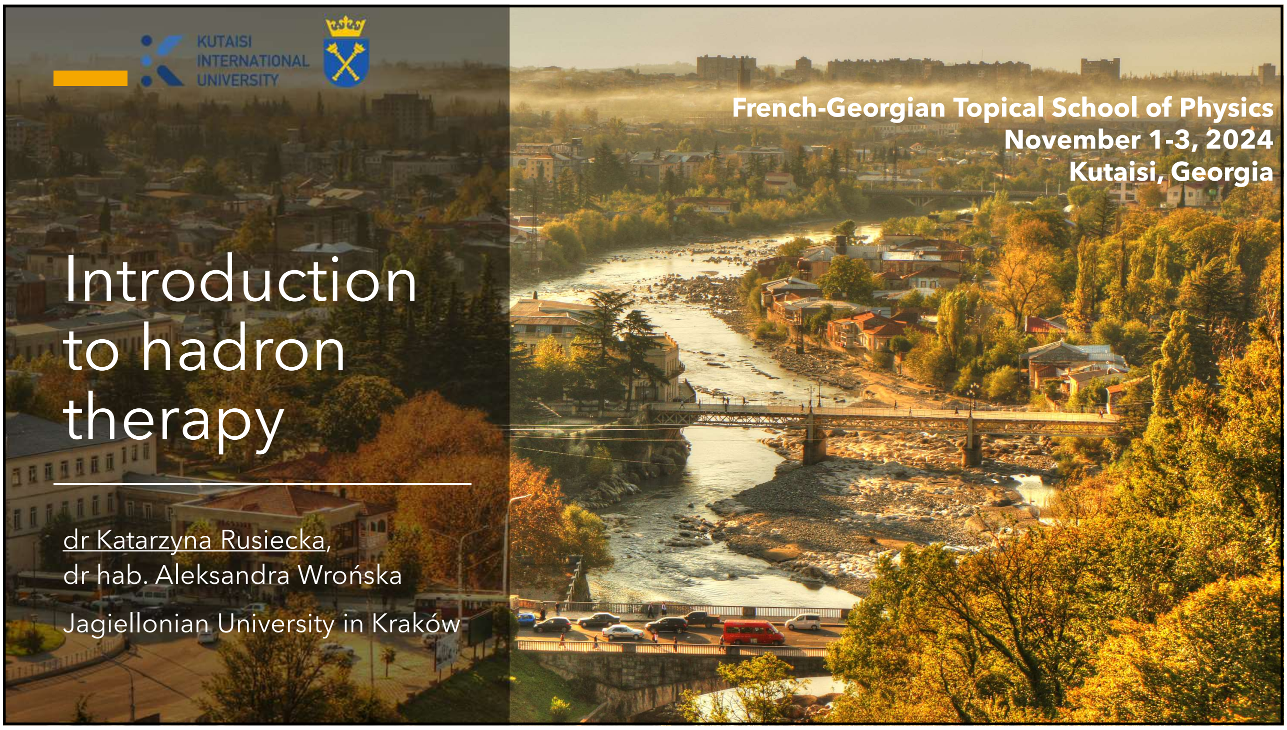


KUTAISI INTERNATIONAL UNIVERSITY

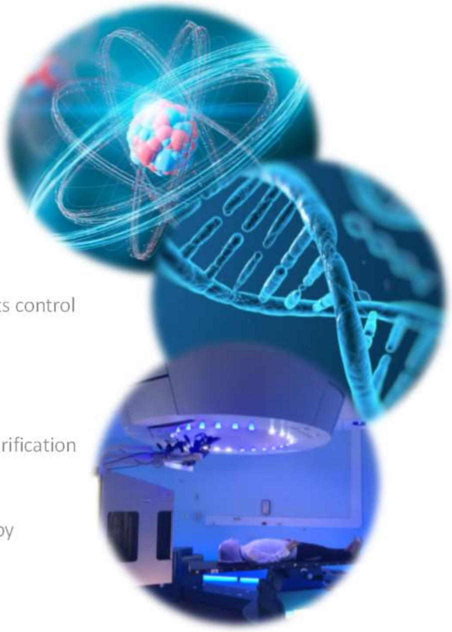
**French-Georgian Topical School of Physics**
**November 1-3, 2024**
**Kutaisi, Georgia**

# Introduction to hadron therapy

dr Katarzyna Rusiecka,
dr hab. Aleksandra Wrońska

Jagiellonian University in Kraków

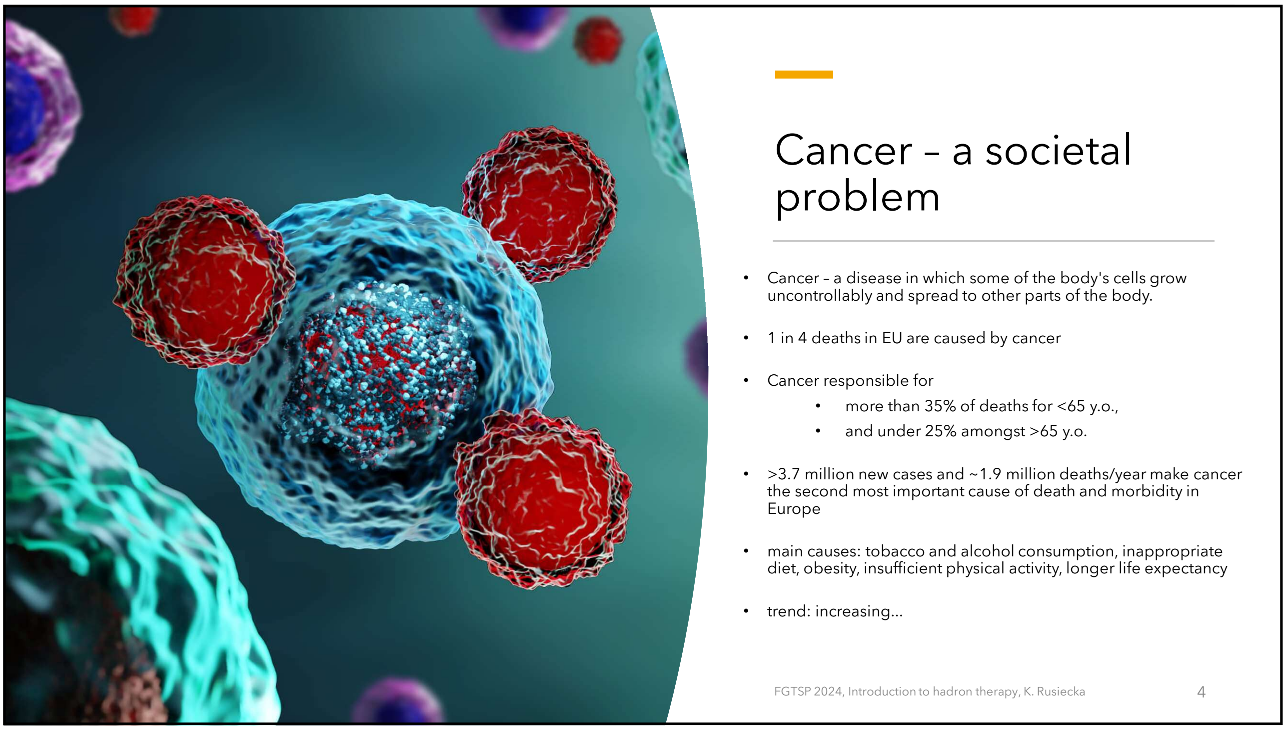
# Outline



Sunday session
Stay tuned!

