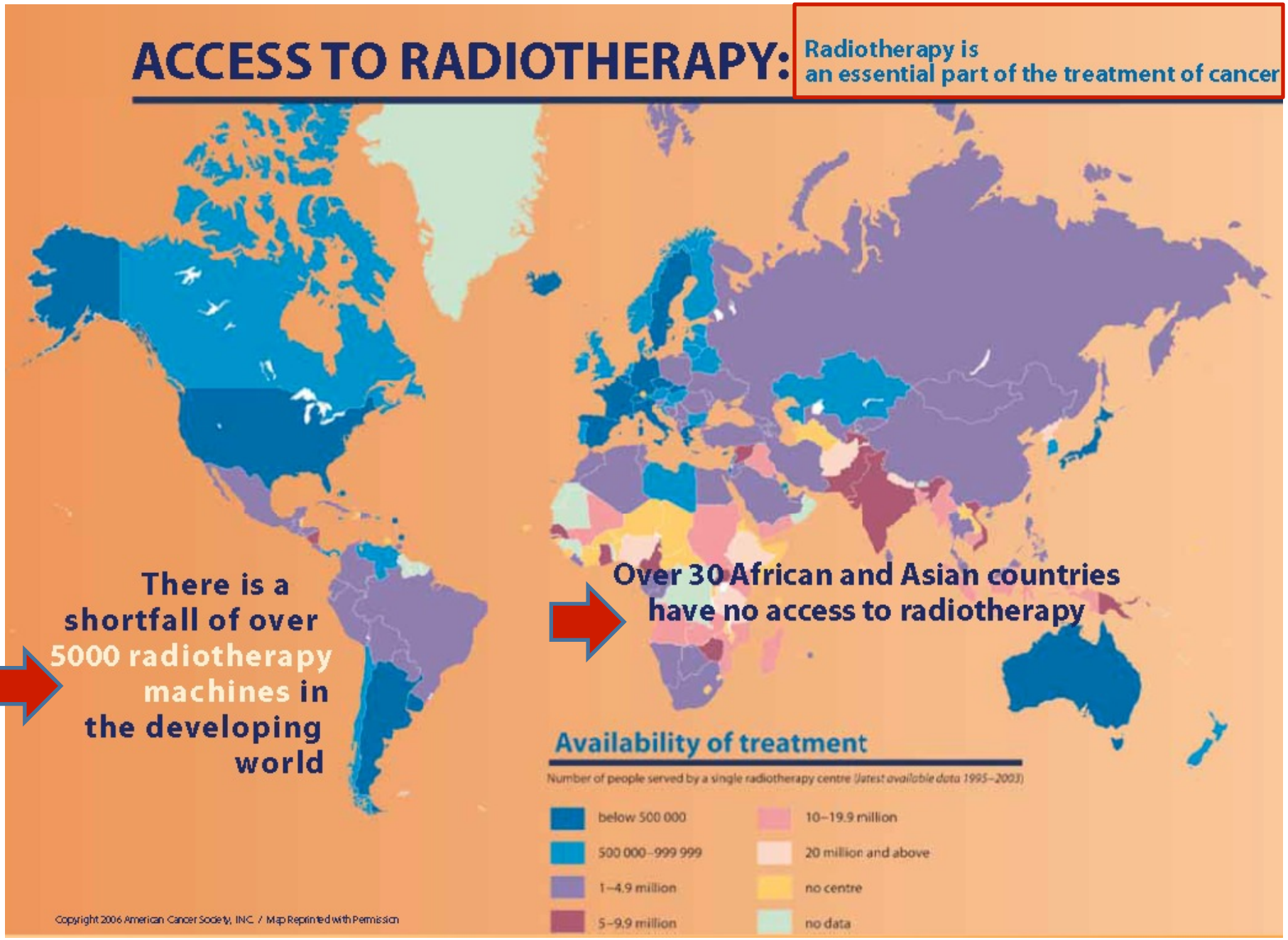
http://www.who.int/healthinfo/global_burden_disease/projections/en/index.html



LMIC cancer death % of global total
2015- **70%**
2030- **75%**

Defining the Problem:

http://www.iceccancer.org



Radiotherapy in the 21st century

3 "Cs" of Radiation

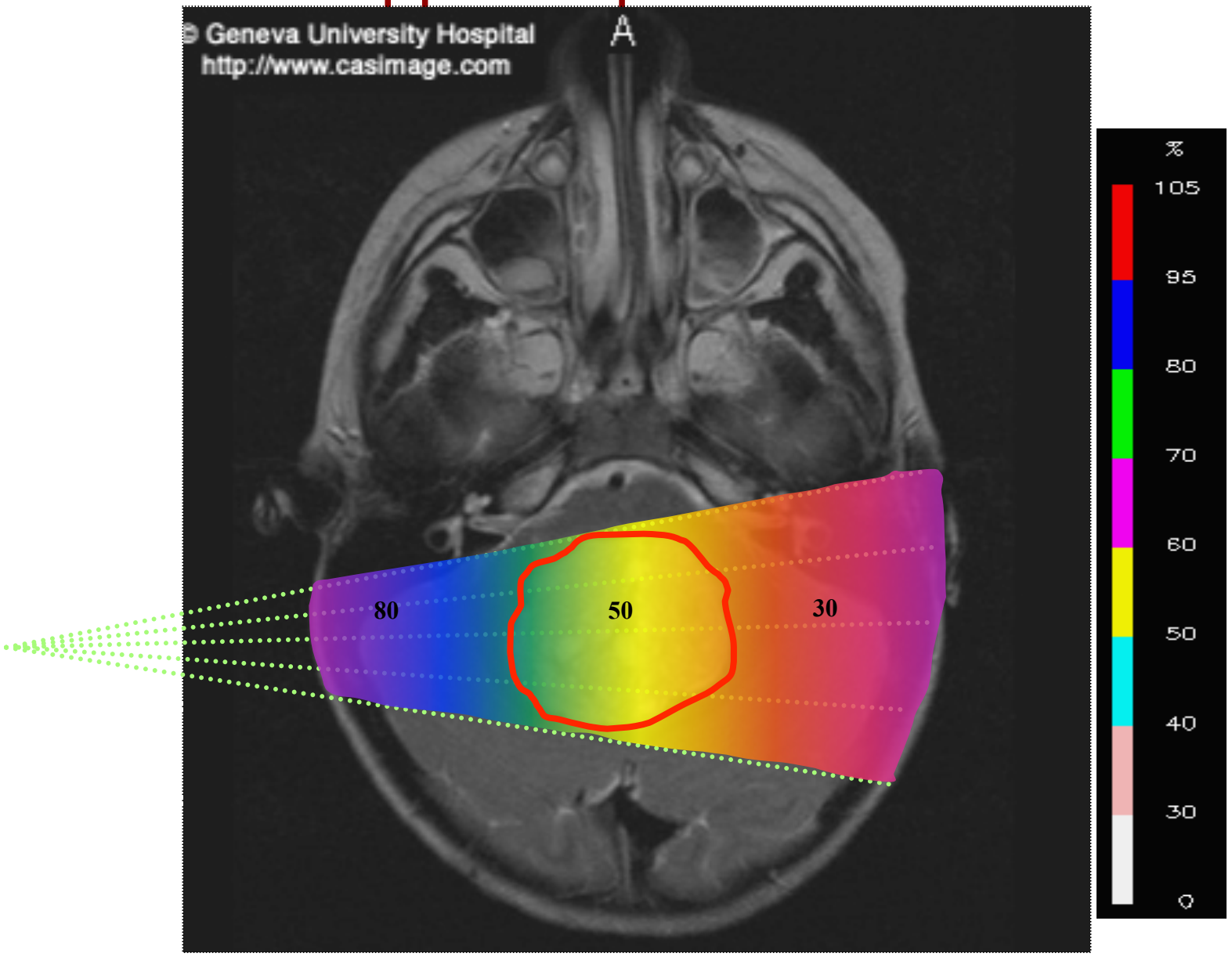
Cure (~ 50-60 % cancer cases are cured)
Conservative (non-invasive, few side effects)
Cheap (5-10% of total cost of cancer on RT)

There is no substitute for RT in the near future
The rate of patients treated with RT is increasing

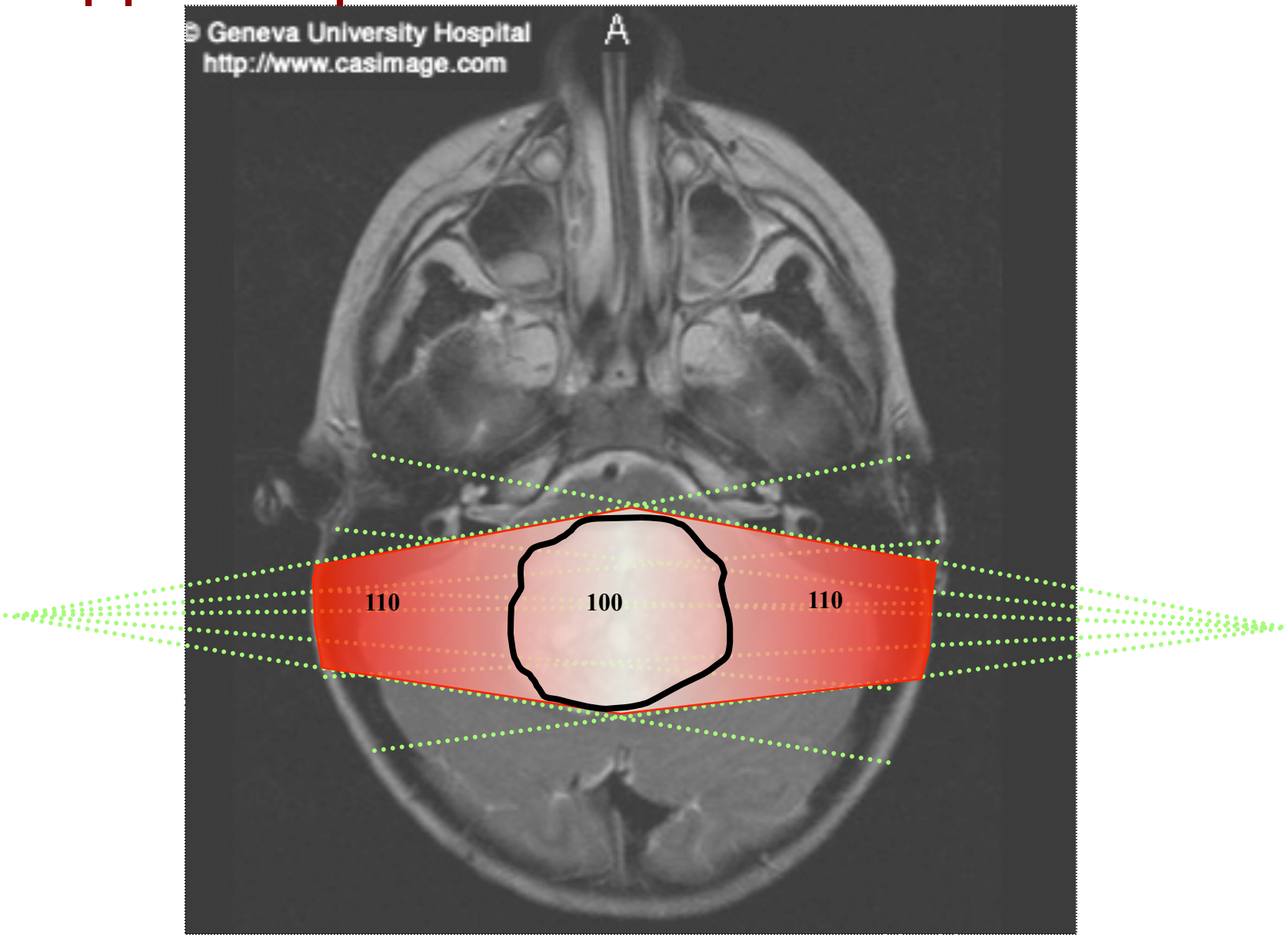
Present Limitation of RT:
~30% of patients treatment fails locally

