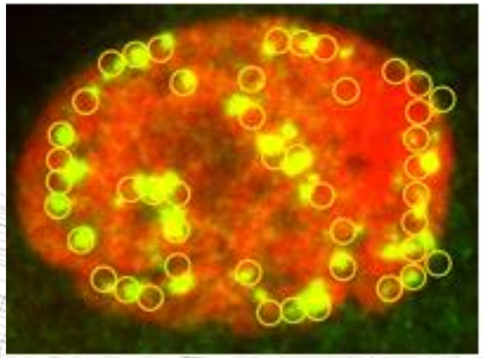
# Future Perspectives in Particle Therapy

Prof. Dr. Marco Durante



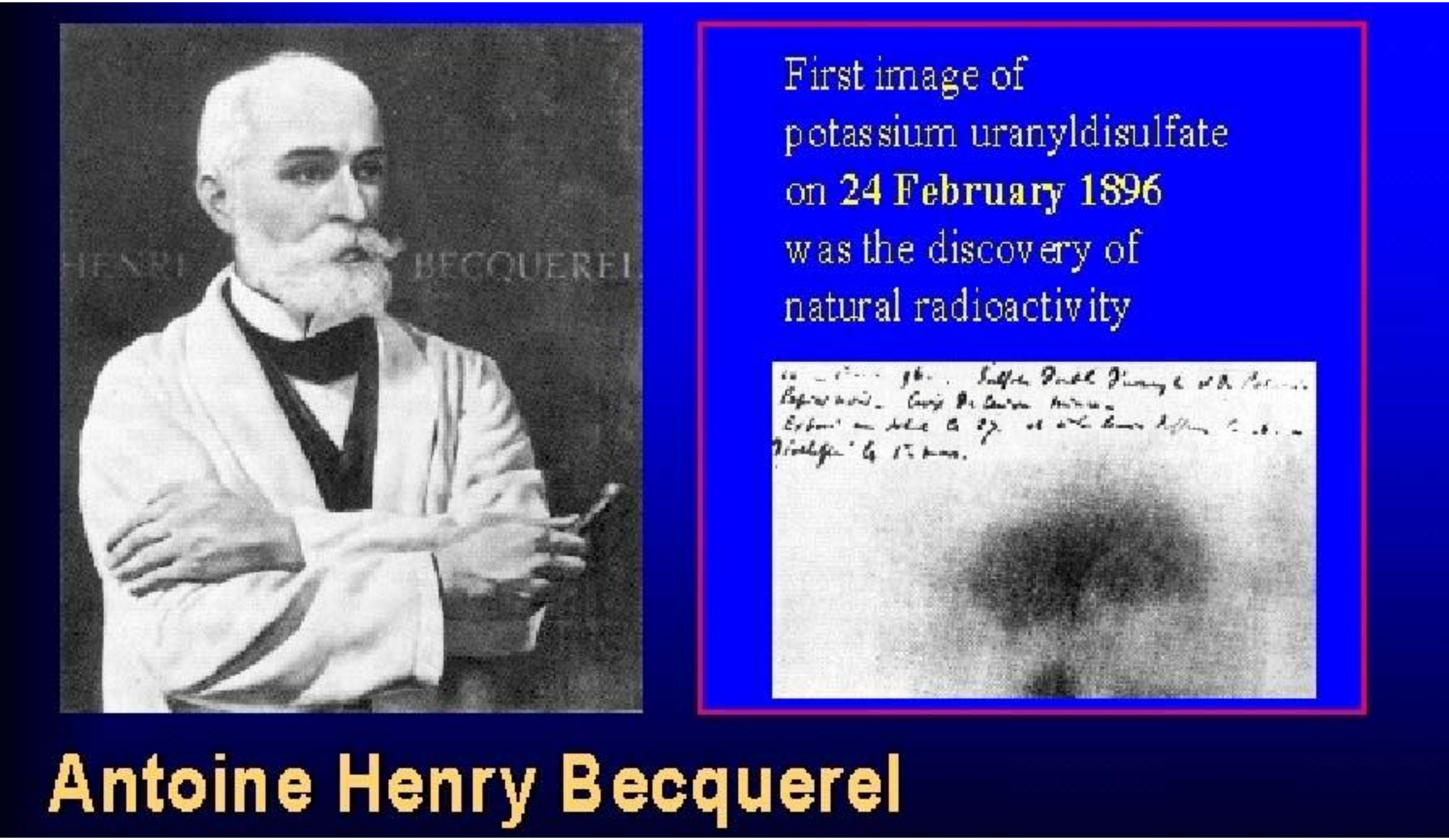
**Saha Nuclear Institute, 24.11.2013**

# Table of contents

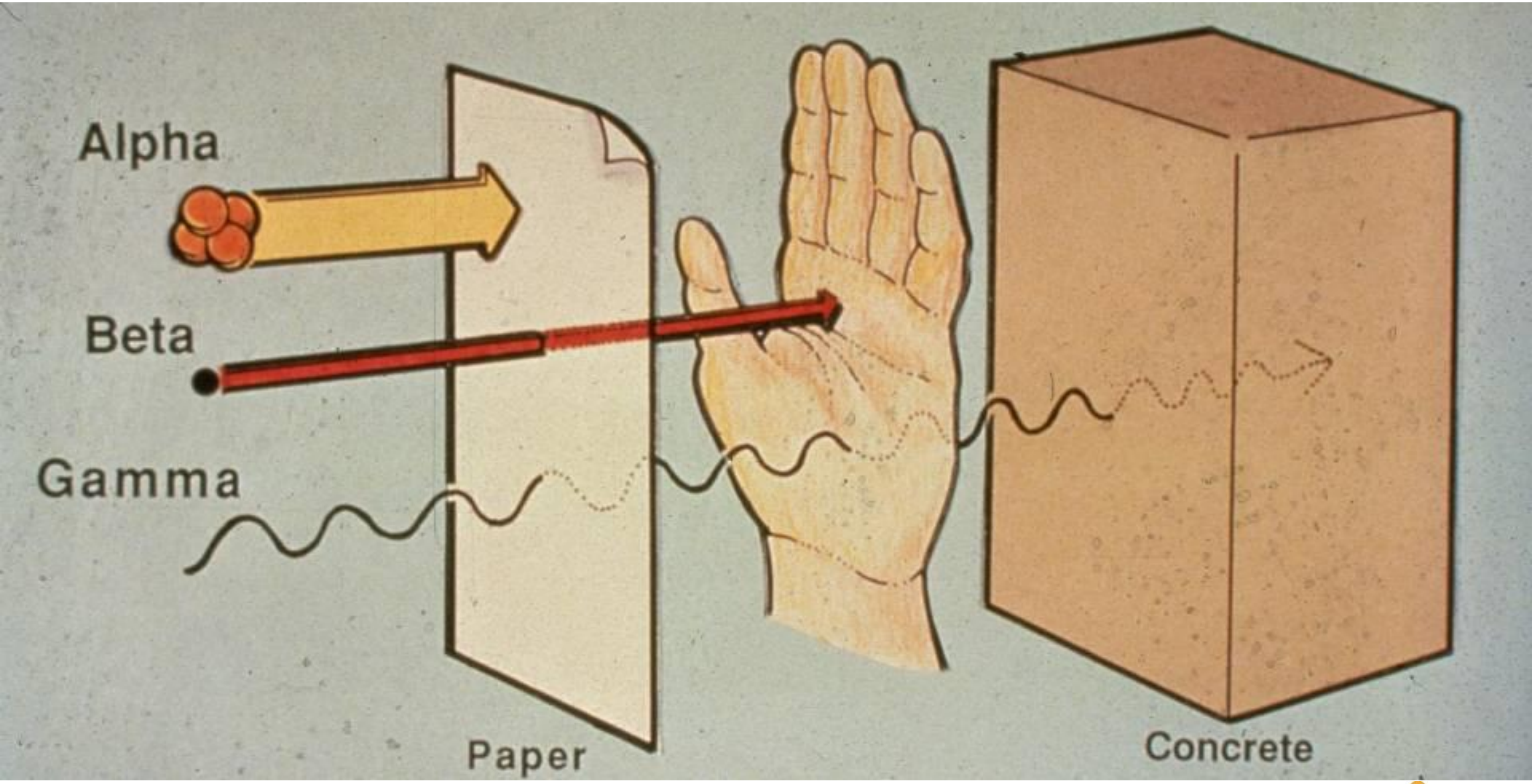
# November 1895: Roentgen discovers x rays

# February 1896: Becquerel discovers radioactivity

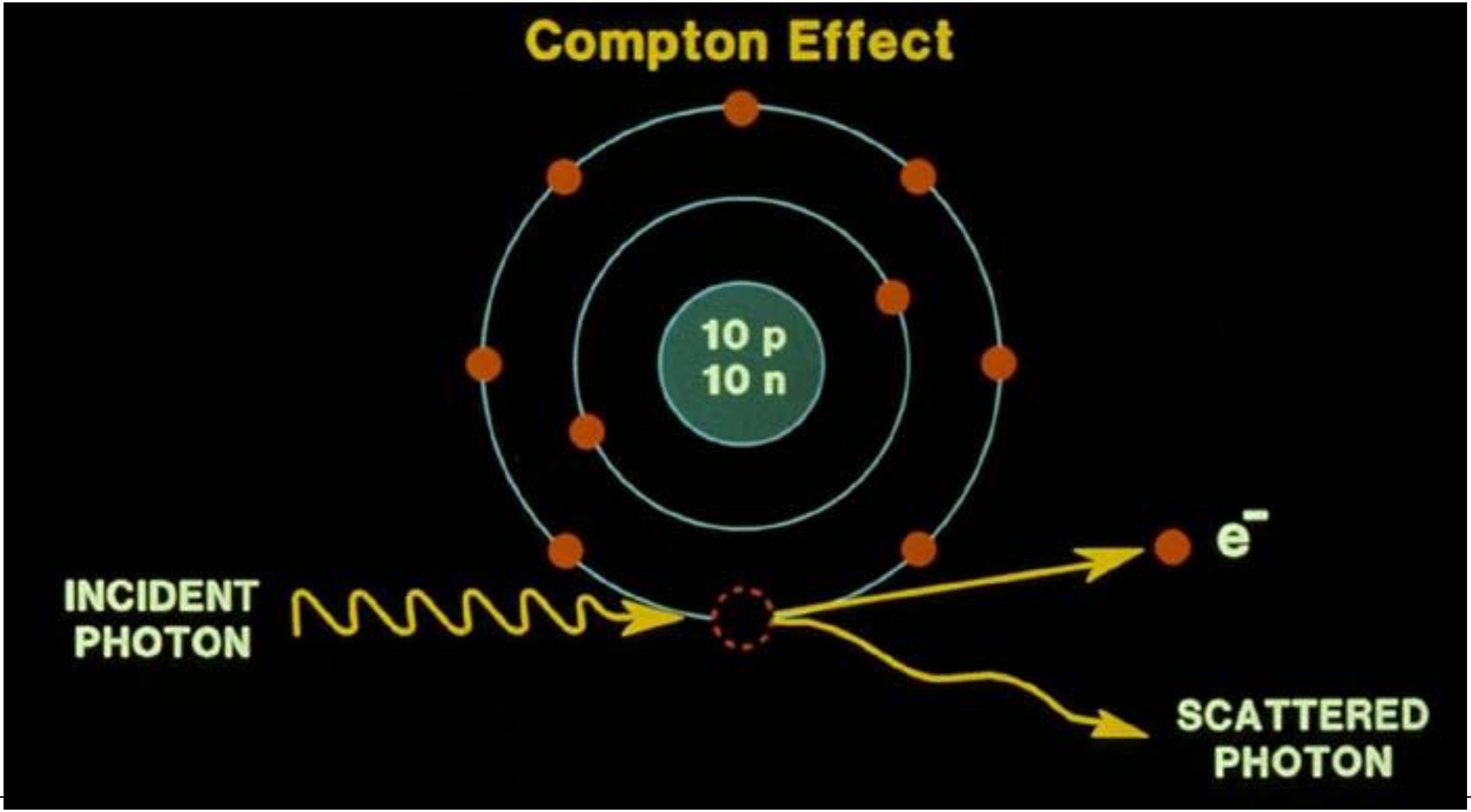
# 1 Bq= 1 disintegration/second



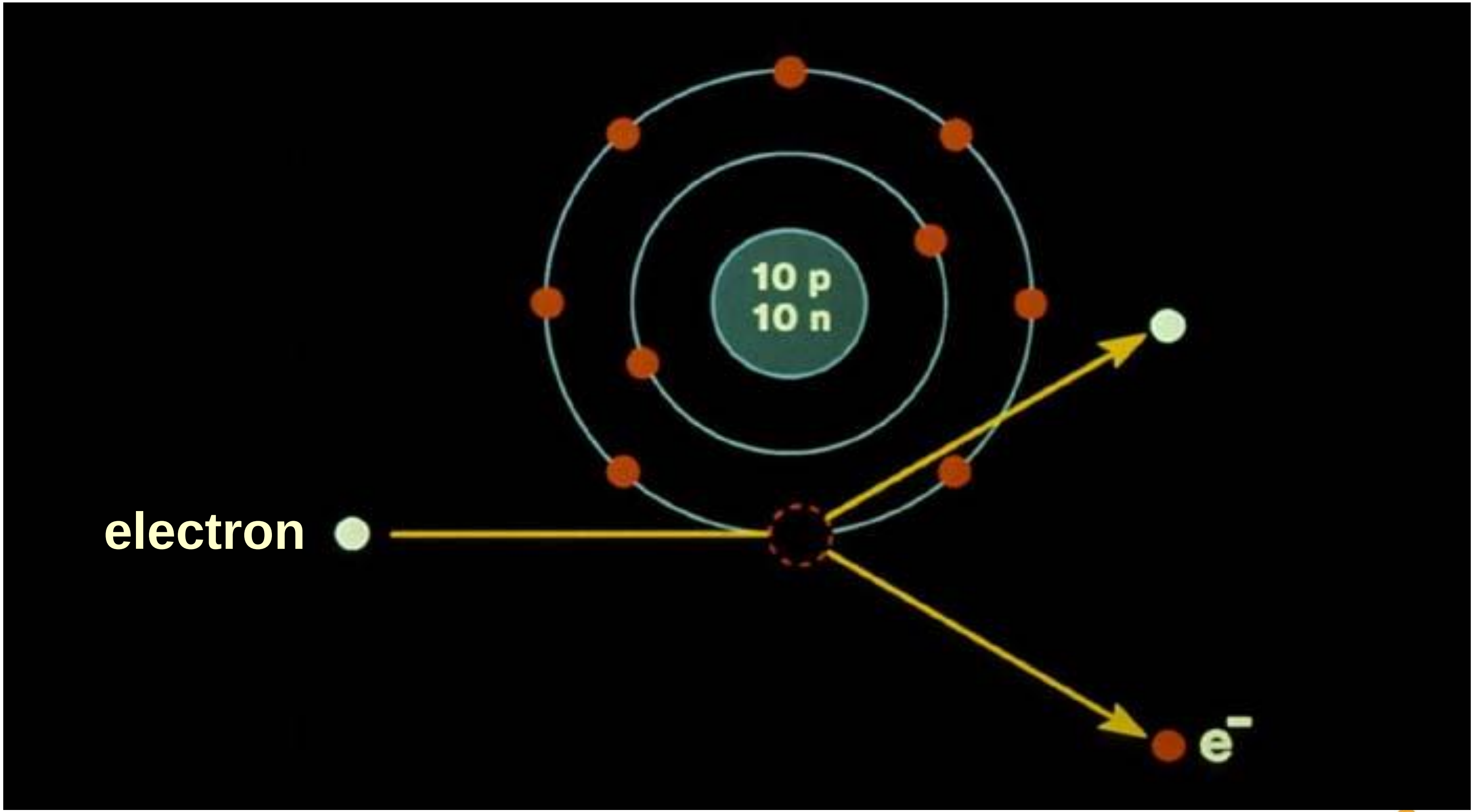
# α, β, γ-rays



# Interaction of x or $\gamma$ rays (photons) with matter: Ionization

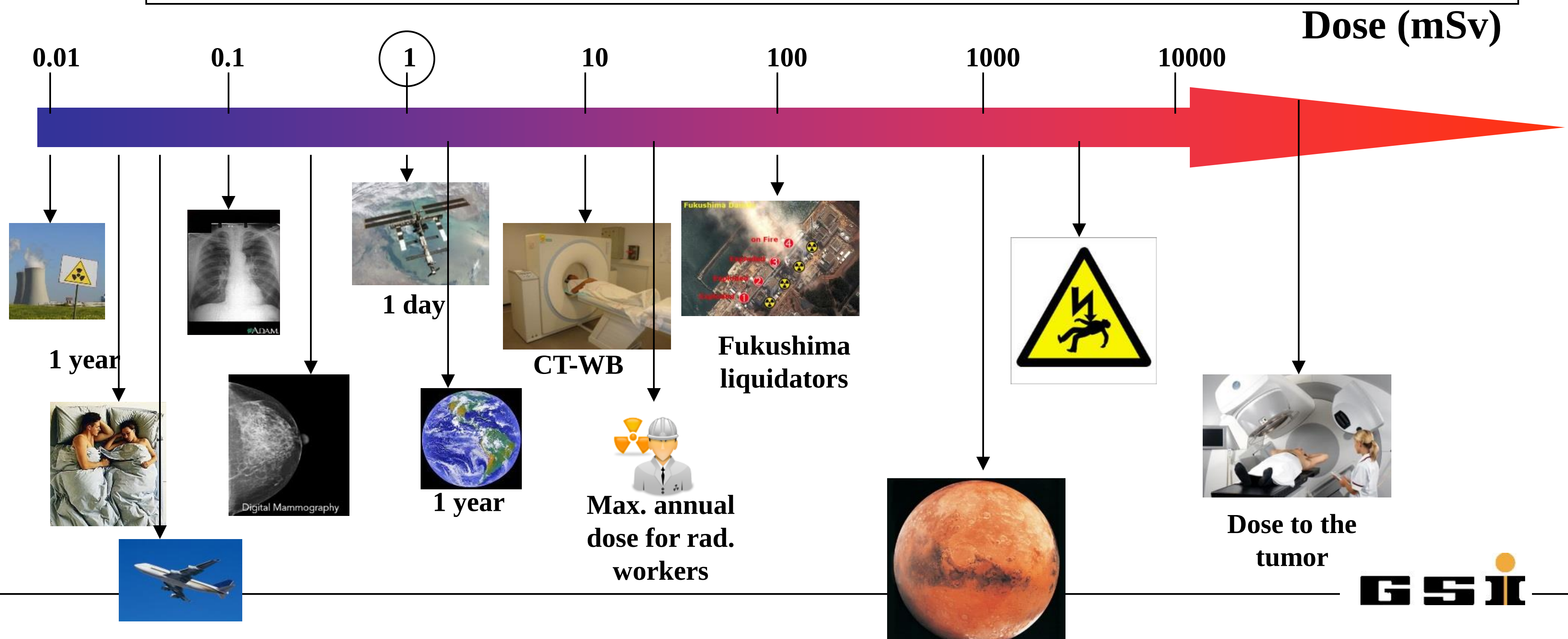


# Interaction of electrons or ions with matter:
# Ionization (Coulomb interaction)

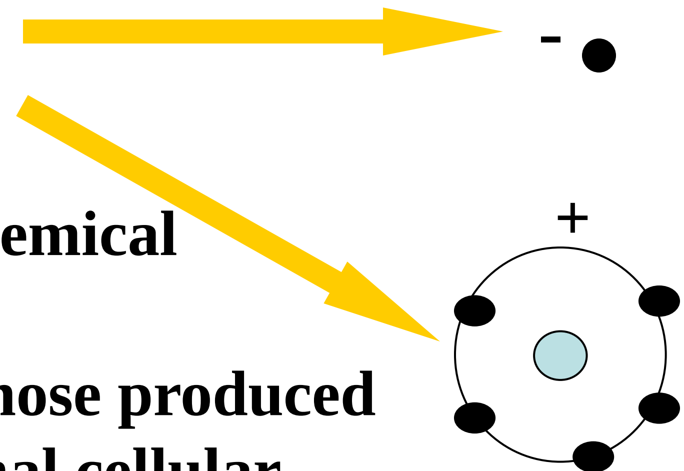


## Radiation Dose

- Radiation effects depends 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-, $\gamma$-rays and electrons: 1 Gy = 1 Sv
- But, for example: 1 mGy $\alpha$-particles= 20 mSv (Q=20)