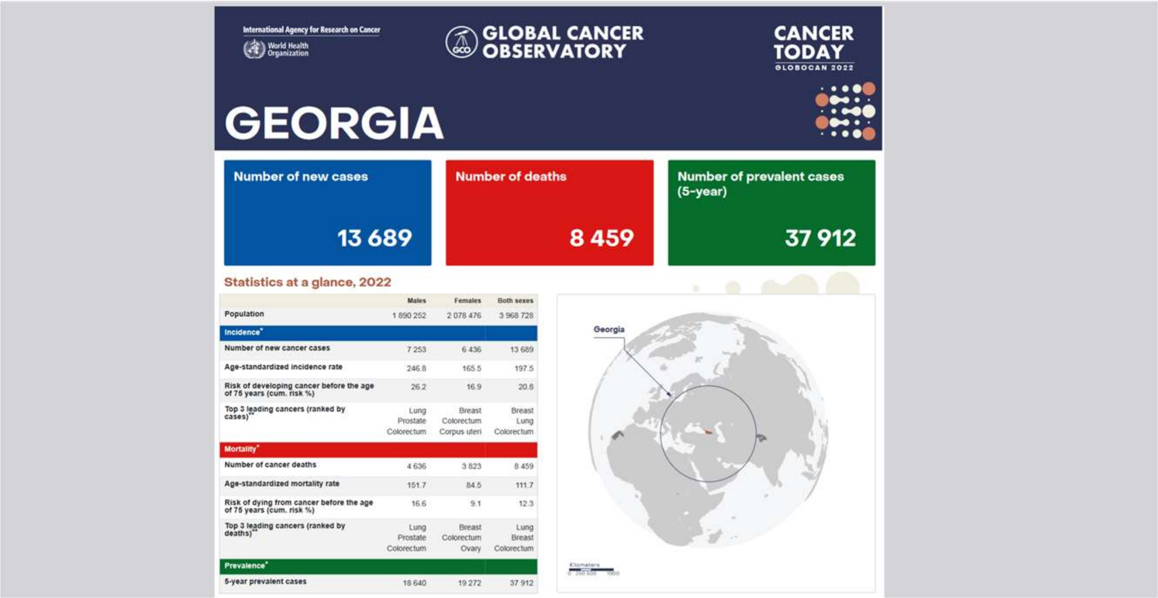
- **Context**
  - Cancer as societal problem
  - Cancer treatment methods and their limitations
- **Physical rationale**
  - Interaction of ionizing radiation with matter
  - Pioneers of proton therapy
- **Biological aspects**
  - Biological effects of irradiation
  - Basic definitions
- **Technologies**
  - Accelerators for hadron therapy
  - Irradiation modes
  - Different ion species
  - Simulations of the interaction of particles with matter
- **Clinical procedures**
  - Clinical workflow
  - Treatment planning
  - Quality control
  - Patient positioning and its control
- **Emerging techologies**
  - Mini beams
  - FLASH
  - Real-time beam range verification
  - Adaptive therapy
  - Proton radiography
  - Big data in hadron therapy

# Hadron therapy - context



## Cancer – a societal problem

- Cancer – a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body.
- 1 in 4 deaths in EU are caused by cancer
- Cancer responsible for
    - more than 35% of deaths for <65 y.o.,
    - and under 25% amongst >65 y.o.
- >3.7 million new cases and ~1.9 million deaths/year make cancer the second most important cause of death and morbidity in Europe
- main causes: tobacco and alcohol consumption, inappropriate diet, obesity, insufficient physical activity, longer life expectancy
- trend: increasing...



International Agency for Research on Cancer
World Health Organization

GLOBAL CANCER OBSERVATORY

CANCER TODAY
GLOBOCAN 2022

GEORGIA

| Number of new cases | Number of deaths | Number of prevalent cases (5-year) |
|---|---|---|
| 13 689 | 8 459 | 37 912 |

Statistics at a glance, 2022

| | Males | Females | Both sexes |
|---|---|---|---|
| **Population** | 1 890 252 | 2 078 476 | 3 968 728 |
| **Incidence*** | | | |
| **Number of new cancer cases** | 7 253 | 6 436 | 13 689 |
| **Age-standardized incidence rate** | 246.8 | 165.5 | 197.5 |
| **Risk of developing cancer before the age of 75 years (cum. risk %)** | 26.2 | 16.9 | 20.8 |
| **Top 3 leading cancers (ranked by cases)**** | Lung<br>Prostate<br>Colorectum | Breast<br>Colorectum<br>Corpus uteri | Breast<br>Lung<br>Colorectum |
| **Mortality*** | | | |
| **Number of cancer deaths** | 4 636 | 3 823 | 8 459 |
| **Age-standardized mortality rate** | 151.7 | 84.5 | 111.7 |
| **Risk of dying from cancer before the age of 75 years (cum. risk %)** | 16.6 | 9.1 | 12.3 |
| **Top 3 leading cancers (ranked by deaths)**** | Lung<br>Prostate<br>Colorectum | Breast<br>Colorectum<br>Ovary | Lung<br>Breast<br>Colorectum |
| **Prevalence*** | | | |
| **5-year prevalent cases** | 18 640 | 19 272 | 37 912 |

# Cancer treatment methods

- Surgery
  radical method, localised tumour in accessible location
- Radiotherapy
  localised tumour, also difficult locations
    - Conventional (X-rays)
    - Ion beams (protons, C-ions)
- Chemotherapy
  cancer with multiple metastases, follow-up treatment
- Immunotherapy (Nobel Prize in 2018)

## Proton therapy? Hadron therapy?

- **Hadrons** – particles made up of two or more quarks, held together by strong interaction
- Protons are hadrons
- Other heavy ions used in radiation therapy are made up of hadrons
- Other term for hadron therapy: ion beam therapy

