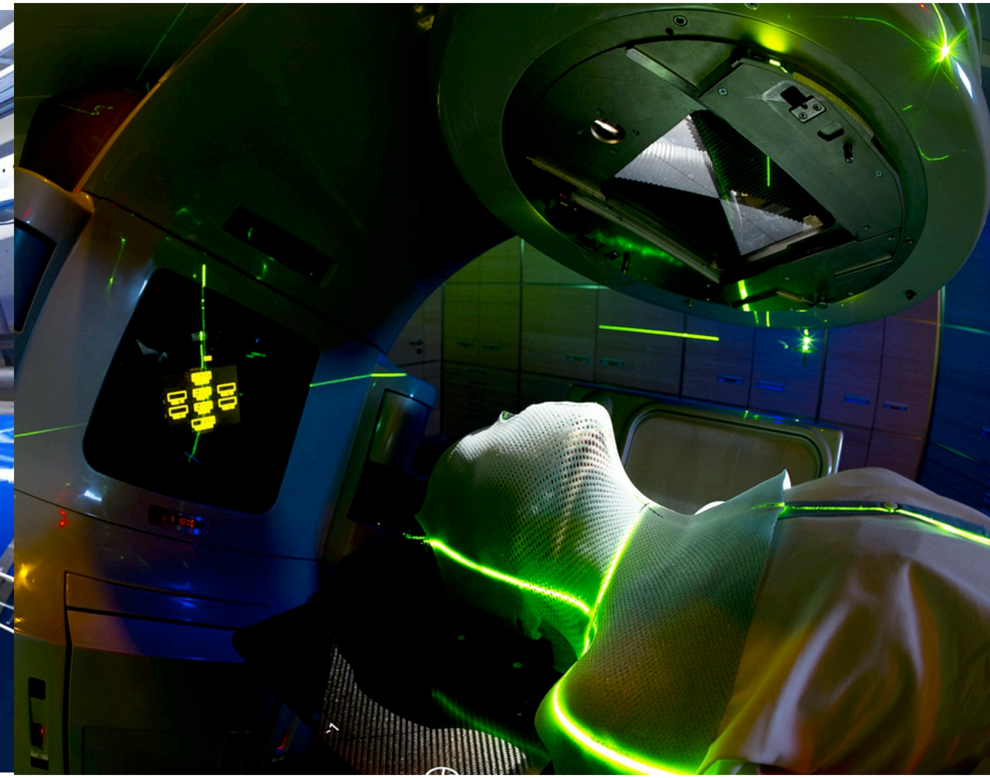
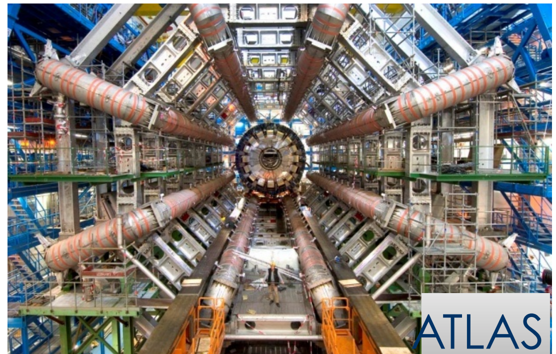
Medical Applications from Physics-1



CERN Summer School Student Lectures, 2017

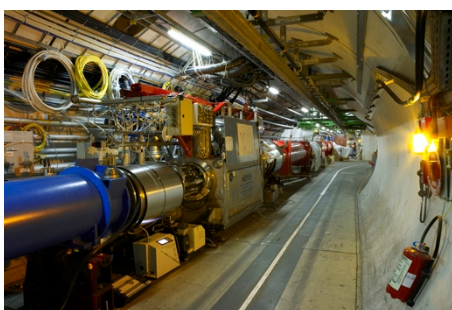
Manjit Dosanjh, CERN
manjit.dosanjh@cern.ch

Physics Technologies



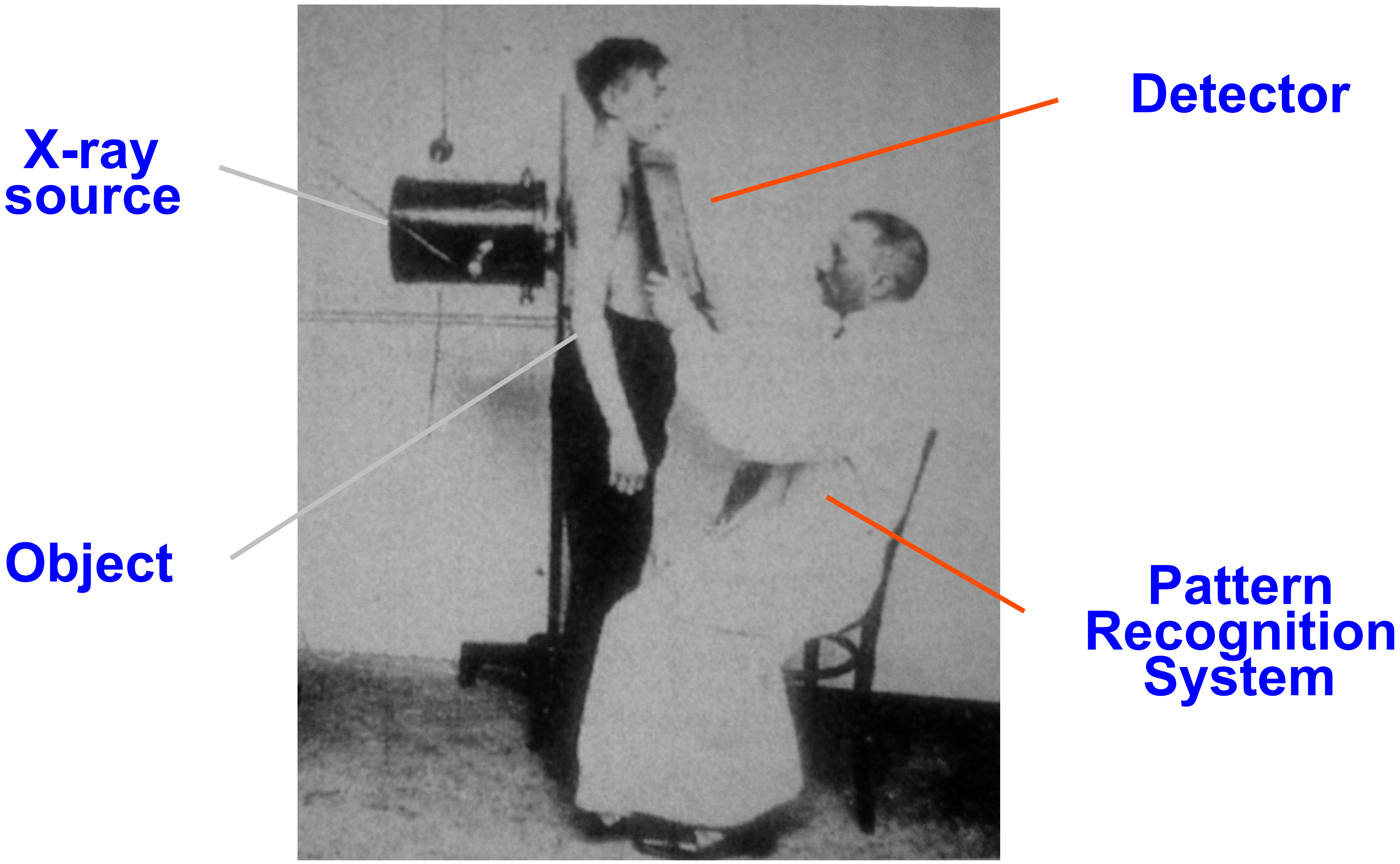
Detecting particles

Accelerating particle beams

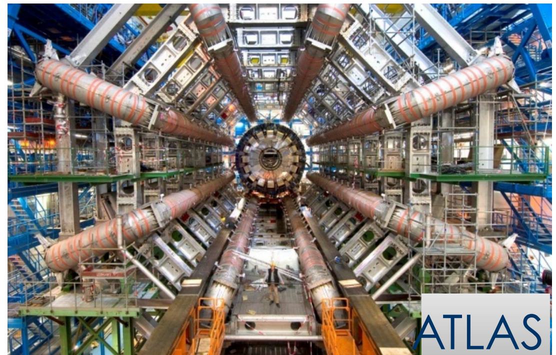


Higgs

Large-scale computing (Grid)

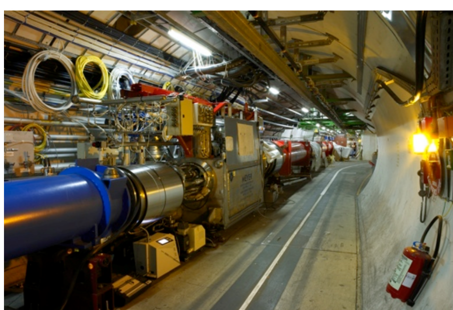

X-ray source
Detector
Object
Pattern Recognition System

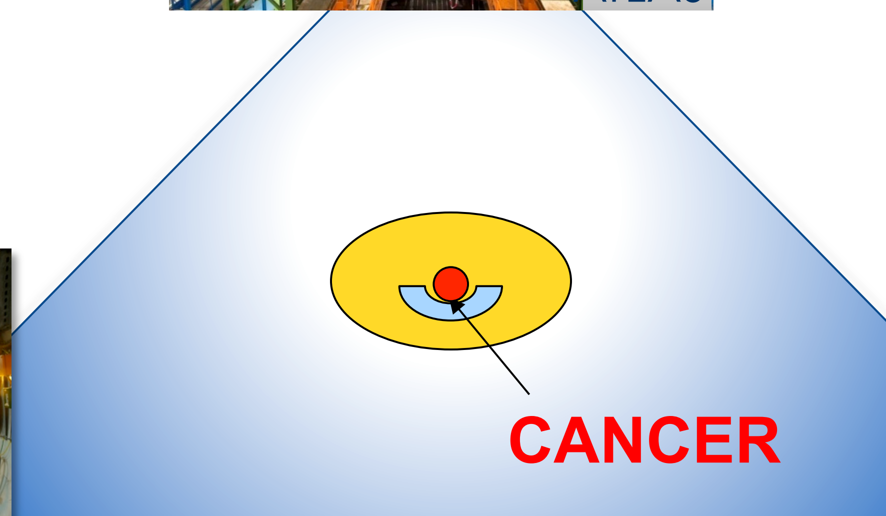
Physics technologies for cancer



Detecting particles

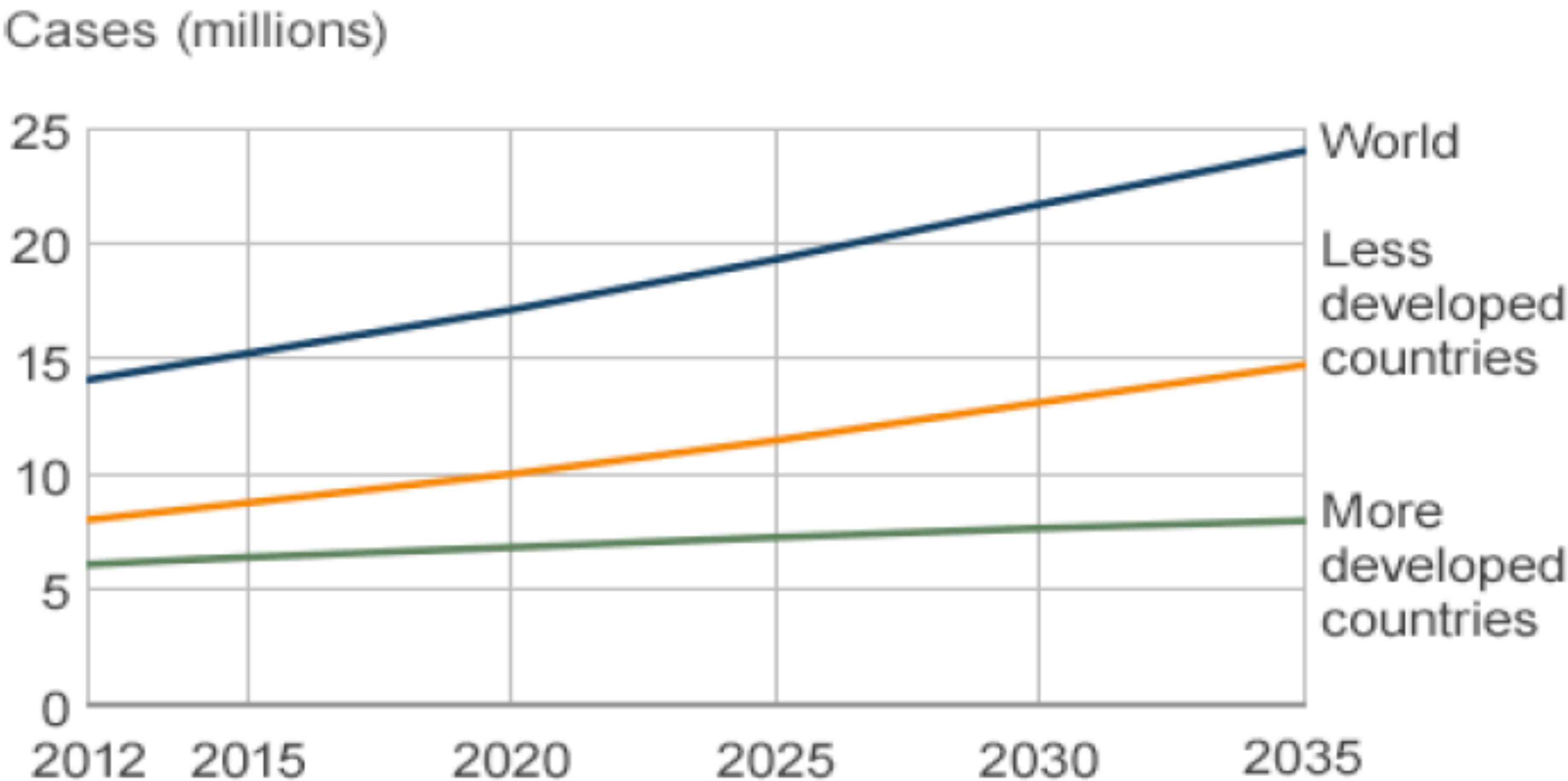
Accelerating particle beams





Large-scale computing (Grid)

Predicted Global Cancer Cases



Source: WHO GloboCan

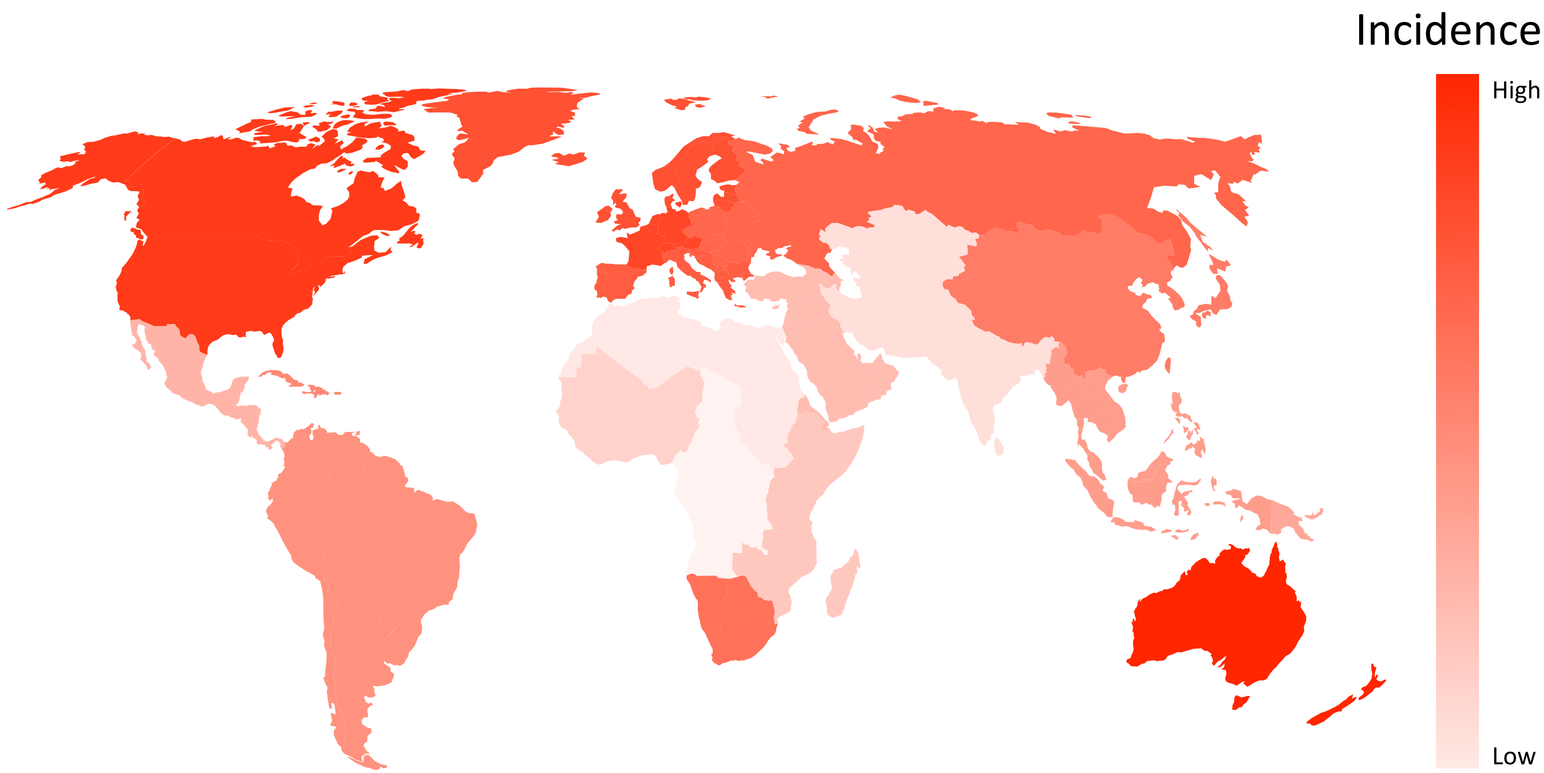
Why is cancer important?