(J.P.Gérard)

Two opposite photon beams

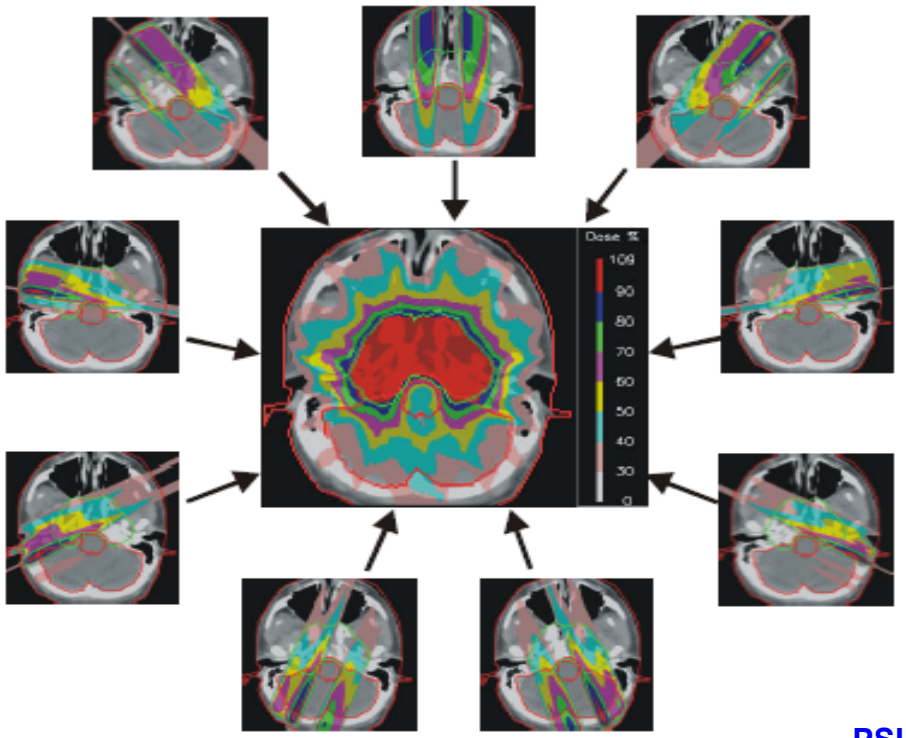


Two opposite photon beams



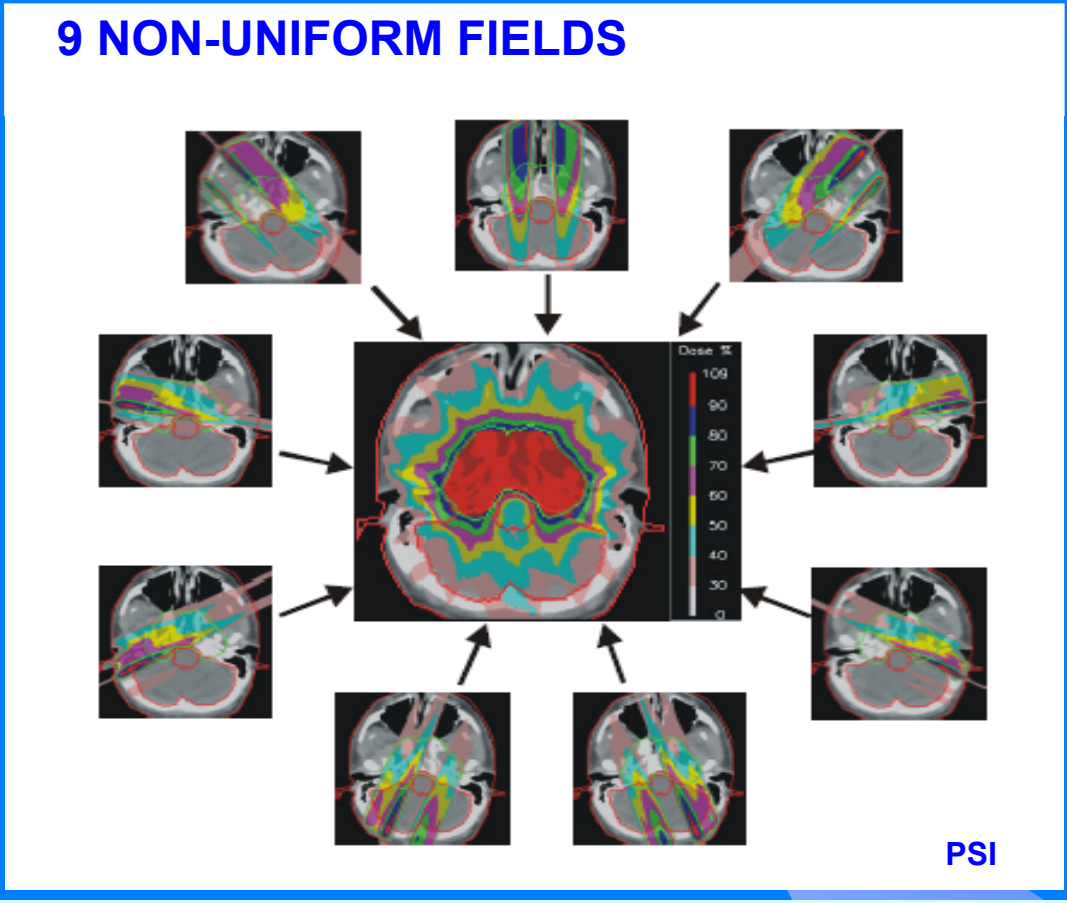
IMRT = Intensity Modulated Radiation Therapy with photons

9 NON-UNIFORM FIELDS



PSI

IMRT = Intensity Modulated Radiation Therapy with photons



60-75 grays (joule/kg) given in 30-35 fractions (6-7weeks)

to allow healthy tissues to repair:

90% of the tumours are radiosensitive

Radiotherapy in the 21st century

3 "Cs" of Radiation

Cure (~ 50 % cancer cases are cured)
Conservative (non-invasive, few side effects)
Cheap (5-10% of total cost of cancer on RT)

There is no substitute for RT in the near future
The rate of patients treated with RT is increasing

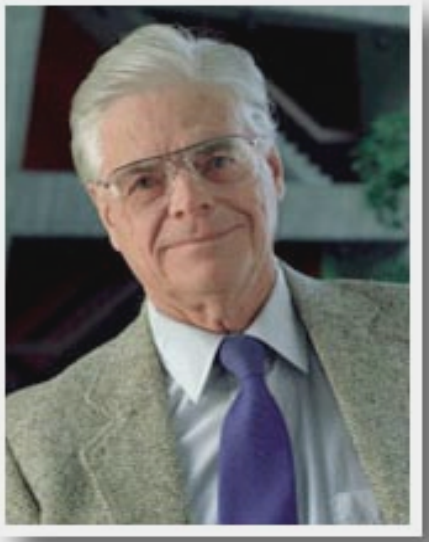
Present Limitation of RT:
~30% of patients treatment fails locally

(J.P.Gérard)

How to improve outcome?

- Physics technologies: better dose distribution, higher dose, more localised
- Imaging: accuracy, multimodality, real-time, organ motion
- Data: storage, analysis, sharing, patient referral, second opinion
- Biology: fractionation, radiobiological effectiveness, radio-resistance, radio-sensitization
- Collaboration: cancer is a multidisciplinary field

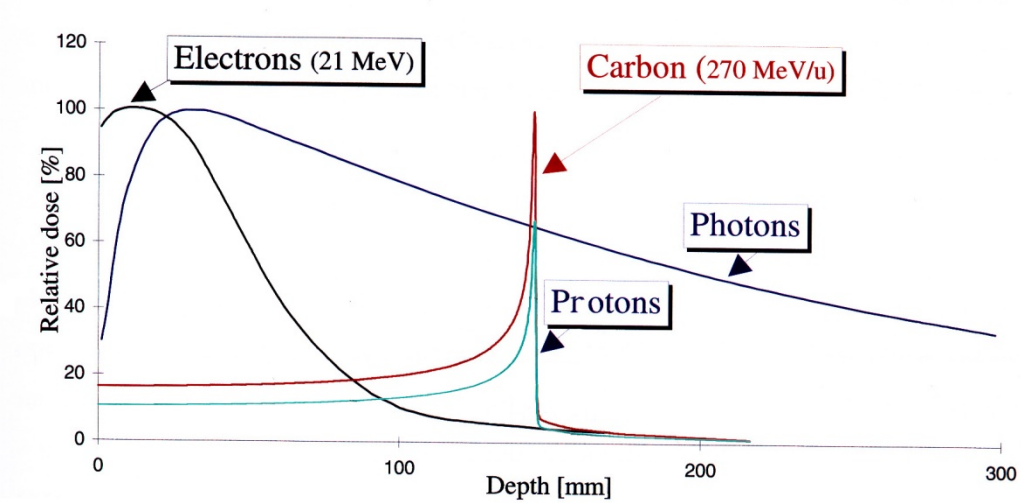
Hadrontherapy: all started in 1946



Founder and first director of Fermilab

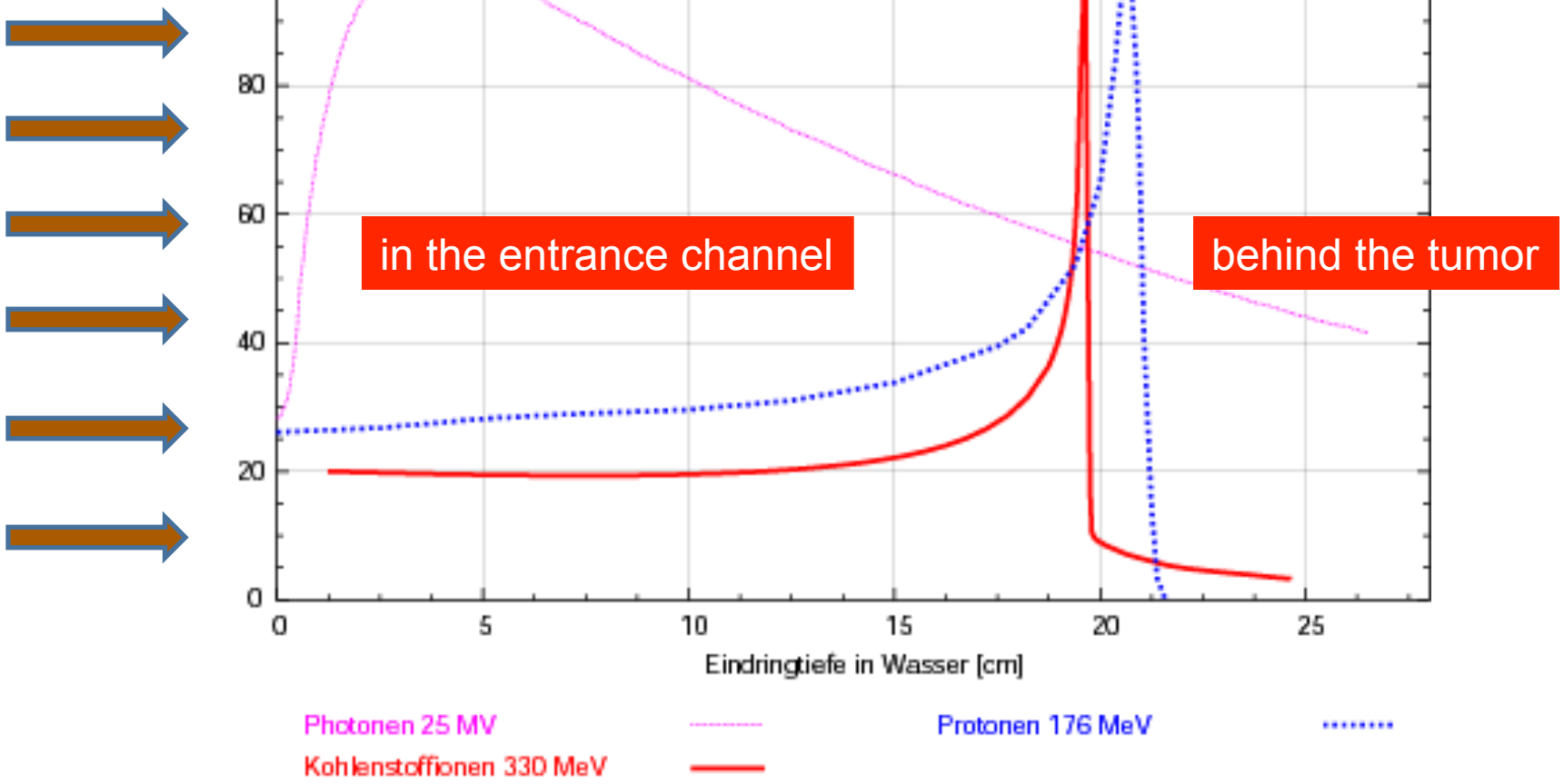
Robert Wilson:

- Protons can be used clinically
- Accelerators are available
- Maximum radiation dose can be placed into the tumour
- Particle therapy provides sparing of normal tissues



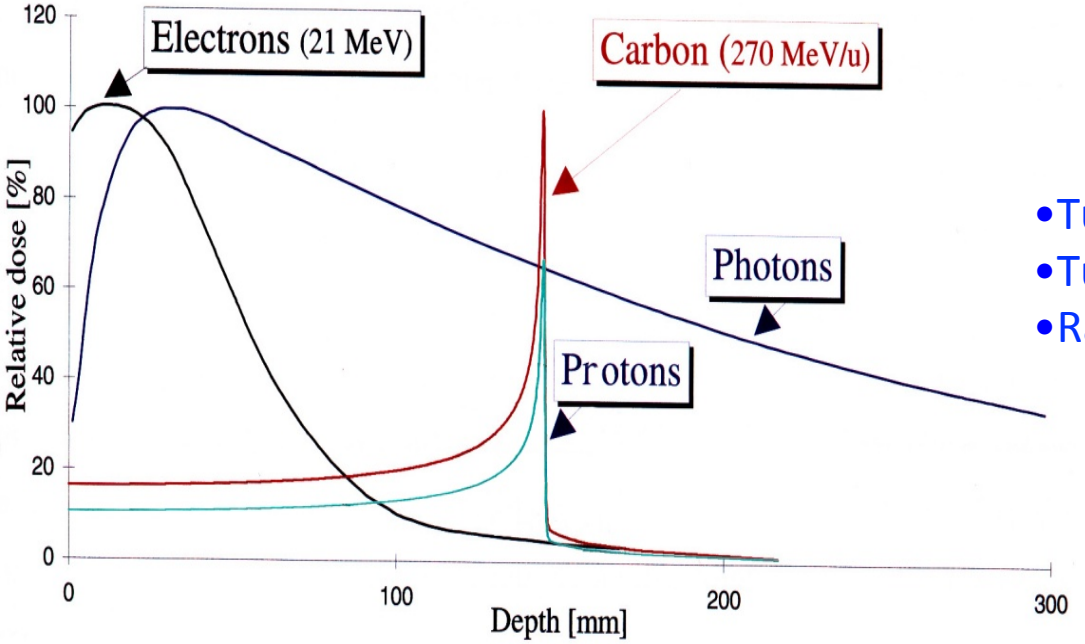
Wechselwirk

Due to the physical selectivity
improved sparing of normal tissue



in the entrance channel

behind the tumor



- Tumours close to critical organs
- Tumours in children
- Radio-resistant tumours

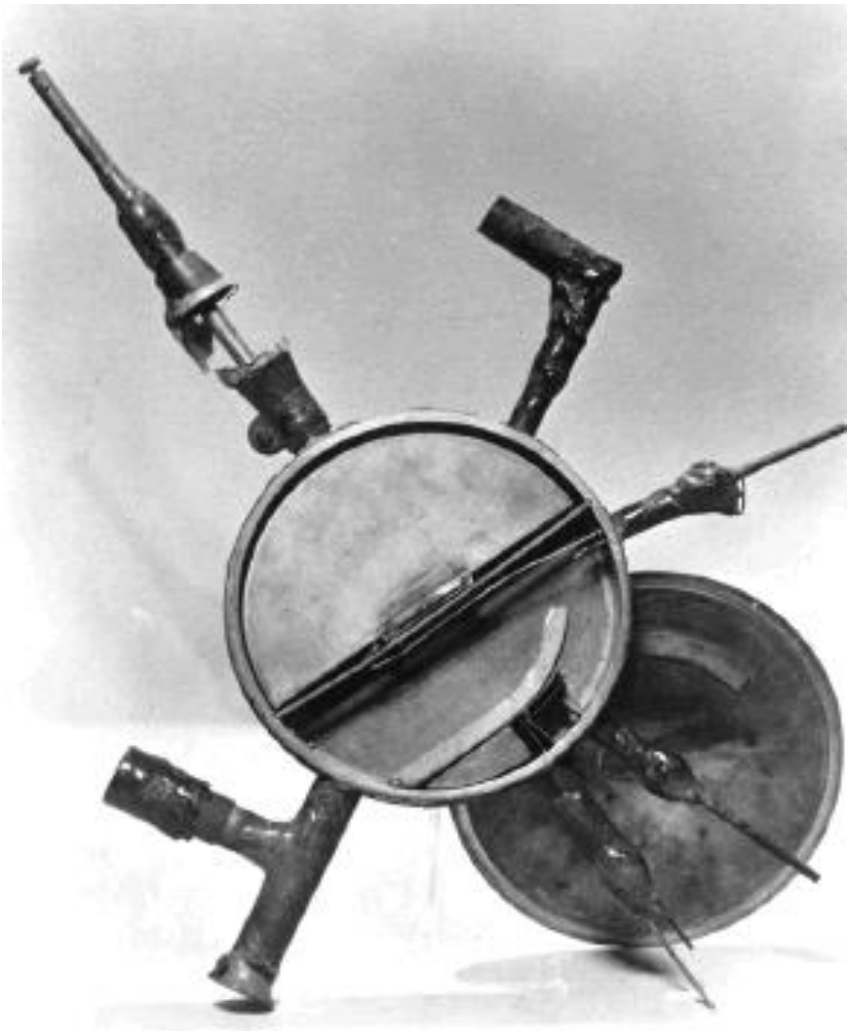
Energy deposition

Photons and Electrons vs. Hadrons

- Physical dose high near surface
- DNA damage easily repaired
- Biological effect lower
- Need presence of oxygen
- Effect not localised

- Dose highest at Bragg Peak
- DNA damage not repaired
- Biological effect high
- Do not need oxygen
- Effect is localised

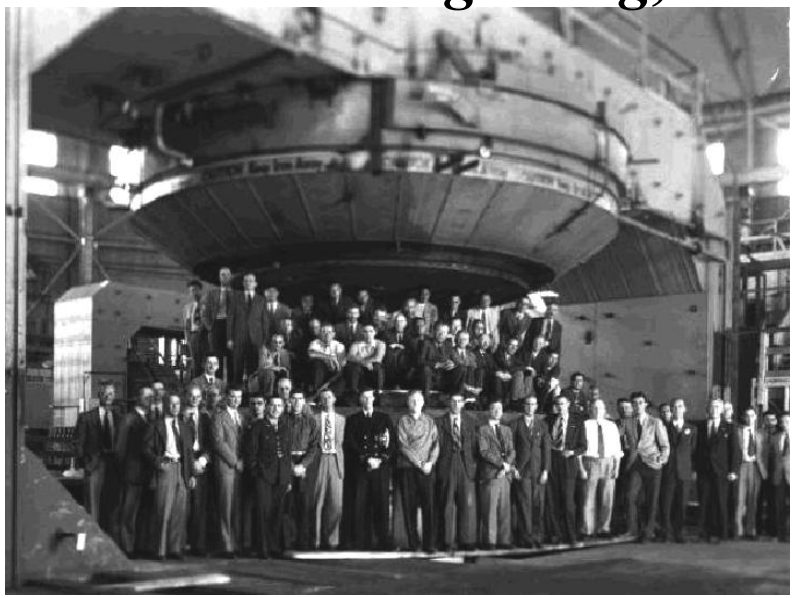
First Cyclotron *(Lawrence& Livingston, 1930)*



Nobel Prize 1939

184-Inch Cyclotron and Hadron Therapy

The beginning, 1947



The first beam, November 1, 1947

E. Blakely, LBNL

FIRST PROTON THERAPY PATIENT TREATED
September 1954

Prof. Cornelius A. Tobias

- *1948: Biology experiments using protons*
- *1954: Human exposure to accelerated proton, deuteron and helium ion beams*
- *1956-1986: Clinical Trials– 1500 patients treated*

CERN WAS FOUNDED
29 September 1954

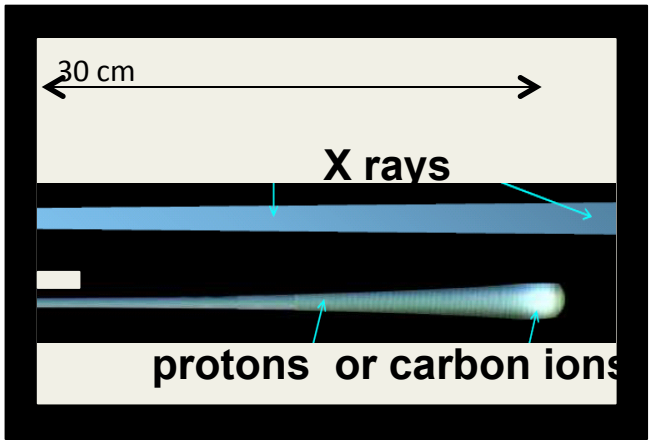
- ***The first meeting of the provisional CERN Council 15 Feb 1952 Key people: Sir Ben Lockspeiser, Edoardo Amaldi, Felix Bloch, Leew Kowarski, Cornelis Bakker, and Niels Bohr***