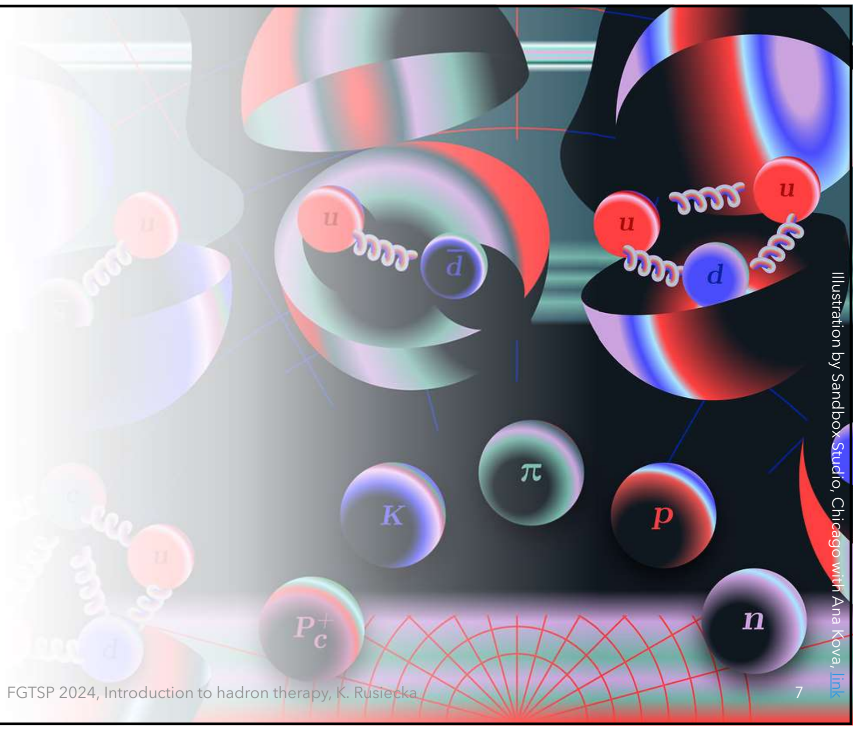


Illustration by Sandbox Studio, Chicago with Ana Kova, link

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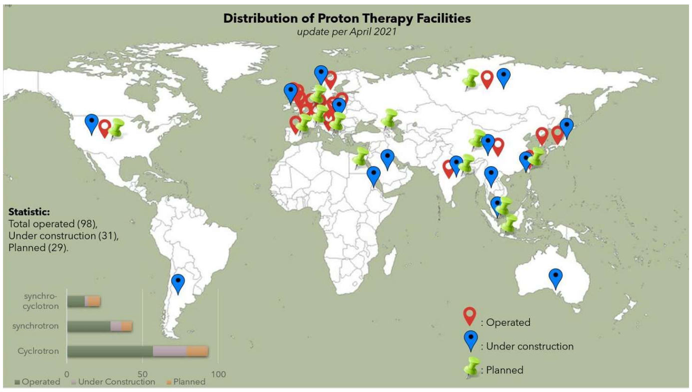
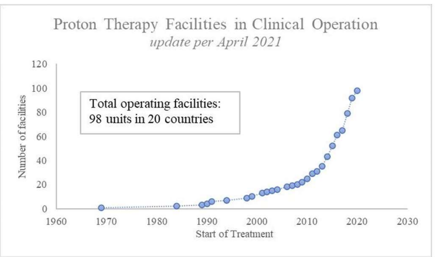
## Ion beam therapy - status

Figures: status for April 2021

Currently (November 2024):
- 136 facilities in clinical operation
- 32 facilities under construction
- 33 centres in planning phase

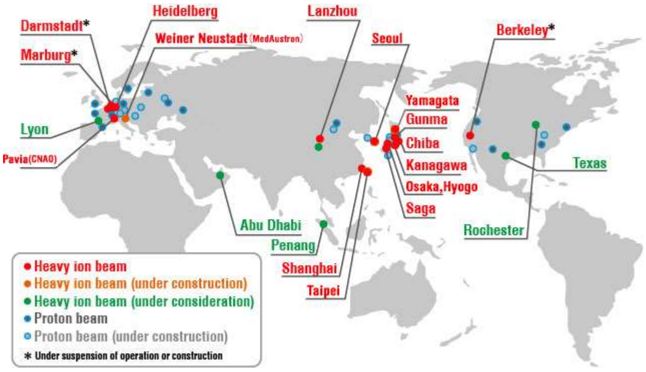




http://doi.org/10.1088/1755-1315/927/1/012042

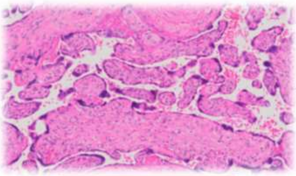
# Ion beam therapy - status

Heavy ion therapy centers…



https://www.particle.or.jp/hirtjapan/en/medical/current/world.html

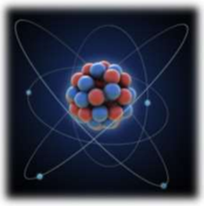
# Structure of living matter



Tissue (macroscopic)

Cells (10-100 μm)

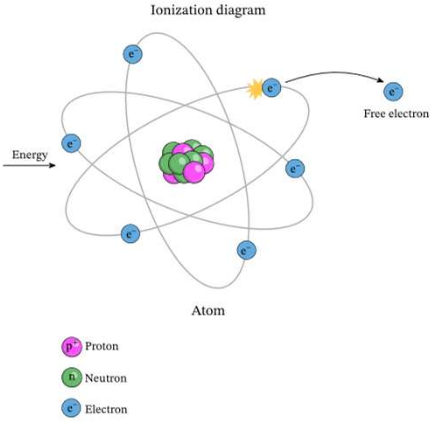
DNA molecules (2 nm x 2 m)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6391780/



atoms (~1 Å)
atomic nuclei (~1 fm)
electrons (point-like)

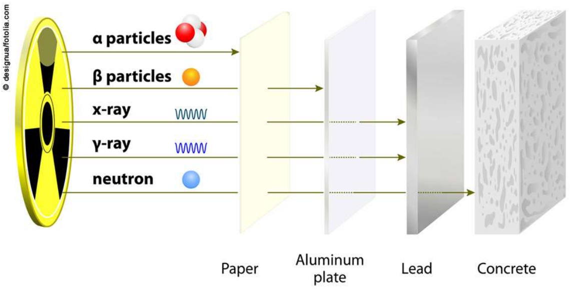
Nucleons:
protons & neutrons (~1 fm)

# Atoms



- Atoms are bound states of atomic nuclei and electrons
- Molecules (including DNA) are bound states of atoms
- Atoms can be **ionized**, i.e. their electrons may be released when provided enough energy; this is called **ionisation energy**
- For hydrogen, ionisation energy is 13.6 eV, in general it depends on the atomic numer of an element and an electron quantum state
- Radiation, whose quanta carry enough energy to ionise matter, is called **ionising radiation**
- Ionisation is a way to deposit radiation energy in matter and invoke **biological effects** in living organisms
- **Mean ionisation energy** for an element/compund/mixture is averaged over all electrons
- Example values:
  Air: 85 eV, Aluminum: 164 eV
  Graphite: 78 eV, Lead: 812 eV