Cancer, increasing huge global mortality, which has an Astronomical Cost

A leading cause of death worldwide

25m new cancer cases by 2030

$286bn, the global economic cost of new cancer cases in 2009



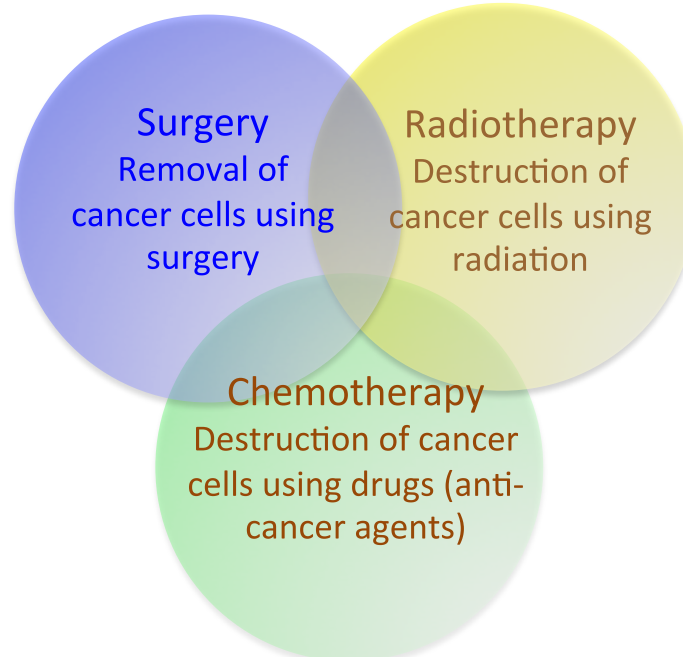
Cure from cancer achieved for only 45% of patients

8m people likely to die as a result of cancer p.a.

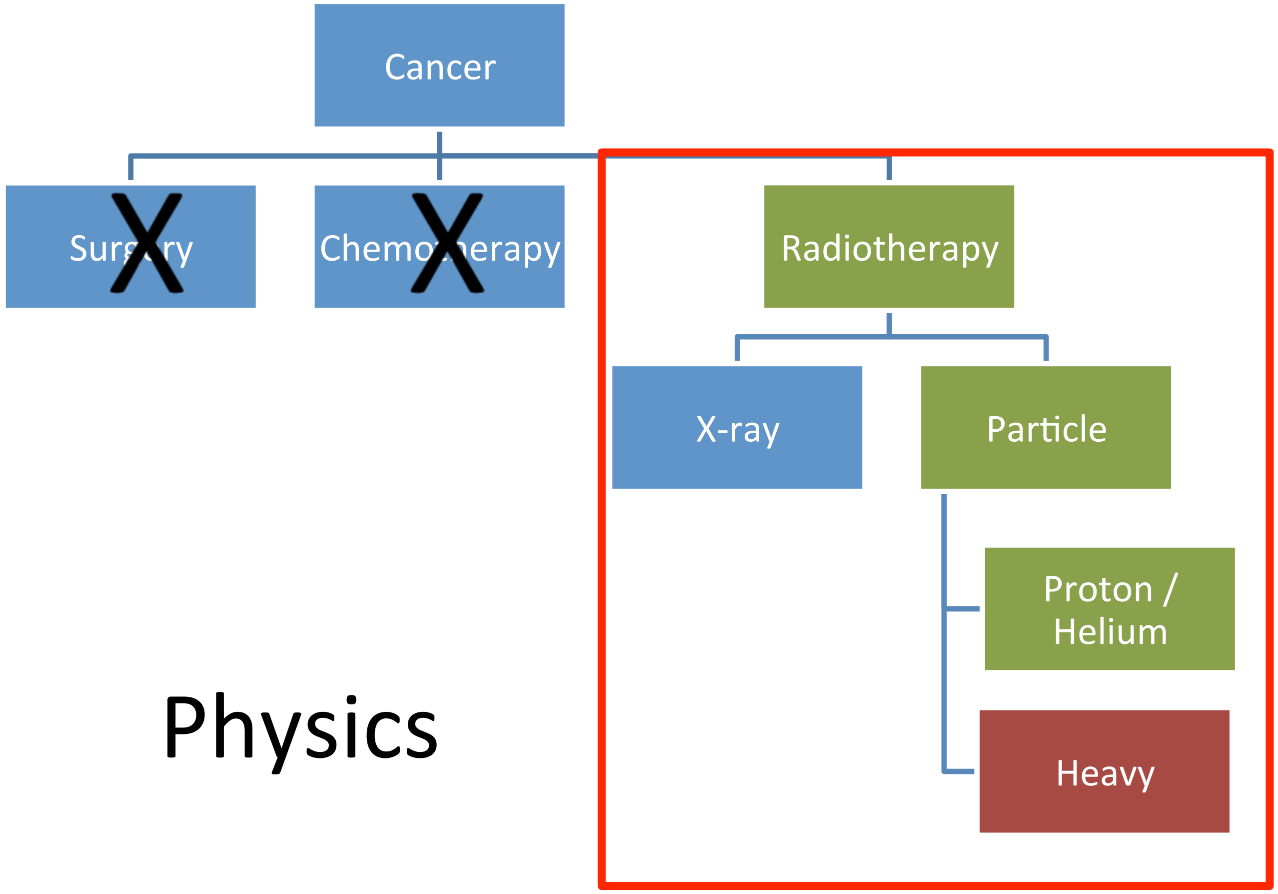
1. *Alone or in combination with other modalities*
2. *By 1934 Coutard had developed a protracted, fractionated process that remains the basis for current radiation therapy*
3. *GLOBOCAN 2008, Cancer incidence and Mortality Worldwide. IARC, 2010 (http://globocan.iarc.fr) http://info.cancerresearchuk.org/cancerstats/*

Some facts about Cancer

- Tumour: why?
  - Abnormal growth of cells
  - Malignant: uncontrolled, can spread → cancer
  - Age expectancy
- Treatment: how?
  - Surgery
  - Radiation
  - Chemotherapy



Cancer treatment



Physics

The Challenge of Treatment

Ideally one needs to treat:

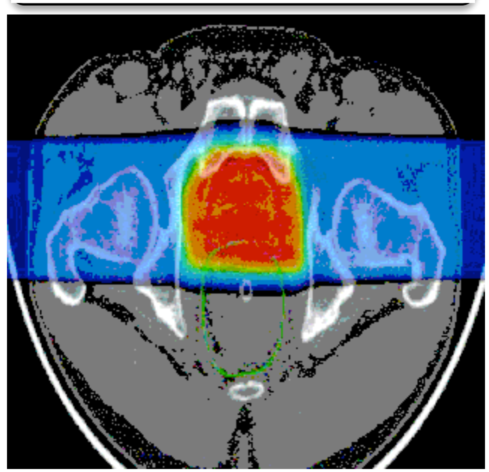
- The tumour
- The whole tumour
- And nothing BUT the tumour”

Radiotherapy has two equally important goals to destroy the tumour and protect the surrounding normal tissue. Therefore “seeing” in order to know where and precise “delivery” to make sure it goes where it should are key.

Treatment options

Surgery

Radiotherapy



X-ray, IMRT, Brachytherapy, Hadrontherapy

Chemotherapy (+ others)

Hormones; Immunotherapy; Cell therapy; Genetic treatments; Novel specific targets (genetics..)

AIM:
Survival, Quality of life

Although cancer is a common disease, each tumour and each patient is an individual: need patient specific approach leading to personalised medicine

Radiotherapy in 21st Century

3 "Cs" of Radiation

Cure (40-50% cancer cases are cured)

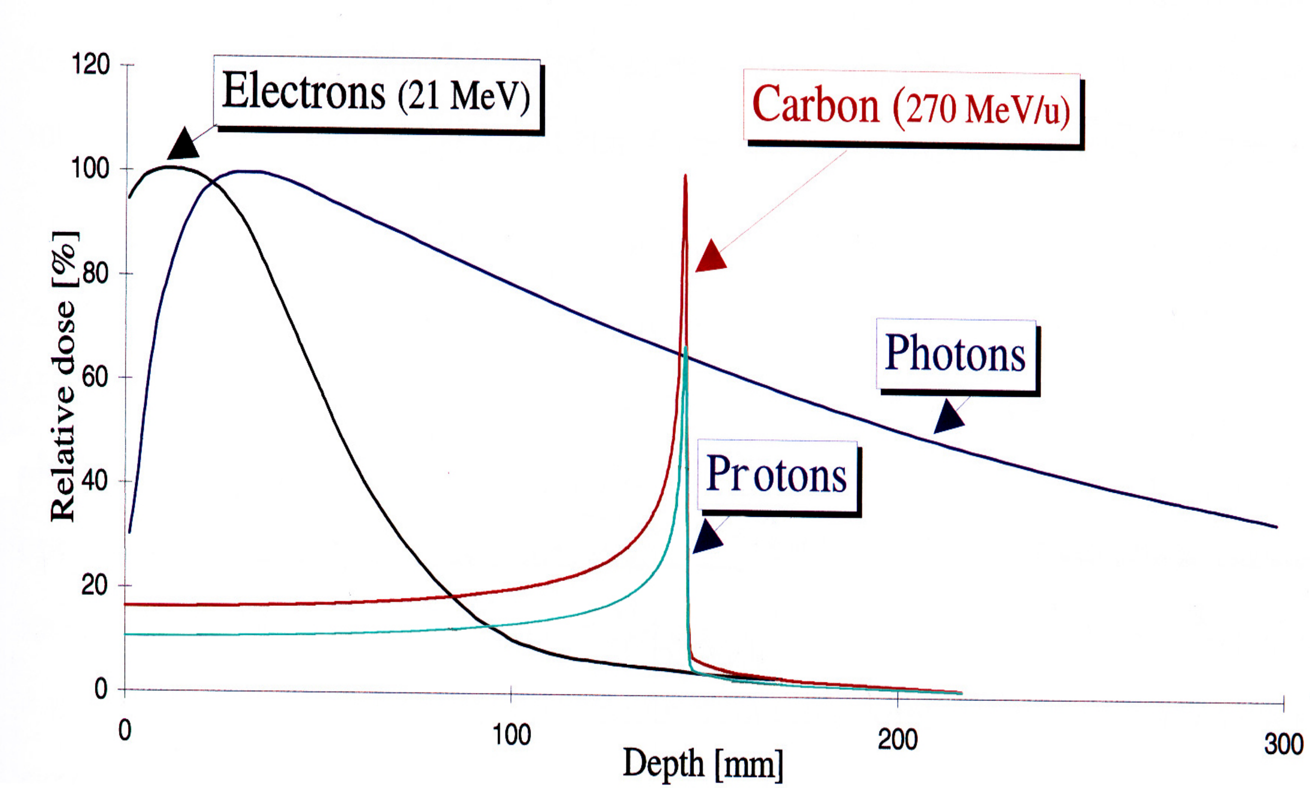
Conservative (non-invasive, fewer side effects)

Cheap (about 10% of total cost of cancer on radiation)

(J.P.Gérard)

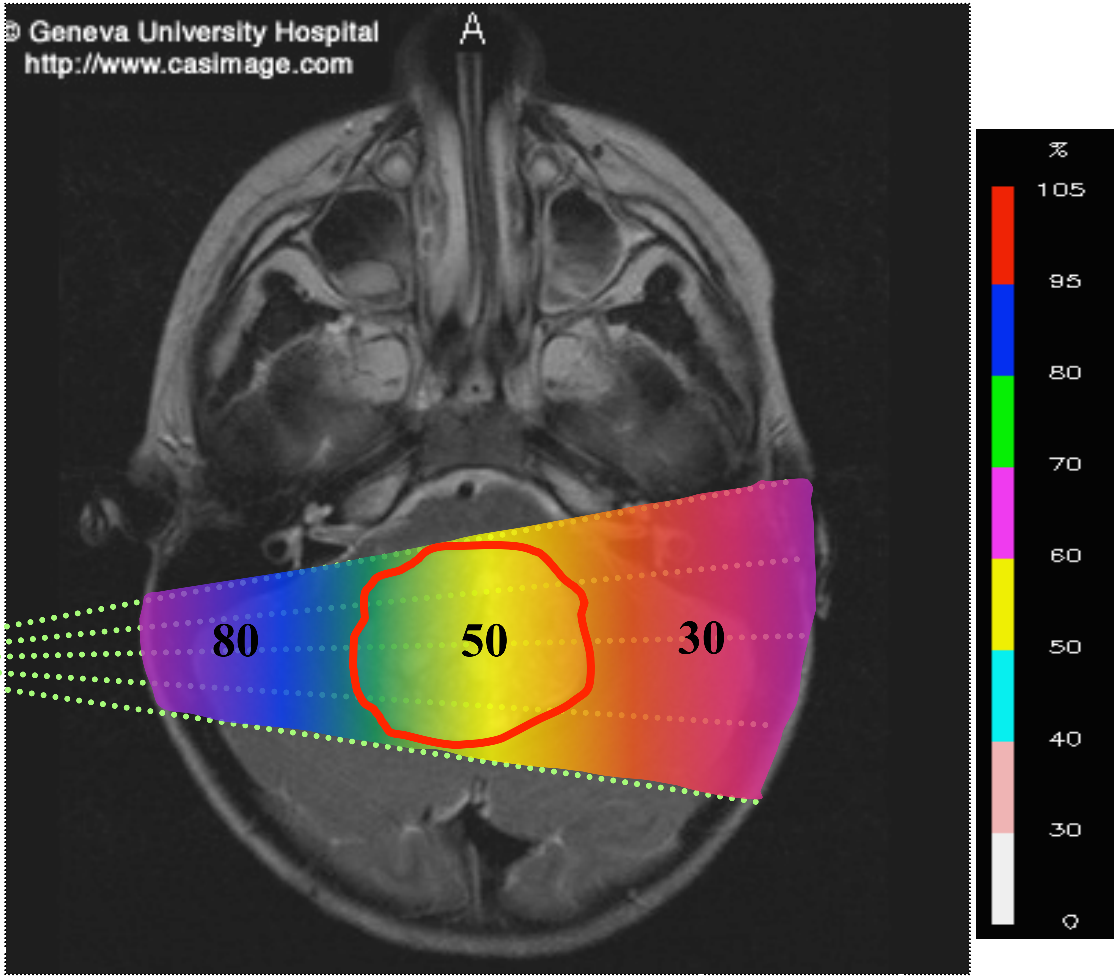
- About 50% patients are treated with RT
- No substitute for RT in the near future
- No of patients is increasing