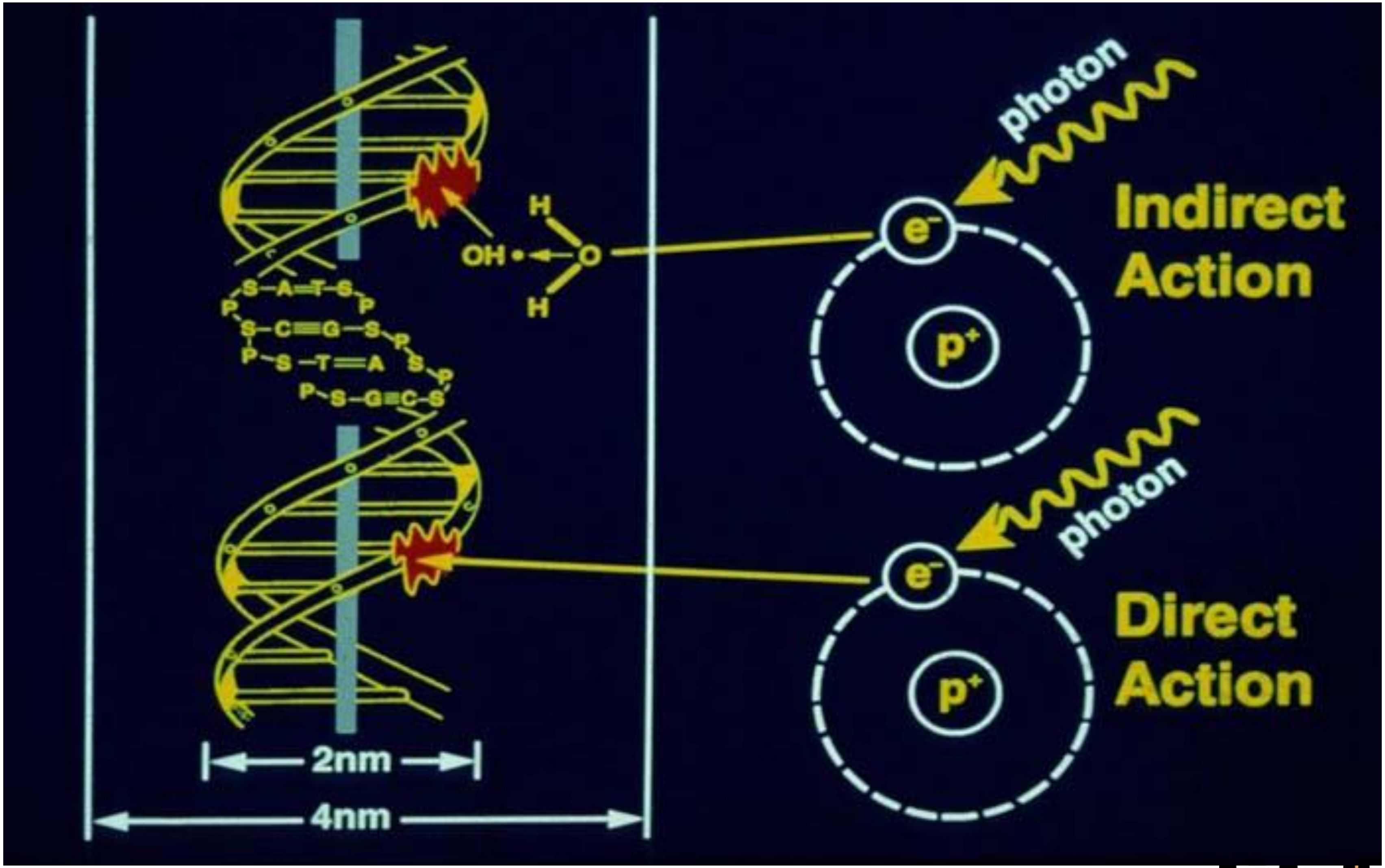
# How does radiation injure people?



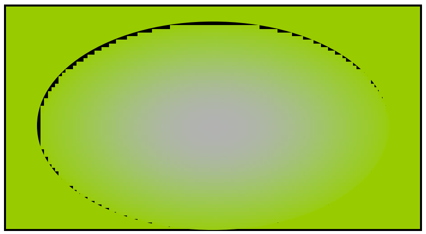
- High energy radiation breaks chemical bonds.
- This creates free radicals, like those produced by other insults as well as by normal cellular processes in the body.
- The free radicals can change chemicals in the body.

# The most unkindest cut of all

(W. Shakespeare, Julius Caesar)

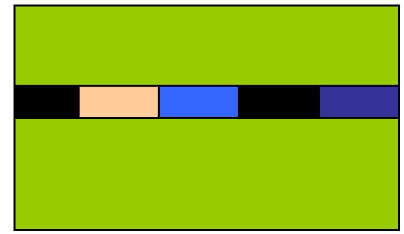


# How does this damage from ionizing radiation effect our bodies?

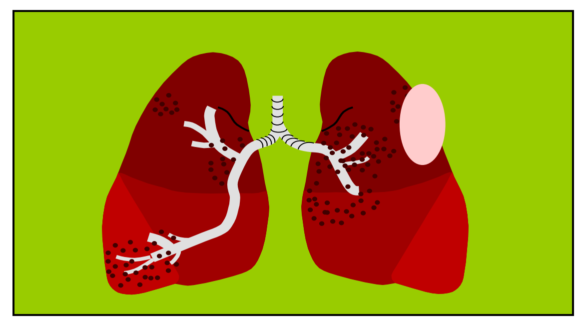


Sufficient Cell Killing

Radiation Sickness



Sufficient Genetic Alterations



Cancer

# RADIATION SICKNESS

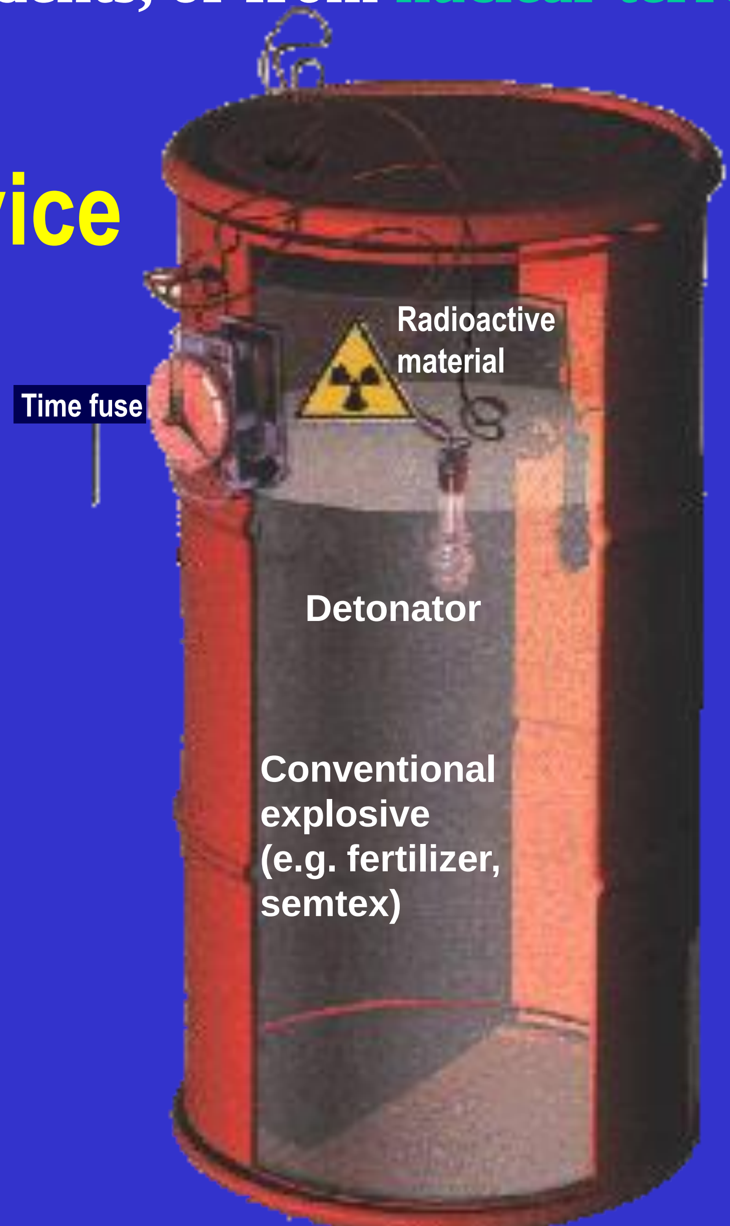
| System effected/ Syndrome | Symptoms | Dose |
|---|---|---|
| **Nervous system**<br>CNS or Cerebrovascular Syndrome | Shock, severe nausea, disorientation, seizures, coma | 100 Gy |
| **G.I. system**<br>Gastrointestinal Syndrome | Nausea, vomiting, diarrhea, dehydration | 10 Gy |
| **Blood cells /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

# Radiation sickness is possible during radiotherapy, in nuclear accidents, or from nuclear terrorism

## Radioactive Dispersal Device (RDD)

Alexander Litvinenko was poisoned in 2006 with the α-radioactive $^{210}Po$

(166 TBq/g and 0.5 μSv/Bq by ingestion → 50 ng are enough to give a lethal dose of 4.5 Sv!)




Argun, Chechnya, 1999 – A container filled with radioactive materials found attached to an explosive mine hidden near a railway line. It is safely defused.

The location is Argun, near the Chechen capital of Grozny, where a Chechen group, led by Shamil Basayev, operated an explosives workshop.

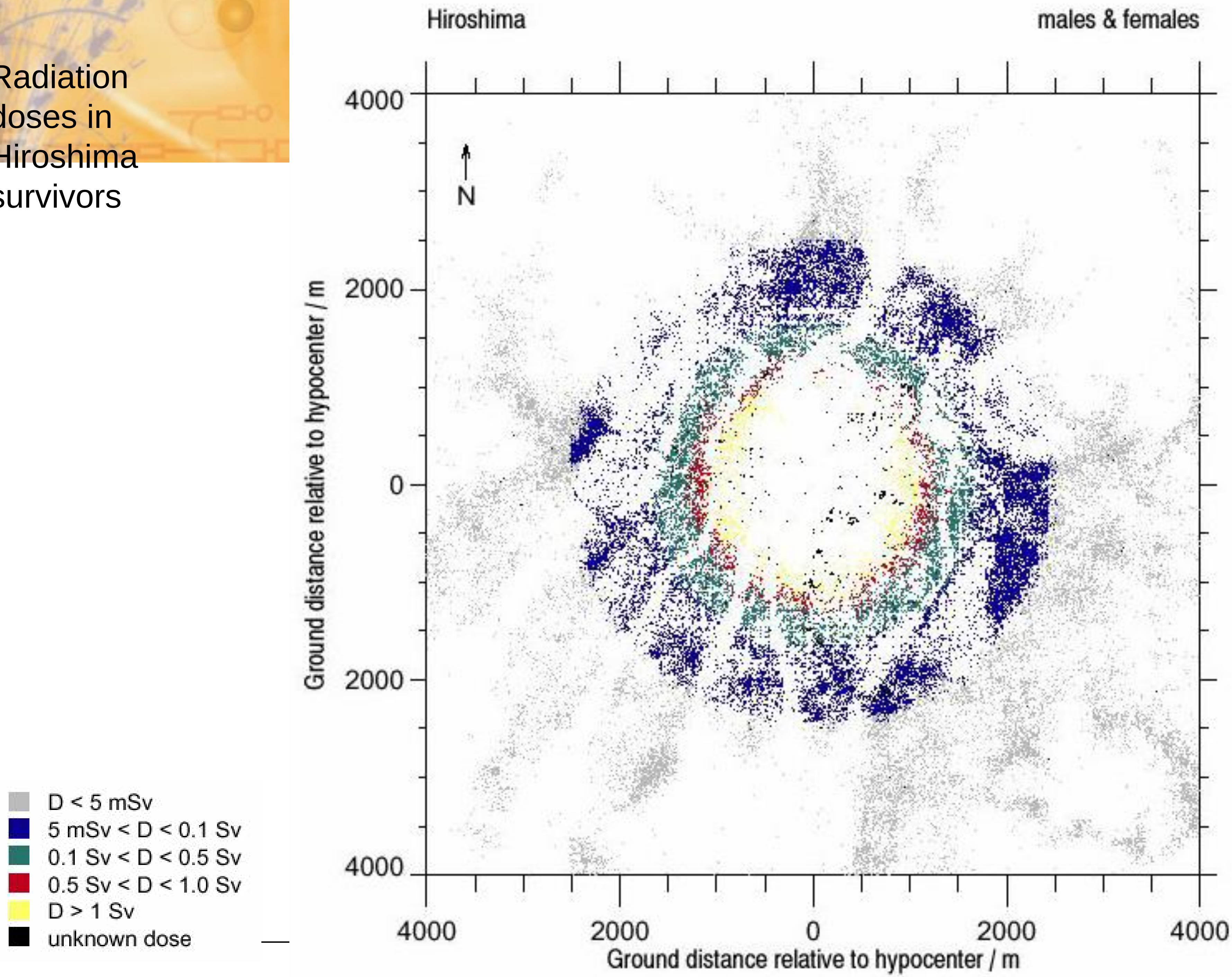
# Stochastic late effects

# Radiation and Cancer:
## A-bomb survivors

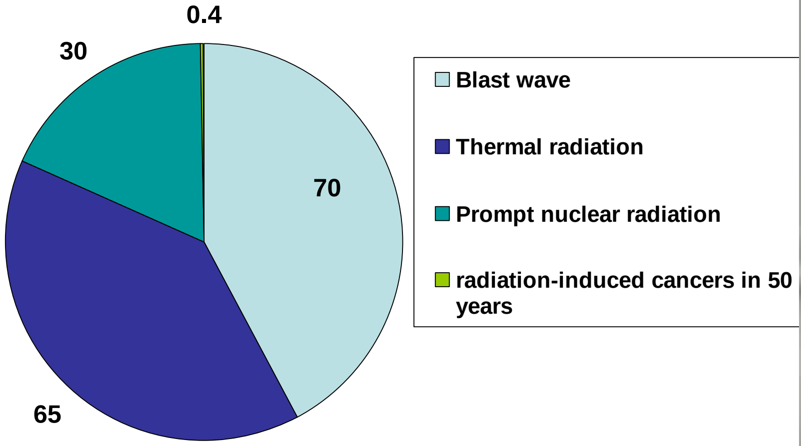
- 86,661 survivors followed (Life Span Study)
- 58% of this population died between 1950 (RERF foundation) and 2003 (last analysis in report 14, published in March 2012)
- 10,929 solid cancer deaths observed
- Approximately 644 (6%) attributed to radiation
- Approximately 1% of noncancer deaths are radiation-induced

Source: LSS report 14, RERF, March 2012

# Radiation doses in Hiroshima survivors



# Death causes distribution in % (total>100% because of multiple concurrent causes)




# Chernobyl Disaster 26.4.1986

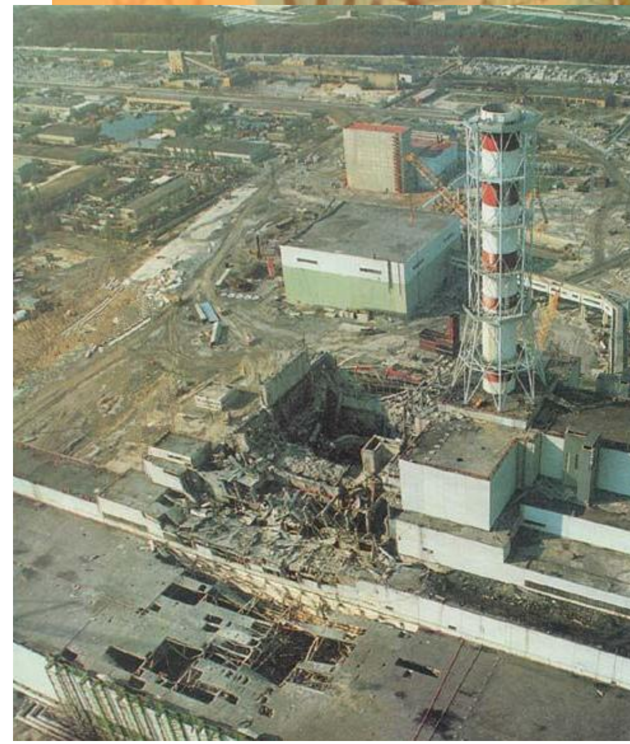
**Table III.** Emergency workers with acute radiation sickness following the Chernobyl accident. Dose estimates come from biological dosimetry. Adapted from [18].

| Degree of acute radiadion sickness | Dose range (Gy) | Number of patients treated | Number of deaths |
|---|---|---|---|
| Mild | 0.8-2.1 | 41 | 0 |
| Moderate | 2.2-4.1 | 50 | 1 |
| Severe | 4.2-6.4 | 22 | 7 |
| Very severe | 6.5-16 | 21 | 20 |

**Table IV.** Mean cumulated doses from the Chernobyl accident during the period 1986-1995 in contaminated areas. Thyroid doses are not included. Contaminated areas are regions with initial radiocesium concentration in excess of 37 kBq/$m^2$. Adapted from [19].

| State | Region | Population (thousands) | Mean cumulated dose (mSv) |
|---|---|---|---|
| Belarus | All | 1,881 | 8 |
| | Brest | 167 | 6 |
| | Gomel | 1,465 | 7 |
| | Gomel* | 78 | 40 |
| | Grodno | 28 | 5 |
| | Minsk | 25 | 6 |
| | Mogilev | 195 | 18 |
| | Mogilev* | 20 | 72 |
| Russia | All | 1,983 | 7 |
| | Bryansk | 451 | 17 |
| | Bryansk* | 95 | 36 |
| | Tula | 724 | 4 |
| Ukraine | All | 1,296 | 11 |
| | Zhytomyr | 313 | 14 |

* Radiocesium concentrations greater than 555 kBq/$m^2$.




**6000 excess childhood thyroid cancer cases (15 fatal)**

**Source: UNSCEAR, 2011 (data updated to 2005)**

# Indirect Effects of Human Abandonment

Pripyat
Abandoned

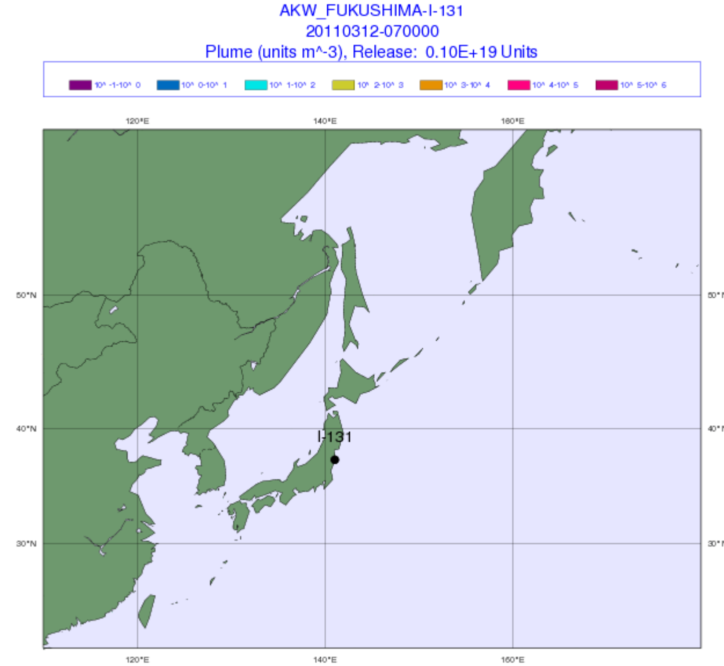
135,000 people and 35,000 cattle evacuated

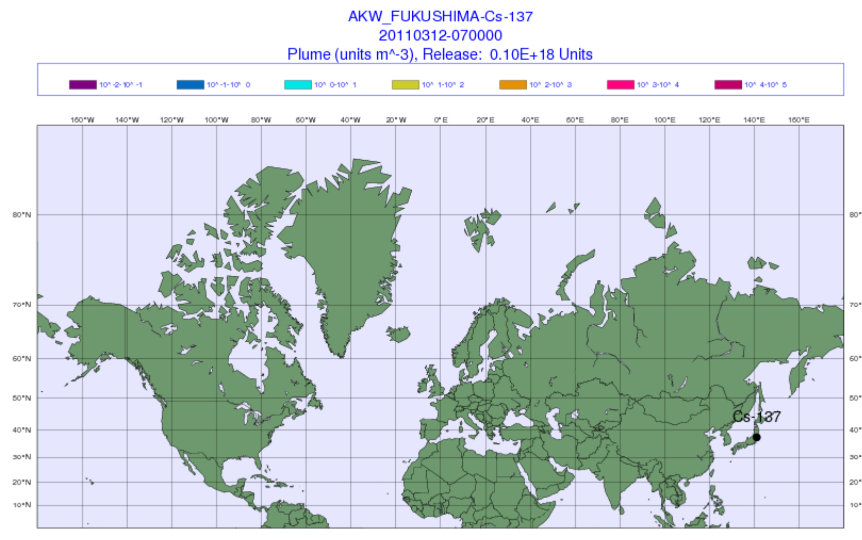
Dozens of towns and villages deserted.