# Ionising radiation

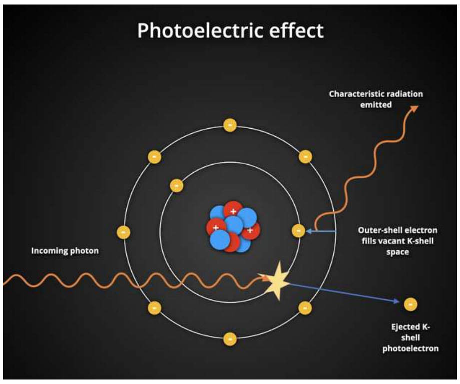


- Nuclei of some isotopes (either naturally present on the Earth or man-made) may be instable
- When they decay, they emit ionising radiation of different types:
  - α (helium nuclei)
  - β (electrons or positrons)
  - γ (high-energetic photons, i.e. electromagnetic)
- We can also form beams of ionising radiation/particles:
  - Accelerated beams of protons and heavier ions
  - Accelerated electron beams
  - By a sudden deceleration of fast electron we make them emit bremstrahlung, which can be in the X-ray or even gamma domain
- **How do they interact with matter?**

# Physical rationale for hadron therapy

## Interaction of gamma radiation with matter

**photoelectric effect**
Compton scattering
pair creation



$$E_\gamma = E_{\text{kinetic e-}} + E_{\text{binding e-}}$$

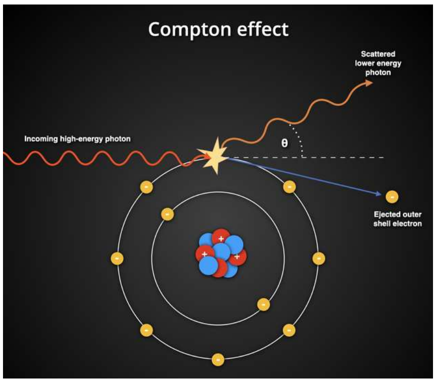
A gamma quantum (photon) interacts with a medium atom and dissapears. Whole energy of the gamma quantum is transferred to an electron of the atom, usually on one of the inner shells. After the photoeffect the electron is released from the atom, and an X-ray cascade follows.

The probability of photoeffect is:

- largest for gamma quanta of small energies
- largest for high-Z media

## Interaction of gamma radiation with matter

photoelectric effect
**Compton scattering**
pair creation



$E_g = E_{g'} + E_{e-}$

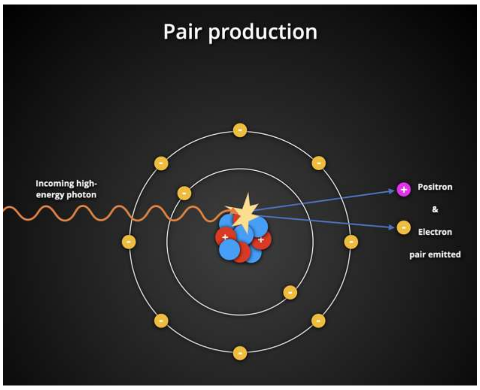
Compton effect is a scattering of a photon on a (quasi-) free electron. Photon behaves here like a particle – it transfers part of its energy to the electron and moves on, with a smaller energy and in a different direction.

Cross section for Compton scattering drops with increasing energy of the photon, but not as fast as for photoeffect. Compton scattering dominates for photon energies from 0.05 MeV to 5 MeV.

Moreover, the cross section increases linearly with the medium atomic numer Z, since it defines the spatial density of electrons.

## Interaction of gamma radiation with matter

photoelectric effect
Compton scattering
**pair creation**



$E_\gamma = 1.022\text{ MeV} + E_{e+} + E_{e-}$

When the energy of a photon exeeds twice the rest energy of an electron ($2m_ec^2$=1.022 MeV), a proces becomes possible, in which a photon converts into a $e^+e^-$ pair. This proces is important for photons of high energies, larger than the threshold energy 1.022 MeV.

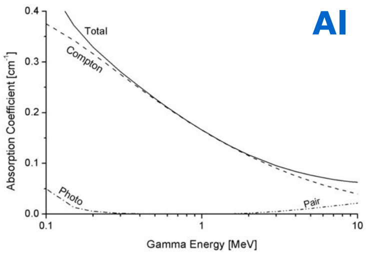
Its cross section:

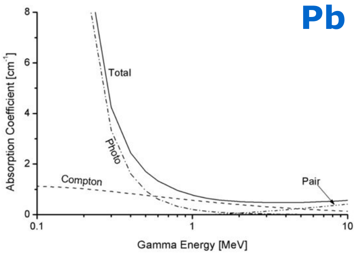
- Increases with photon energy,
- Increases with medium atomic numer like $Z^2$.

# Interaction of gamma radiation with matter

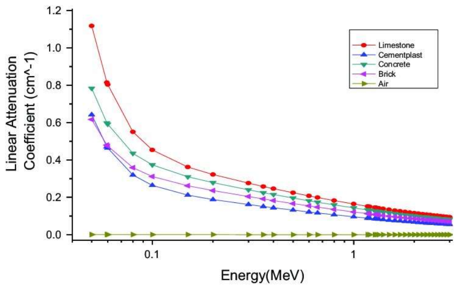
In aluminium, (smaller Z) photoelectric effect becomes negligible already at 200 keV, while Compton scattering dominates the total cross section in the whole depicted energy range (up to 10 MeV).

In lead, up to 600 keV photoelectric effect dominates, then Compton scattering takes over until 5 MeV, when pair creation becomes significant.





# Attenuation of gamma radiation



https://doi.org/10.1016/j.radphyschem.2015.01.031

$$dN = -N\,\mu\,dx$$
$$N = N_0\,e^{-\mu x}$$

**dN** – number of photons absorber in the layer **dx** of a material

**N(x)** – number of photons downstream of the material layer of thickness **x**

**$N_0$** – number of impinged photons

**μ** – linear absorption coefficient

# Interaction of electrons with matter

**Ionisation**

- An electron traversing through a medium has the same mass as orbital electrons in the medium. Thus, in a single act of interaction, it can transfer a large part or even its whole energy to the orbital electron.
- This leads to an **entirely different (compared to protons) characteristics** of passing through matter.
- In case of electrons, **energy loss occurs in leaps and bounds**, but with a smaller frequency. Electron trajectory is all but a straight line, with many kink points.
- Electron **range is not well defined**.

**Bremsstrahlung**

- Electrons may deposit their energy in another proces. As every charged particle, it emits electromagnetic radiation when its velocity changes.
- The proces is important during braking of light particles.
- Bremsstrahlung becomes competitive to ionisation when electrons have high energy and traverse high-Z medium (e.g. Pb).
- This process is used to generate X-rays for conventional radiotherapy.

Energy loss for Bremsstrahlung in a material layer of thickness $dx$ for a particle of mass $m$ and charge $ze$:

$$-\frac{dE}{dx} \approx 4\alpha N_A \frac{Z^2}{A} z^2 \left(\frac{1}{4\pi\varepsilon_0} \cdot \frac{e^2}{mc^2}\right)^2 \cdot E \cdot \ln\frac{183}{\sqrt[3]{Z}}$$

Note the inverse proportionality to $m^2$.