Tumours treated by HT at LBNL

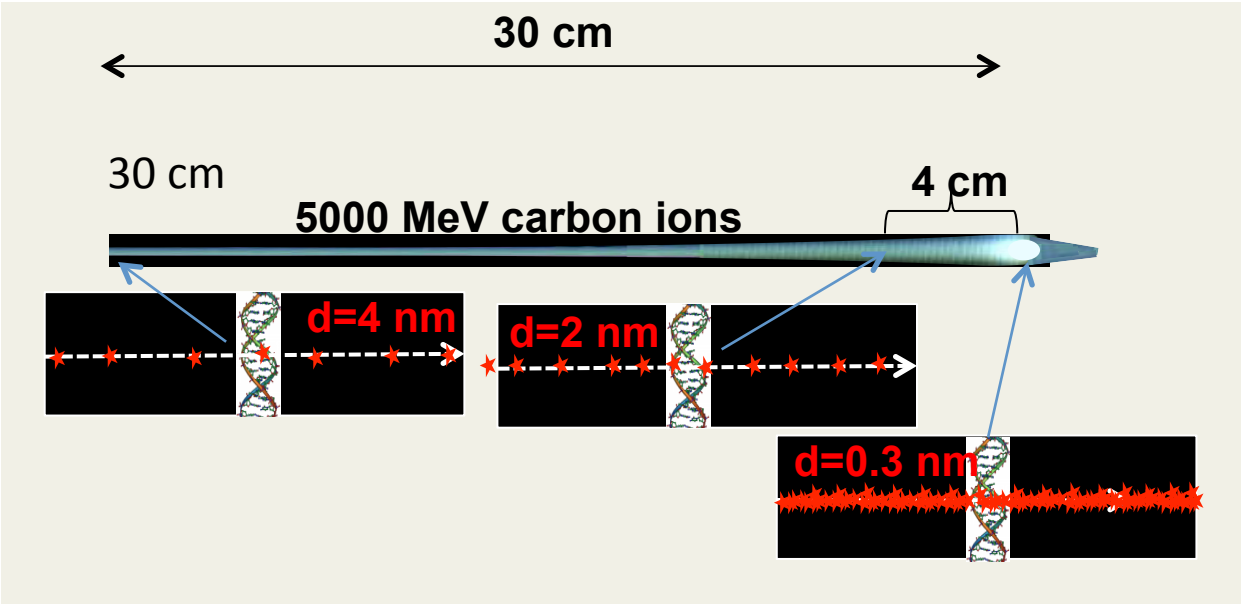
1955	1975	1976	1977	1982	1987	1992
Pituitary Treatment	1st He pt		1st C, Ne pt			
			Eye treatment			
		Phase-1 He		Phase I-II Ne	Phase I-II Ne & He	
		1st Comp Tx Plan			3D planning	
			LBNL CT	LBNL MRI		
					Image Correlation	

Avantages of protons and carbon ions

protons: 230 MeV
C ions : 5000 MeV



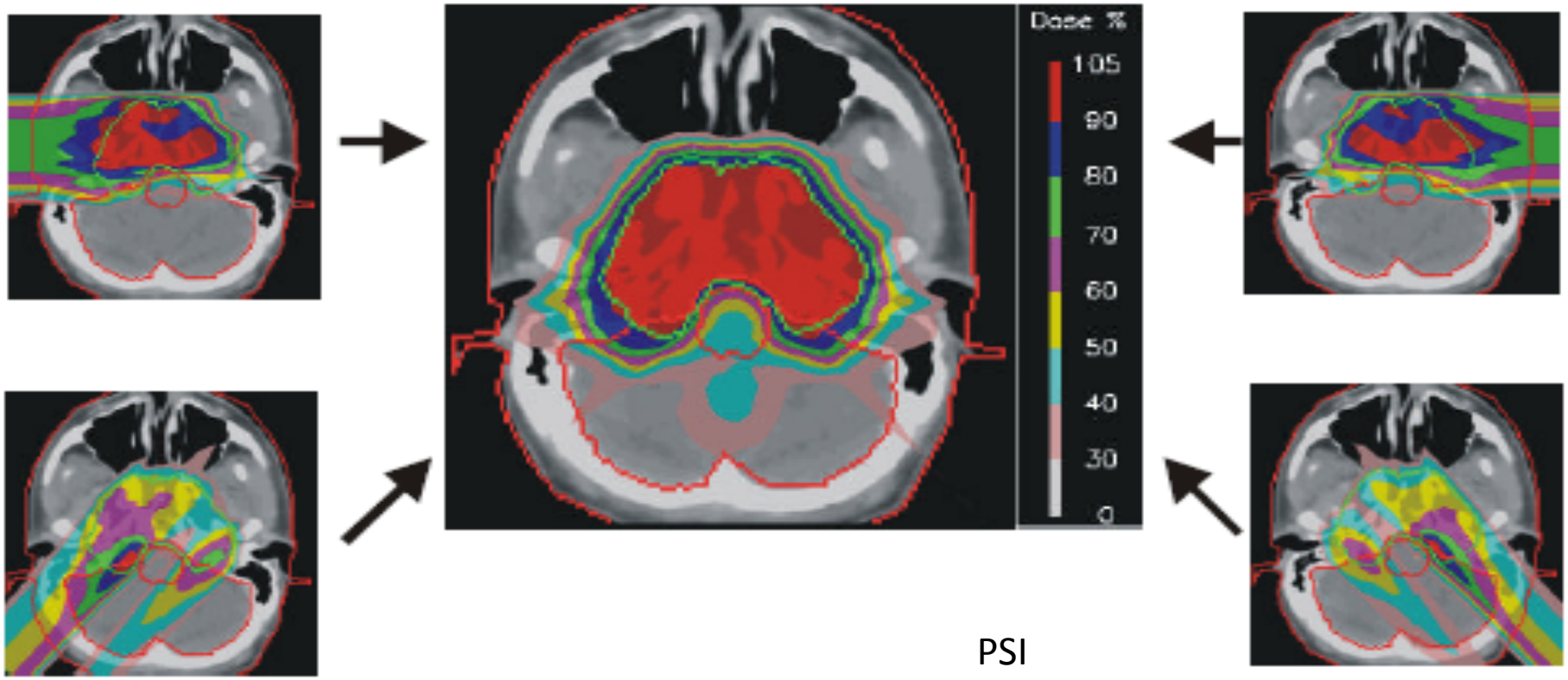
1. Healthy tissues are spared by protons and carbon ions



2. Carbon ions have charge = 6 and produce in the DNA clustered unrepairable damages thus killing at the end of the range the cells which are radioresistant to both X rays and protons.

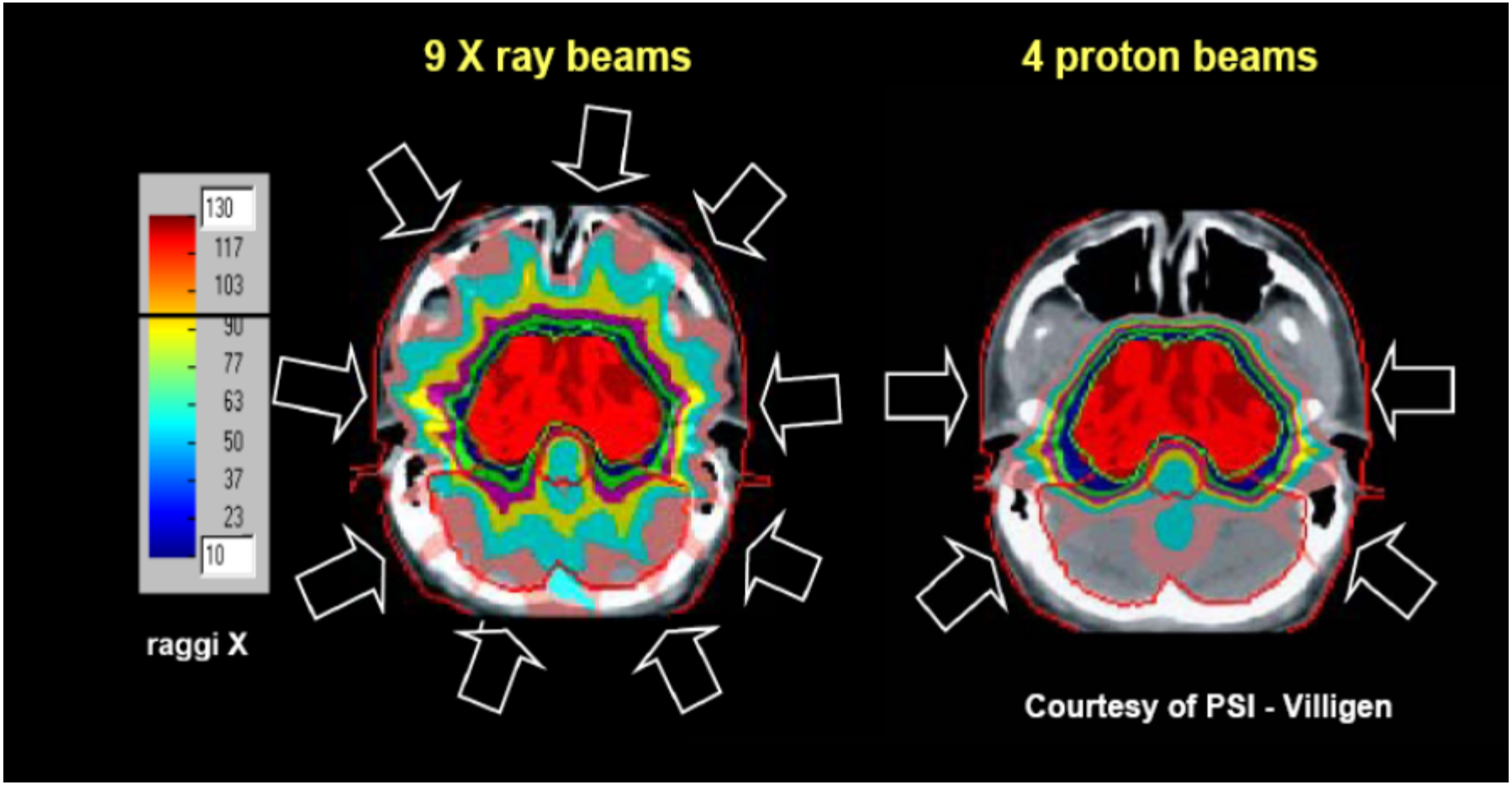
IMPT = Intensity Modulated Particle Therapy with protons