48 endangered species listed in the international Red Book of protected animals and plants are now thriving in the Chernobyl Exclusion Zone

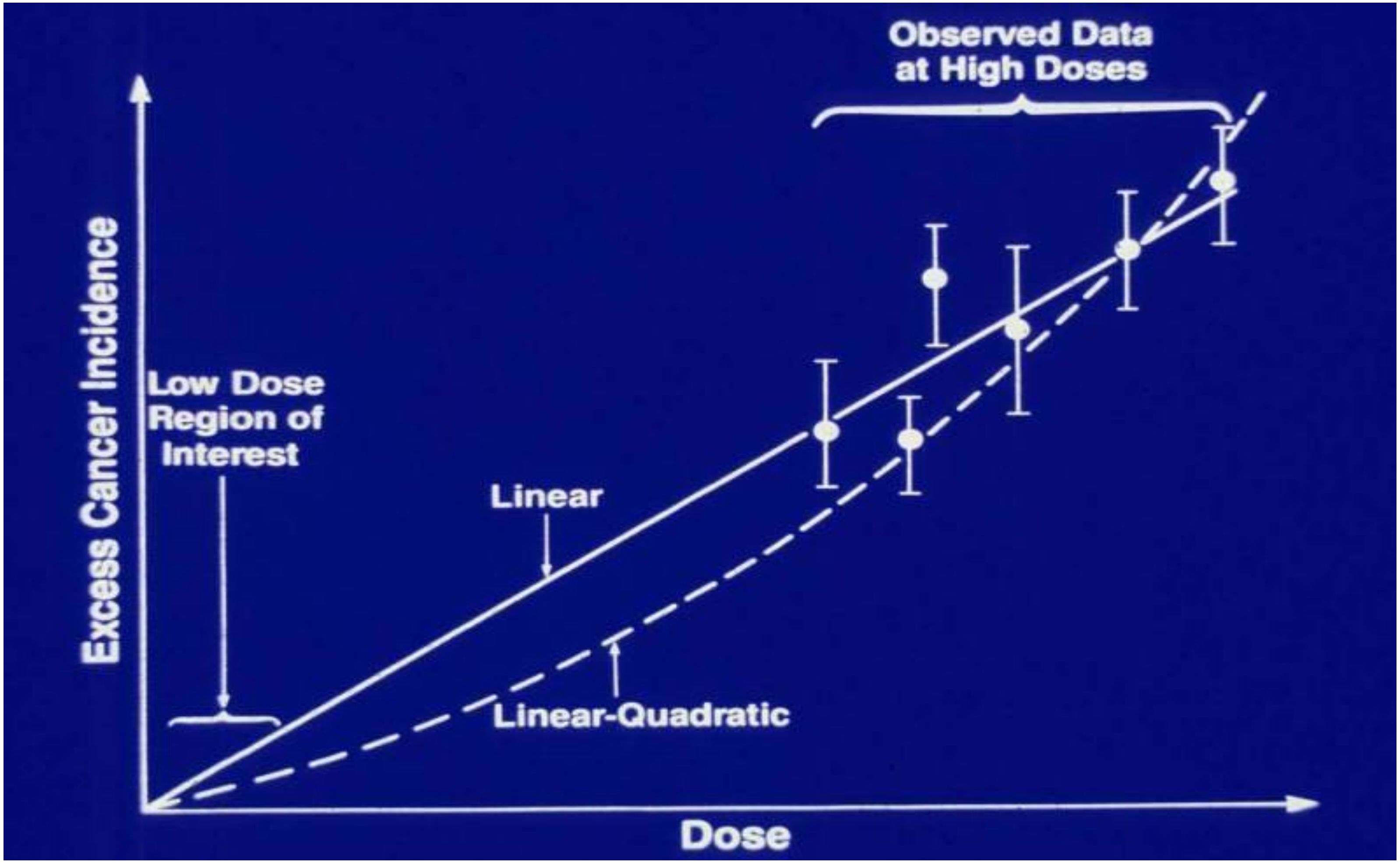
# The Fukushima radioactive cloud

Fukushima Daiichi Nuclear Power Station **(**Japan) – the aftermath of the March 11, 2011, 9.0 earthquake and tsunami



# Extrapolating radiation risks from high to low doses



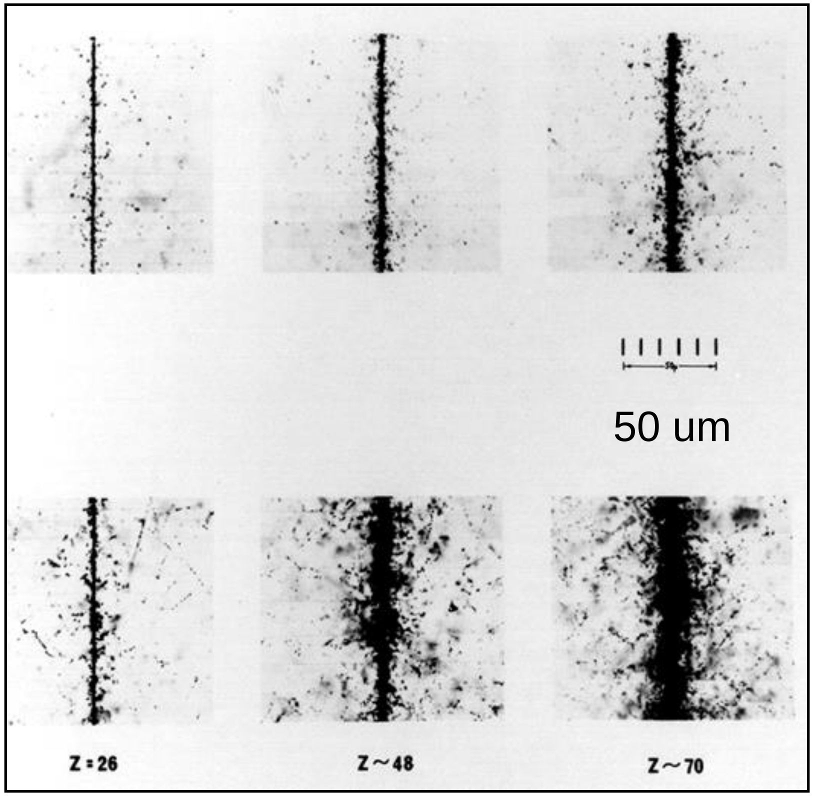
# Hereditary Effects

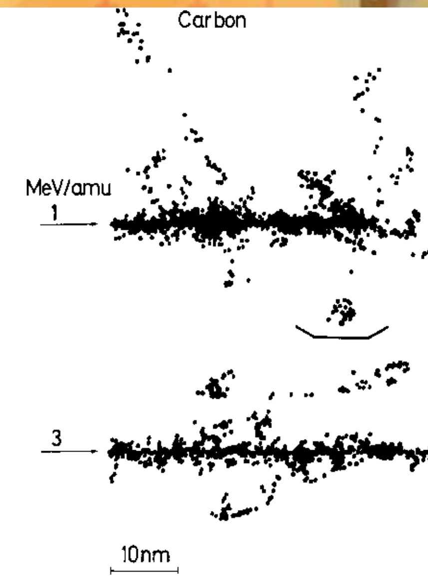
Children of the survivors of the A-bomb attacks have been studied for:

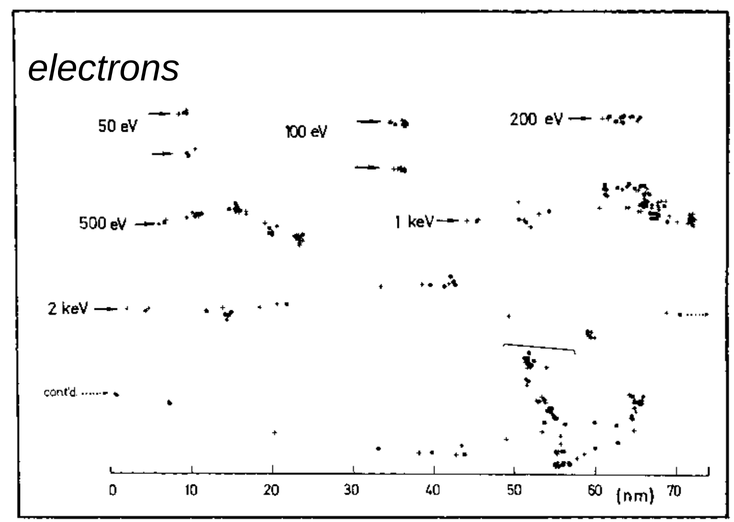
- Untoward pregnancy outcomes
- Death of live-born children
- Sex chromosome abnormalities
- Electrophoretic variants of blood proteins

But no statistically significant effects have been observed

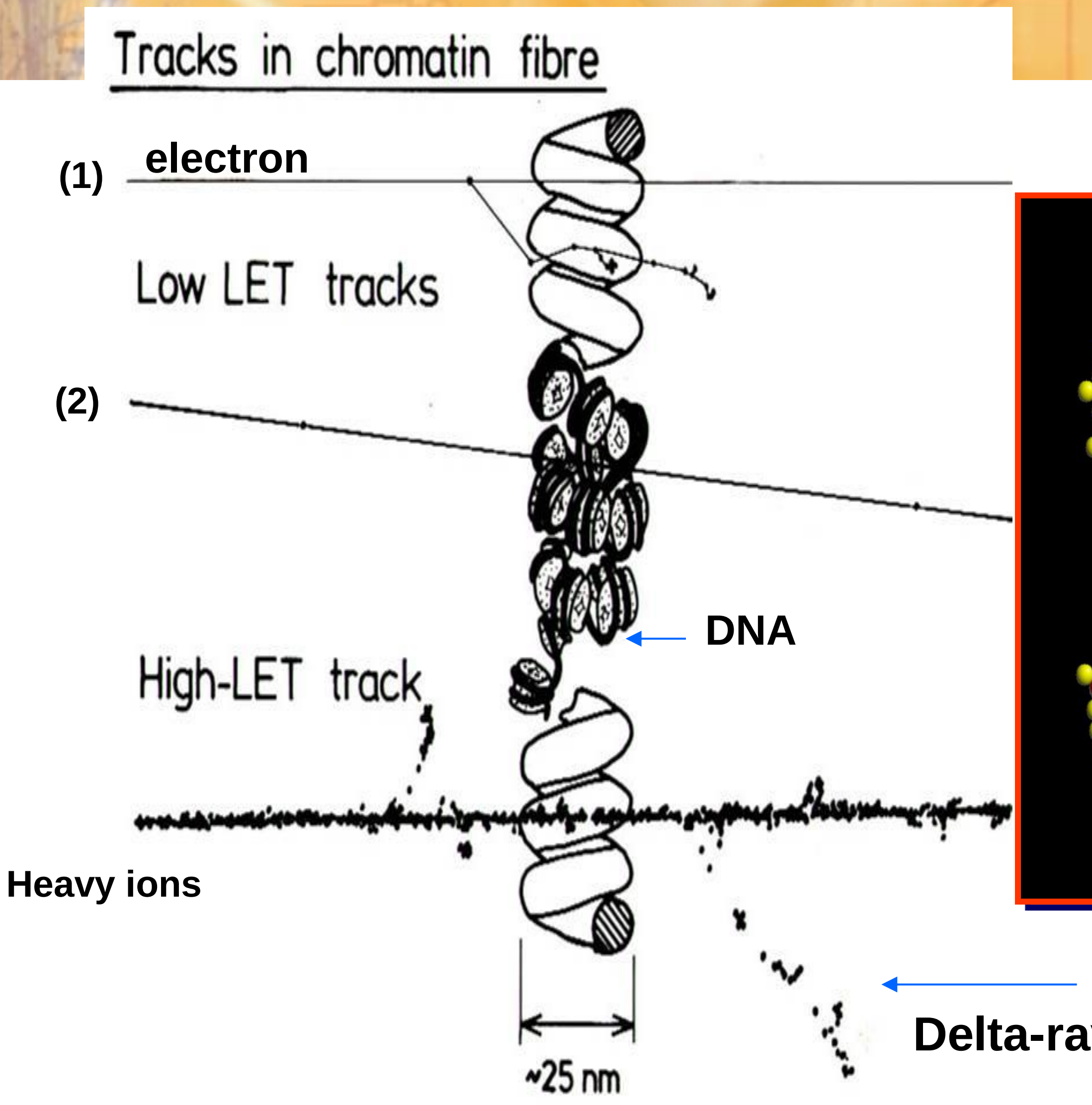
# High-energy heavy ions

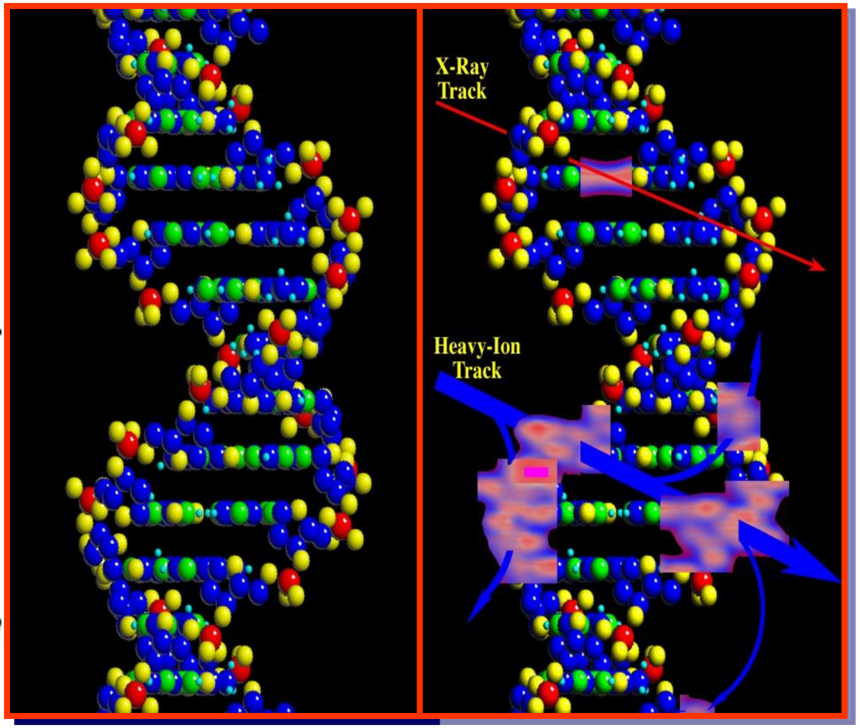


# All radiation tracks are highly structured on the scale of DNA



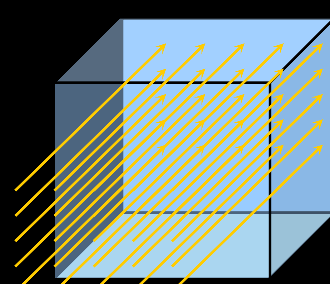
## An Analogy for Structured Energy Deposition and its Consequences

Low LET radiation produces isotropic damage to organized targets.

High LET radiation produces correlated damage to organized targets.

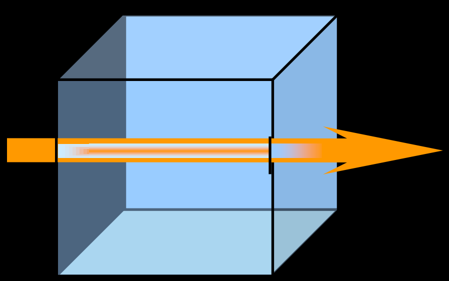
## LET: Linear Energy Transfer

1 Dose Unit



Low LET radiation deposits energy in a uniform pattern

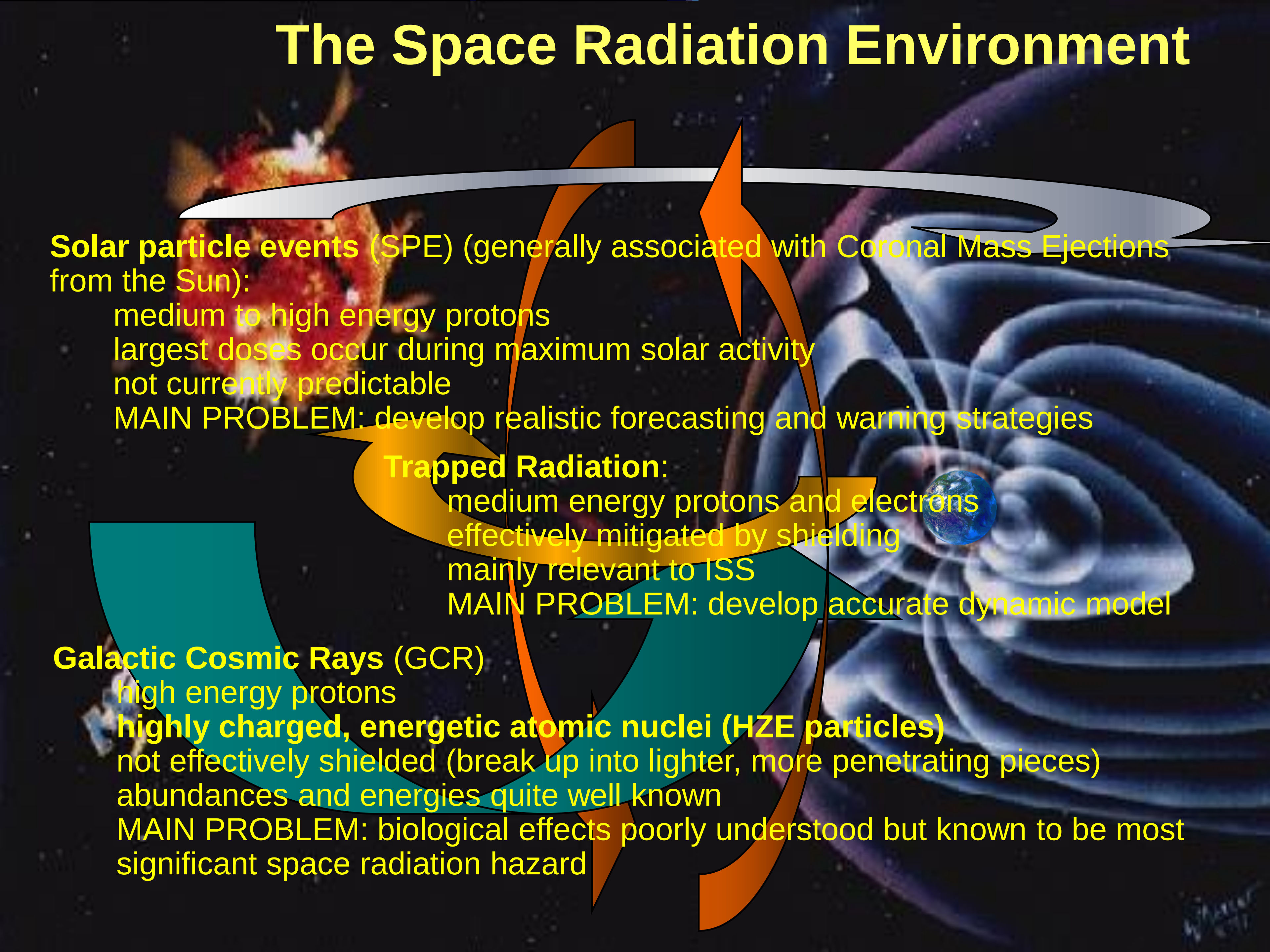
1 Dose Unit



High LET radiation deposits energy in a non-uniform pattern

# Why are we interested in energetic heavy ions?

**Heavy ion radiation is not present naturally on Earth**



# The Space Radiation Environment

**Solar particle events** (SPE) (generally associated with Coronal Mass Ejections from the Sun):

- medium to high energy protons
- largest doses occur during maximum solar activity
- not currently predictable
- MAIN PROBLEM: develop realistic forecasting and warning strategies