# Interaction of heavy charged particles with matter

**Interactions with electrons**
In interactions with electrons, protons lose a small part of their energy, still sufficient to release electrons from atoms (ionisation). A pair of an electron and a positively charged ion is created. Proton continues its motion with a slightly smaller energy, in almost undisturbed direction.

**Interactions with atomic nuclei**
When colliding with objects of similar mass, protons can be scattered even backwards (180°); in a single act of interaction proton can transfer its whole energy, or a significant part, to the nucleus.

**Interactions with electrons are much more frequent** thus almost all beam protons:

- have straight-line trajectories,
- lose their energy gradually, ionizing many atoms along their trajectory.

# Quantitative description – Bethe-Bloch formula

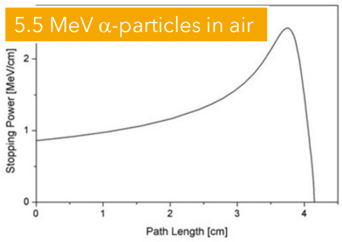
$$-\frac{dE}{dx} = Kz^2\frac{Z}{A}\frac{\rho}{\beta^2}\left[\frac{1}{2}\ln\frac{2m_ec^2\beta^2\gamma^2T_{max}}{I^2} - \beta^2 - \frac{\delta(\gamma\beta)}{2}\right]$$

| | |
|---|---|
| **$E$** | Particle kinetic energy |
| **$m_e$** | Electron mass 511 keV/$c^2$ |
| **$r_e$** | Electron classical radius 2,817 fm |
| **$K = 4\pi N_A r_e^2 m_e c^2$** | Combination of constants, $N_A = 6{,}022 \times 10^{23}$ mol $^{-1}$ |
| **$T_{max} = 2m_e(\gamma\beta c)^2$** | Maximum Energy transfer |
| **$A$** | Medium molar mass |
| **$Z$** | Medium atomic numer |
| **$z$** | Particle electric charge (in units of e) |
| **$\rho$** | Medium density |
| **$I$** | Medium ionisation potential |
| **$\gamma = 1/\sqrt{1 - v^2/c^2}$** | Lorentz factor |
| **$\beta = v/c$** | Particle velocity (in units of c) |
| **$\delta(\gamma\beta)$** | Medium density correction |

Energy loss per unit length of trajectory in a medium (absorber) depends on the particle's **velocity** (kinetic energy) and **electric charge**, as well as on the type and properties of traversed medium.

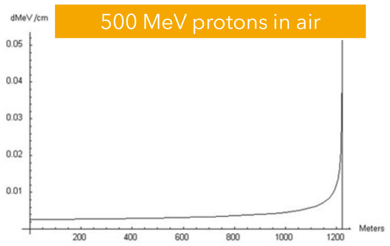
When discussing this quantity as a property of the medium, it is referred to as **stopping power**.

# Interaction of heavy charged particles with matter

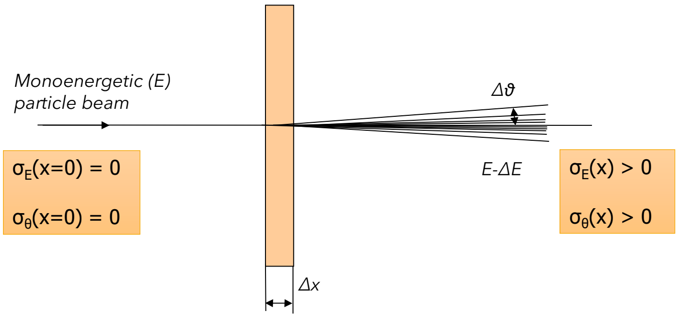

5.5 MeV α-particles in air

α particles lose their energy gradually. **At the end of their trajectory, their energy loss per unit length of trajectory has a maximum**. Then, the particle stops.

Protons at first lose only ~3 keV per 1 cm of their trajectory, but just before stopping it rises up to ~60 keV/cm!


500 MeV protons in air

# Energetic and angular straggling



$\sigma_E(x=0) = 0$

$\sigma_\theta(x=0) = 0$

$\sigma_E(x) > 0$

$\sigma_\theta(x) > 0$

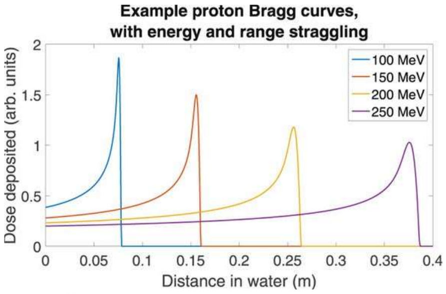
**Straggling** = (usually Gaussian) smearing resulting from the statistical nature of interaction between beam particles and the medium – its electrons and nuclei

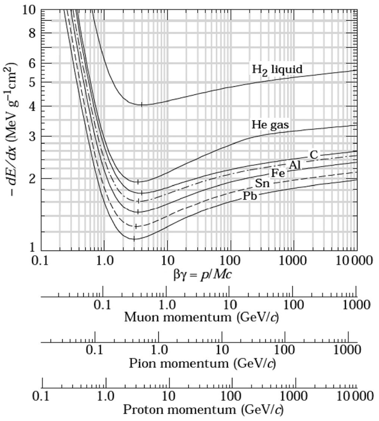
$\sigma_E$ – energetic straggling

$\sigma_\theta$ – angular straggling

# Energy loss and range of heavy charged particles

- -dE/dx depends on the particle velocity βγ, but not its mass
- -dE/dx reaches minimum for βγ = p/Mc ≈ 4, so-called **minimum of ionisation**
- Bethe-Bloch formula has a precision of a few percent for 0.1 ≤ βγ ≤ 1000
- **Particle range** in medium is given by its properties and those of the medium and is well defined – typically at the **80% of the maximal dose**