Radiation therapy

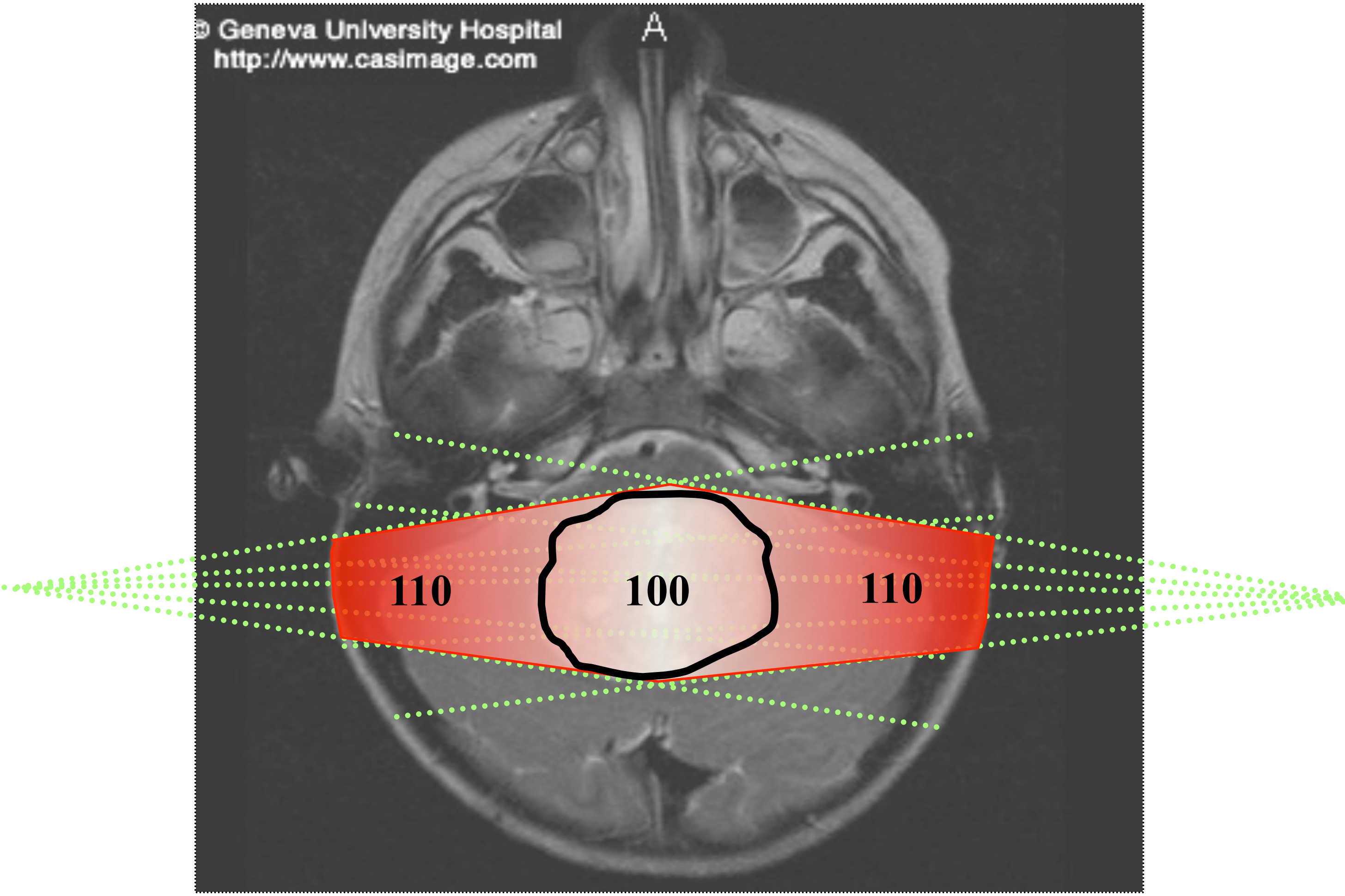


Depth in the body (mm)

Single beam of photons



2 opposite photon beams



Improving Cancer Outcome

Earlier diagnosis, better tumour control, fewer side-effects

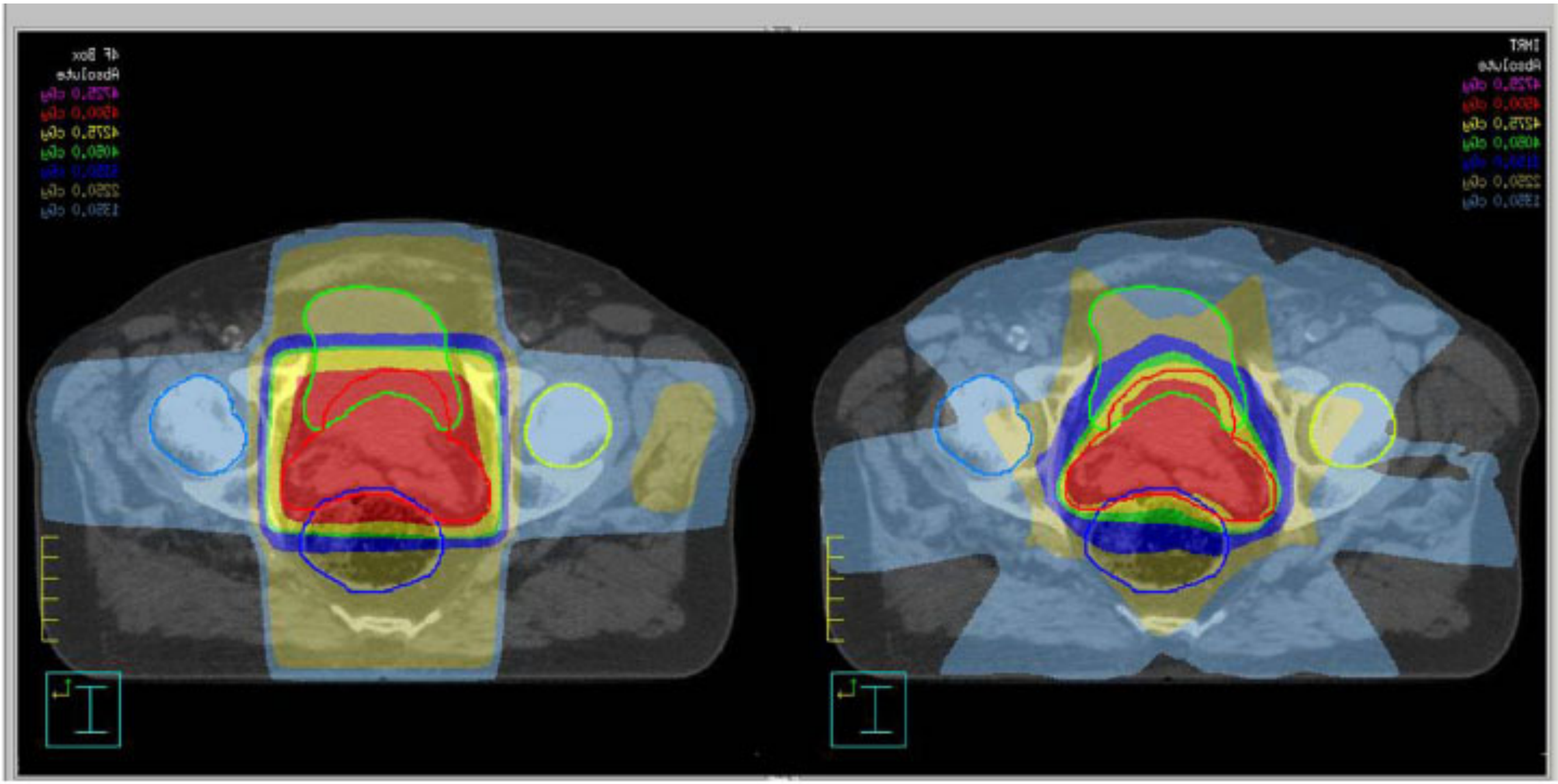
- Imaging: accuracy, multimodality, real-time, organ motion
- Accelerator technologies: higher dose, more localised, real time targeting
- Data: analysis, image fusion/reconstruction, treatment planning, sharing, screening, follow-up patient ….
- Biology: basic research, fractionation, radio-resistance, radio-sensitization

Advances in Radiation Therapy

In the past two decades due to:

- huge improvements in imaging modalities
- powerful computers and software and delivery systems have enabled:
  - Intensity Modulated Radiotherapy (IMRT),
  - Image Guided Radiotherapy (IGRT),
  - Volumetric Arc Therapy (VMAT) and
  - Stereotactic Body Radiotherapy (SBRT)
- advances in accelerator technologies: better treatment machines for conventional RT as well as new modalities e.g. HT

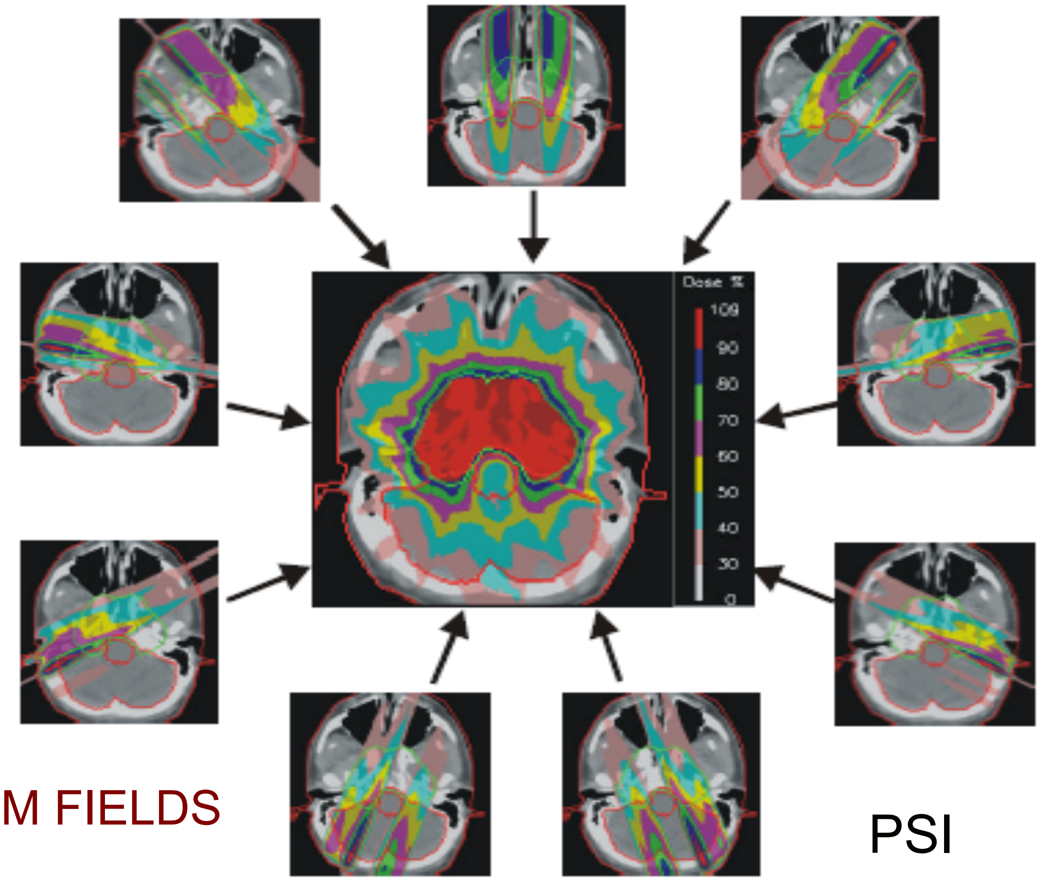
Improved Delivery



1990s: 4 constant intensity fields

Current state of RT: Intensity Modulated Radiotherapy (IMRT) – Multiple converging field with planar (2D) intensity variations

Intensity Modulated Radiation Therapy



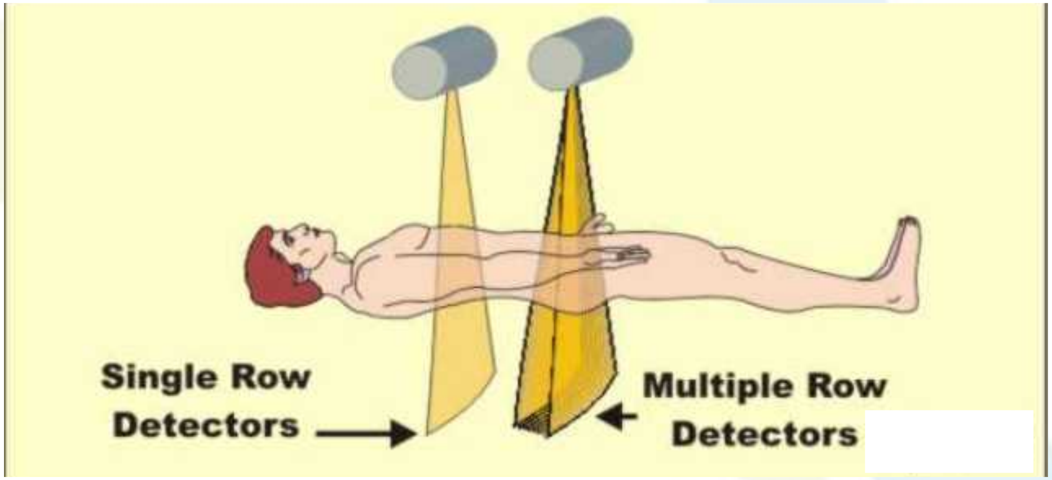
9 NON-UNIFORM FIELDS

PSI

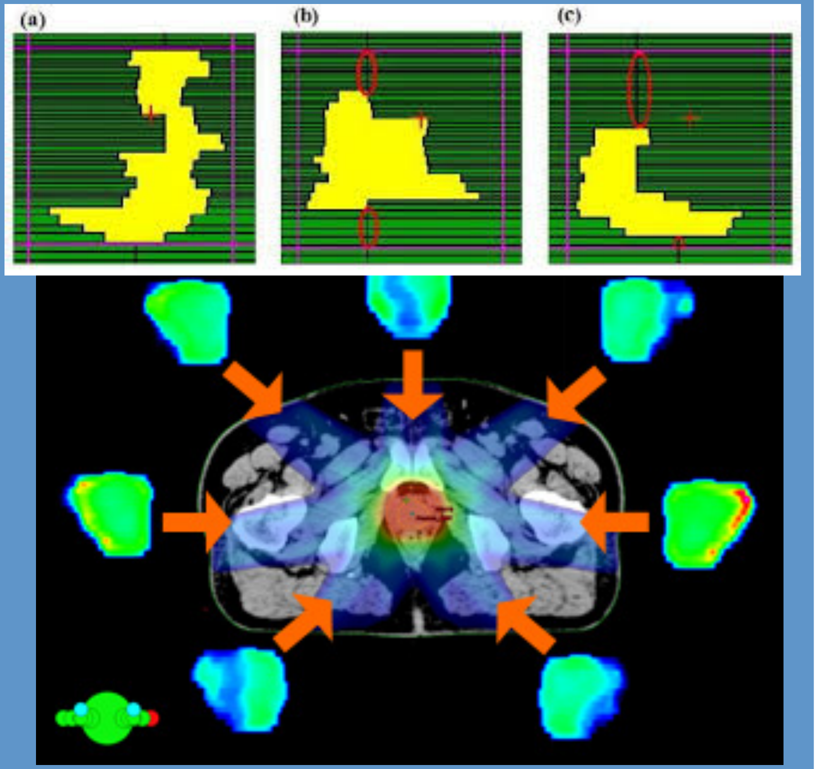
CT is a key driver of change

2000-2008 “CT Slice War”