**Trapped Radiation**:

- medium energy protons and electrons
- effectively mitigated by shielding
- mainly relevant to ISS
- MAIN PROBLEM: develop accurate dynamic model

**Galactic Cosmic Rays** (GCR)

- high energy protons
- **highly charged, energetic atomic nuclei (HZE particles)**
- not effectively shielded (break up into lighter, more penetrating pieces)
- abundances and energies quite well known
- MAIN PROBLEM: biological effects poorly understood but known to be most significant space radiation hazard

## 4-6 crew to lunar surface for extended-duration stay

**CEV**:Earth-moon cruise – 4 days
Low lunar orbit (LLO) operations- 1 day
Untended lunar orbit operations – 4-14 days
Low lunar orbit operations – 1 day
Moon-Earth cruise – 4 days

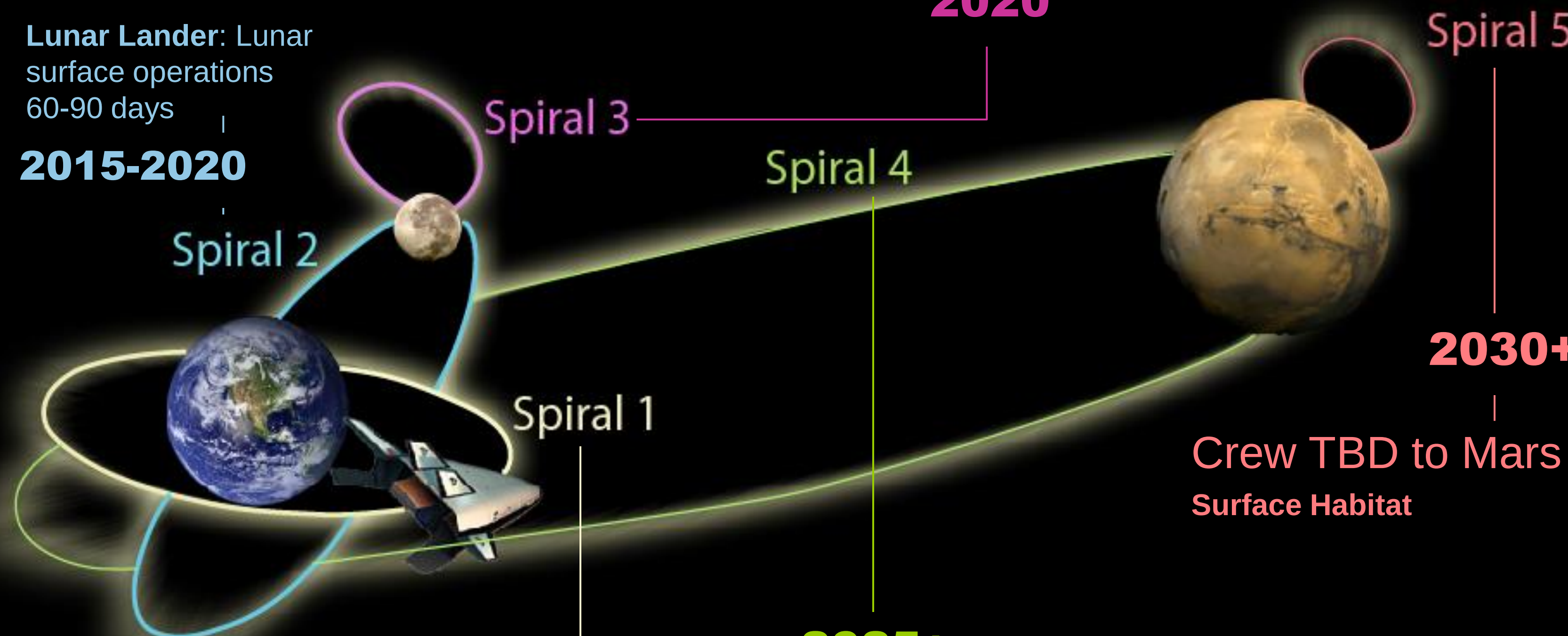
**Lunar Lander**: Lunar surface operations 60-90 days

**2015-2020**

## 4-6 crew to lunar surface for long-duration stay

**Lunar Habitat:** Lunar surface operations 60-90 days

**2020**




**2030+**

## Crew TBD to Mars surface

**Surface Habitat**

**2025+**

## Crew TBD to Mars Vicinity

**Transit vehicle**: Earth-Mars cruise – 6-9 months
Mars vicinity operations – 30-90 days
Mars-Earth cruise – 9-12 months

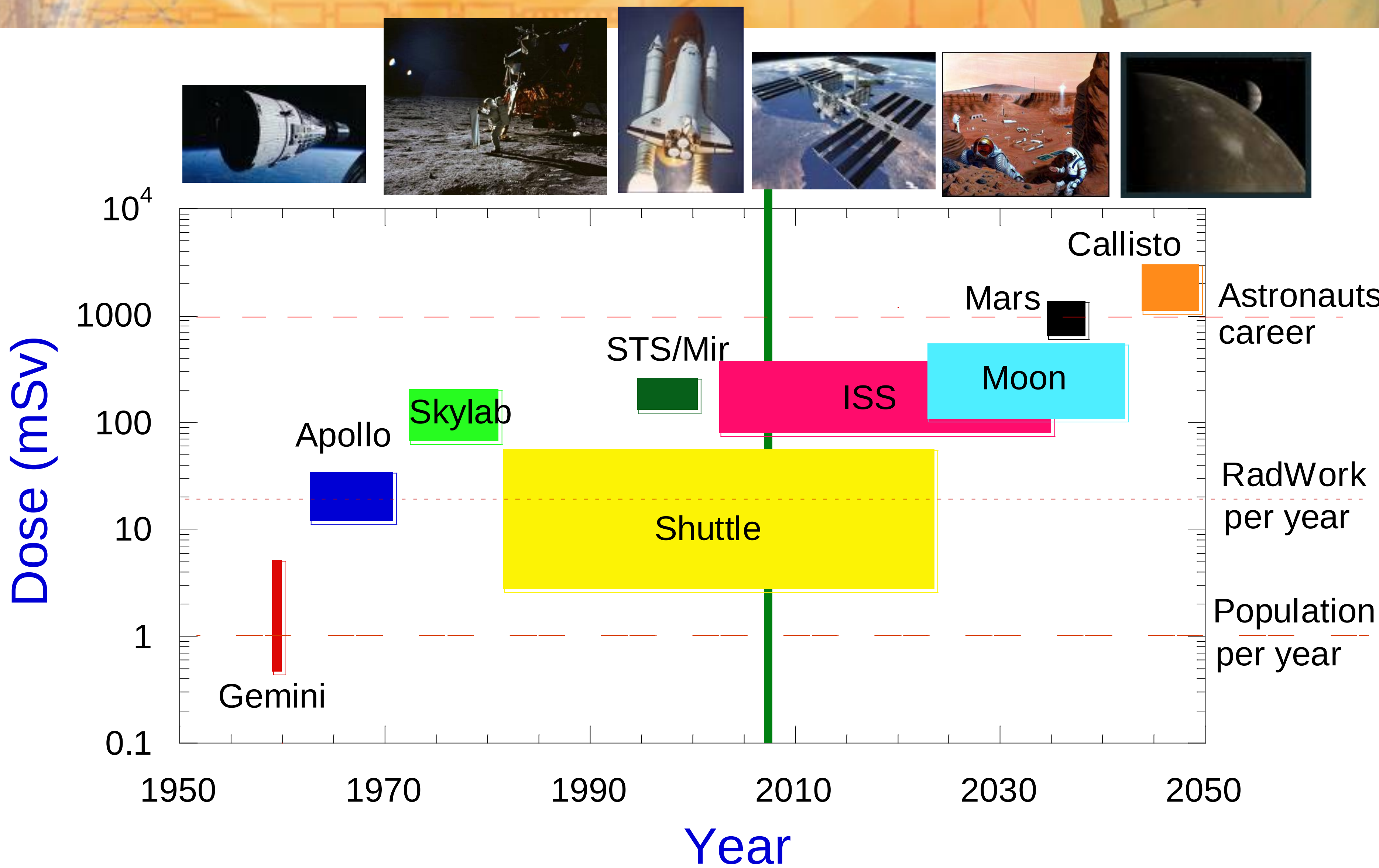
**2014**

## 4-6 crew to Low Earth Orbit

**Crew Exploration Vehicle**: Launch Environment
LEO Environment
Earth entry, water (or land) recovery

*NASA ESMD*

# Radiation doses in different missions




# Health in Deep Space

1. Protection from space radiation (particularly very high energy heavy ions)
2. Psychosocial and behavioural problems
3. Physiological changes caused by microgravity

**Modified by Mike Lockwood**

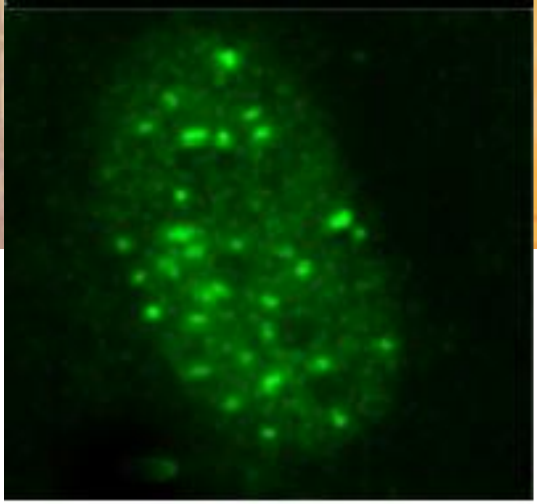
# Biological effects of heavy ions

**No human epidemiological data**

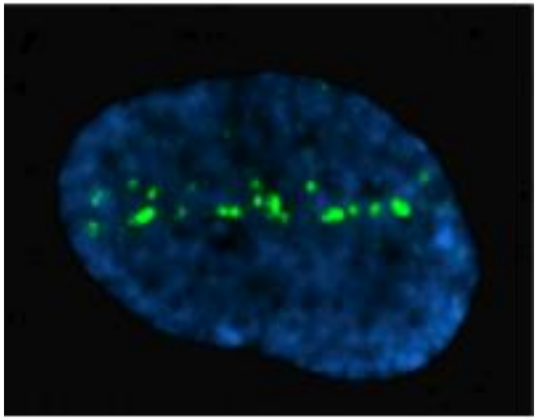

**γ-rays**


**heavy ions**

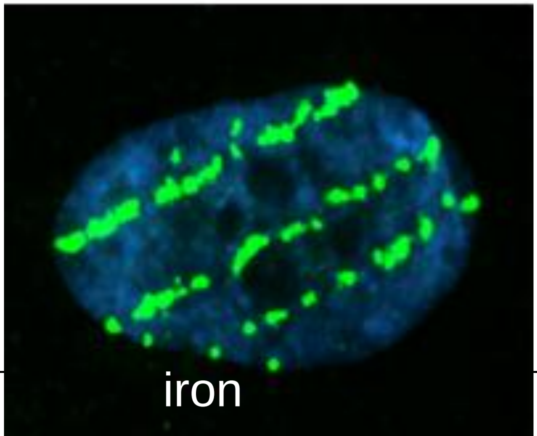
# Tracks in cells



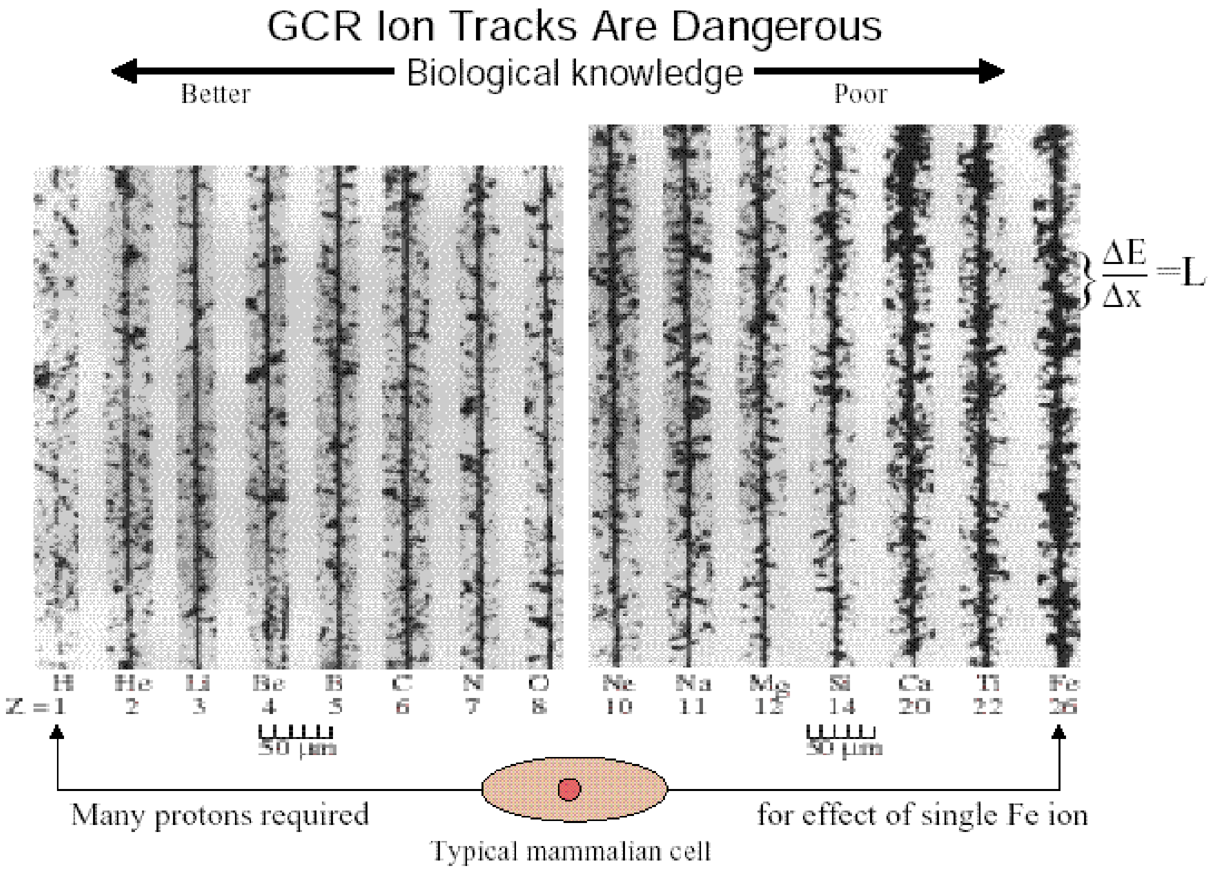
γ-rays



silicon

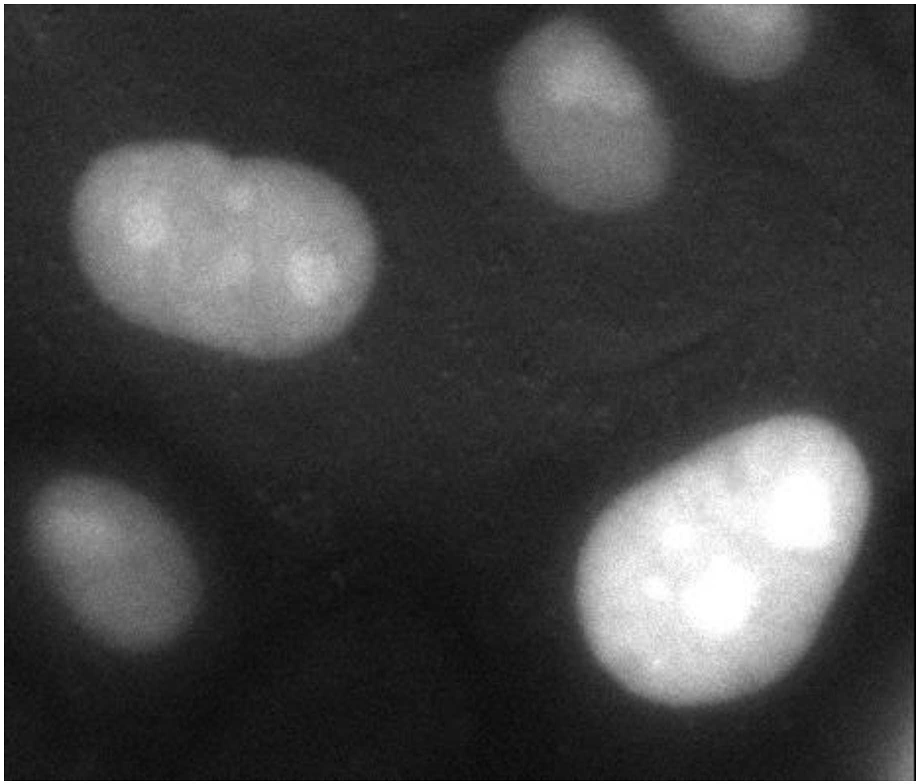


iron




Cucinotta and Durante, *Lancet Oncol.* 2006

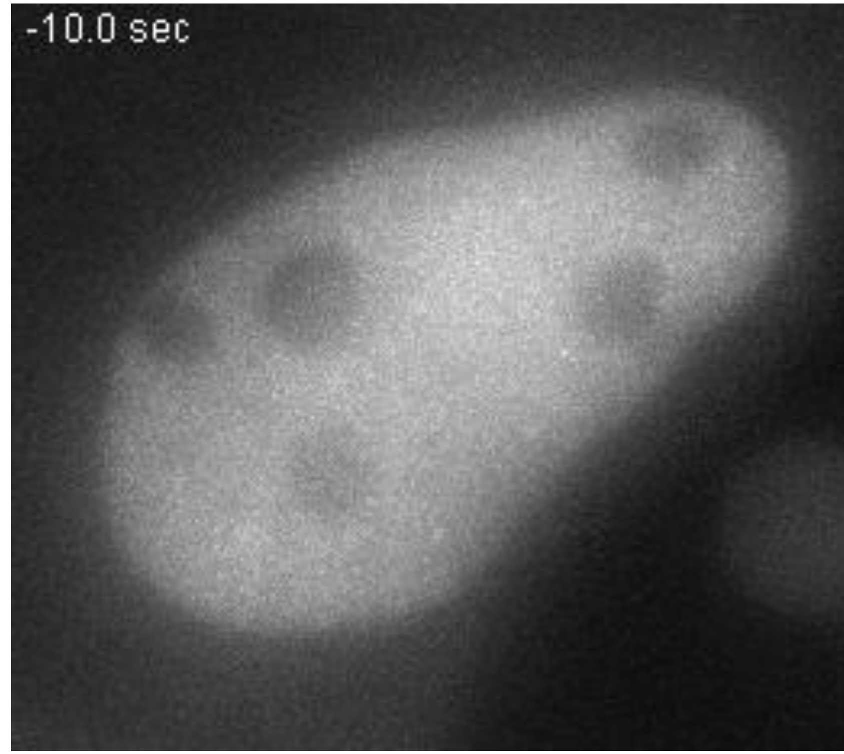
# Beamline live cell imaging



Uranium 11 MeV/n, 90°

Human cells

GFP- APTX (Aprataxin)