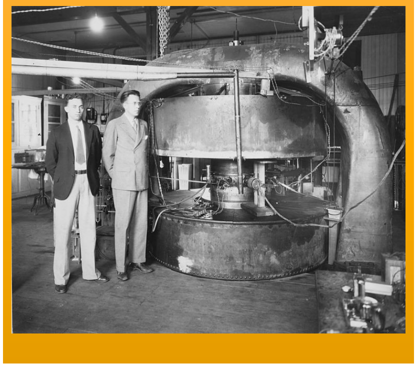


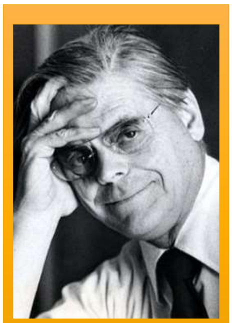


# Fathers of proton therapy

Hans Bethe, 1930
Theoretical description of proton interaction with matter

Ernest O. Lawrence, 1932
Construction of a cyclotron





Robert Wilson, 1946
Proposal to use proton beams for cancer treatment

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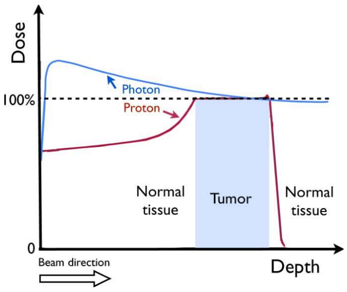
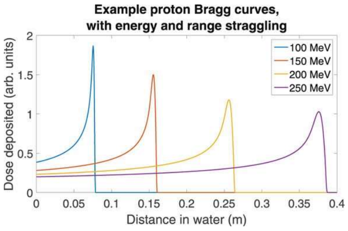
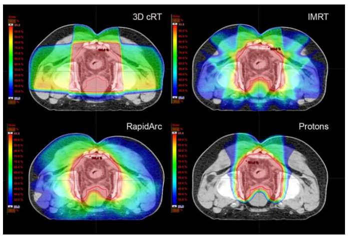
# Rationale for proton therapy

- Local tissue damage depends on the local energy deposit
- For **X-rays**, dose maximum is close to the surface
- For **protons**, dose maximum at a certain depth, just before stopping, in the so-called **Bragg peak**
- Bragg peak depth can be adjusted by tuning of the proton beam energy – better dose conformality, less dose in the healthy tissue
- Different radiation types lead to different biological effects at the same delivered dose: **relative biological effectivness (RBE)**

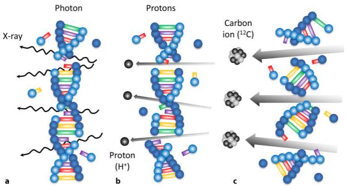


DOI: 10.1038/s41391-019-0140-7

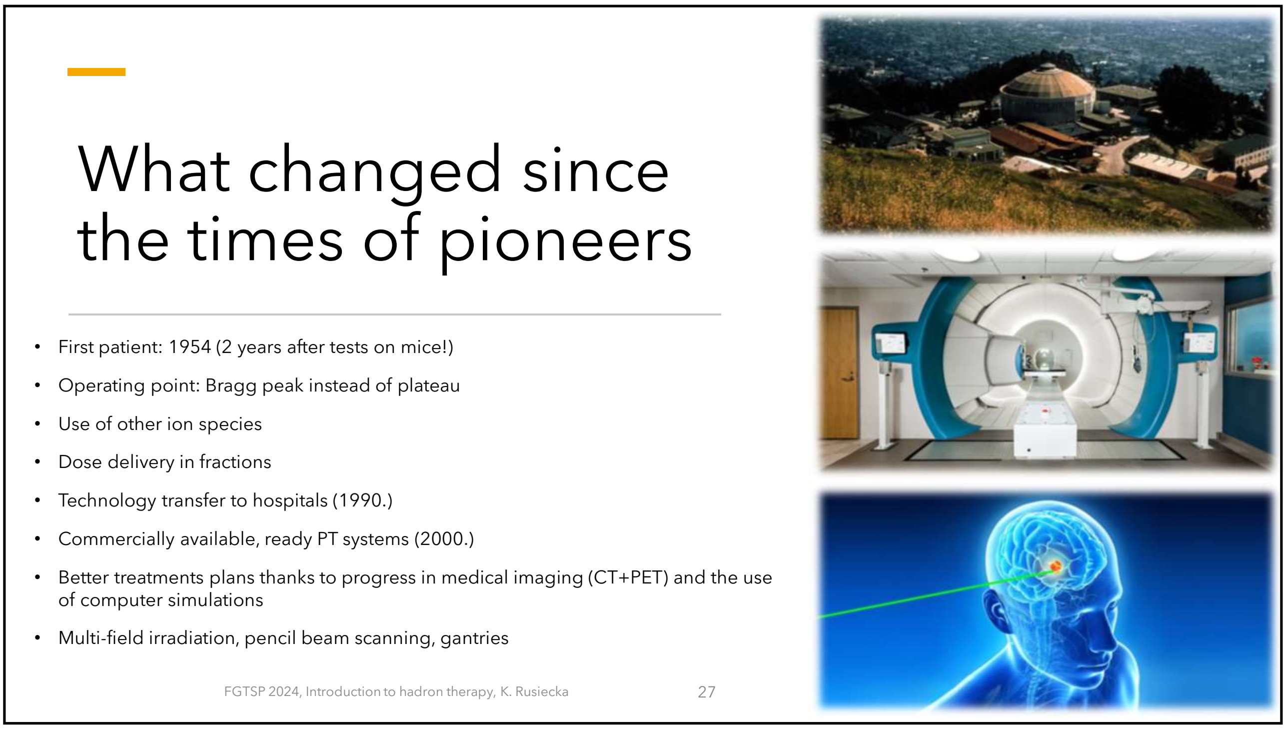




Wolff et al, DOI: 10.1016/j.radonc.2011.10.018



DOI: 10.1007/s12254-020-00623-y

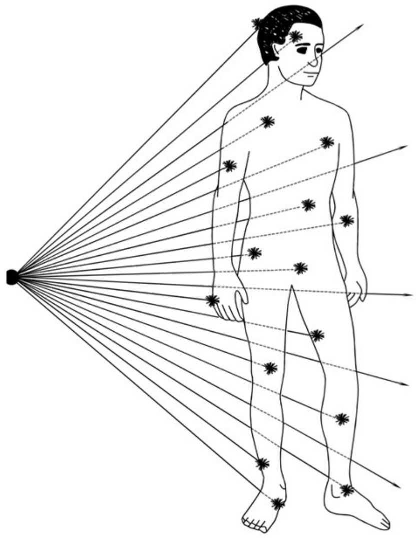


# What changed since the times of pioneers

- First patient: 1954 (2 years after tests on mice!)
- Operating point: Bragg peak instead of plateau
- Use of other ion species
- Dose delivery in fractions
- Technology transfer to hospitals (1990.)
- Commercially available, ready PT systems (2000.)
- Better treatments plans thanks to progress in medical imaging (CT+PET) and the use of computer simulations
- Multi-field irradiation, pencil beam scanning, gantries

# Biological aspects

Reactor Concepts Manual, Biological Effects of Radiation



# Radiation damage in biological systems

- Ionisation
- Excitation
- Chemical effects
- Thermal damage

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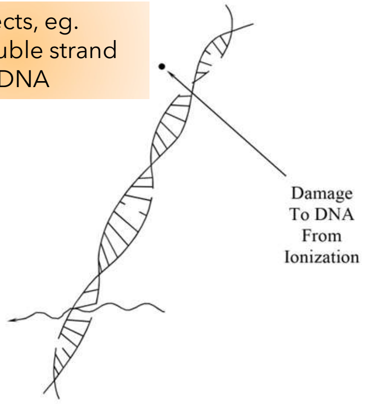
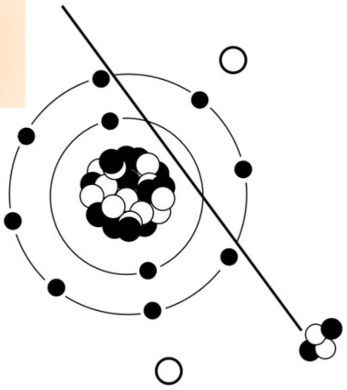
# Radiation damage in biological systems