- *CT became very fast with small voxel / pixels*
  - 2000: acquire a single transverse slice per rotation
  - 2012: acquire up to 64-500 slices per rotation



Modern Coventional Therapy

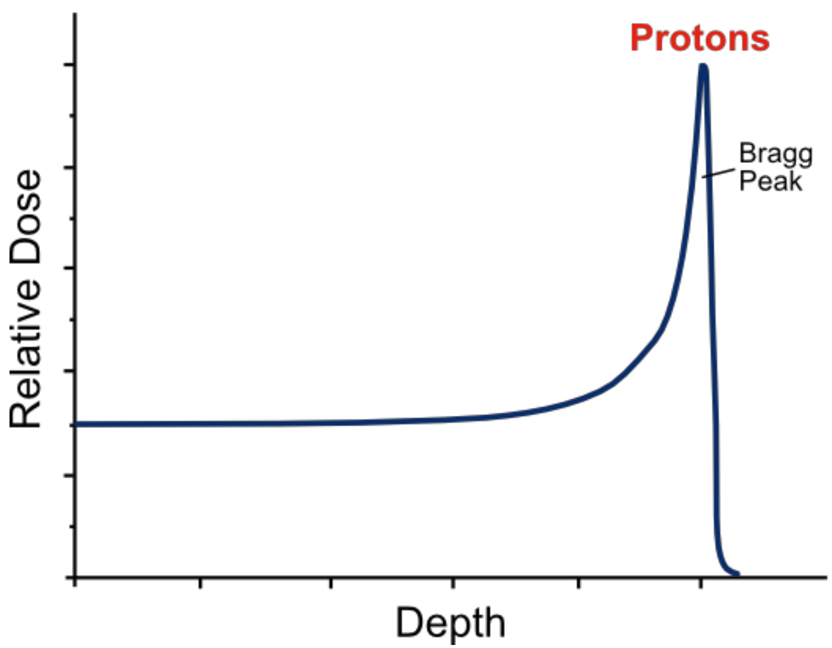


Current accelerator system with gantry, patient positioner and X-ray panels to acquire CBCT and planar X-rays.
Intensity modulation is achieved by changing the multi-leaf collimator (MLC) patterns (right), gantry rotation and dose rate. Thus, intensity modulation is achieved through mechanical (slow) means.

Future: Hadron Therapy?

- 1946: Robert Wilson

  Protons can be used clinically

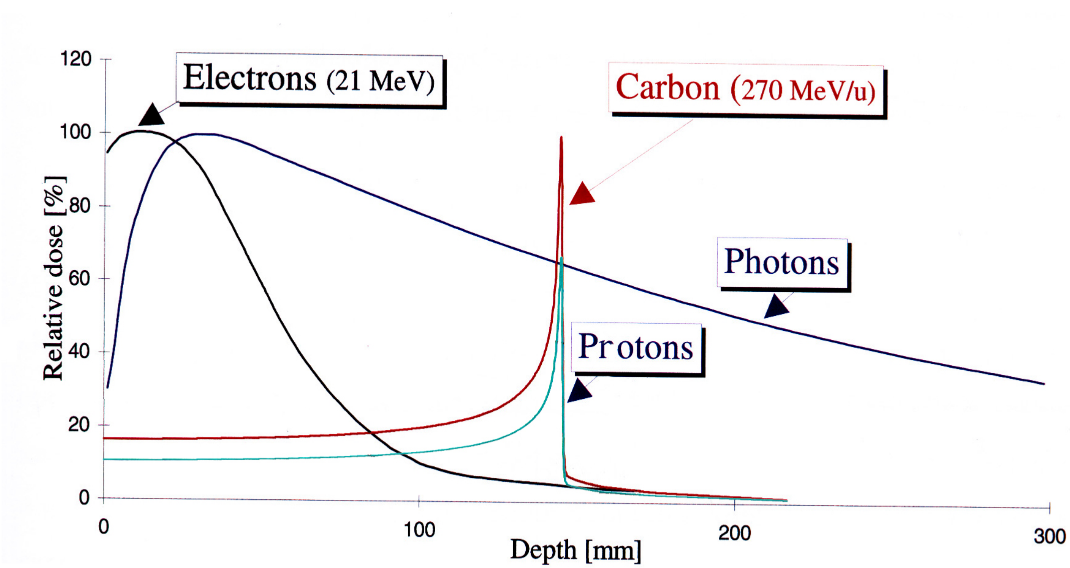


Robert Wilson

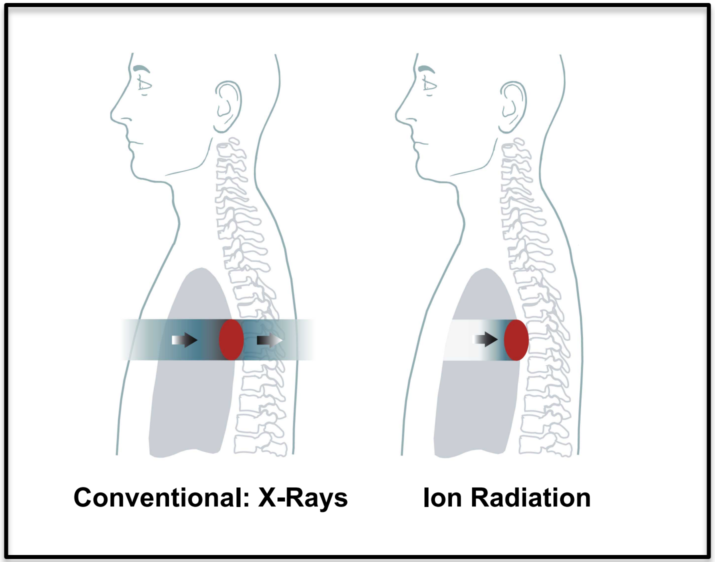
Hadron Therapy

In 1946 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**

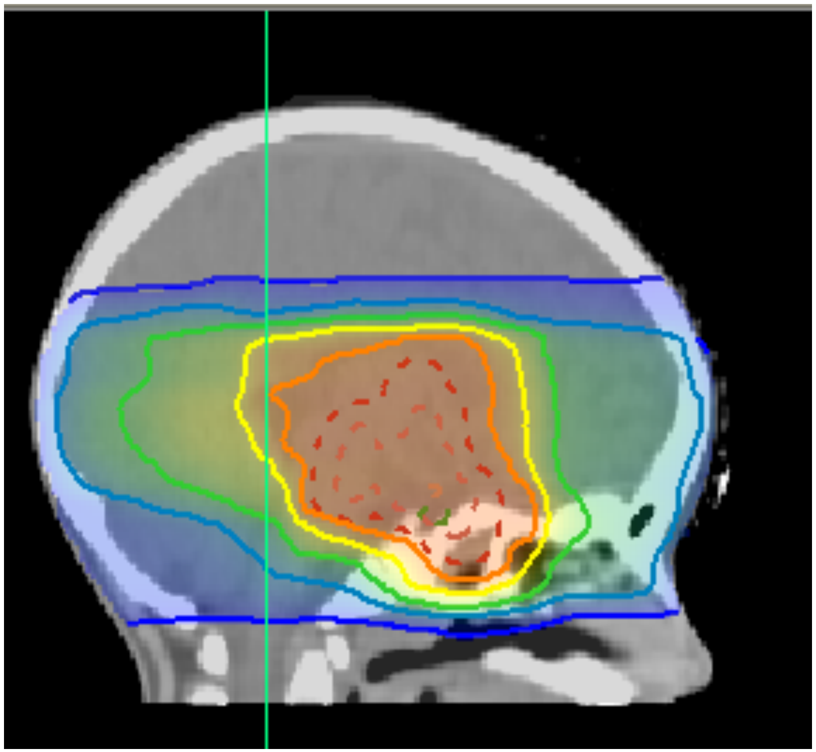


Depth in the body (mm)



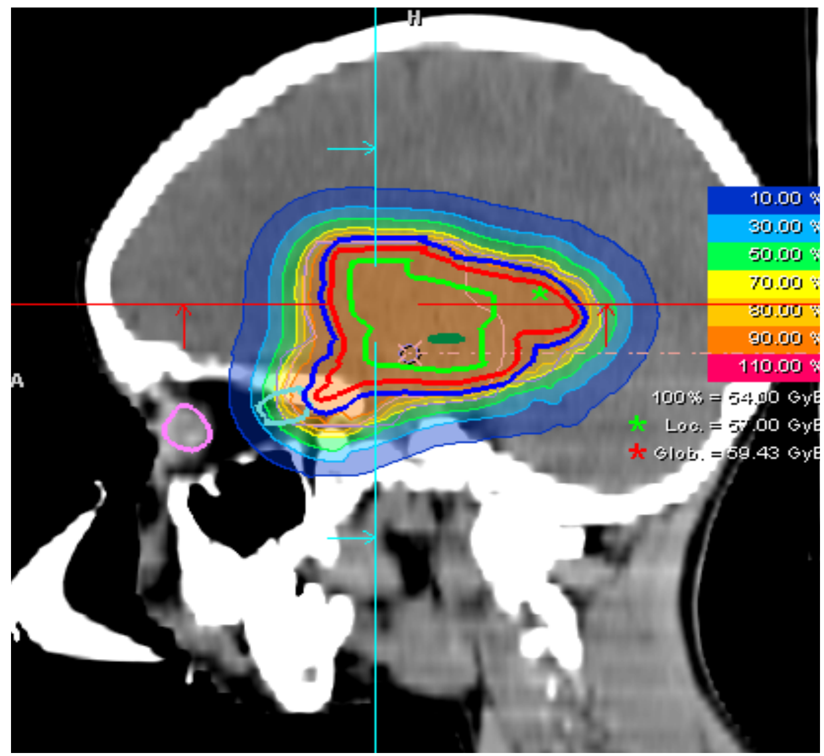
Potential of particle therapy

Photon-IMRT



Universitätsklinikum Dresden

Protons



HIT, Heidelberg

Two sides of Radiation

Radiation Dose

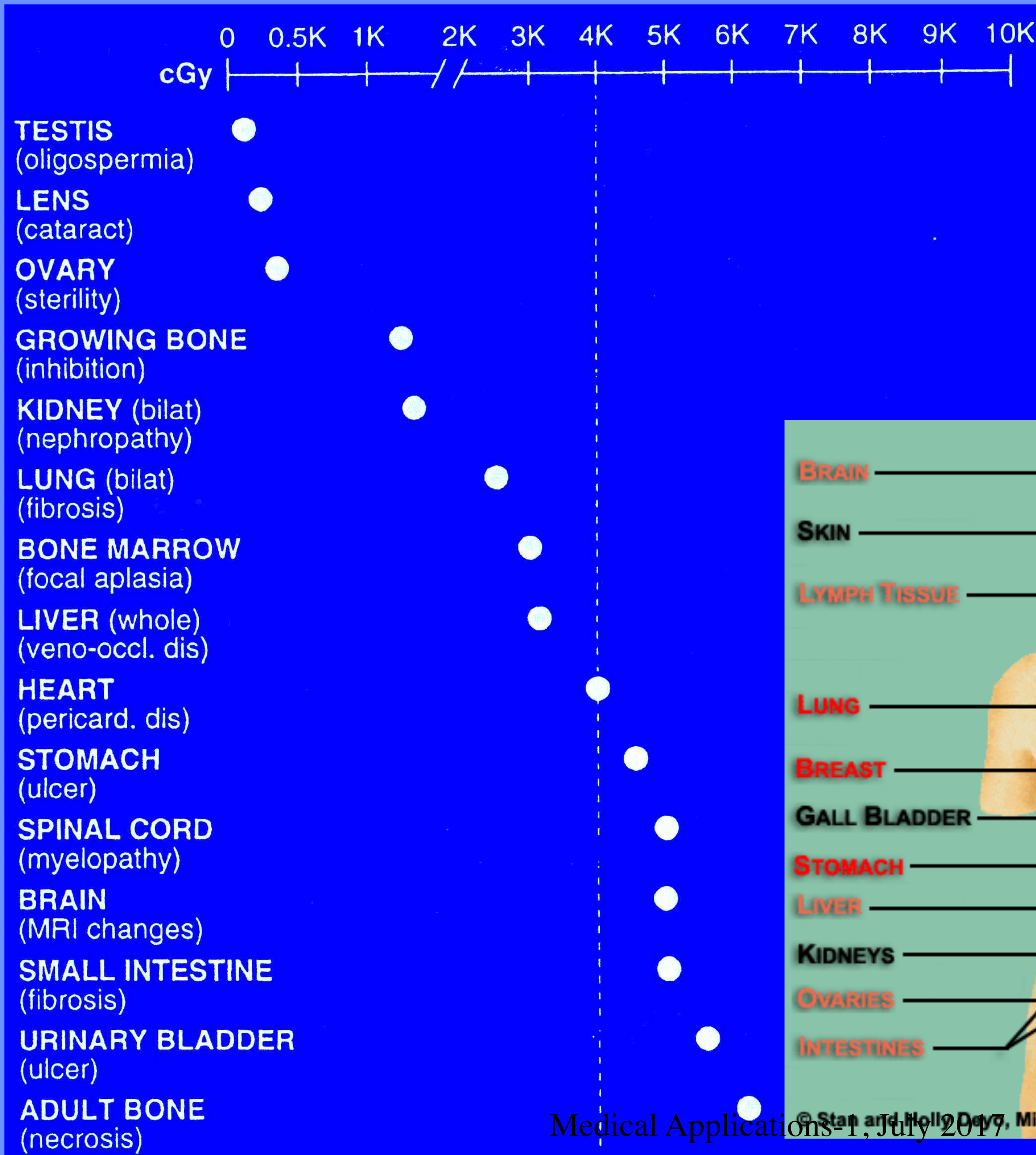
- Radiation effects depend on DOSE= Energy Deposited by Radiation per Unit Target Mass
- **Dose is measured in Gray (Gy) (=1 joule / kg)**
- ..but different radiations have different effectiveness (Q)
- **Equivalent dose= QxD is measured in Sievert (Sv)**
- For X-, γ-rays and electrons: 1 Gy = 1 Sv
- But, for example: 1 Gy α-particles= 20 Sv (Q=20)

- Mammography= 0.01 mSv
- Average background radiation dose on Earth= 3 mSv/year
- Occupational limit= 50 mSv/year
- Lethal dose= 4.5 Sv
- Radiotherapy= 60-70 Gy (to the tumour)
- Average background radiation dose in space = 1 mSv/day