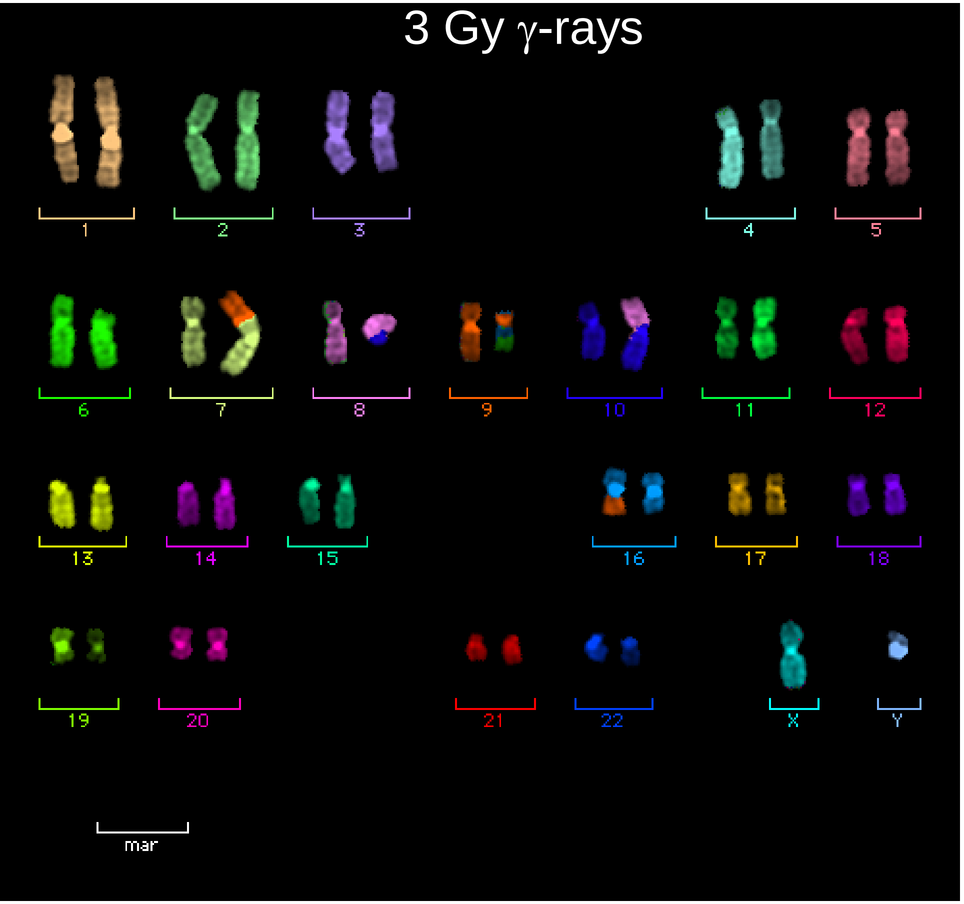

Iron 1 GeV/n, 0°

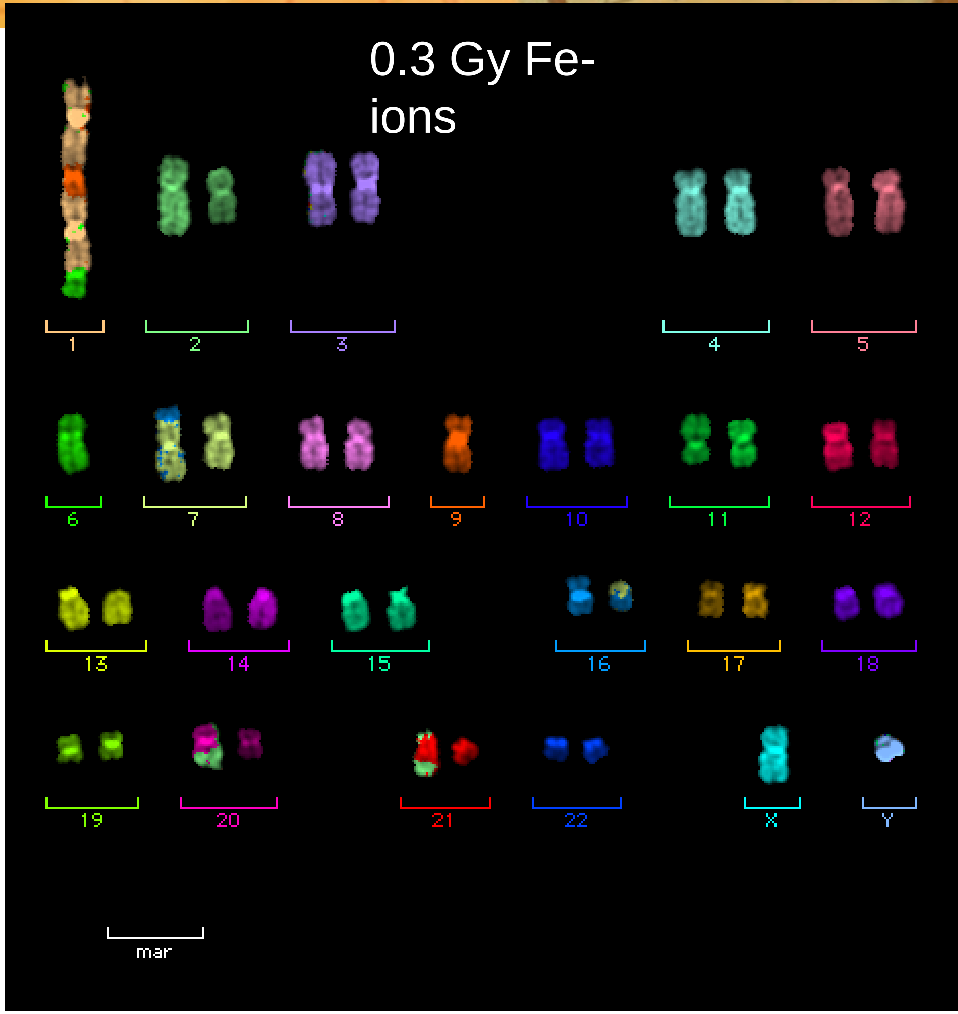
Human cells

GFP-Nijmegen breakage syndrome 1 (NBS1)

Jakob *et al. Proc. Natl. Acad. Sci. USA* (2009)

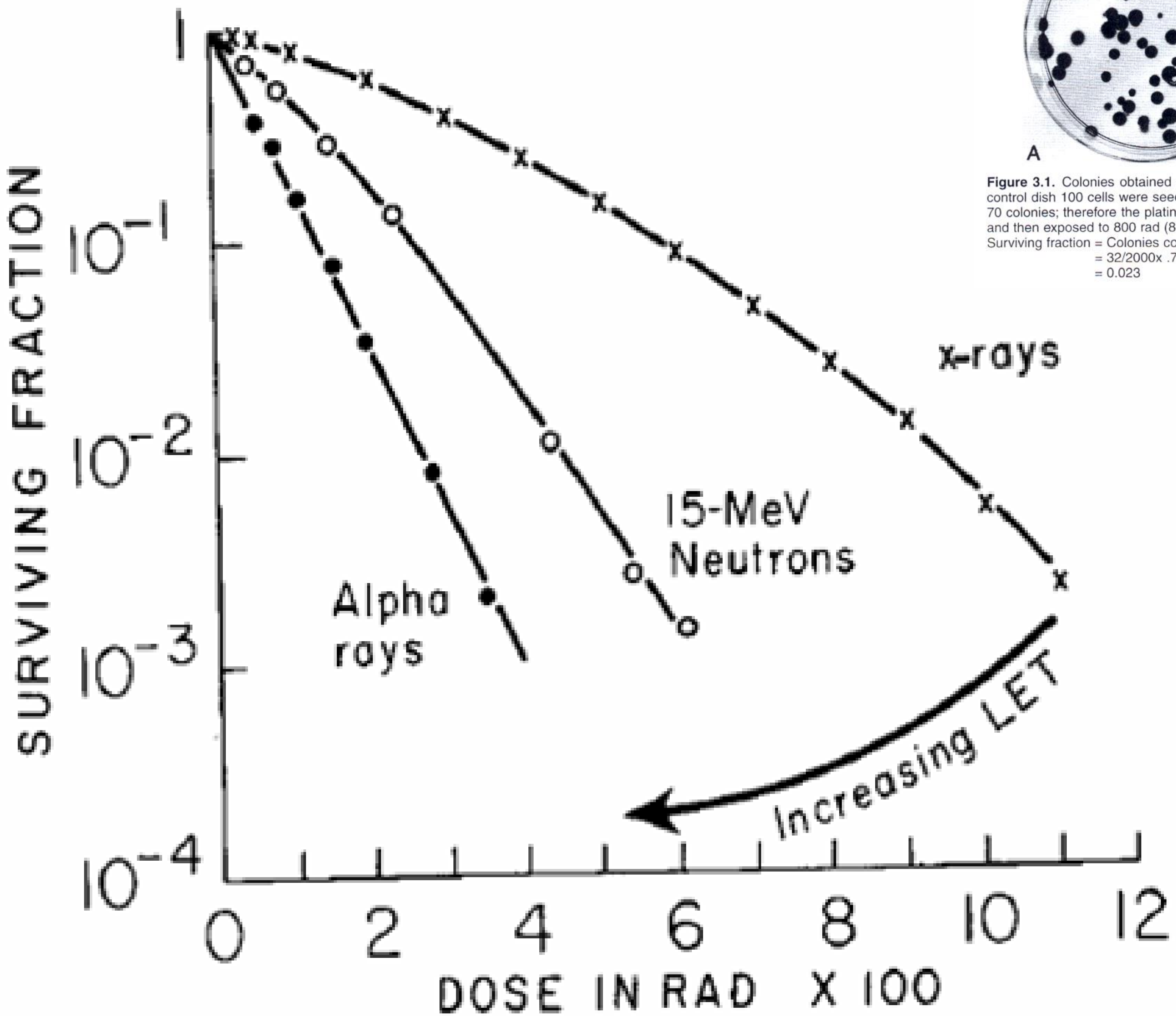
# Chromosomal aberrations induced by heavy ions




Durante *et al.*, *Radiation Research* 2002

# Cell killing by different radiation types



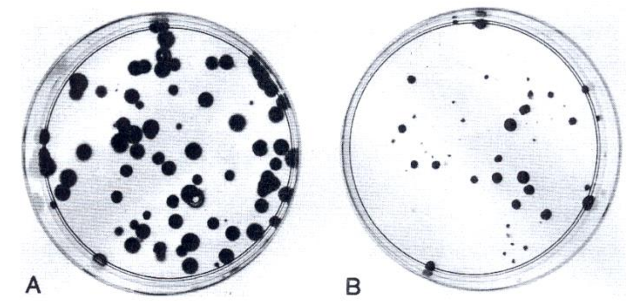
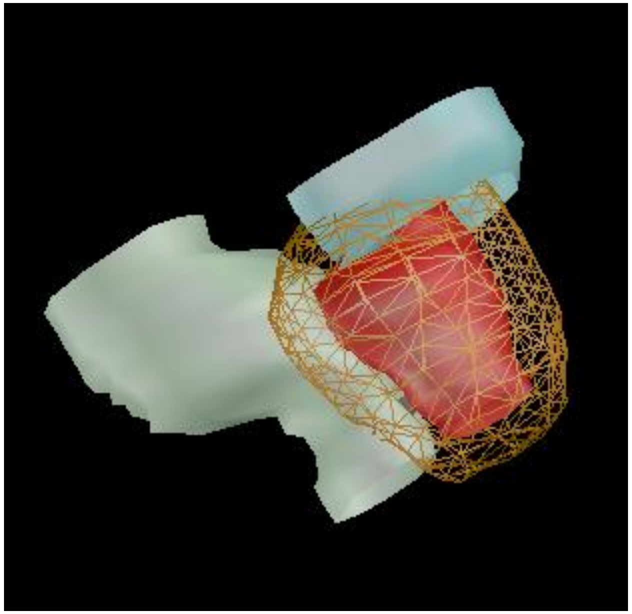
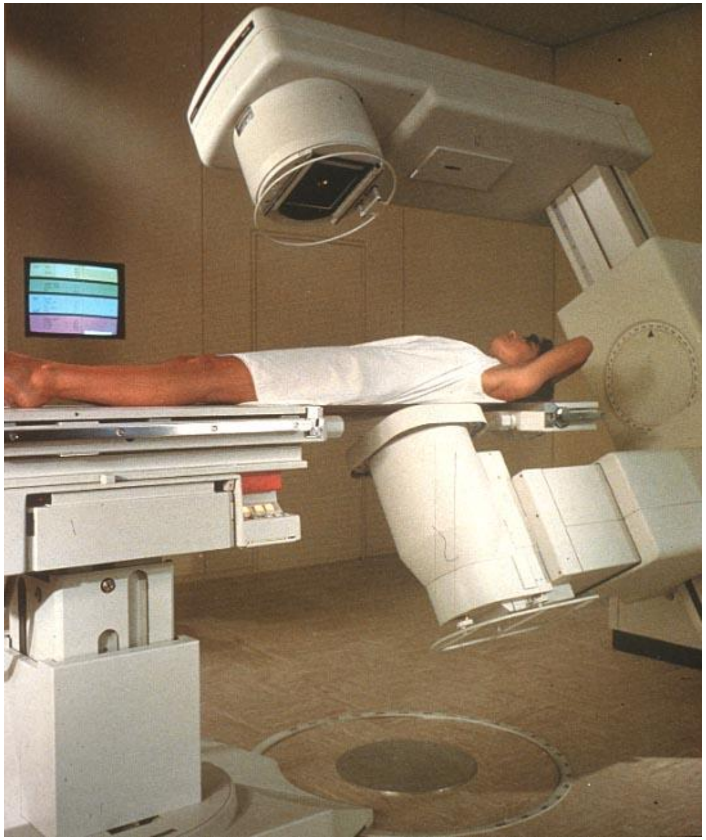




**Figure 3.1.** Colonies obtained with Chinese hamster cells cultured in vitro. **A:** In this unirradiated control dish 100 cells were seeded and allowed to grow for 7 days before being stained. There are 70 colonies; therefore the plating efficiency is 70/100, or 70%. **B:** Two thousand cells were 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

# The good side of radiation: radiotherapy

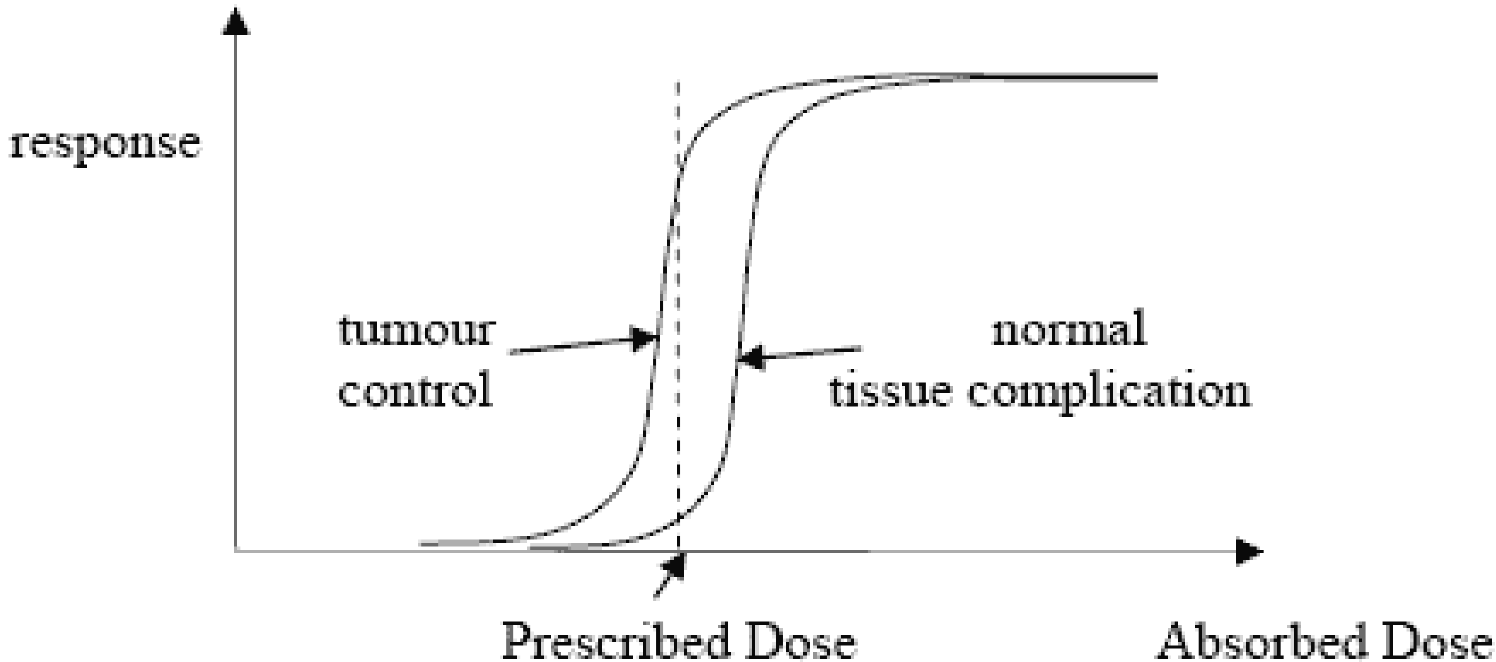




# Radiotherapy

- Also called “Radiation Therapy”
- Part of multi-disciplinary approach to cancer care
- Useful for 50-60% of all cancer patients
- Can be given for cure or palliation
- Mainly used for loco-regional treatment
- Benefits and side-effects are usually limited to the area(s) being treated

# Therapeutic window



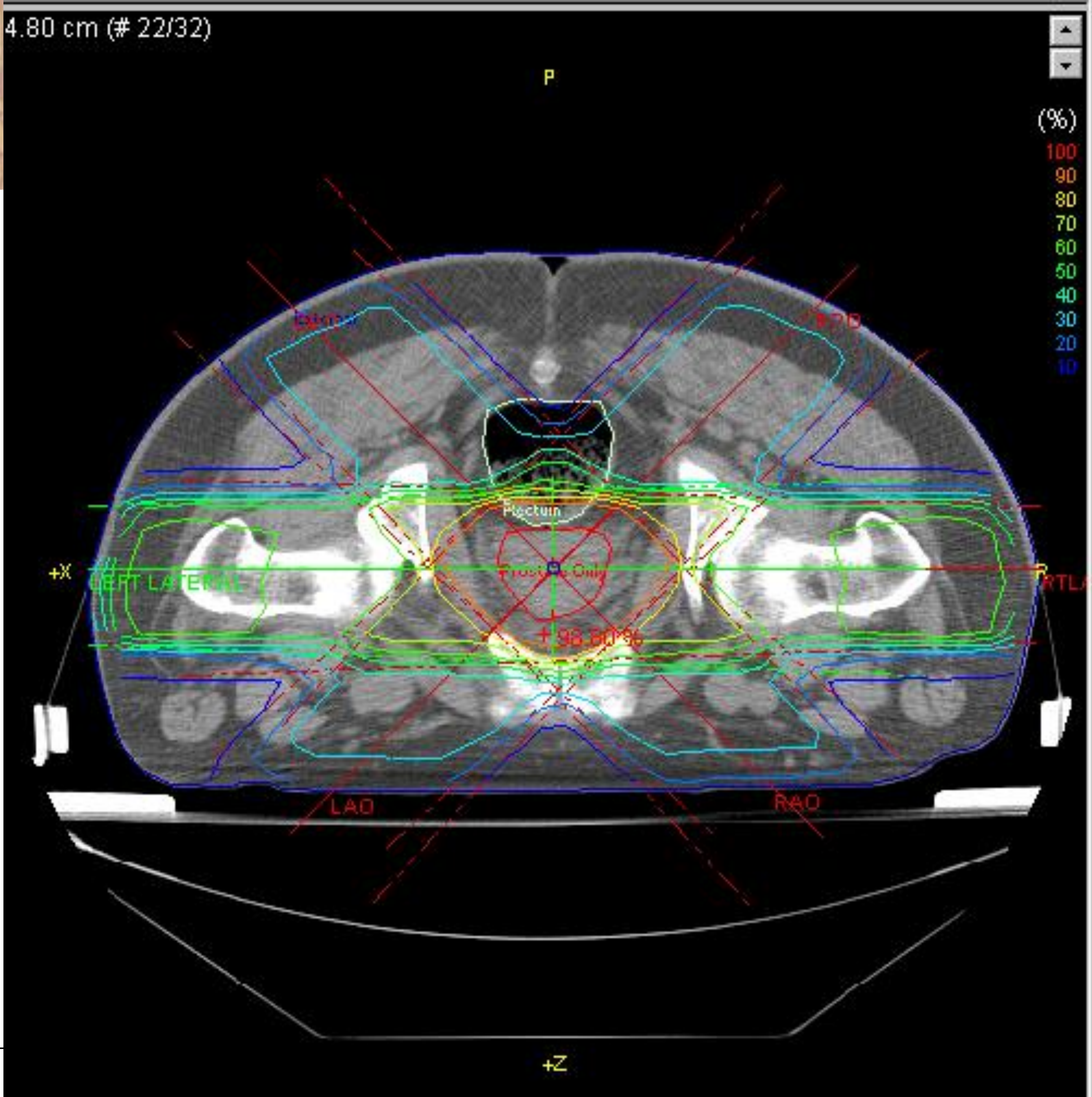

*Dose-Response Curves for tumour and normal tissues*

# Types of radiotherapy

| Radiosensitive | Radioresistant |
| --- | --- |
| Lymphomas | Melanoma |
| Germ cell tumours | Sarcomas |
| Small cell carcinomas | Glioblastomas |