4 NON-UNIFORM FIELDS



PSI

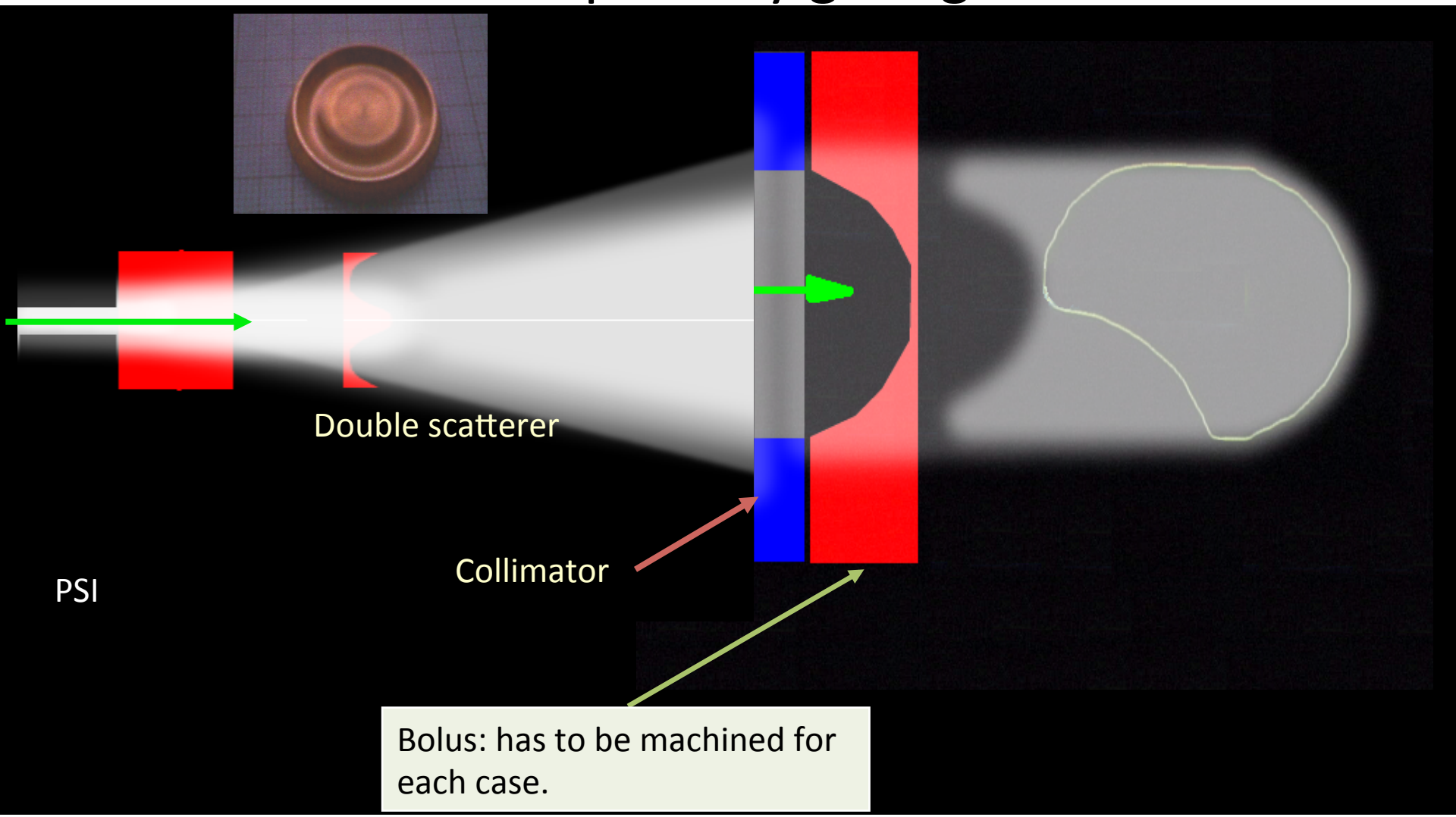
Comparison of Collateral Damage



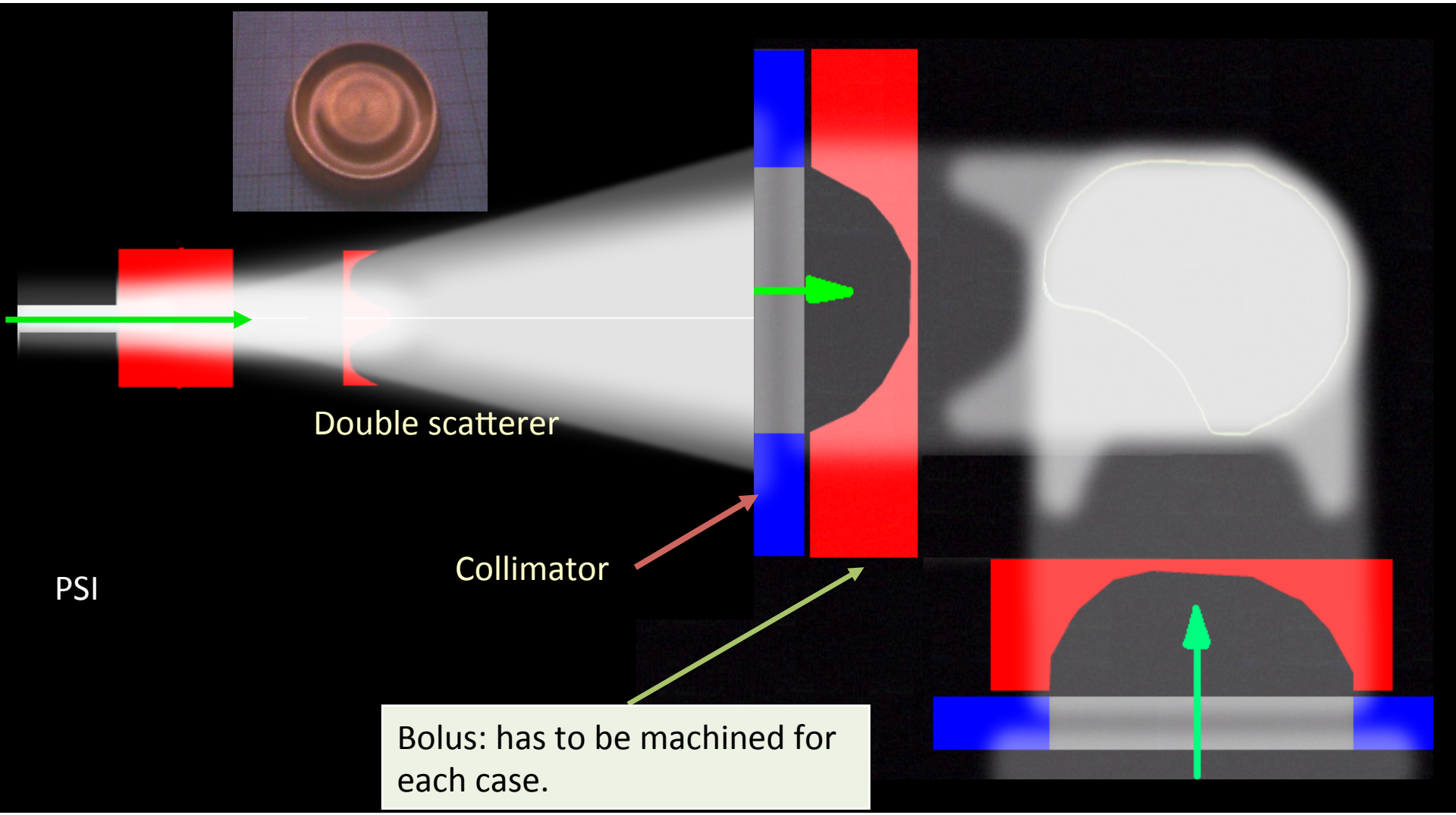
The Bragg Peak

- Allows more precise allocation of the dose to the tumour
- BUT makes dosimetry and diagnostics more difficult because the energy is deposited preferentially inside the patient
- To take full advantage, we need improved diagnostics
    - To steer the beam spot by measurement of the location of the energy deposition
    - To control the dose (dosimetry)

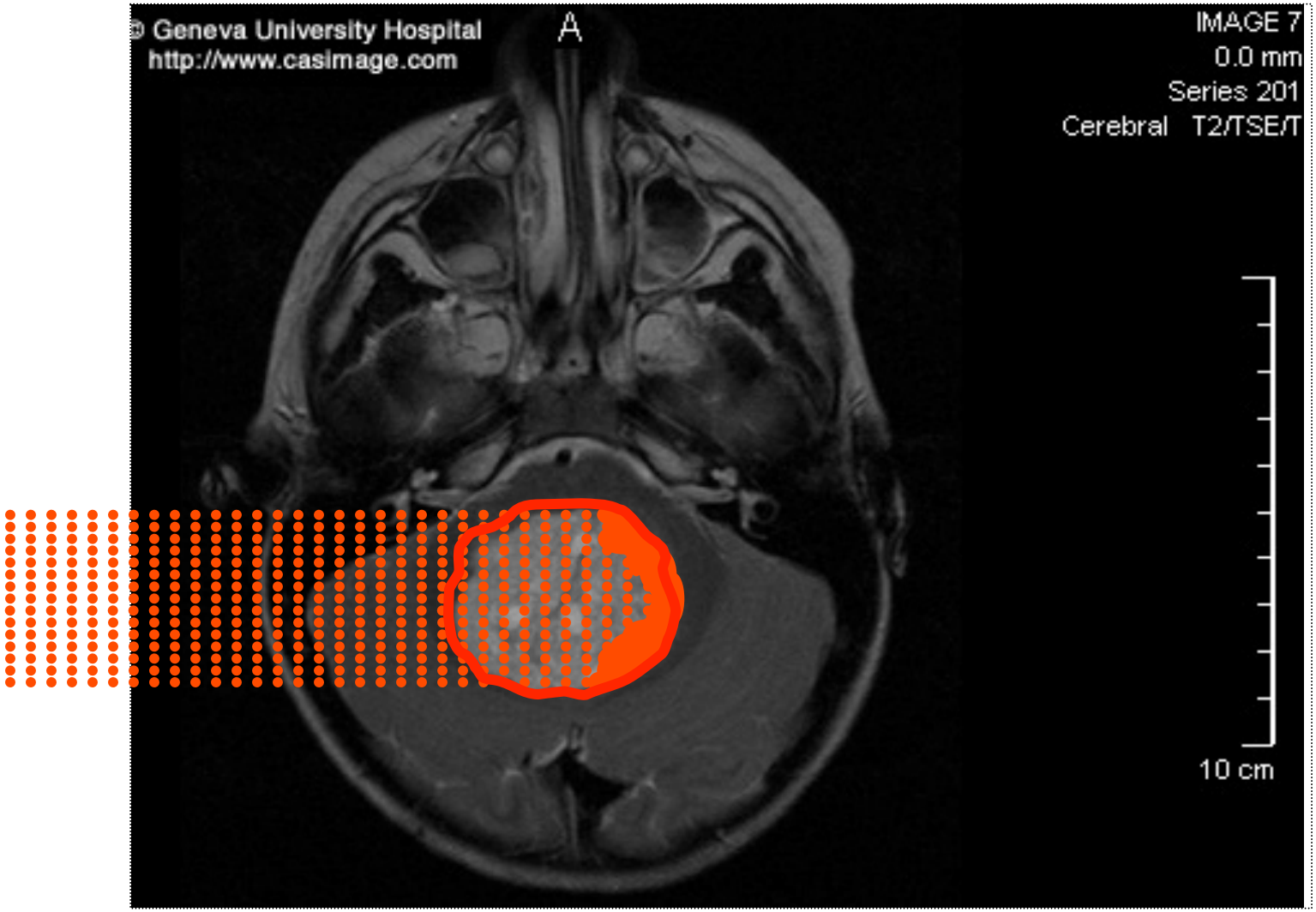
Standard procedure: Passive beam spreading with respiratory gating



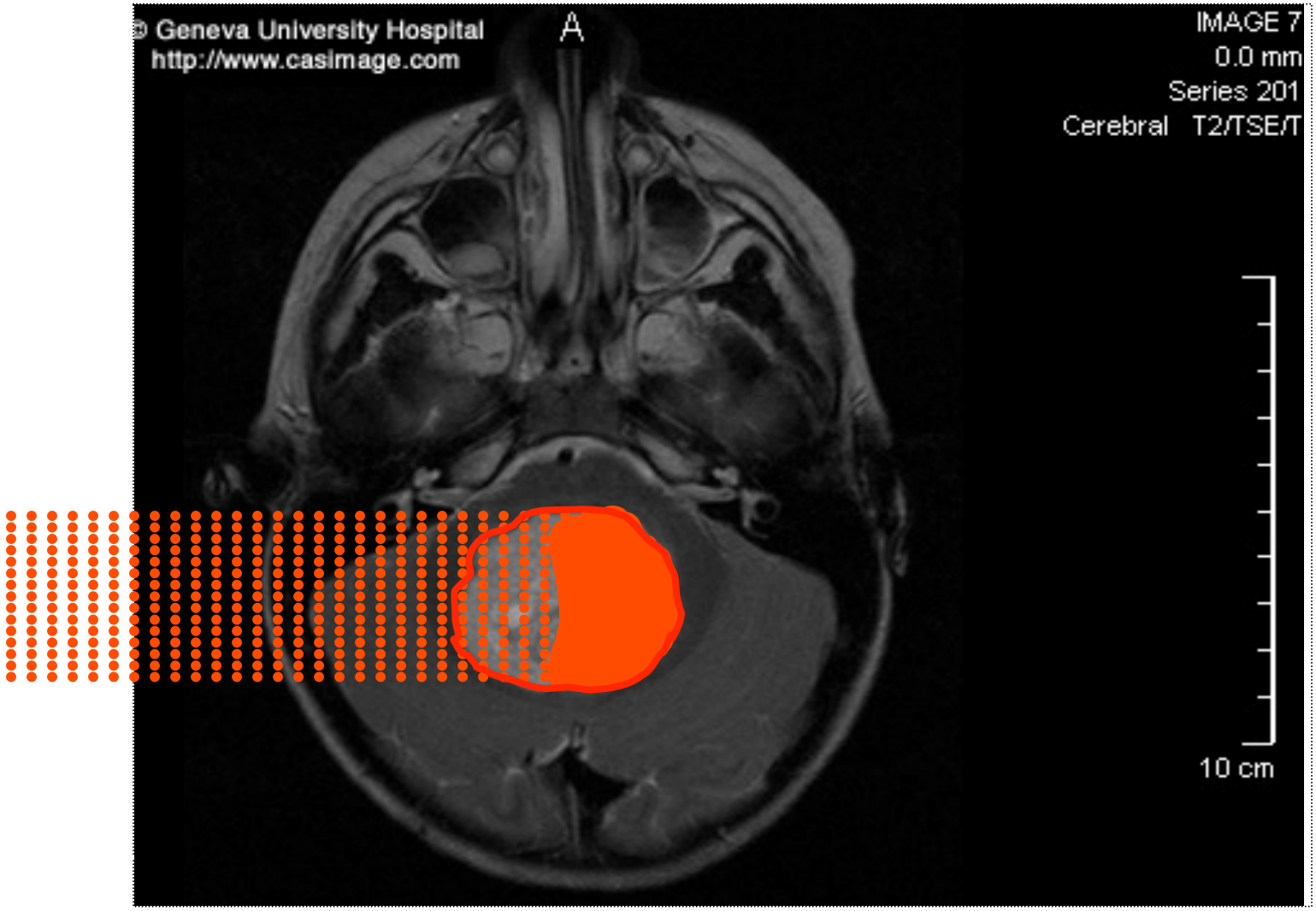
Standard procedure: Passive beam spreading