Direct effects, eg. single/double strand breaks of DNA



Indirect effects, eg. hydrolysis of water molecules, creation of free radicals



Reactor Concepts Manual, Biological Effects of Radiation

# Descritption of irradiation

**Delivered dose** – measure of the energy deposited in matter by ionizing radiation per unit mass.

$$D = \frac{E}{m}$$

$$[D] = \frac{\mathrm{J}}{\mathrm{kg}} = \mathrm{Gy}$$

**Equivalent dose** – takes into account the biological effectivness of the radiation, which is dependent on radiation type and energy.

$$H_T = \Sigma_R (W_R \cdot D_{RT})$$

$$[H_T] = \frac{\mathrm{J}}{\mathrm{kg}} = \mathrm{Sv}$$

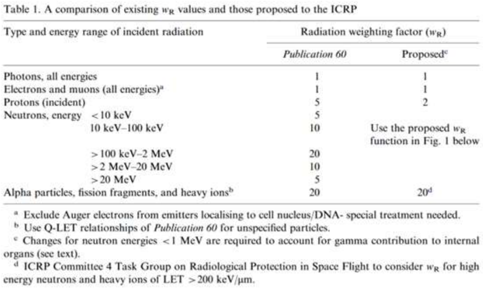


Table 1. A comparison of existing $w_R$ values and those proposed to the ICRP

| Type and energy range of incident radiation | | Radiation weighting factor ($w_R$) | |
|---|---|---|---|
| | | *Publication 60* | Proposed[c] |
| Photons, all energies | | 1 | 1 |
| Electrons and muons (all energies)[a] | | 1 | 1 |
| Protons (incident) | | 5 | 2 |
| Neutrons, energy | <10 keV | 5 | |
| | 10 keV–100 keV | 10 | Use the proposed $w_R$ function in Fig. 1 below |
| | >100 keV–2 MeV | 20 | |
| | >2 MeV–20 MeV | 10 | |
| | >20 MeV | 5 | |
| Alpha particles, fission fragments, and heavy ions[b] | | 20 | 20[d] |

[a] Exclude Auger electrons from emitters localising to cell nucleus/DNA- special treatment needed.

[b] Use Q-LET relationships of *Publication 60* for unspecified particles.

[c] Changes for neutron energies <1 MeV are required to account for gamma contribution to internal organs (see text).

[d] ICRP Committee 4 Task Group on Radiological Protection in Space Flight to consider $w_R$ for high energy neutrons and heavy ions of LET >200 keV/μm.

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# Descritption of irradiation

**Relative Biological Effectivness (RBE)**

$$RBE = \frac{D_X}{D_R}$$

$D_X$ – reference absorbed dose of radiation of standard type X

$D_R$ – absorber dose of radiation type R, which causes the same amount of biological damage

**Delivered dose** – measure of the energy deposited in matter by ionizing radiation per unit mass.

$$D = \frac{E}{m}$$

$$[D] = \frac{\mathrm{J}}{\mathrm{kg}} = \mathrm{Gy}$$

**Equivalent dose** – takes into account the biological effectivness of the radiation, which is dependent on radiation type and energy.

$$H_T = \Sigma_R (W_R \cdot D_{RT})$$

$$[H_T] = \frac{\mathrm{J}}{\mathrm{kg}} = \mathrm{Sv}$$

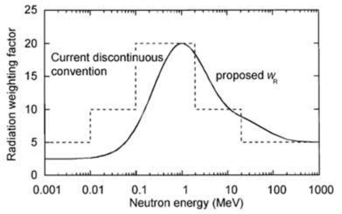

Fig. 1. The radiation weighting factor $w_R$ for neutrons introduced in *Publication 60* (ICRP, 1991) as a discontinuous function of the neutron energy (- - -) and the proposed modification (—).

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$$H_T = \Sigma_R (W_R \cdot D_{RT})$$

$$[H_T] = \frac{\mathrm{J}}{\mathrm{kg}} = \mathrm{Sv}$$

**Effective dose** – tissue-weighted sum of equivalent doses in all specified tissues and organs.

$$E = \Sigma_T (W_T \cdot H_T)$$

$$[E] = \frac{\mathrm{J}}{\mathrm{kg}} = \mathrm{Sv}$$

| Tissue | Tissue weighting factor wT | Σ wT |
|---|---|---|
| Bone-marrow (red), Colon, Lung, Stomach, Breast, Remainder tissues* | 0.12 | 0.72 |
| Gonads | 0.08 | 0.08 |
| Bladder, Oesophagus, Liver, Thyroid | 0.04 | 0.16 |
| Bone surface, Brain, Salivary glands, Skin | 0.01 | 0.04 |
|  | Total | 1.00 |

https://www.euronuclear.org/glossary/tissue-weighting-factor/

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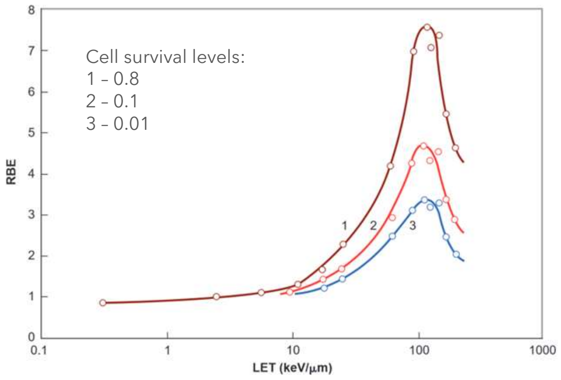
# Descritption of irradiation

**Linear energy transfer (LET)**– amount of energy that is deposited by the ionizing radiation per unit distance traversed in matter.

$$LET = \frac{dE}{dl}$$

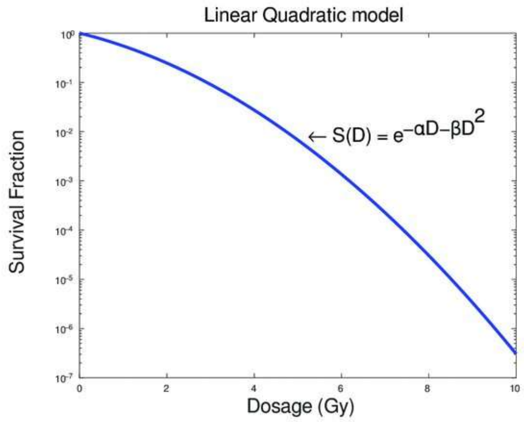
- Closely related to stopping power
- LET depends on the radiation type and medium type
- Larger LET → more radiation damage
- BUT approx. LET 100 keV/μm is optimal for biological effectivness