- External beam (teletherapy)

  - Conformal therapy, IMRT (X-rays), hadrontherapy (protons or C-ions)
- Brachytherapy
  - Intracavitary
  - Interstitial
  - Surface molds
- Systemic
  - Radioactive Iodine, Strontium, Radio-labeled antibodies

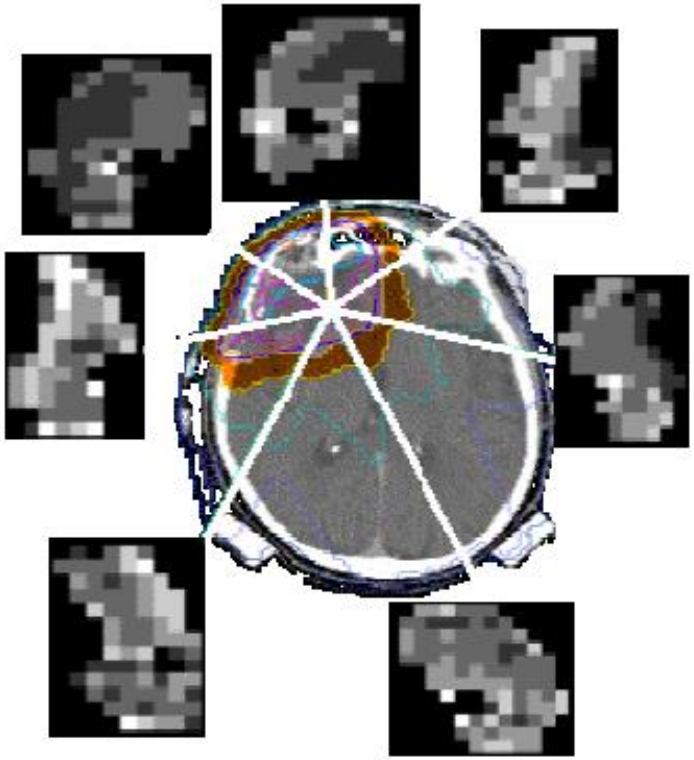


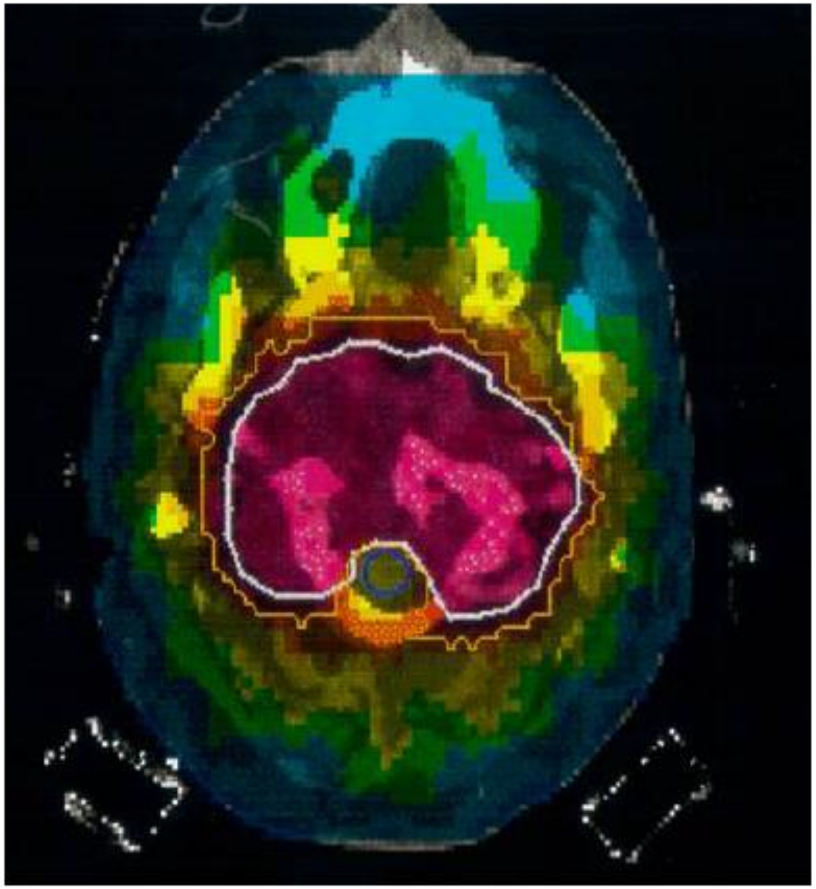

**Treatment planning**

**Generally, the total dose to the tumor is about 60 Gy, given in daily fractions of 2 Gy to spare the normal tissue**

**X-rays produced by LINACS (6-15 MV) are normally used**

# State of the art: IMRT

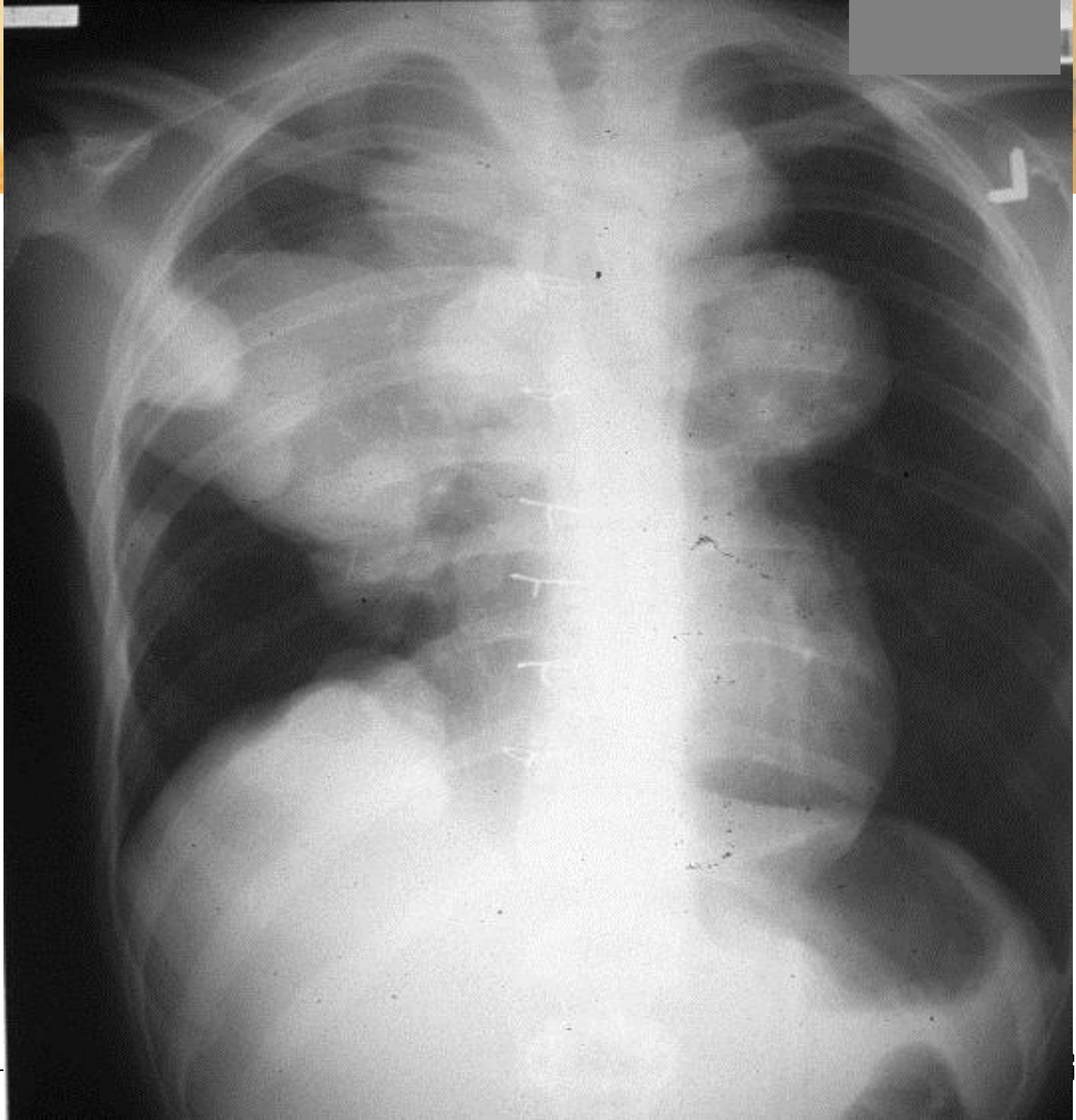


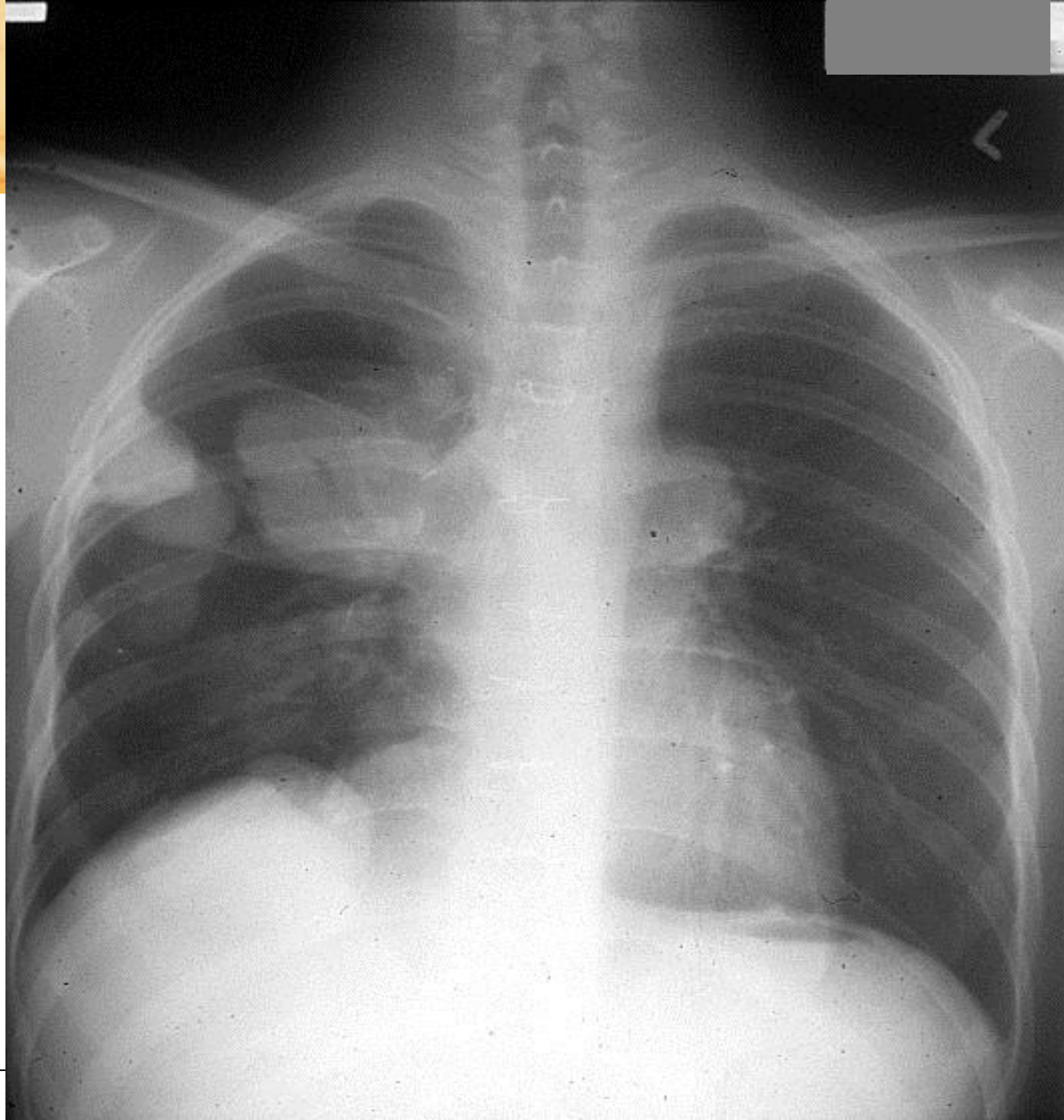


Intensity modulated radiation therapy (IMRT)


01 OCT 93
EXNR 47584
106
R
TM 10-13-36.6
KV 120 FIL 0
MA 201 EXT 2.4
TYP SCT 9.6
TH 4.5 FOV 131
AN 1.8 CF 4
SP 23.3 HFS
L
GREWAL
WW 400
WL +70
-130


60 92 62 25 5019
BD:12 08 26 F
ED:19 NOV 93
EXNR: 48194
SN: 107
R
TM: 08-46-31.5
KV:120 FIL: 0
MA:201 EXT:2.4
TYP: SCT:9.6
TH:4.5 FOV:110
AN: 2.0 CF: 4
SP: 28.0 HFS
FILING
+250
CONTRAST
L






April 11, 2001

(just prior to 1000cGy/1fr/1day orthovoltage treatment using 300kvp photons)

Treated area close-up (1 year post radiation)