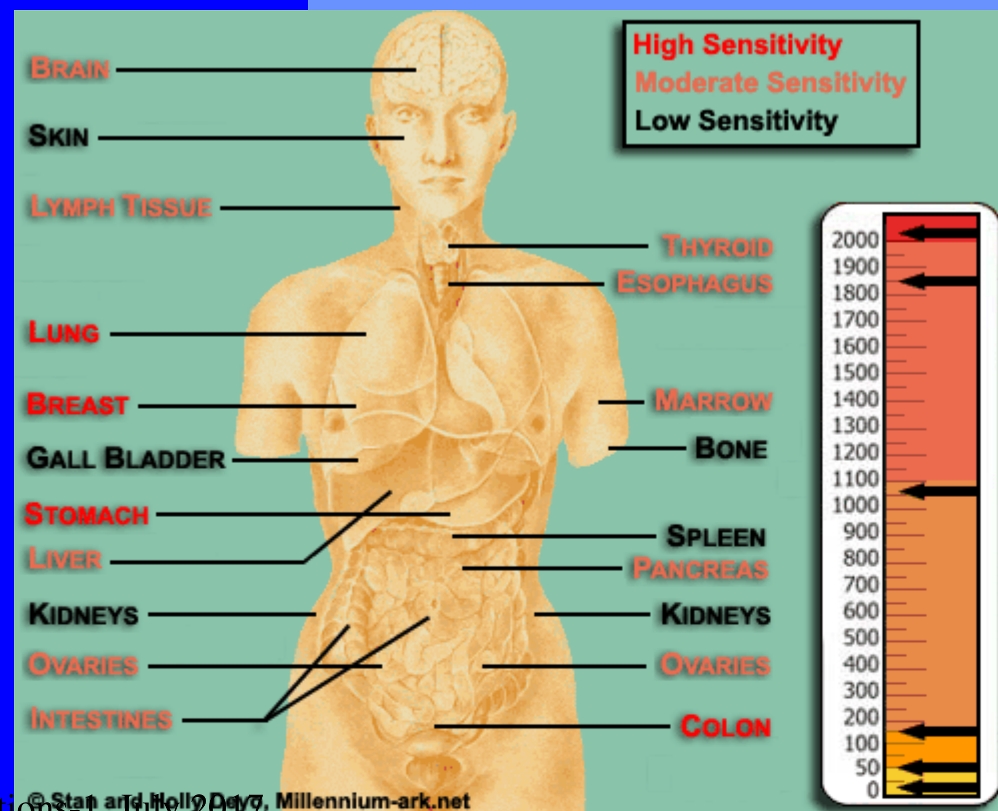
Radiation Sickness

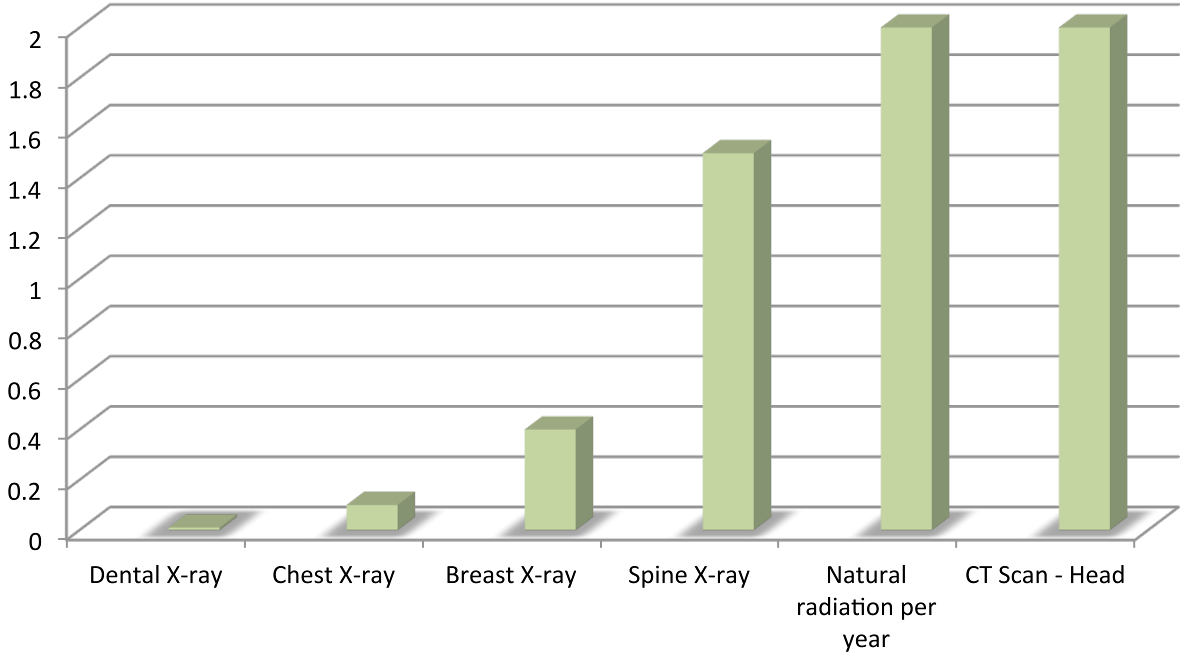
System effected/ Syndrome	Symptoms	Dose
Nervous system CNS or Cerebrovascular Syndrome	Shock, severe nausea, disorientation, seizures, coma	100 Gy
G.I. system Gastrointestinal Syndrome	Nausea, vomiting, diarrhea, dehydration	10 Gy
Blood cells / bone marrow Hematopoietic Syndrome	Chills, fatigue, hemorrhage, ulceration, infections, anemia	3-8 Gy
Skin Erethema	Burning/ infection, sloughing of skin, hair loss	10 Gy
Ovaries/ Testes	Sterility	0.6-0.8 Gy 2-6 Gy

Variation in Radiation Sensitivity Among Adult Human Organs

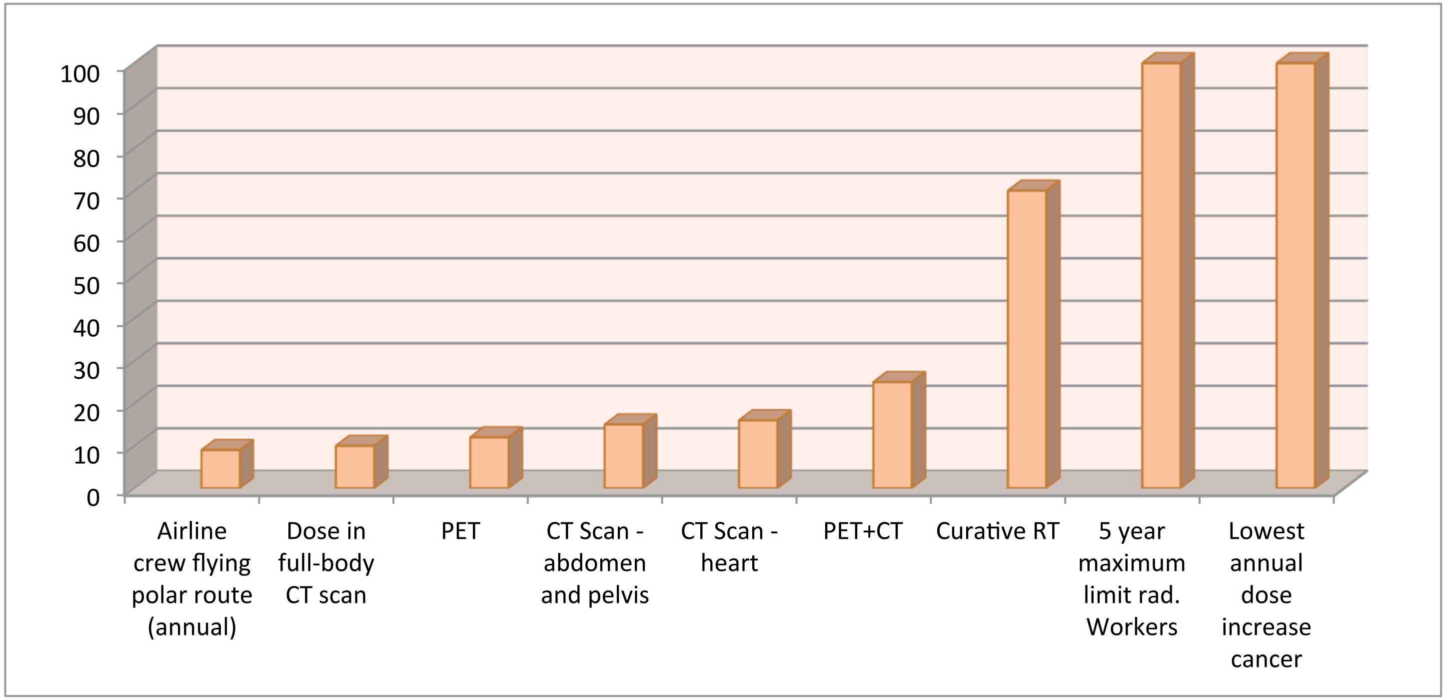


Approximate Tolerance Dose (TD) beyond which there is a high probability of delayed injury, e.g. 5% clinical injury within 5 years after exposure.





Typical doses in mSv



Questions

- What is radiobiology?
- Why do we need biology for radiotherapy?
- What kinds of biology are important for radiotherapy?
- How do you investigate biological effects of particle beams?
- What do the data tell you?
- Do we know everything we need to know?

What is radiobiology?

Radiobiology is a branch of science which concerns the action of radiation on biological cells, tissues and living organisms

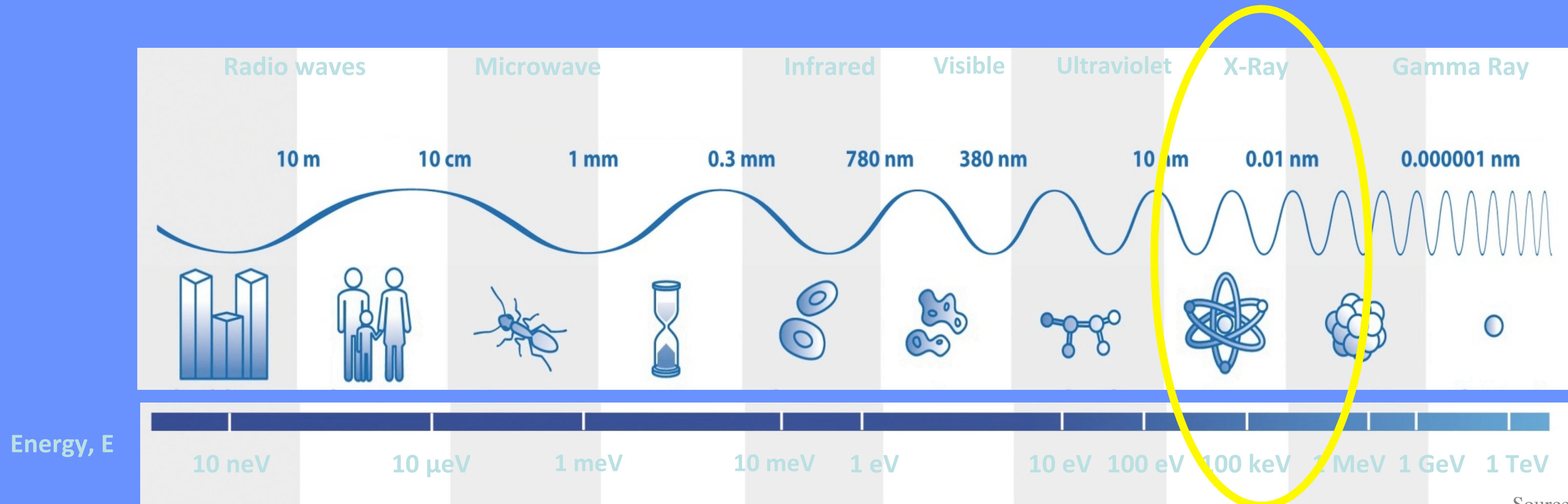
Radiobiology enables understanding of radiotherapy

It plays an important role in safe and effective application of radiation in cancer treatment i.e. radiotherapy, imaging

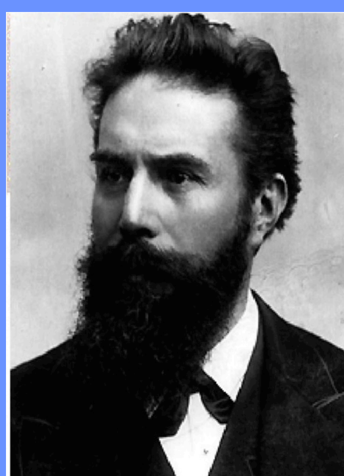
Role of radiobiology in radiotherapy?

- Radiobiology provides a rationale for implementation of treatment strategies, especially new treatment strategies
- Treatment outcome depends on:
  - clinical situation (extent of cancer, type of tumour, node, metastasis)
  - total dose delivered
  - fractionation scheme
    - Dose per fraction
    - Intensity of dose delivery
    - Treatment time

The Beginning ……………..



Source: ESA



Wilhelm Röntgen

X-rays

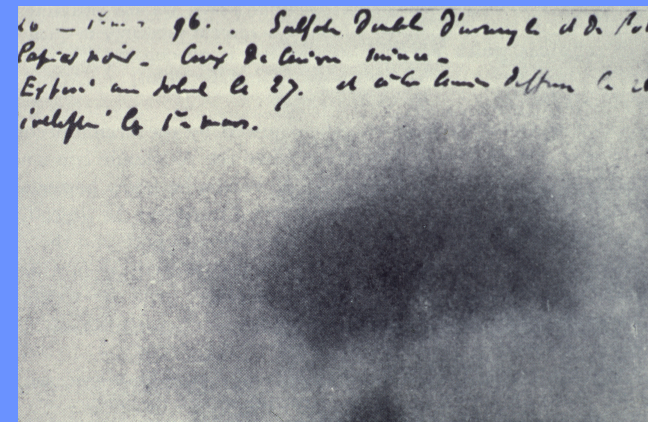
– November 1895:

– 1901: first physics Nobel prize

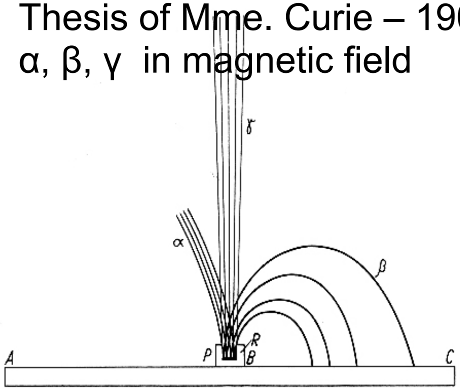
………..of radiation biology

Henri Becquerel
(1852-1908)

1896:
Discovery of natural radioactivity

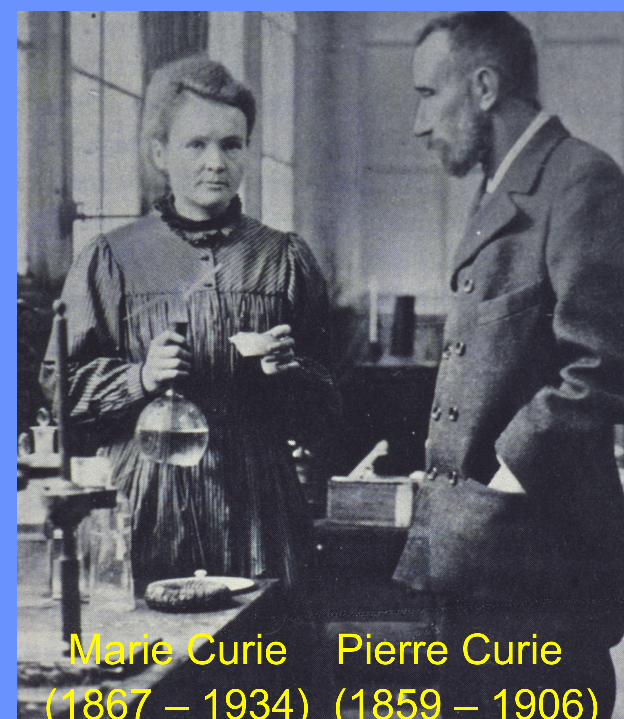


Thesis of Mme. Curie – 1904
α, β, γ in magnetic field



1898: Discovery of radium

used immediately for "Brachytherapy"



Marie Curie (1867 – 1934) Pierre Curie (1859 – 1906)

First radiobiology experiment: Pierre Curie

The first radiobiology experiment. Pierre Curie using a radium tube to produce radiation ulcer on his arm. Hall fig. 1-2

Early results.....