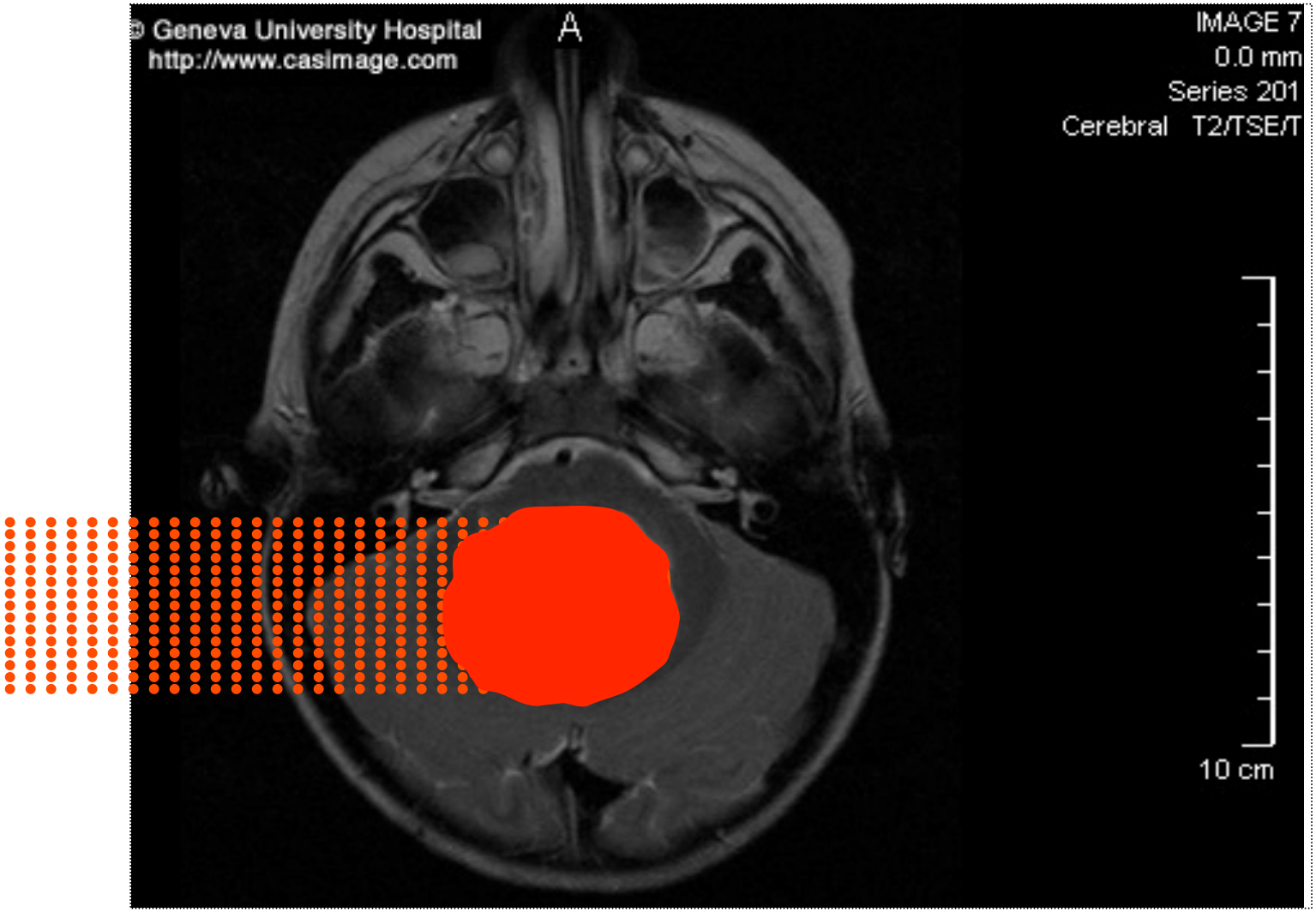
Spot scanning with a proton beam



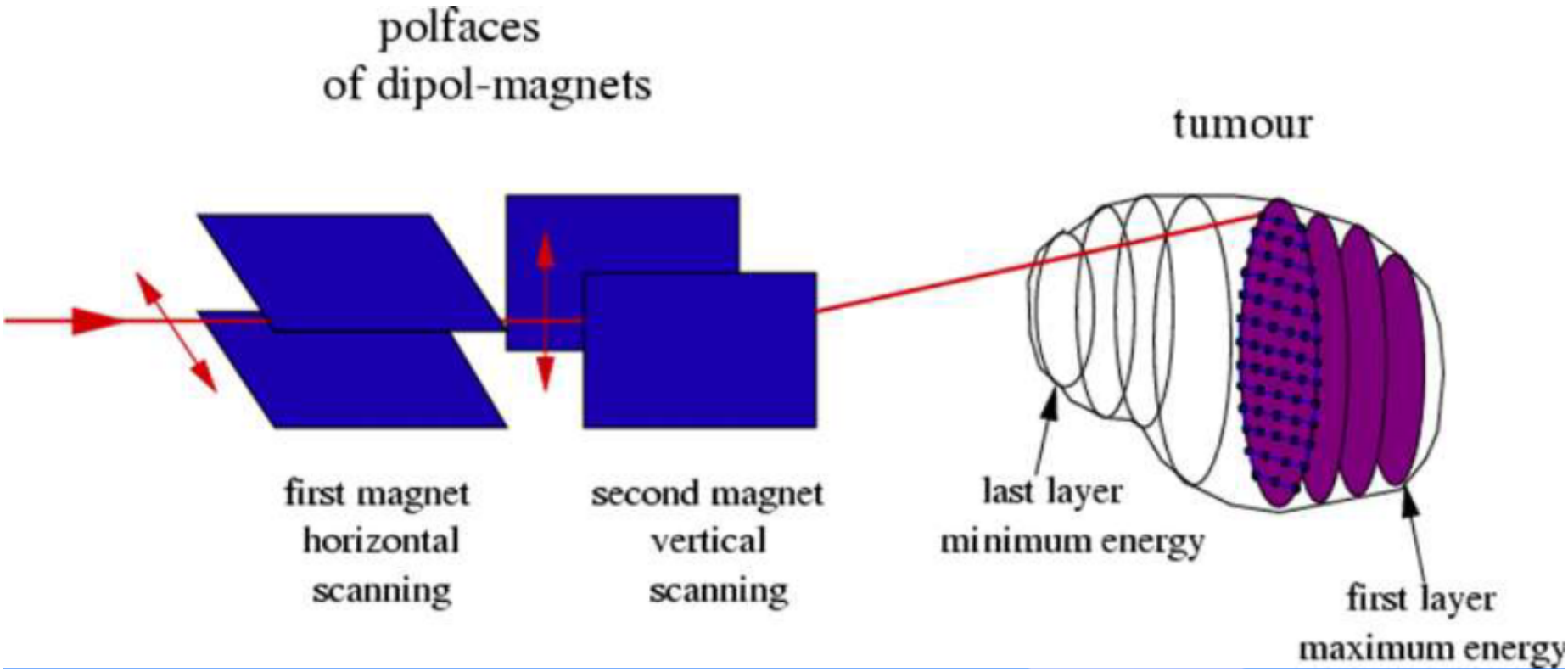
Spot scanning with a proton beam



Spot scanning with a proton beam



2B. Active “raster scanning” technique by GSI with respiratory gating (Villigen)



The synchrotron beam is moved continously

3 crucial years for HT

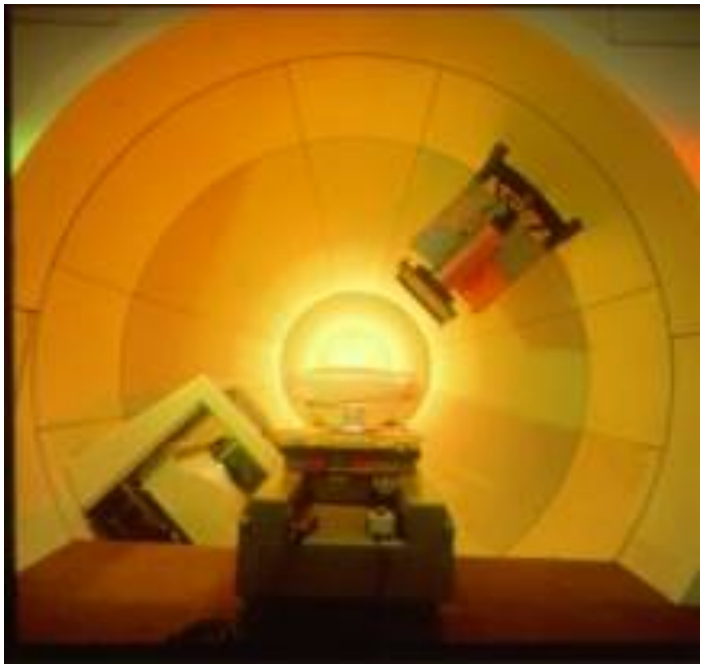
In the years 1992-1994 the rate of progress changed:

- 1992 at Loma Linda first proton patient
- 1993 MGH (Boston) orders the first commercial protontherapy centre
- 1993 GSI starts the carbon ion 'pilot project'
- 1994 HIMAC first carbon ion patient

Key Milestones of Hadron therapy

1991 — First hospital based *Proton* facility
Loma Linda University Medical Center, CA, USA

360^0 Gantry



HIMAC in Chiba is the pioneer of carbon therapy

Yasuo Hirao

First patient1994

Hirohiko Tsujii

Since the cells do not repair. less fractions are possible

HIMAC: reduced fractions! Even single fraction

The Darmstadt GSI ‘pilot project’ (1997-2008)