# Side-effects of Radiotherapy


## Acute (<1 month)

Depend on area(s) being treated

Often fatigue can occur

mucositis/esophagitis, nausea, diarrhea and redness of skin

## Late (>1 month)

Pneumonitis/fibrosis of lungs

Hypothyroidism

Xerostomia

Enteritis

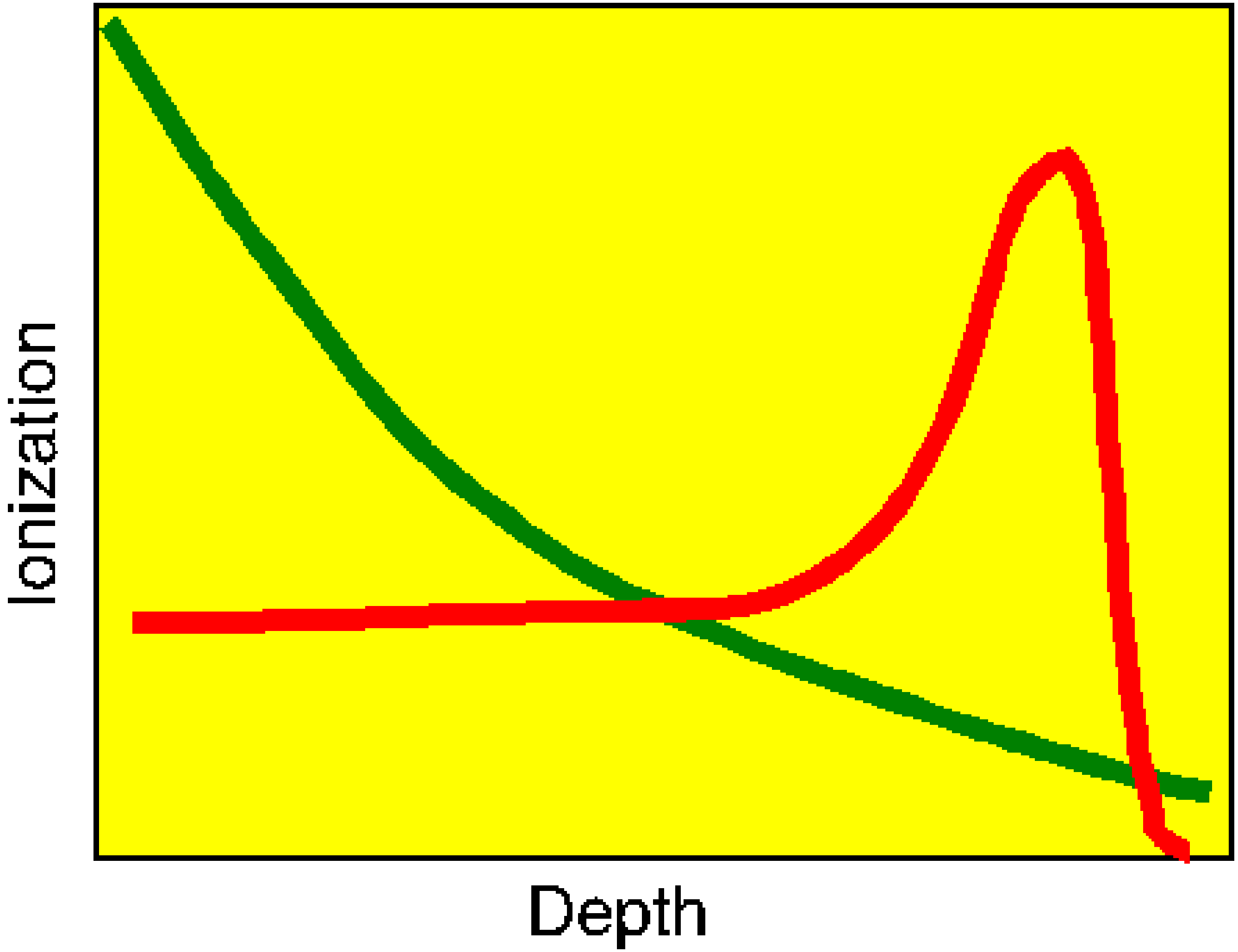
Infertility/menopause

## Long-term (10-20 years)

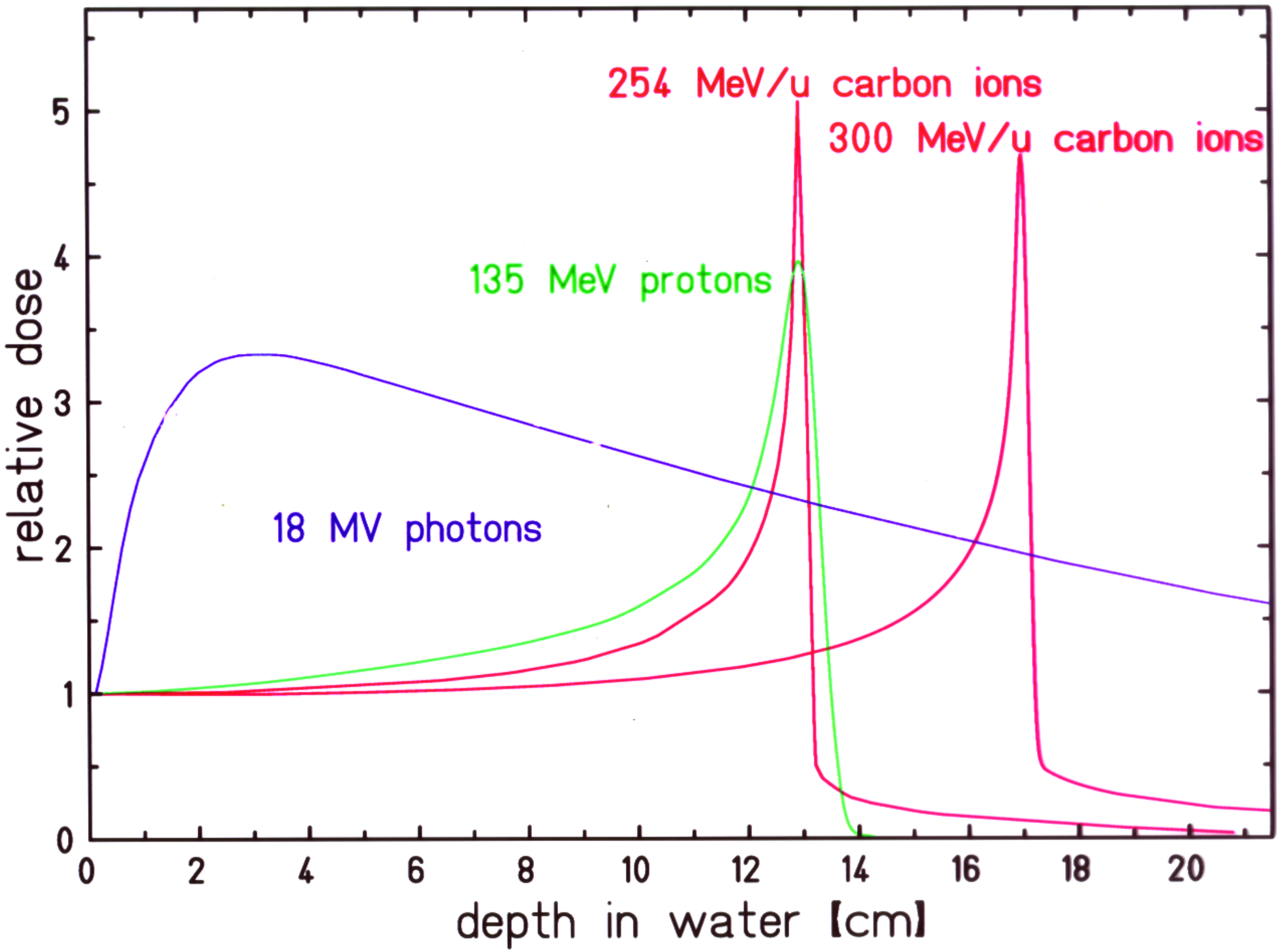
Increased risk of secondary cancers

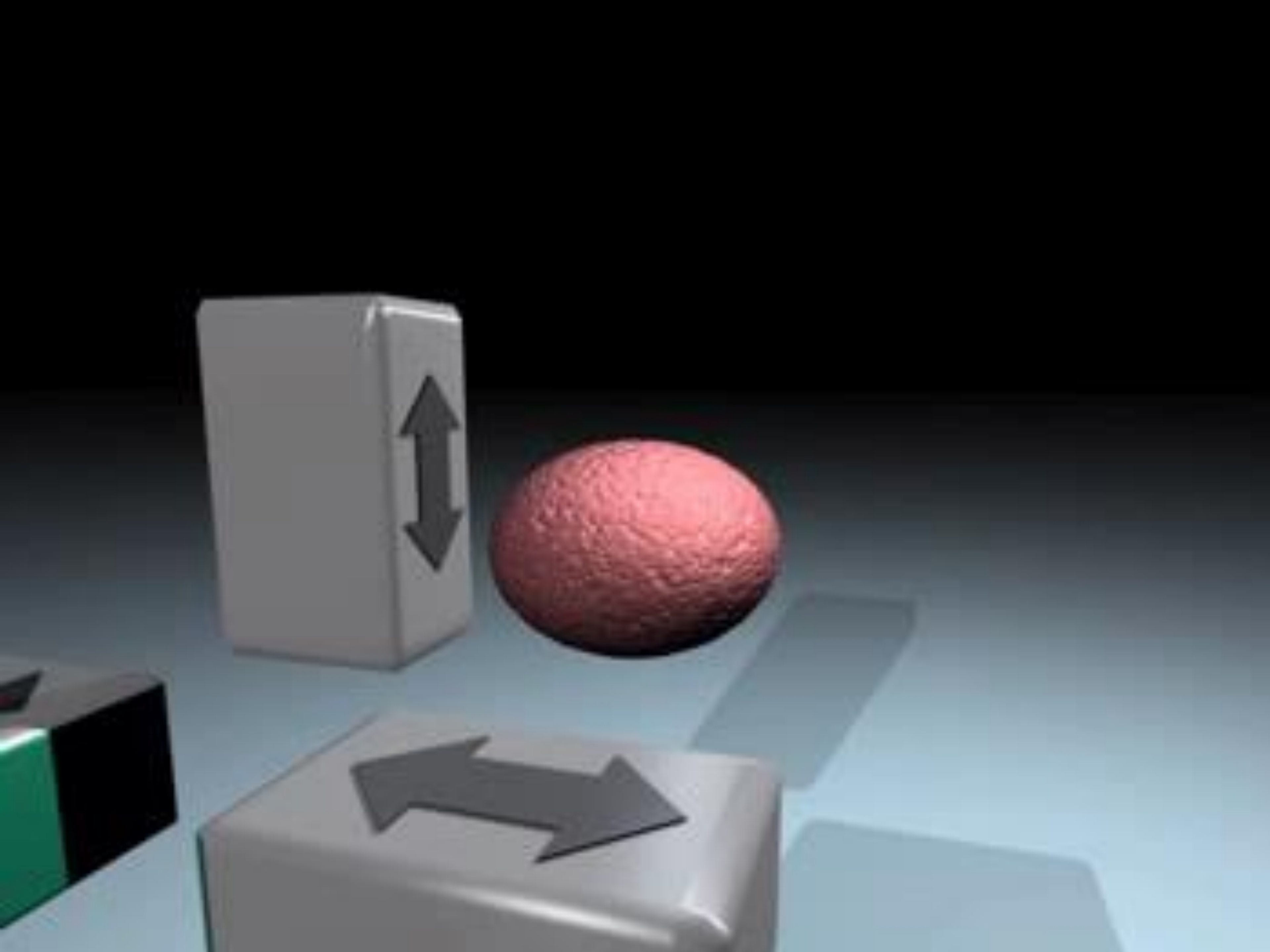
Increased heart disease if chest region treated

# Charged particles for therapy

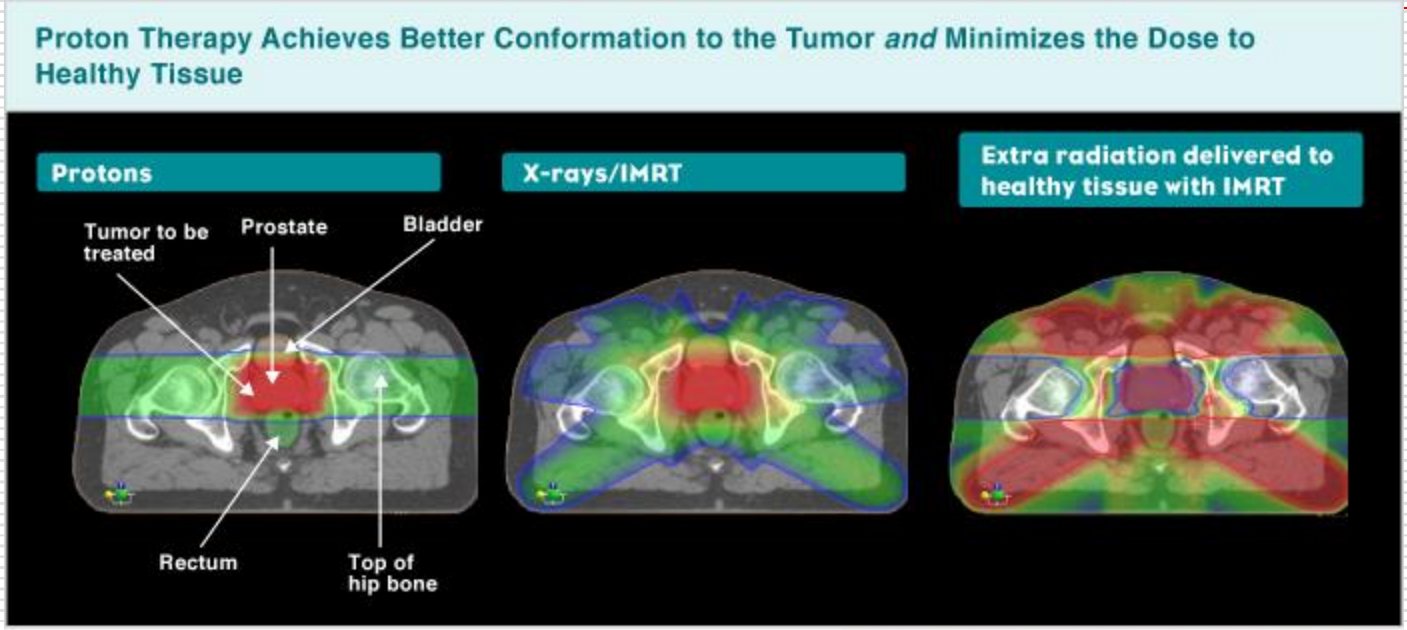


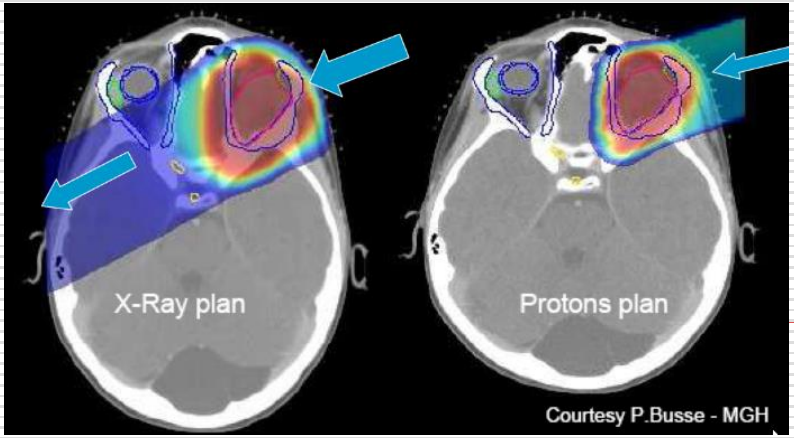
# Depth dose distribution of various radiation modalities

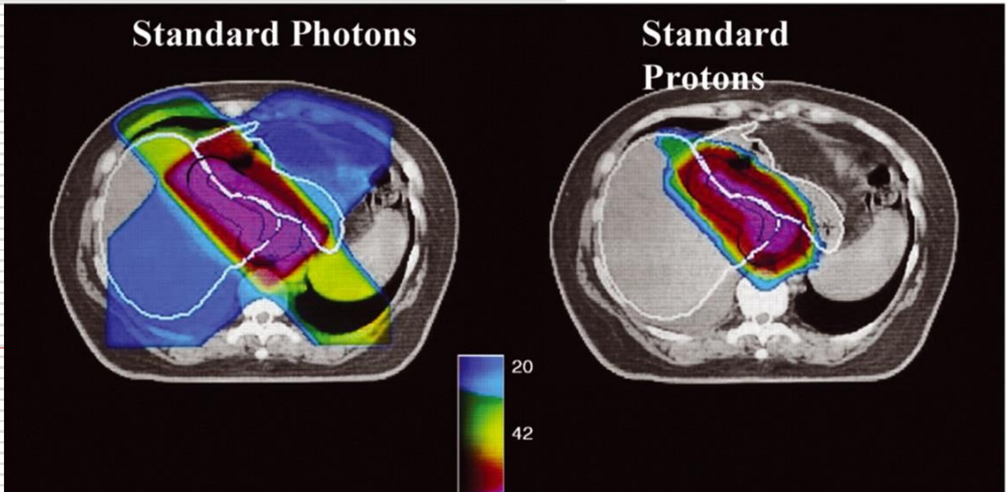




# Treatment plans with protons: sparing of normal tissue, recommended especially for pediatric patients

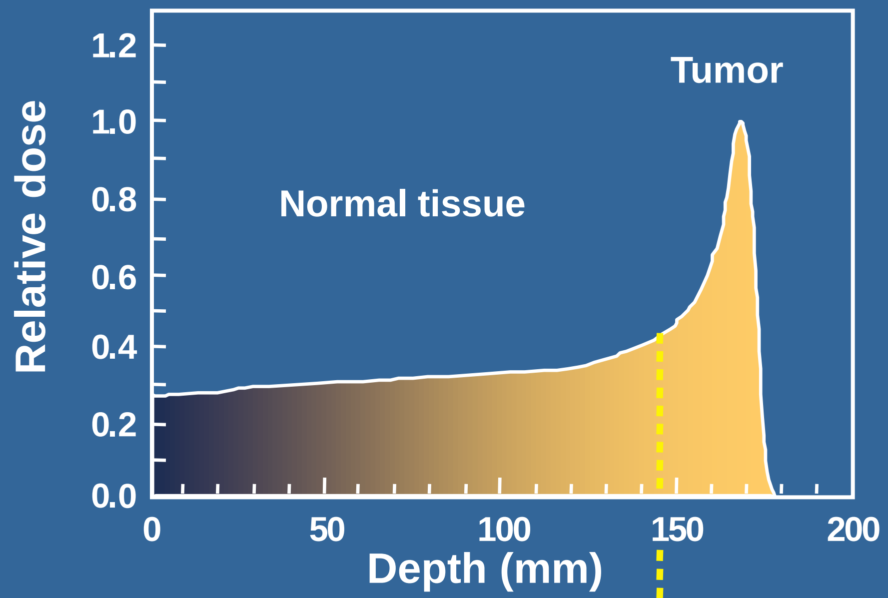


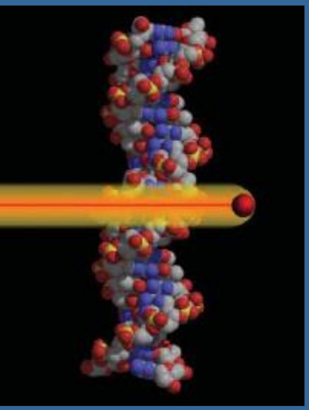



Durante & Loeffler,

*Nature Rev Clin Oncol* 2010

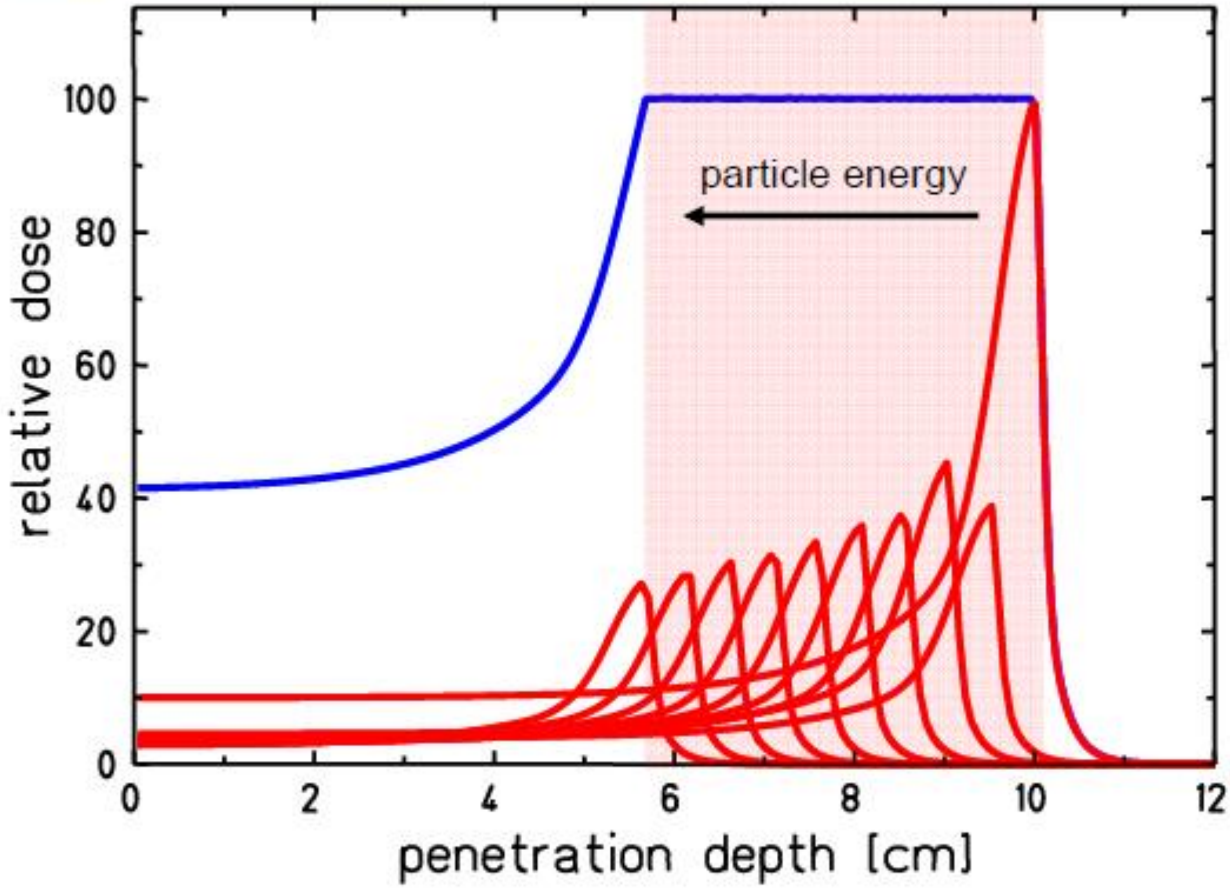



**Potential advantages**

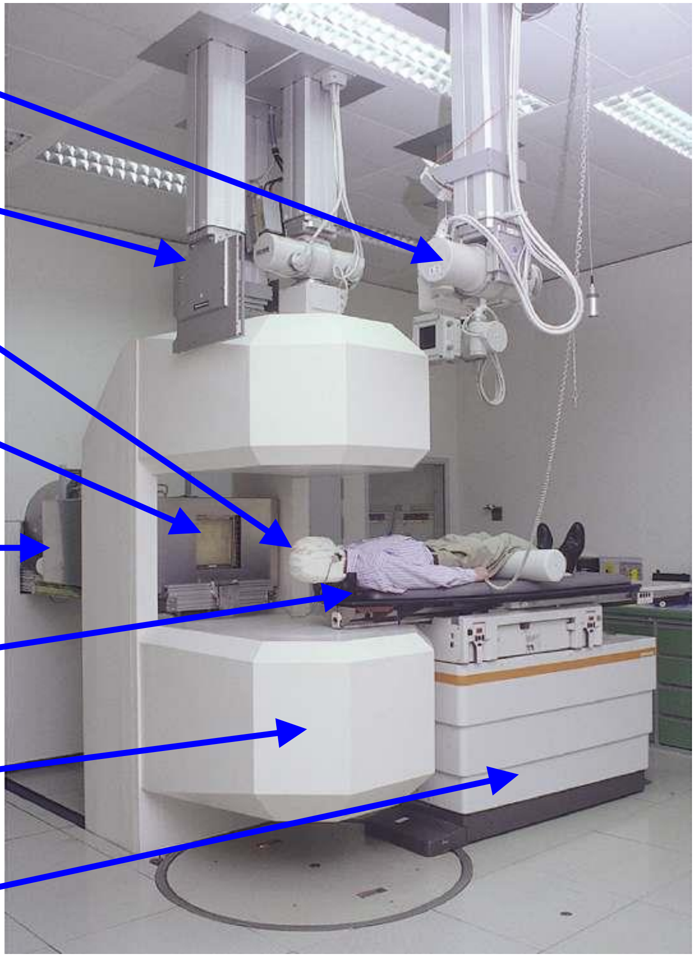


| | | | |
|---|---|---|---|
| Energy | high | low | |
| LET | low | high | |
| Dose | low | high | High tumor dose, normal tissue sparing |
| RBE | ≈ 1 | > 1 | Effective for radioresistant tumors |
| OER | ≈ 3 | < 3 | Effective against hypoxic tumor cells |
| Cell-cycle dependence | high | low | Increased lethality in the target because cells in radioresistant (S) phase are sensitized |
| Fractionation dependence | high | low | Fractionation spares normal tissue more than tumor |
| Angiogenesis | Increased | Decreased | Reduced angiogenesis and metastatization |
| Cell migration | Increased | Decreased | |