1896 -The first radiation therapy of a cancer patient (Victor DESPEIGNES, *Lyon)*

1896: First diagnostic use Kaiser, Vienna

1899 - The first successful radiation treatment of tumour -Thor Stenbeck, Stockholm

1900 – Palliation of tumour

1902- radium used to treat pharyngeal carcinoma in Vienna

1904 - Patients in New York undergoing implantation of radium tubes in the tumours

1904 - Chromosomal damage caused by radiation in embryos

1907-The first described fatal cases (11) of cancer

1910 - Hypothesis - Cancer arises from damage on the chromosomes (Muller)

1911 - The first specification of skin cancer (94 cases) - Herman Hesse

1911 - Report on radiation causes mutation in fruit fly Drosophila - Herman Muller

1917 – Observations of sterility among radiologists

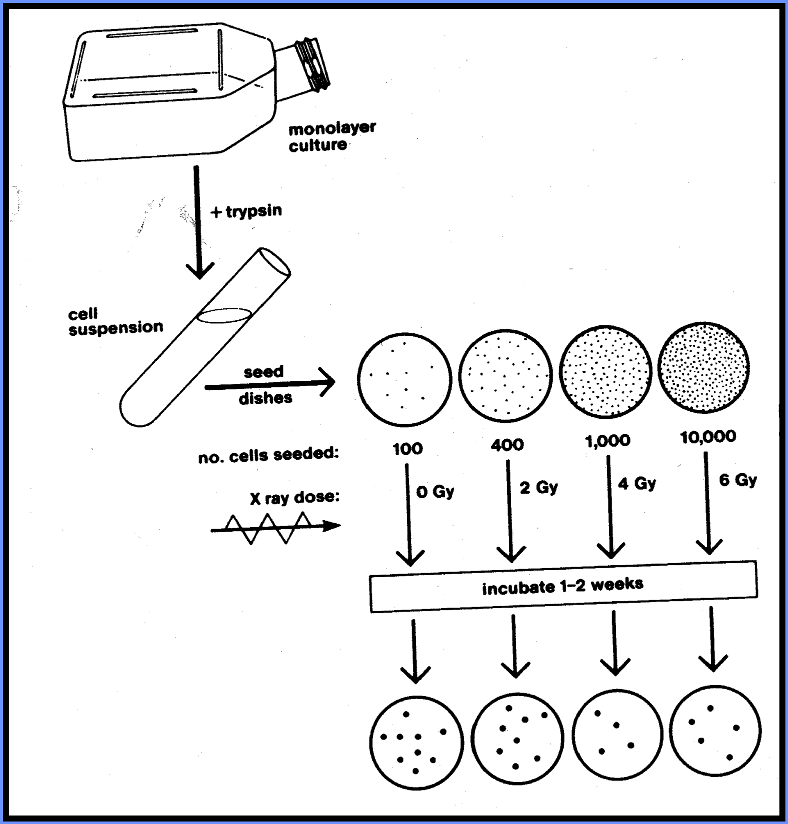
1921 – The 100^{th} death among radiologists

1926 - Muller showed radiation's role in mutation and that chromosomes are target https://youtu.be/dKubyIRiN84

https://youtu.be/8nlfP03bdxo

HeLA Cells: Immortal Life of Henrietta Lacks

Cell culture techniques and cell survival curves



Puck and Marcus promoted the study of radiation on individual cells…cell culture

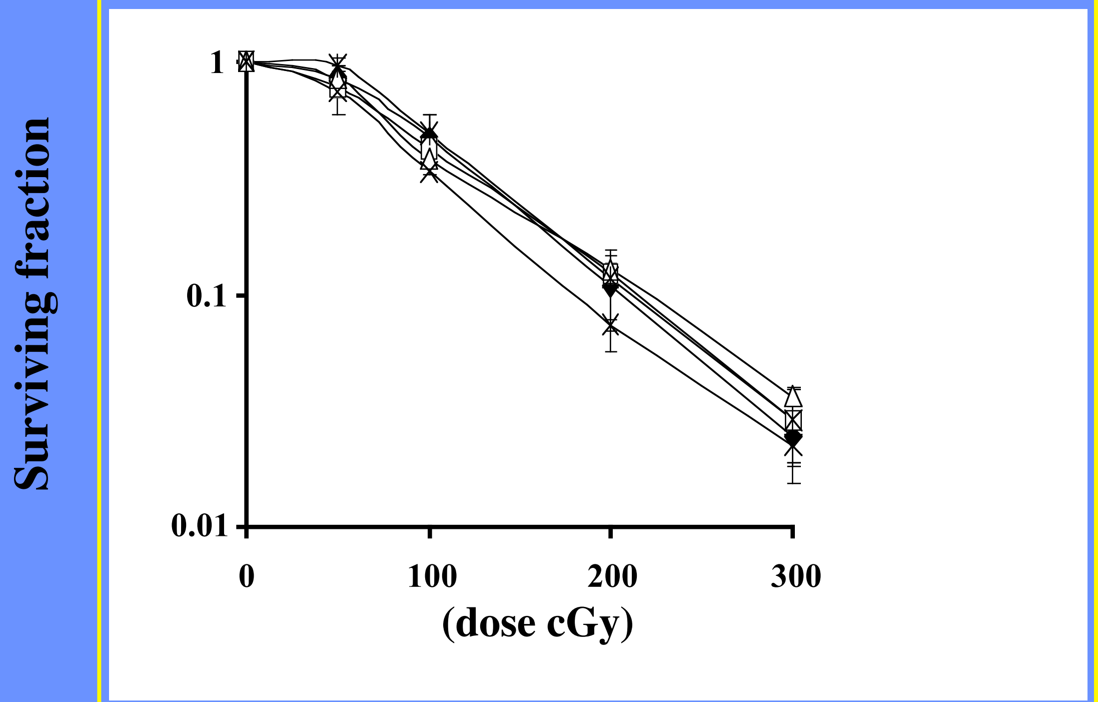
S/S_0 = colonies produced / cells plated * PE
PE = plating efficiency (correction factor derived from control samples)

Cell survival curves

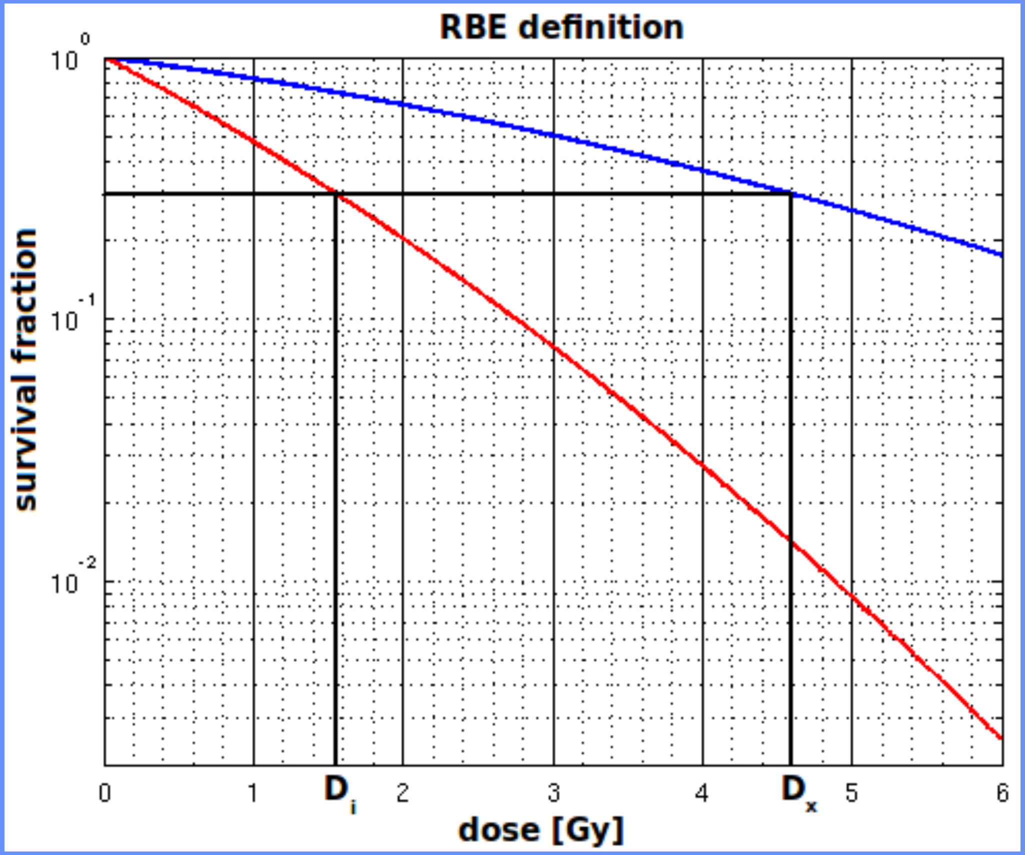
- describe the relationship between the radiation dose and the proportion of cells that survive

- presented with the dose plotted on a linear scale and the surviving fraction on a logarithmic scale

1956: The first in vitro radiation survival curve on mammalian cells by Puck & Marcus



Cellular Survival Curves and Relative Biological Effectiveness

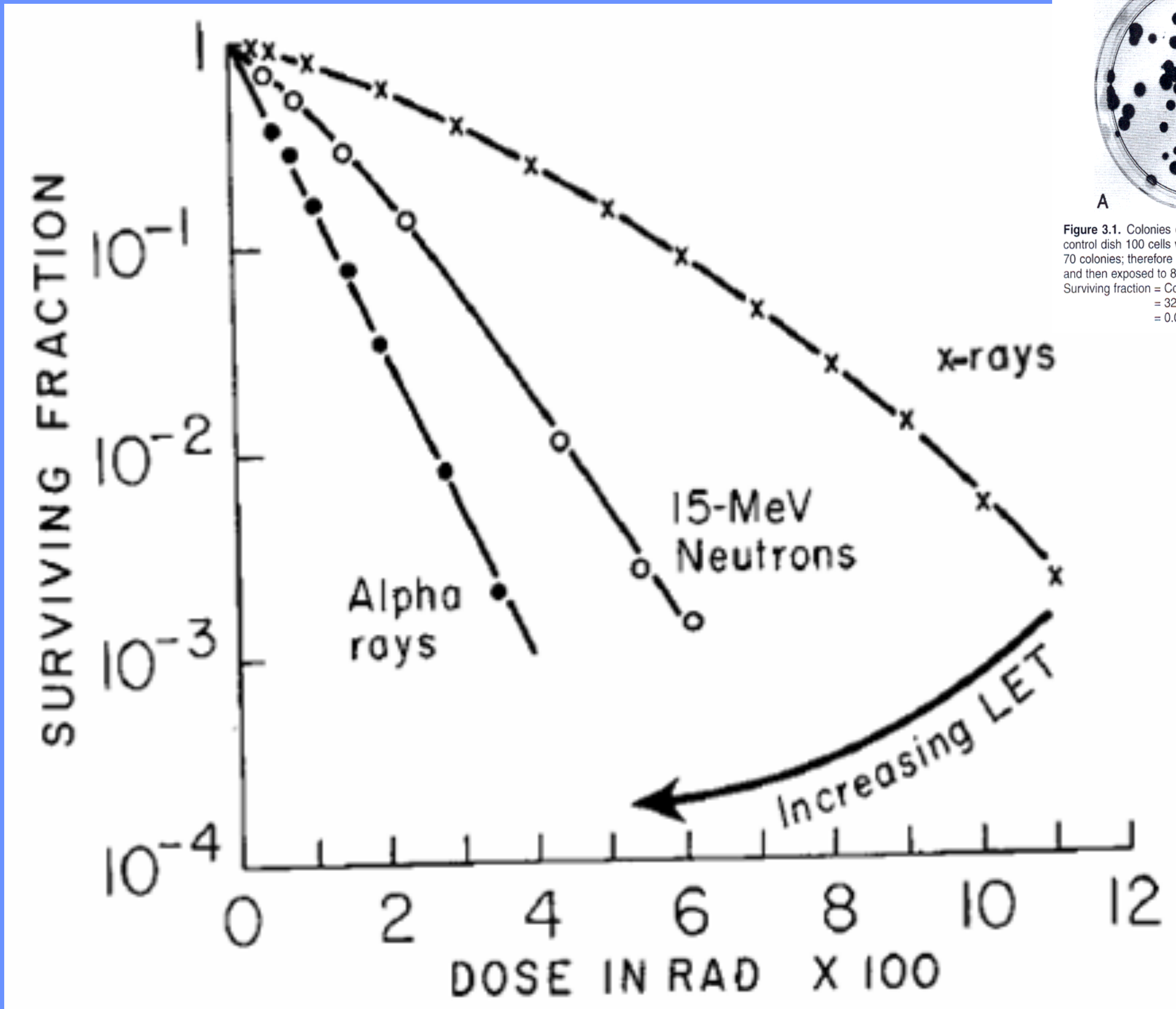


$$\frac{D_x}{D_i} = RBE$$

RBE and how does it vary

- Varies with type of radiation
- Varies with type of cell/tissue
- Varies with the biological effect under investigation
- Varies with dose rate and fractionation
- An increase in RBE in itself does not offer therapeutic advantage unless there is differential effect between normal and tumour tissues
- OER (oxygen enrichment ratio) effects RBE
- Effected by presence of other chemicals present

Cell killing by different radiation types



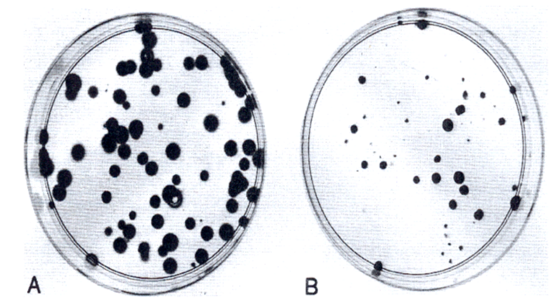
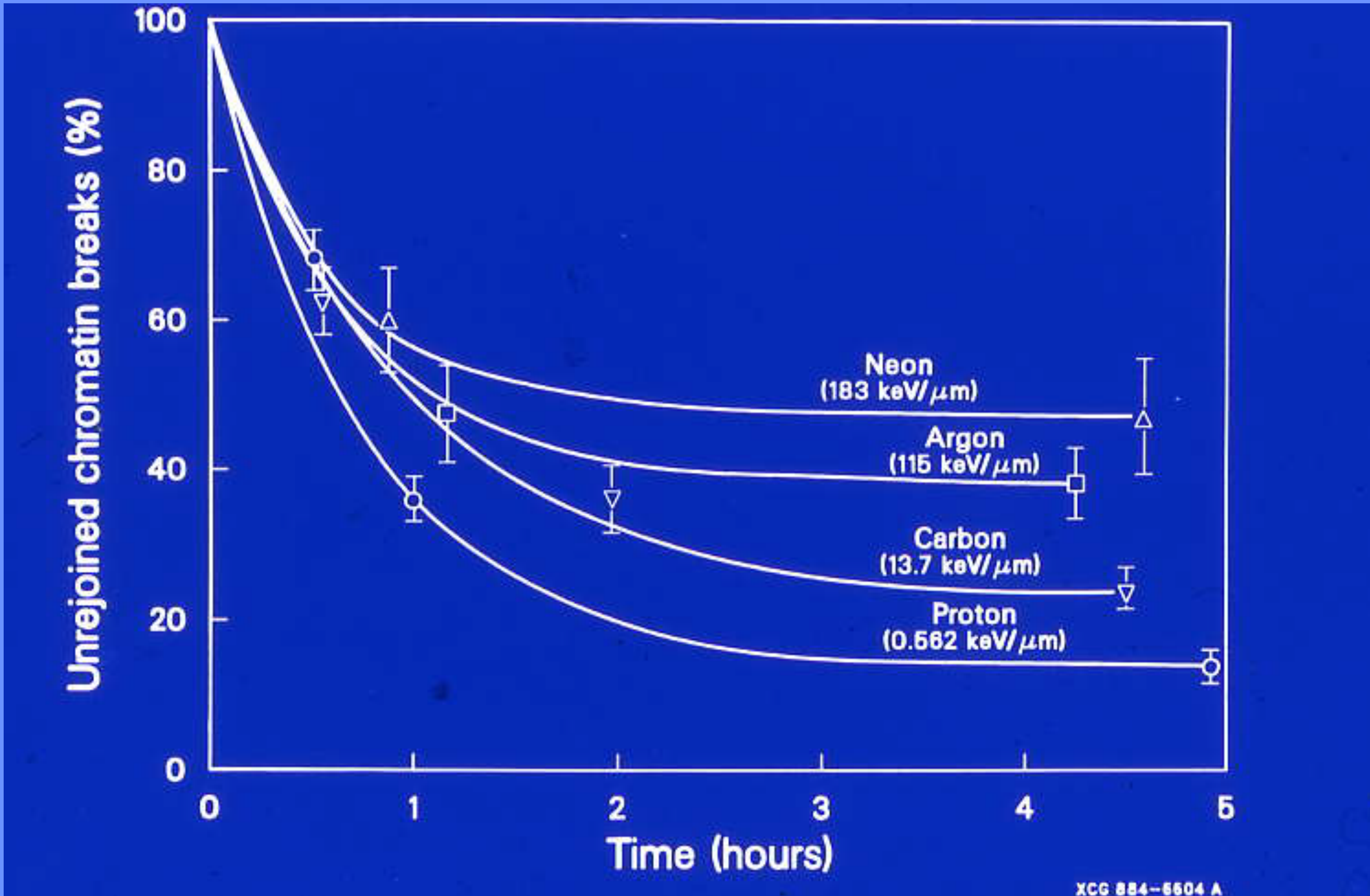