E. J. Hall, A. J. Giaccia, Radiobiology for the Radiologist

# Cell survival

- Dependence of the cel survival on the dose is often described with **linear quadratic model**
- $\alpha D$ – cell death induced by single hits
- $\beta D^2$ – cell death induced by multiple hits



DOI: 10.3390/radiation1010005

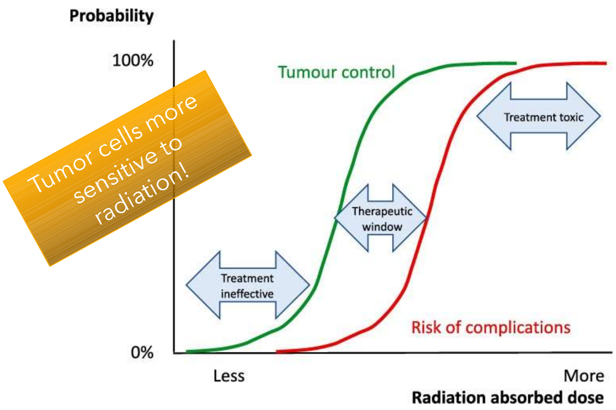
# Principles of radiotherapy

**Tumor control:**

- Tumor control probability (TCP)
- Goal of the therapy – prevent further proliferation of cancer cells, kill existing cancer cells

**Complications**

- Normal Tissue Complications Probability (NTCP)
- Minimize radaition damage to neighbouring healthy tissues



Tumor cells more sensitive to radiation!

# Principles of radiotherapy – 5R

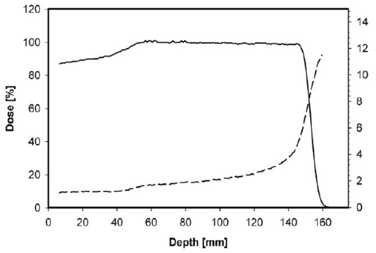
Fractioning of radiotherapy

- **Repair** – cells can rapair DNA damage caused by the radiation
- **Repopulation** – increase in cell divisions in response to radiation
- **Redistribution** in the cell cycle – cells in G2 and M stages are the most sensitive to radaition
- **Reoxygenation** – hypoxic cells are more resistant to radiotherapy, thus oxygen is desired
- **Radioresistance** – different types of cells (tumors) have different radiosensitivity

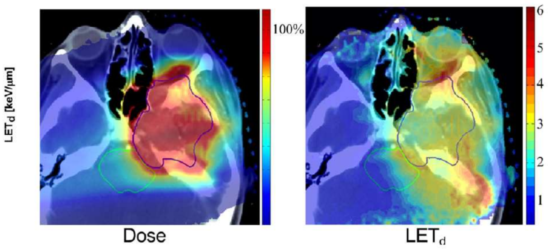
# Radiobiology of hadron therapy

- Radiation oncology currently applies a constant and generic value of protons RBE = 1.1
- That comes from early days of PT and is a conservative estimate.
- But reality more complicated. There is evidence, that **RBE varies** with:
  - LET (linear energy transfer) and dose per fraction $D_P$
  - physiologic and biological factors of protons and reference photon radiation
  - clinical endpoint
- Models from clonogenic cell-survival data from various cell lines

Conclusion: to optimize the treatment, dependence of RBE on LET and other factors should be taken into account.

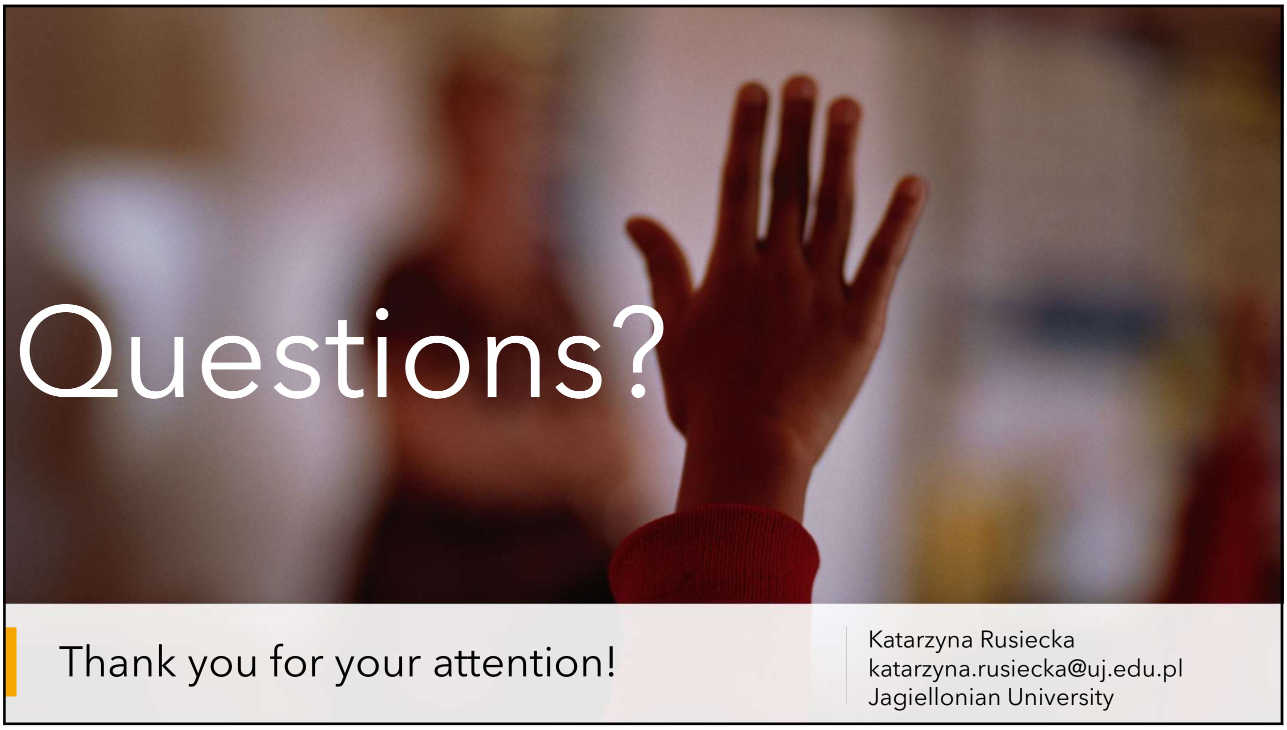


Typical ranges of linear energy transfer (dashed line; dose-averaged LETd) in a spread-out Bragg peak (solid line) in water.



Dose (%) and LET$_d$ (keV/mm) in a chordoma patient based on intensity modulated proton therapy.
LET$_d$ = dose-averaged linear energy transfer.

Paganetti, doi: 10.1016/j.ijrobp.2021.08.015



# Questions?

Thank you for your attention!

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