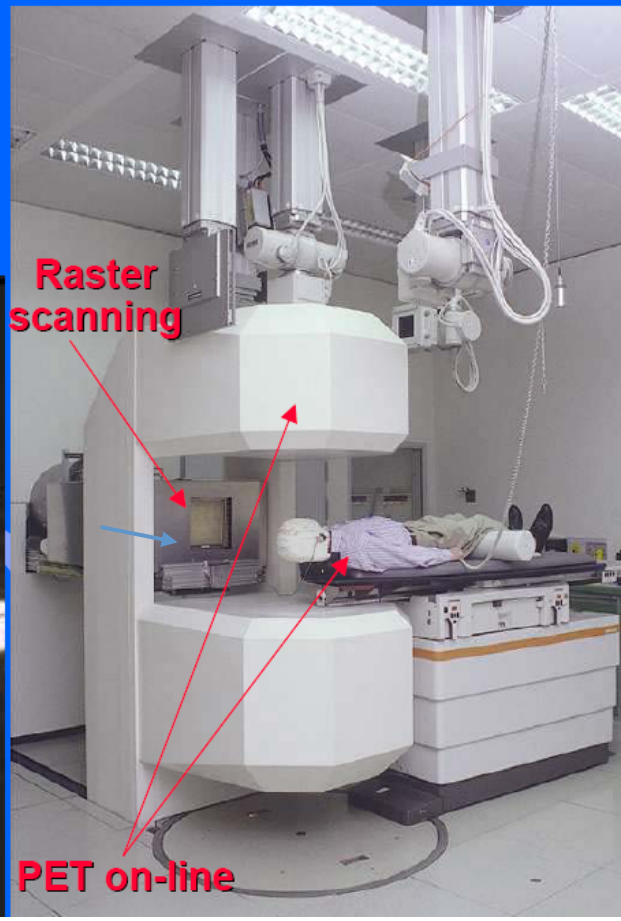
G. Kraft

J. Debus

G. Kraft

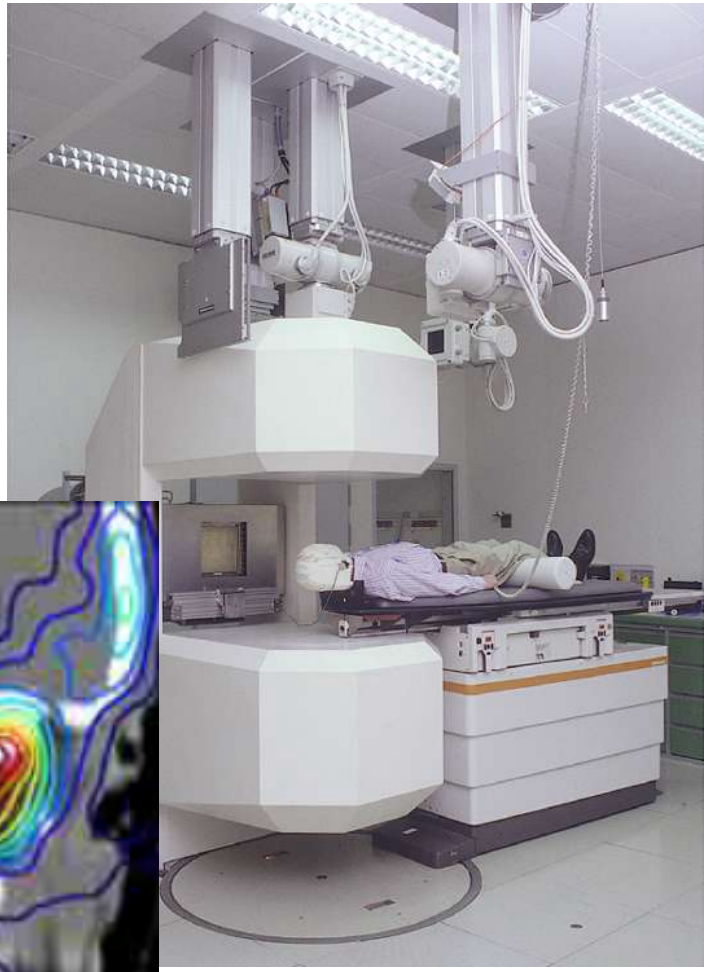
450 patients treated with carbon ions

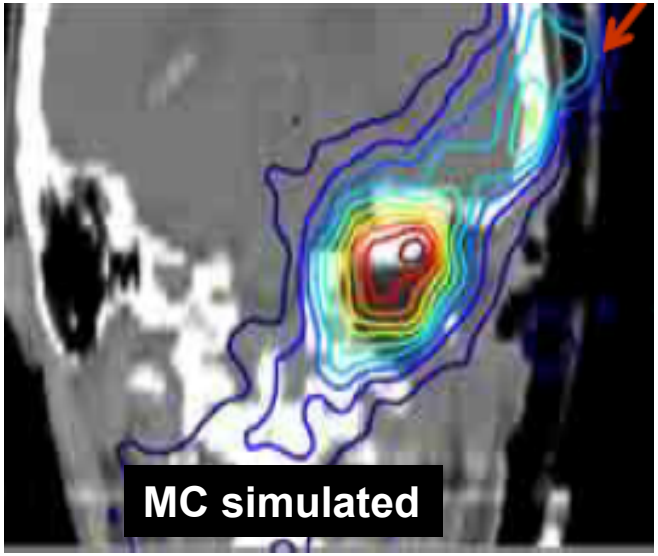
J. Debus (Heidelberg Univ.)

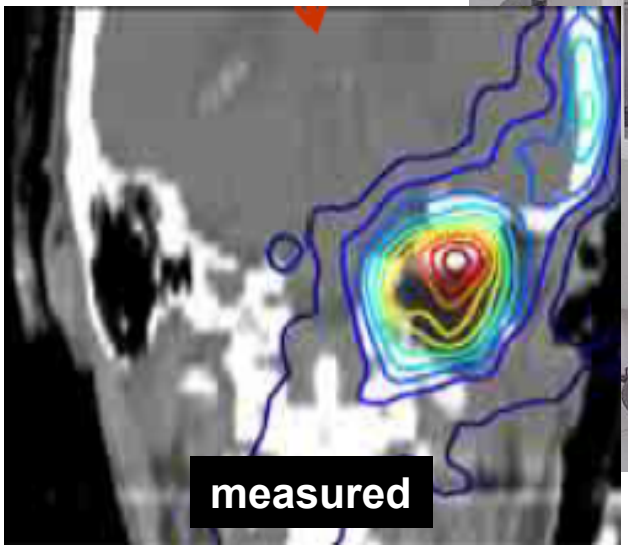


Real-time monitoring

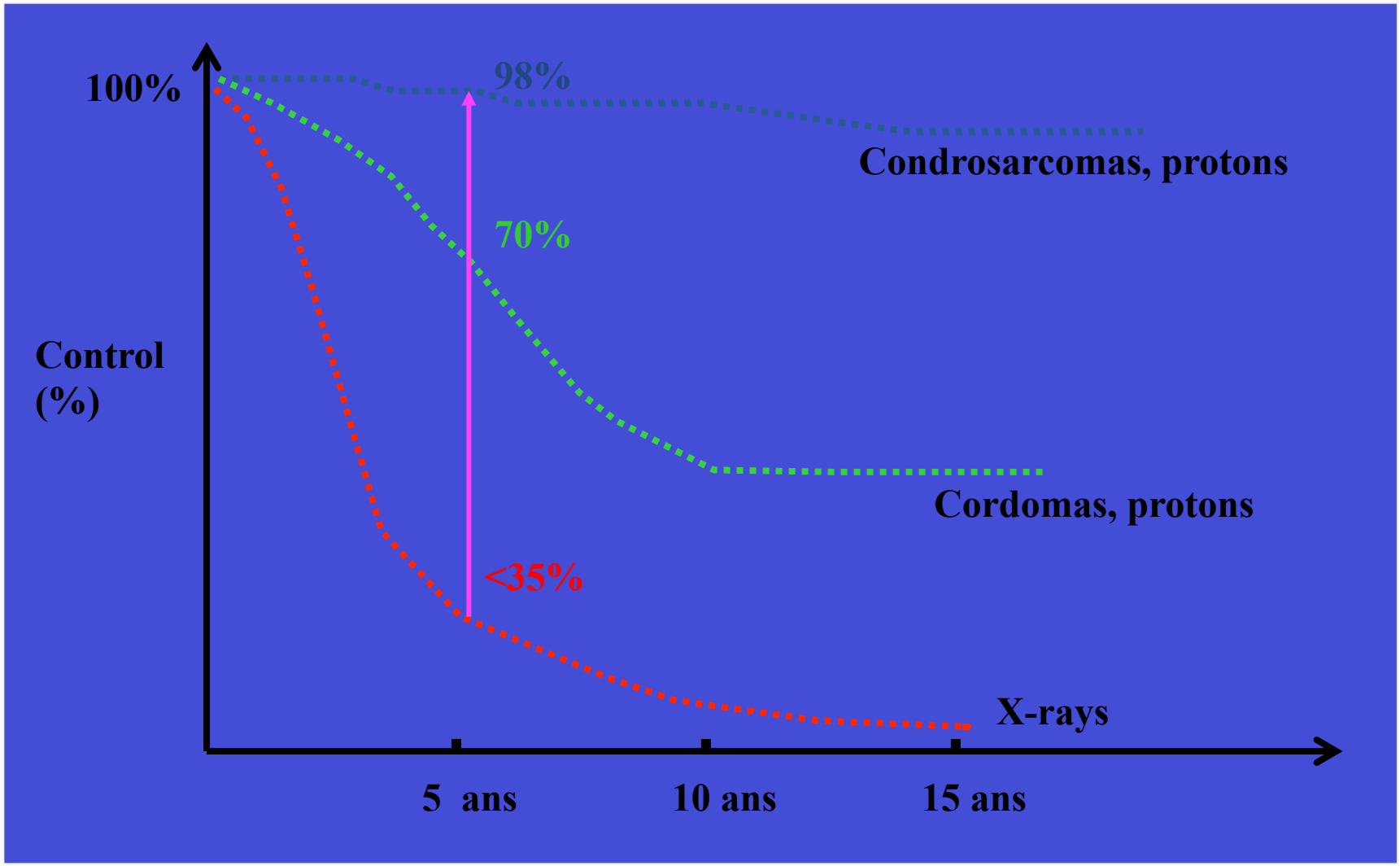
- In-beam PET @ GSI (Germany)
- MonteCarlo simulations
- Organ motion