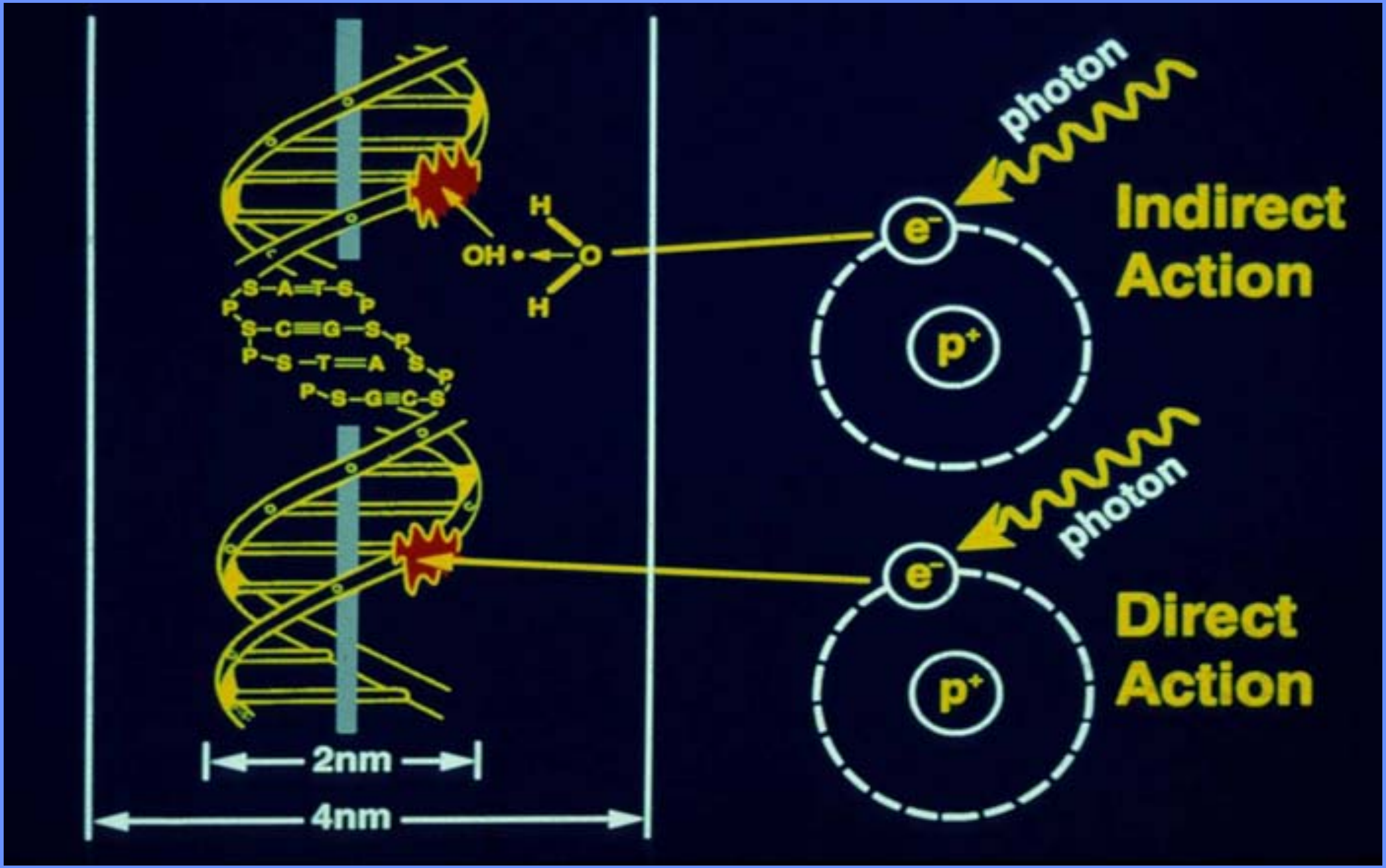
Figure 3.1. Colonies obtained with Chinese hamster cells cultured in vitro. **A:** In this unirradiated control dish 100 cells were seeded and allowed to grow for 7 days before being stained. There are 70 colonies; therefore the plating efficiency is 70/100, or 70%. **B:** Two thousand cells were seeded and then exposed to 800 rad (8 Gy) of x-rays. There are 32 colonies on the dish. Thus:
Surviving fraction = Colonies counted [colonies seeded x (PE/100)]
= 32/2000x .7
= 0.023

Chromatin Rejoining From Heavier Ion Damage is Slower



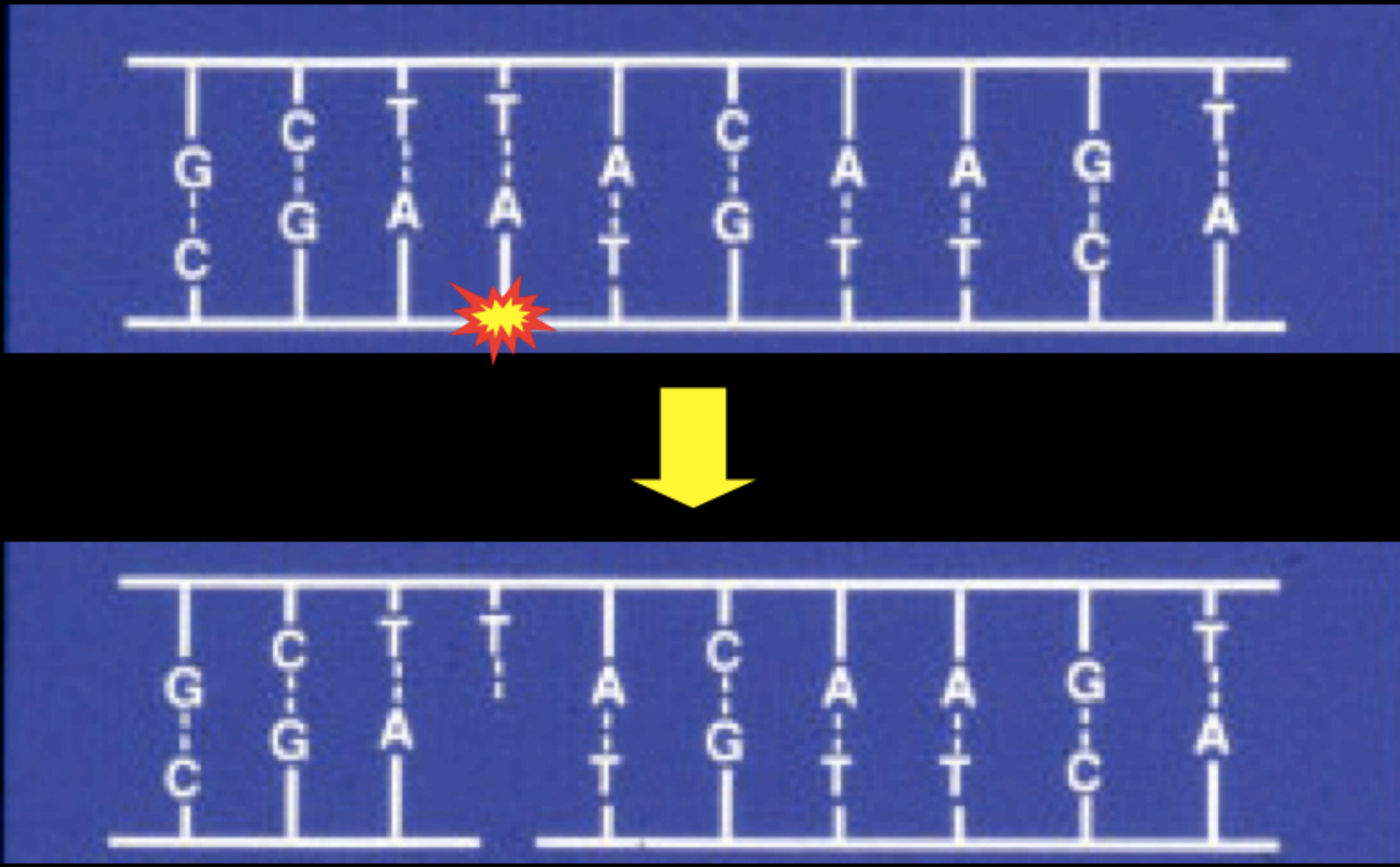
Goodwin et al.

DNA damage

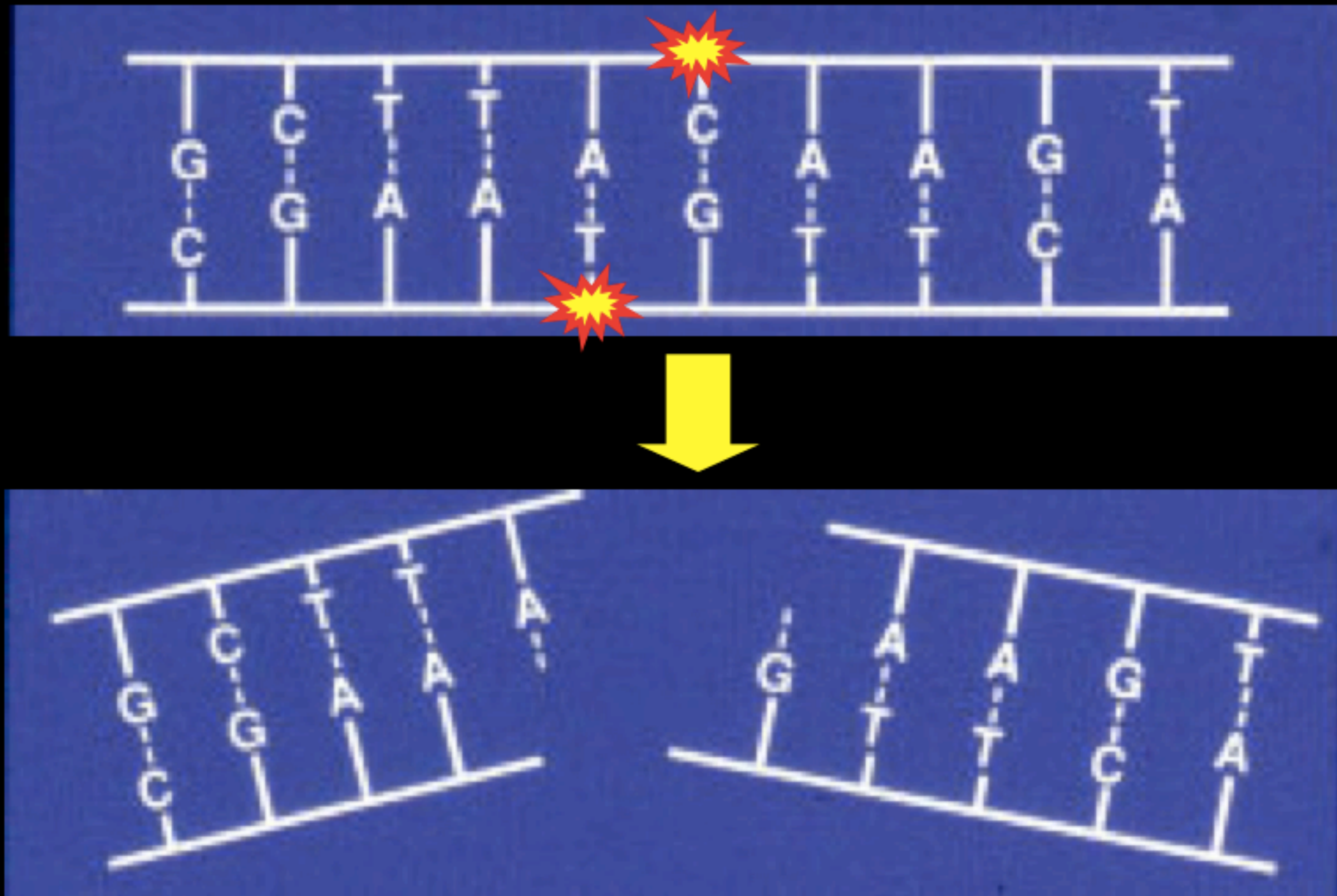

photon
Indirect Action
H
OH
O
H
e⁻
p⁺
S–A=T–S
P
P
S–C≡G–S
P
P–S–T=A S
P
P–S–G≡C–S
photon
Direct Action
e⁻
p⁺
2nm
4nm

Effects on DNA Macromolecules

- Point mutation
  - Ionizing radiation that ruptures the chemical bond of a macromolecule severing one of the sugar-phosphate chain side-rails of the DNA ladder (Single-strand break)
  - Gene mutations may result
  - These can occur with low-LET radiation
  - Repair enzymes can reverse this damage



Single strand break



DNA double break triggers cell death

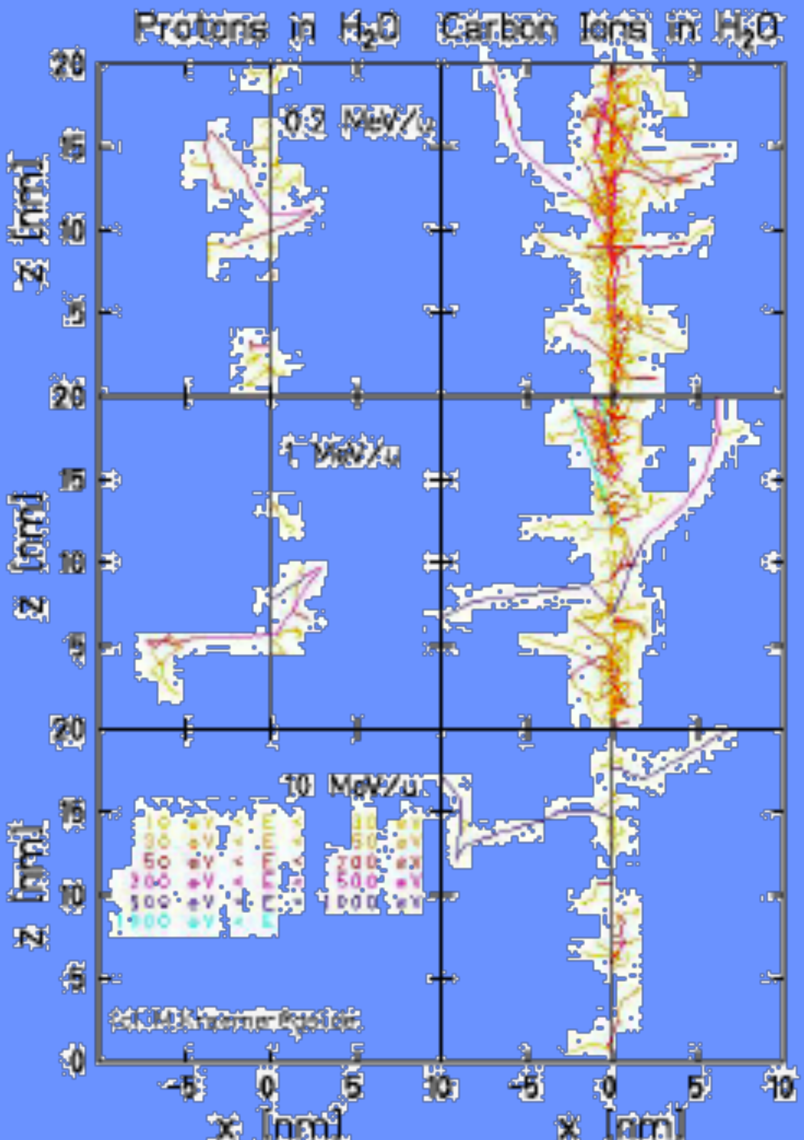
Double Strand Breaks

- One or more breaks in each of the two sugar-phosphate chains
- Not repaired as easily as single strand breaks
- More common with high LET radiation