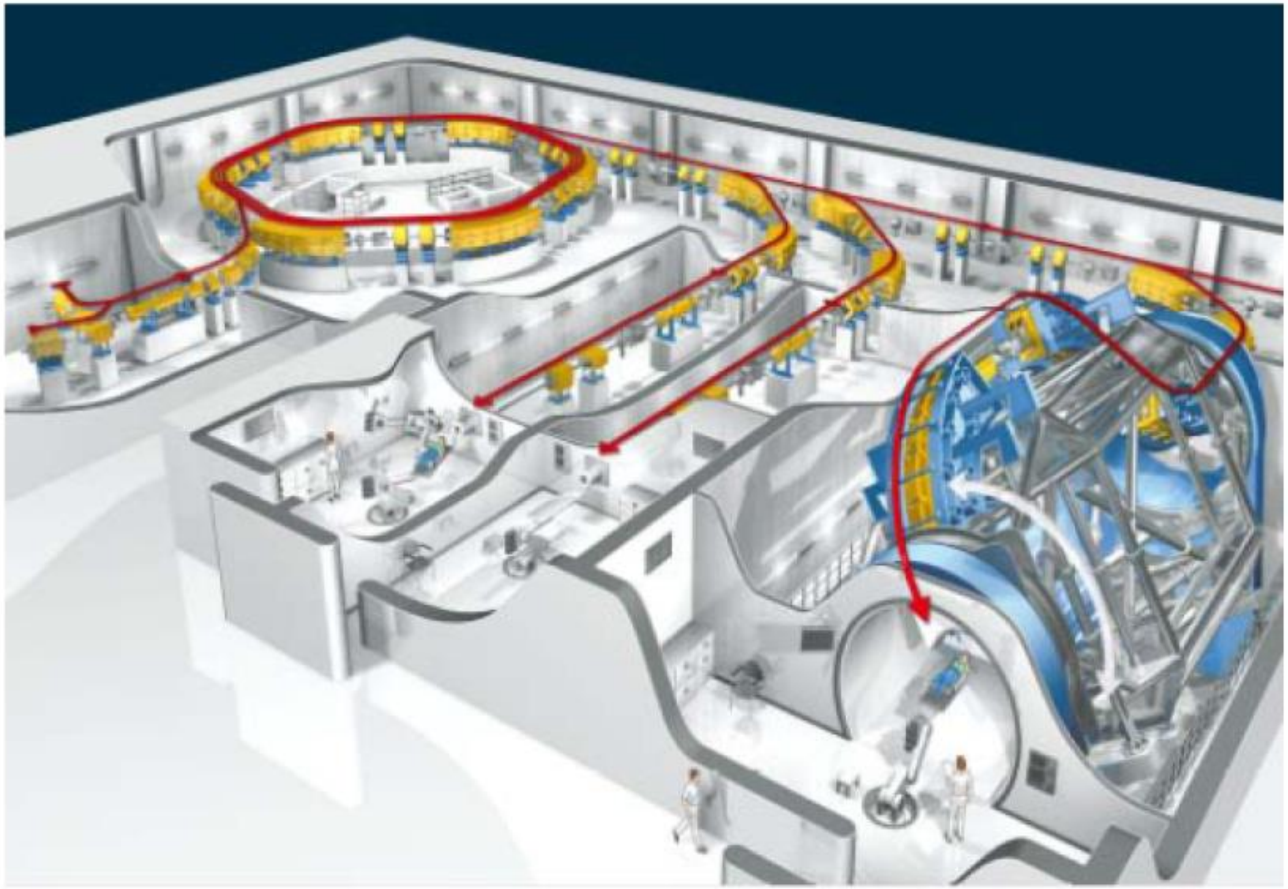
# Longitudinal - Spread out Bragg peak



# Bestrahlungsraum: Cave M



# Heidelberg Ion Beam Therapy

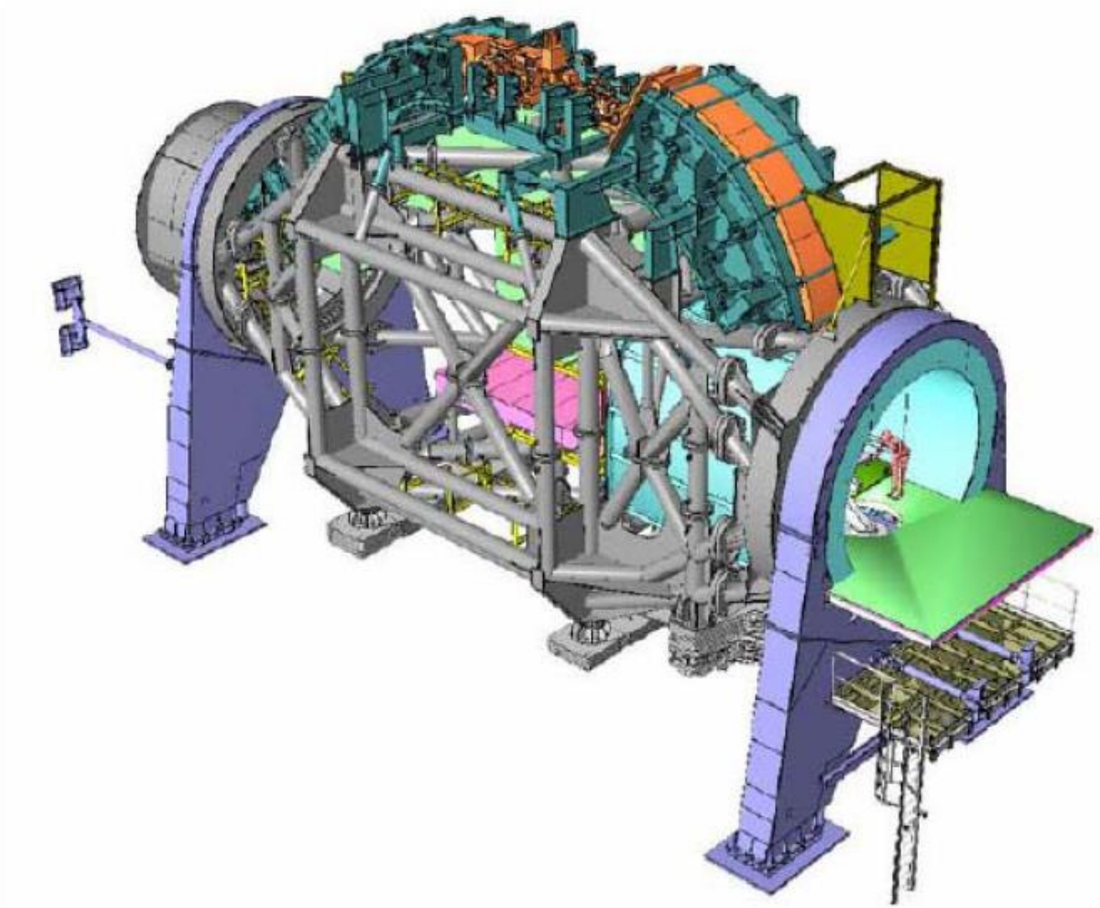




1st patient treated: November 2009

# CNAO: National Centre for Oncological Hadrontherapy
# Pavia, Italy

# Gantry @ HIT



total weight: 670t

length: 22m

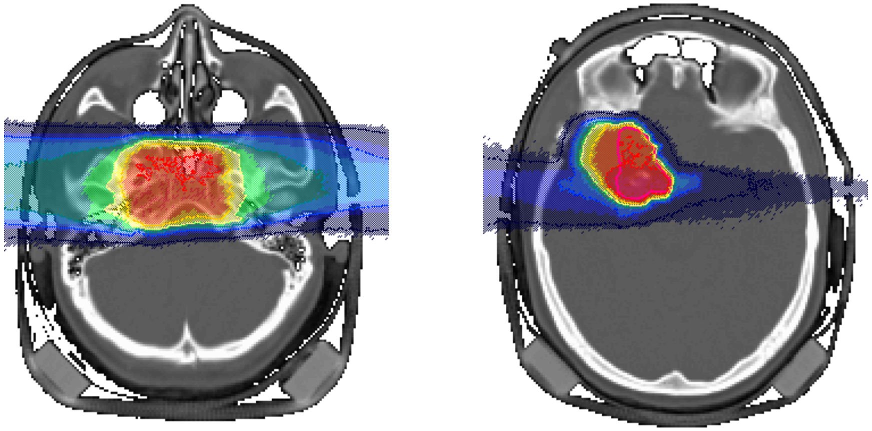
diameter: 14m

precision at isocenter: ~1mm

# • Clivus Chondrosarcomas

- Patient:23 years old
- Diagnosis: Chondrosarcoma
- Subtotal surgery
- Postoperative radiationtherapy:60Gye
- 3 fields with 20 fraction

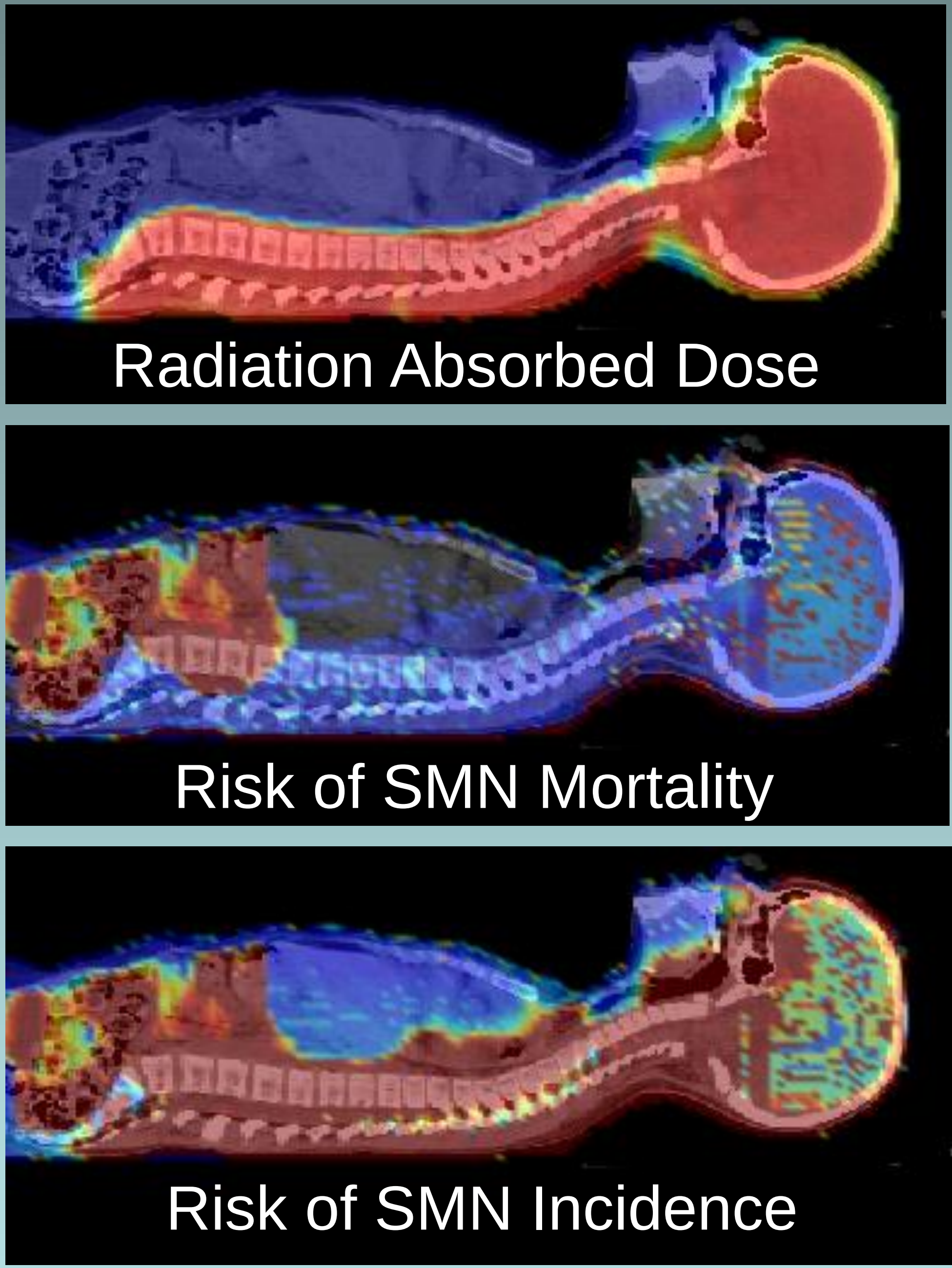
vor Bestrahlung



6 Weeks after carbon
tfeatment with a dose of 60 Gye

D.Schulz-Ertner et al.

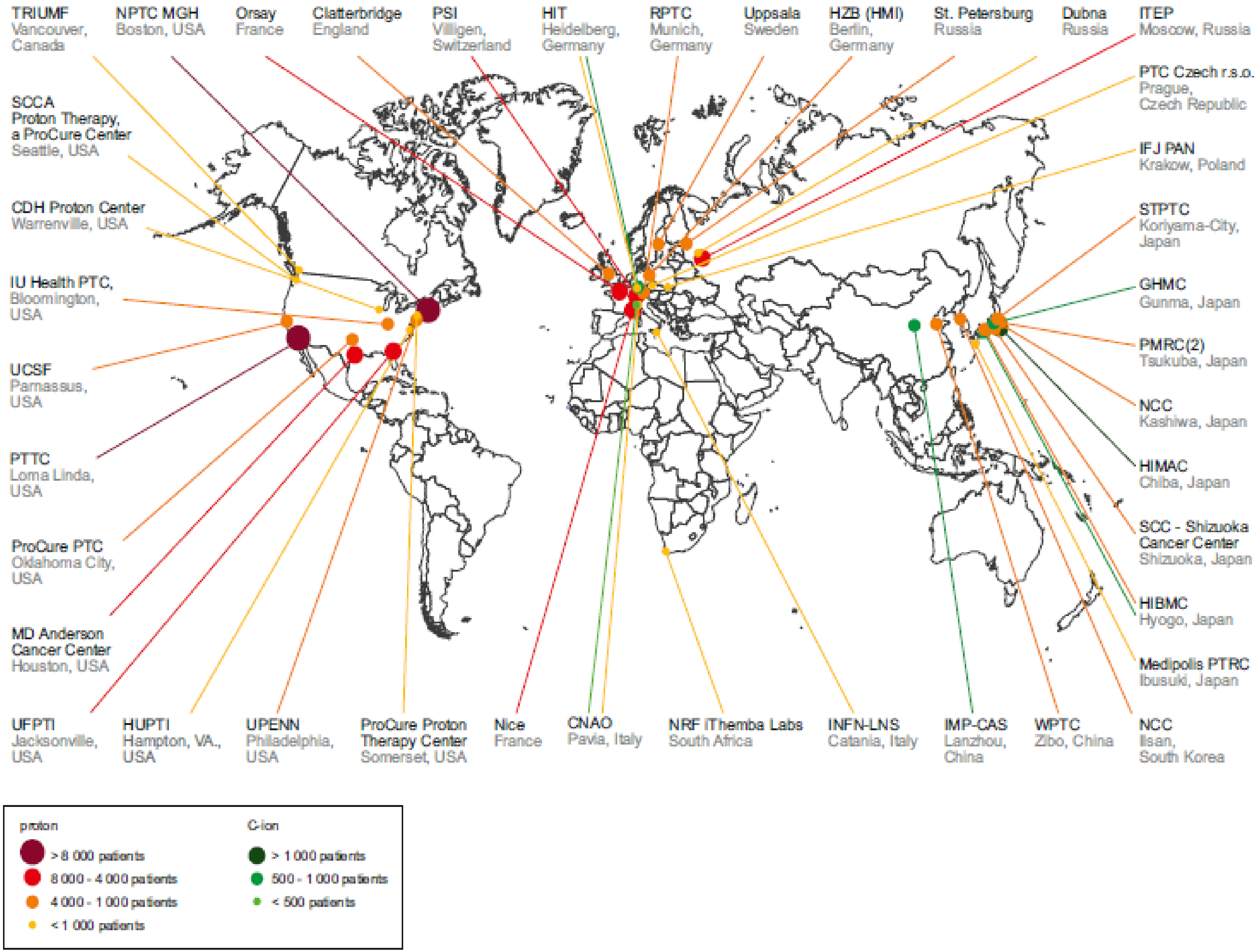
**Secondary Malignant Neoplasms (SMN) in particle therapy**




Comparison of relative radiation dose distribution with the corresponding relative risk distribution for radiogenic second cancer incidence and mortality. This 9-year old girl received craniospinal irradiation for medulloblastoma using passively scattered proton beams. The color scale illustrates the difference for absorbed dose, incidence and mortality cancer risk in different organs.

Newhauser & Durante,

*Nature Rev. Cancer* 2011


TRIUMF
Vancouver, Canada
NPTC MGH
Boston, USA
Orsay
France
Clatterbridge
England
PSI
Villigen, Switzerland
HIT
Heidelberg, Germany
RPTC
Munich, Germany
Uppsala
Sweden
HZB (HMI)
Berlin, Germany
St. Petersburg
Russia
Dubna
Russia
ITEP
Moscow, Russia
PTC Czech r.s.o.
Prague, Czech Republic
IFJ PAN
Krakow, Poland
STPTC
Koriyama-City, Japan
GHMC
Gunma, Japan
PMRC(2)
Tsukuba, Japan
NCC
Kashiwa, Japan
HIMAC
Chiba, Japan
SCC - Shizuoka Cancer Center
Shizuoka, Japan
HIBMC
Hyogo, Japan
Medipolis PTRC
Ibusuki, Japan
SCCA Proton Therapy, a ProCure Center
Seattle, USA
CDH Proton Center
Warrenville, USA
IU Health PTC,
Bloomington, USA
UCSF
Parnassus, USA
PTTC
Loma Linda, USA
ProCure PTC
Oklahoma City, USA
MD Anderson Cancer Center
Houston, USA
UFPTI
Jacksonville, USA
HUPTI
Hampton, VA., USA
UPENN
Philadelphia, USA
ProCure Proton Therapy Center
Somerset, USA
Nice
France
CNAO
Pavia, Italy
NRF iThemba Labs
South Africa
INFN-LNS
Catania, Italy
IMP-CAS
Lanzhou, China
WPTC
Zibo, China
NCC
Ilsan, South Korea
proton
> 8 000 patients
8 000 - 4 000 patients
4 000 - 1 000 patients
< 1 000 patients
C-ion
> 1 000 patients
500 - 1 000 patients
< 500 patients

## Advantages of heavy ion therapy

- Inverse dose profile: higher target dose
  lower dose to normal tissue
- Millimeter-precision treatment
- PET beam verification
- High biological effectiveness in the target
- Low biological effectiveness in the entrance channel
- Biological based treatment planning
- Little side effects
- Good tumor control rates 80-90%

## Future

- Heavy ion center at Heidelberg
- Many projects over the world
- Treatment of moving organs
- Biologically optimized treatment

## Biophysics Department

M. Durante (Director)

G. Kraft (Helmholtz Professor)

G. Taucher-Scholz (DNA damage)

S. Ritter (Stem cells)

C. Fournier (Late effects)

W. Kraft-Weyrather (Clinical radiobiology)

M. Scholz (Biophysical modelling)

M. Krämer (Treatment planning)

C. Bert (Moving targets)

C. La Tessa (Dosimetry)

# Thank you very much!

http://www.gsi.de/biophysik/