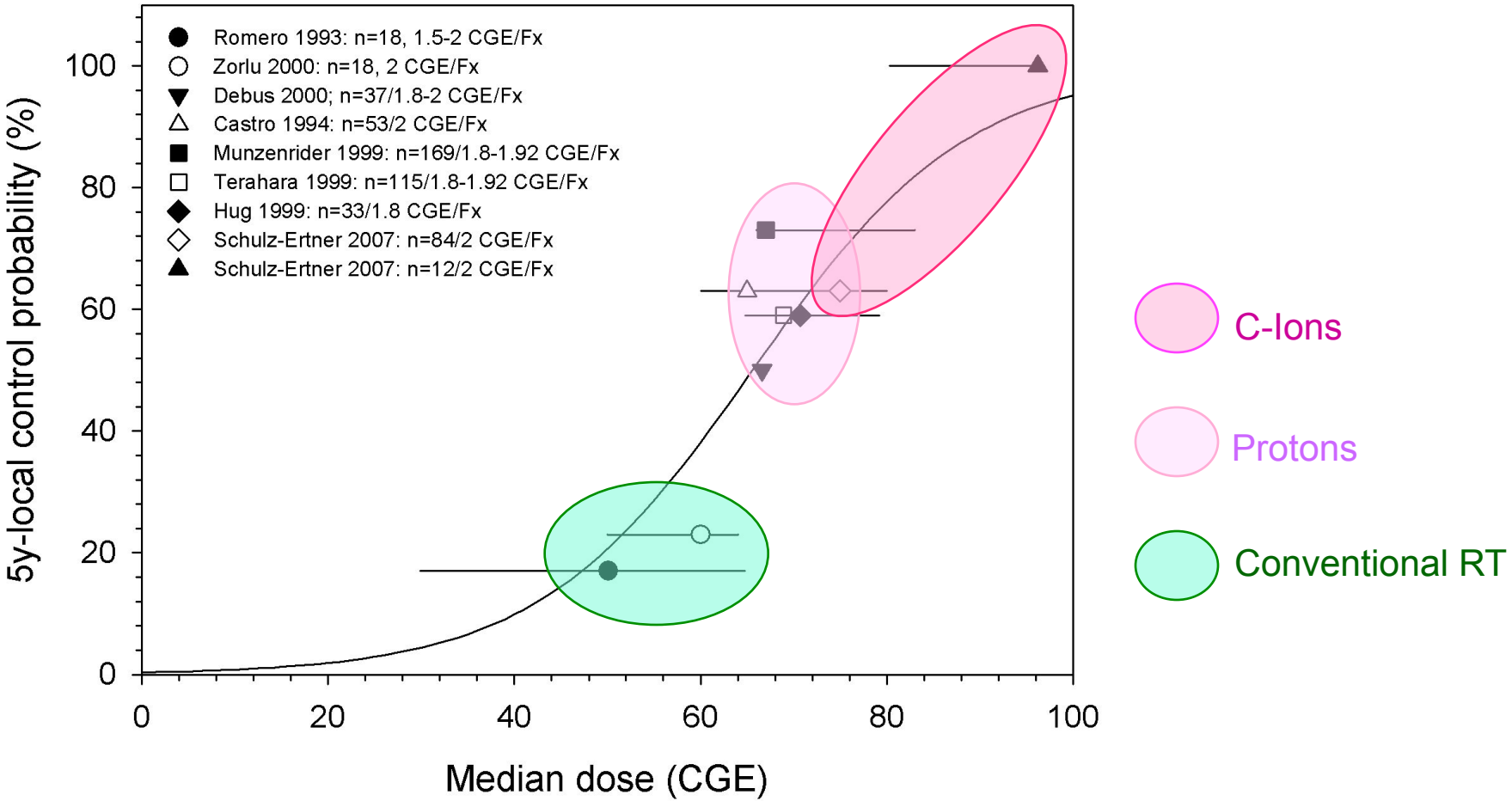




First results at MGH-Harvard with protons



Tumour control Rate: Chordomas



Schulz-Ertner, IJROBP 2007

Numbers of potential patients

- X-ray therapy
  every 10 million inhabitants: 20'000 pts/year

- Protontherapy
  12% of X-ray patients 2'400 pts/year

- Therapy with Carbon ions for radio-resistant tumour
  3% of X-ray patients 600 pts/year

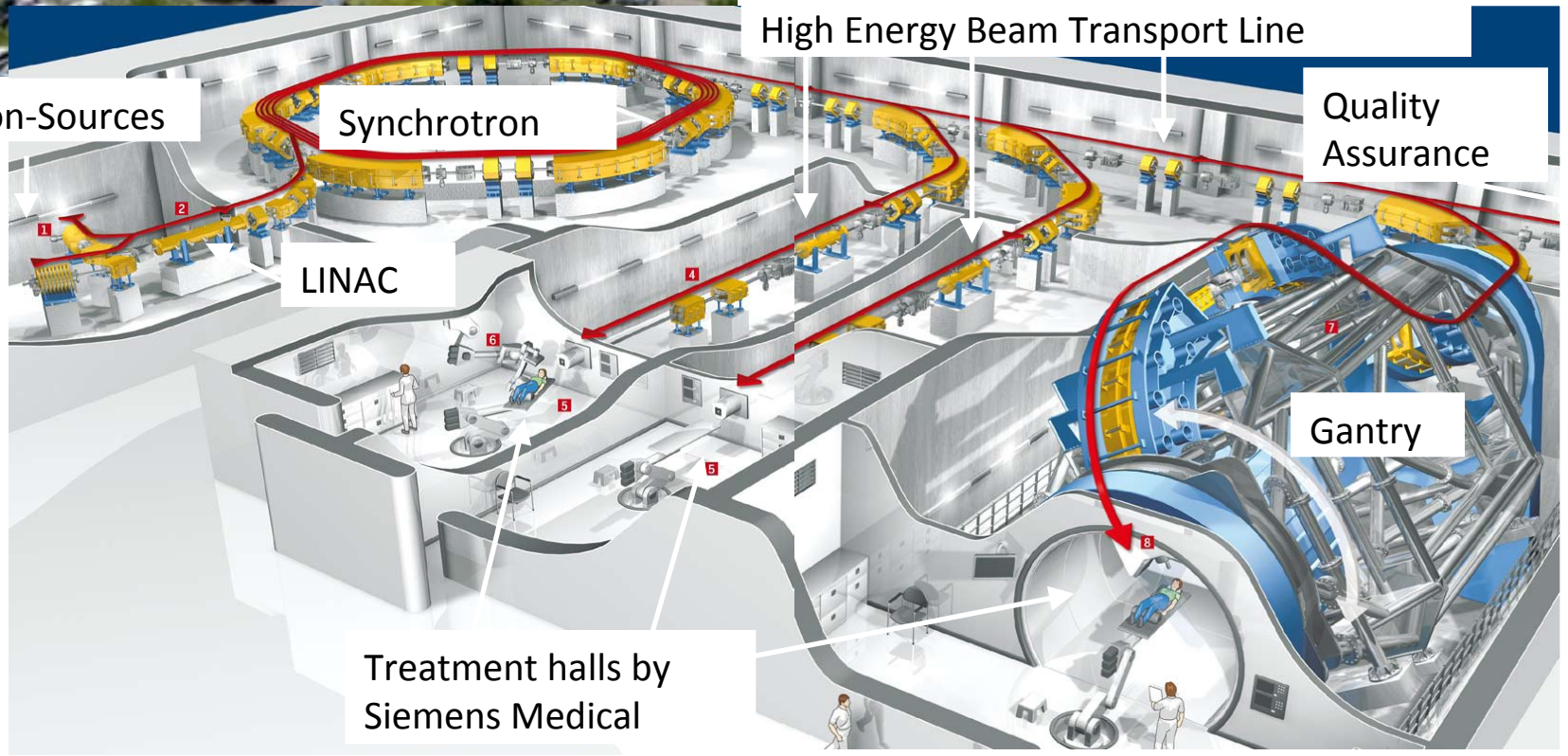
TOTAL every 10 M about 3'000 pts/year

(*) Combining studies made in Austria, Germany, France and Italy in the framework of ENLIGHT - Coordinator: Manjit Dosanjh

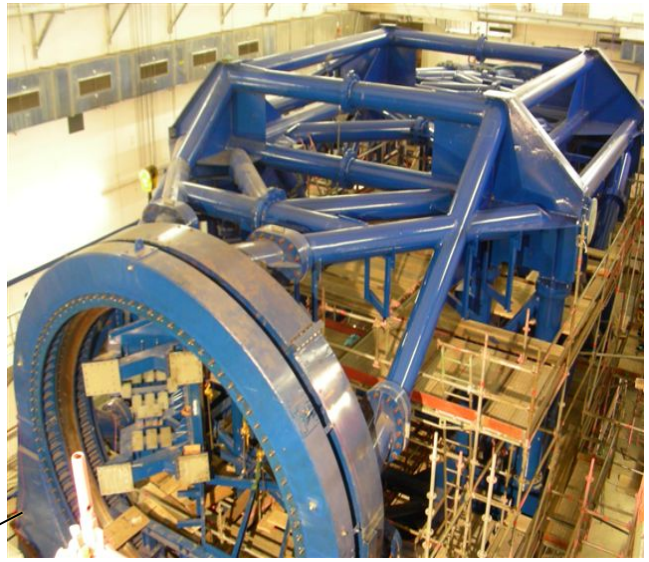
HIT at Heidelberg

Medical Director: J. Debus
Technical Director: T. Haberer

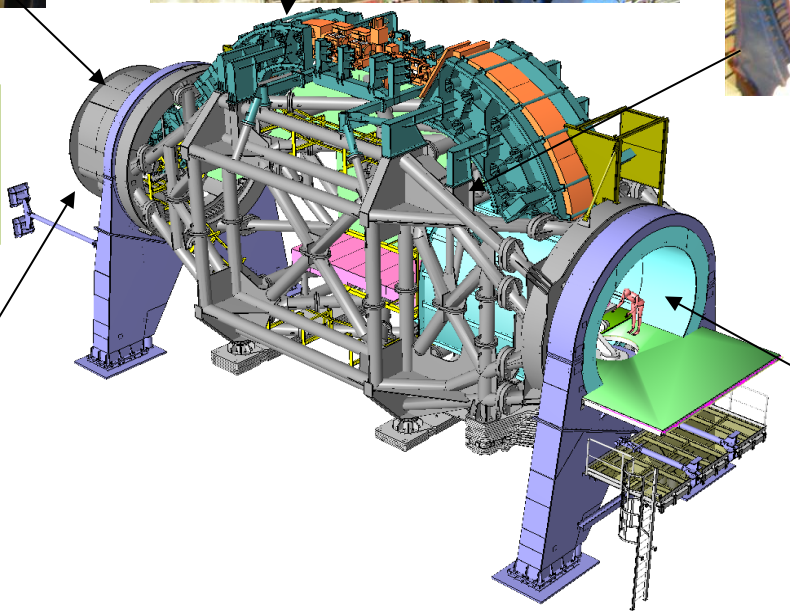
First patient: September 2009

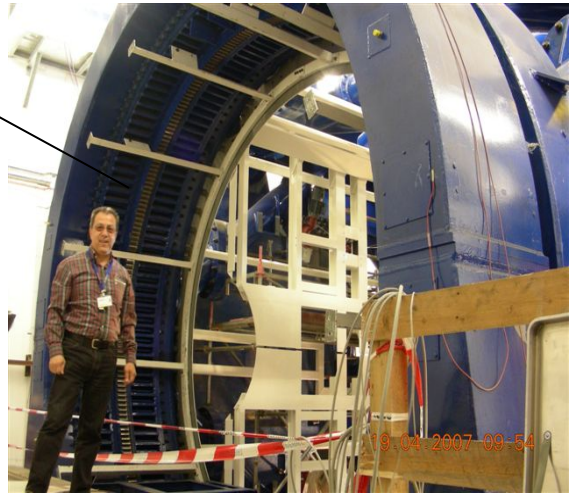


Heidelberg ion gantry: 600 tons and 400 kW



1st Rotation at 21.04.2007





MT AEROSPACE

Many thanks to:

- U. Amaldi, CERN &TERA
- E. Blakely, LBNL, USA
- M Durante, GSI, Germany
- HIT, CNAO, MedAustro, PSI and ENLIGHT colleagues
- Life Sciences Team

Useful links

- *cern.ch/crystalclear*
- *cern.ch/enlight*
- *cern.ch/virtual-hadron-therapy-centre*
- *http://cds.cern.ch/record/1611721*
- *cern.ch/knowledgetransfer*
- *cern.ch/medipix*
- *cern.ch/twiki/bin/view/AXIALPET*
- *cern.ch/medaustron*
- *cern.ch/fluka/heart/rh.html*
- *www.fluka.org/fluka.php*
- *cern.ch/wwwasd/geant*
- *cern.ch/wwwasd/geant/tutorial/tutstart.html*
- www-pub.iaea.org/MTCD/Publications/PDF/TCS-42_web.pdf