Effects of Ionizing Radiation Upon Chromosomes

- If chromosomes are broken, two or more fragments are produced
- Each fragment has a fractured end
- These can join to another fractured end
- These new formations are known as an aberration

Track Structures of Proton vs. Carbon Ions



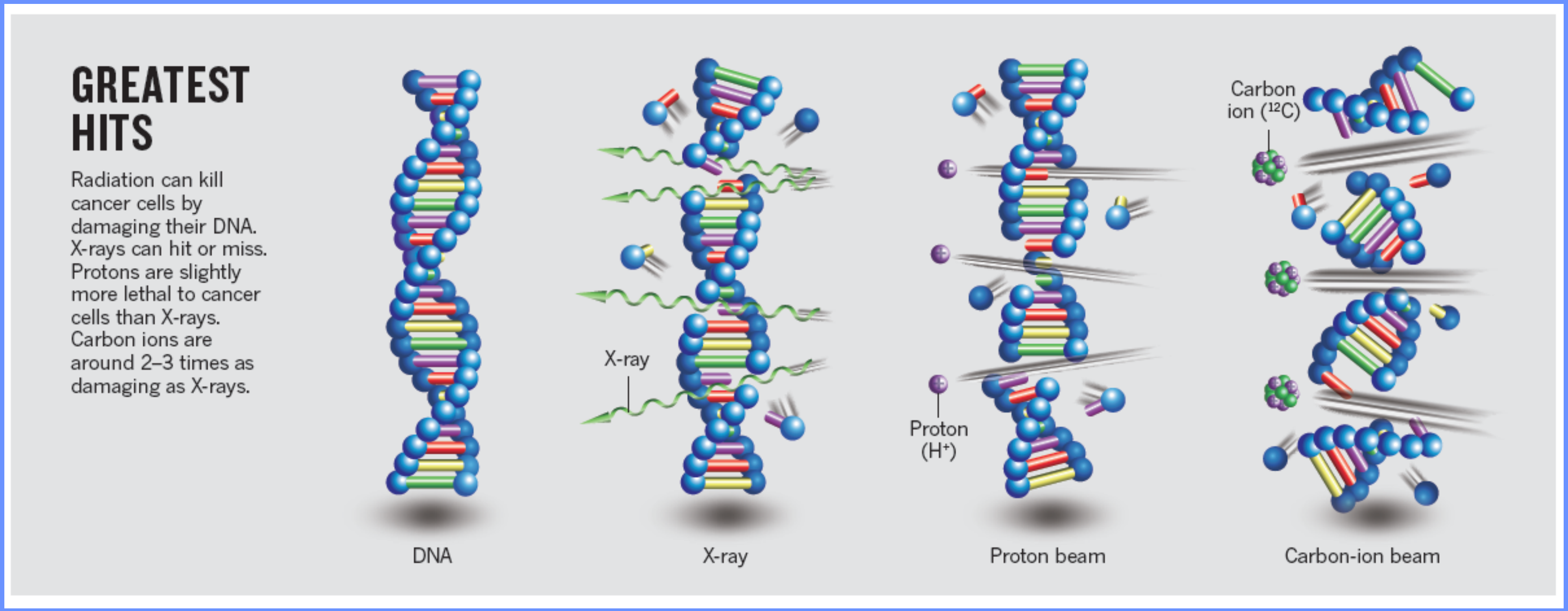
Linear Energy Transfer (LET) stands for the radiation energy deposited per unit length in tissue.

- X-rays and proton beams are low-LET radiations
- Heavy ion beams are high-LET radiation in Bragg peaks

Biological advantages:

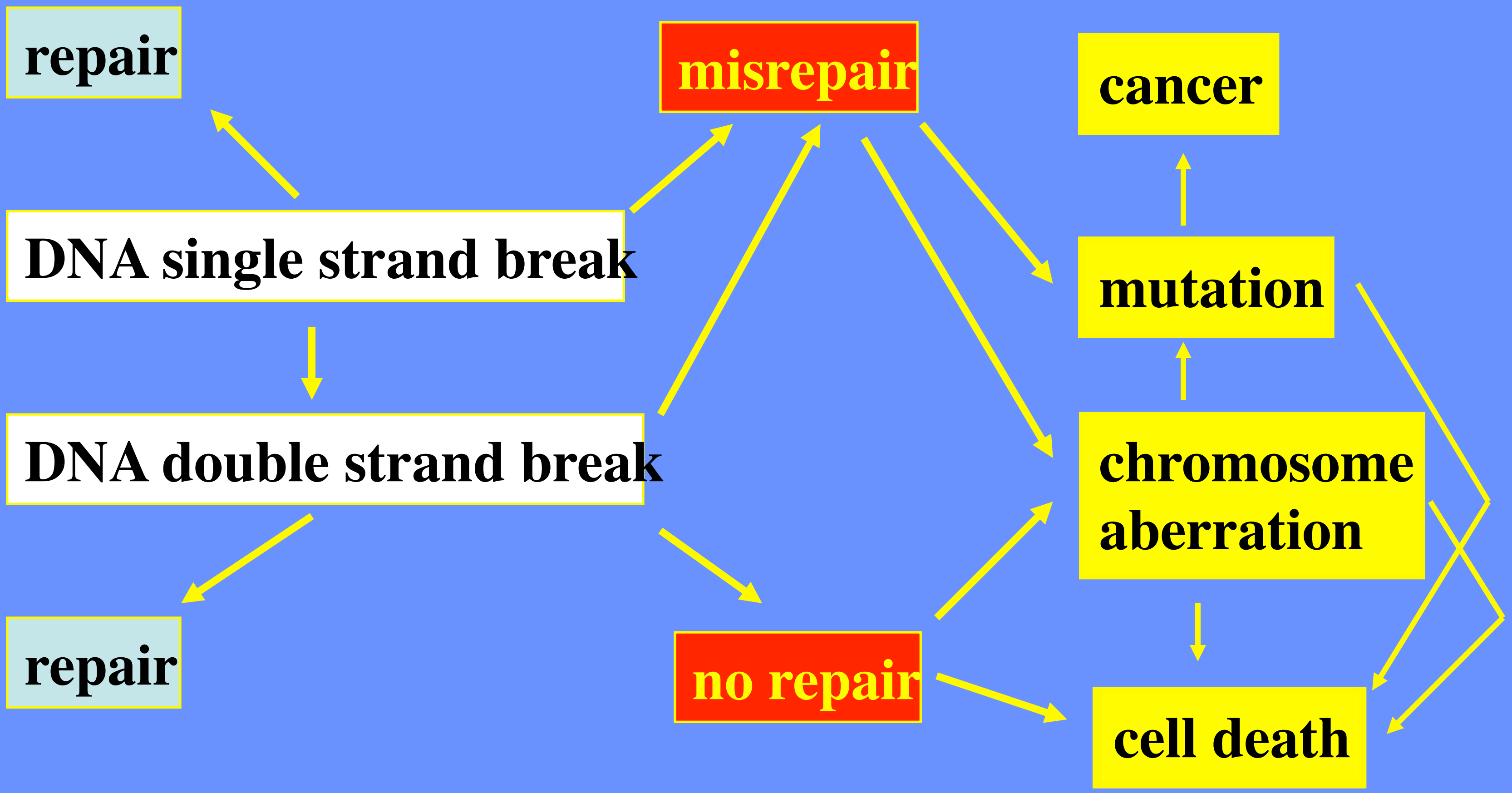
- High LET to provide significant differences in DNA damages
- Suppression of radiation repair
- Yet avoids some complications with higher-Z ions

DNA **X-rays** **Protons** **Carbon ions**



Marx, Nature, 2014

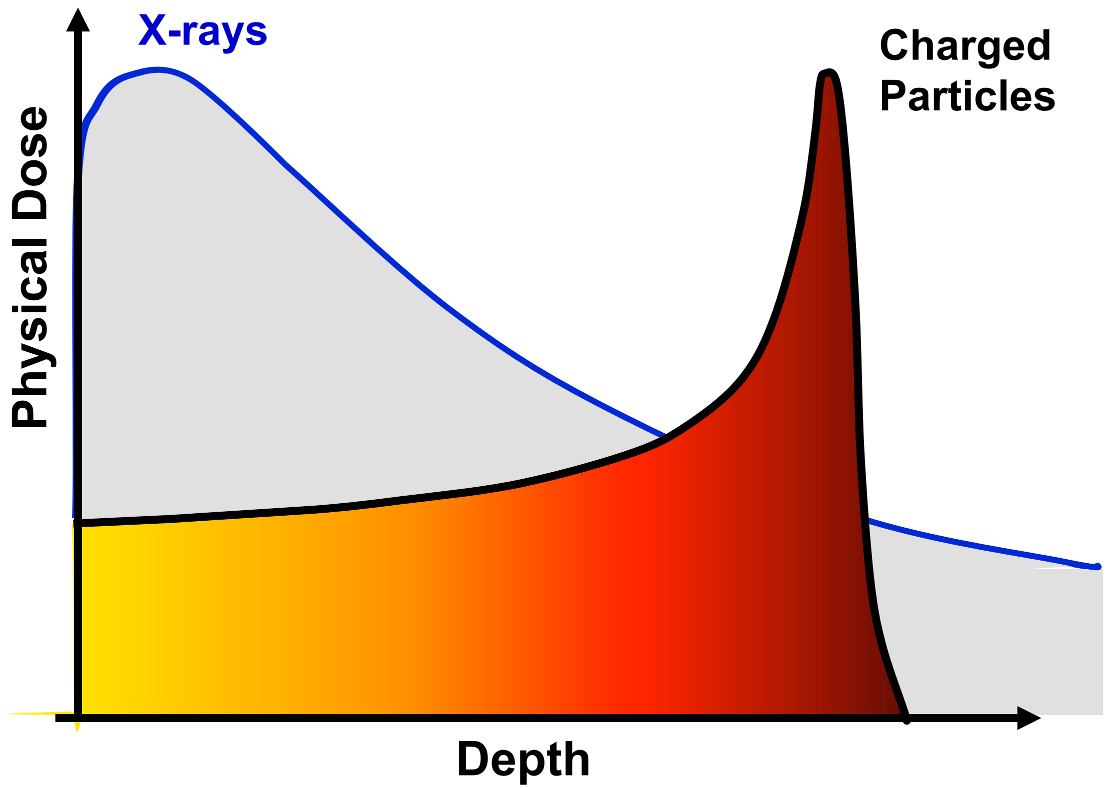
DNA damage and its consequences



Hadrons are being increasingly used in cancer treatment

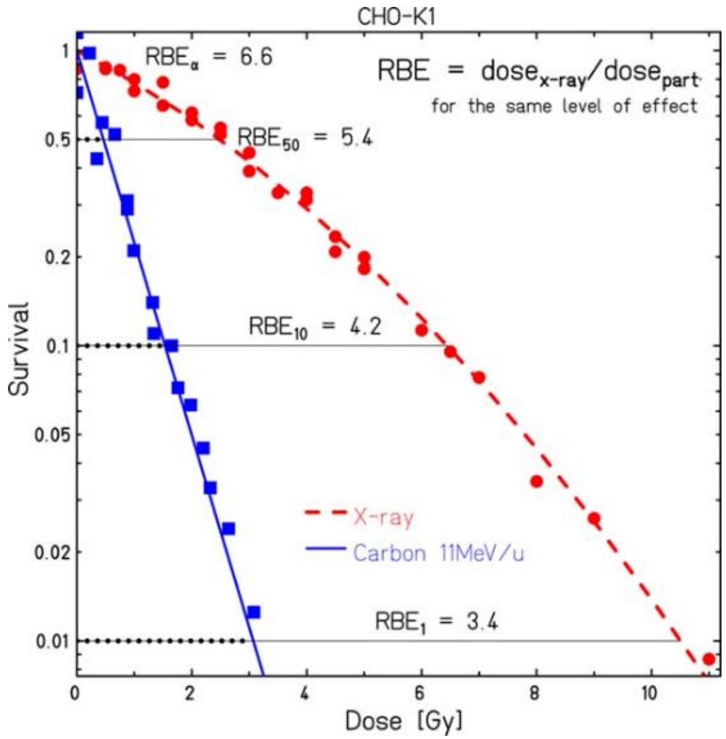
- Inverse energy deposition
- Elevated RBE for cell killing

→ Selective dose localization
Improved tumour control



Kevin Prise, ENLIGHT 2017

RBE: Relative Biological Effectiveness



RBE critically depends on both physical and biological parameters:

- **Dose & Dose Rate**
- **Cell line radiosensitivity**
- **Ion mass**
- **Ion energy**
- **SOBP shape/size**

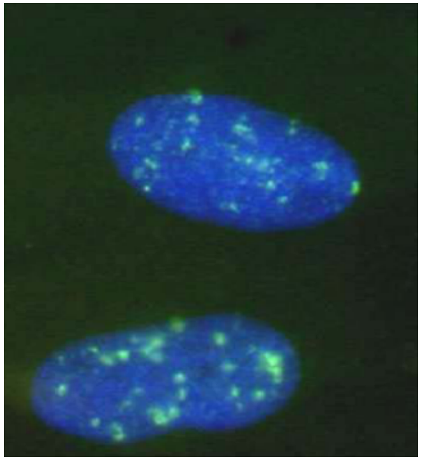
.....

Kevin Prise, ENLIGHT 2017

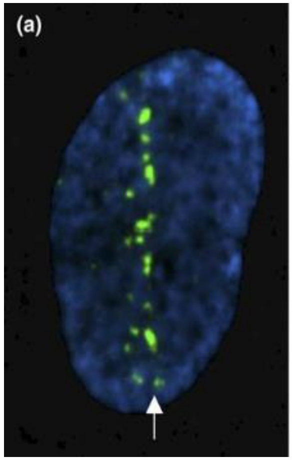
CCRCB

Dose, LET and RBE

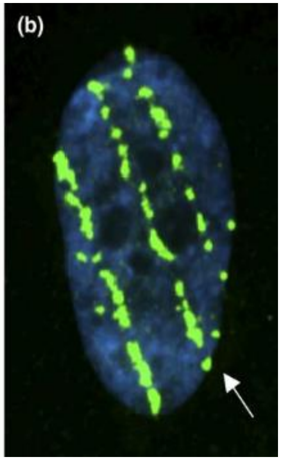
- Cellular response is determined by the level and quality of DNA damage, which reflects the energy deposition pattern.



X-rays



54 keV/µm Si ions



174 keV/µm Fe ions

- Severity of DNA damage depends on lesion proximity and repairability, hence it is not a constant value but depends on physical (particle type, LET, dose) and biological (cell type, oxygenation status, repair capacity) parameters.
- RBE varies with the particle energy and the change of the beam composition (SOBP and nuclear fragmentations): its distribution is not homogenous across a treatment field.

Kevin Prise, ENLIGHT 2017

CCRCB

Thanks to:

- U. Amaldi, CERN &TERA
- E. Blakely, LBNL, USA
- M Durante, Trento, Italy; Kevin Prise, Queens, UK
- HIT, CNAO, MedAustron, PSI, ENLIGHT colleagues
- KT. Medipx, Crytal Clear, Fluka, GEANT
- E-Book: From Particle Physics to Medical Applications

http://iopscience.iop.org/book/978-0-7503-1444-2

Useful links

- *cern.ch/crystalclear*
- *cern.ch/enlight*
- *cern.ch/virtual-hadron-therapy-centre*
- *https://cds.cern.ch/record/2002120?ln=en*
- *http://cds.cern.ch/record/1611721*
- *cern.ch/knowledgetransfer*
- *cern.ch/medipix*
- *cern.ch/twiki/bin/view/AXIALPET*
- *cern.ch/medaustron*
- *www.fluka.org/fluka.php*
- *http://geant4.cern.ch/*