Introduction to Radiobiology, with a little on particle therapy

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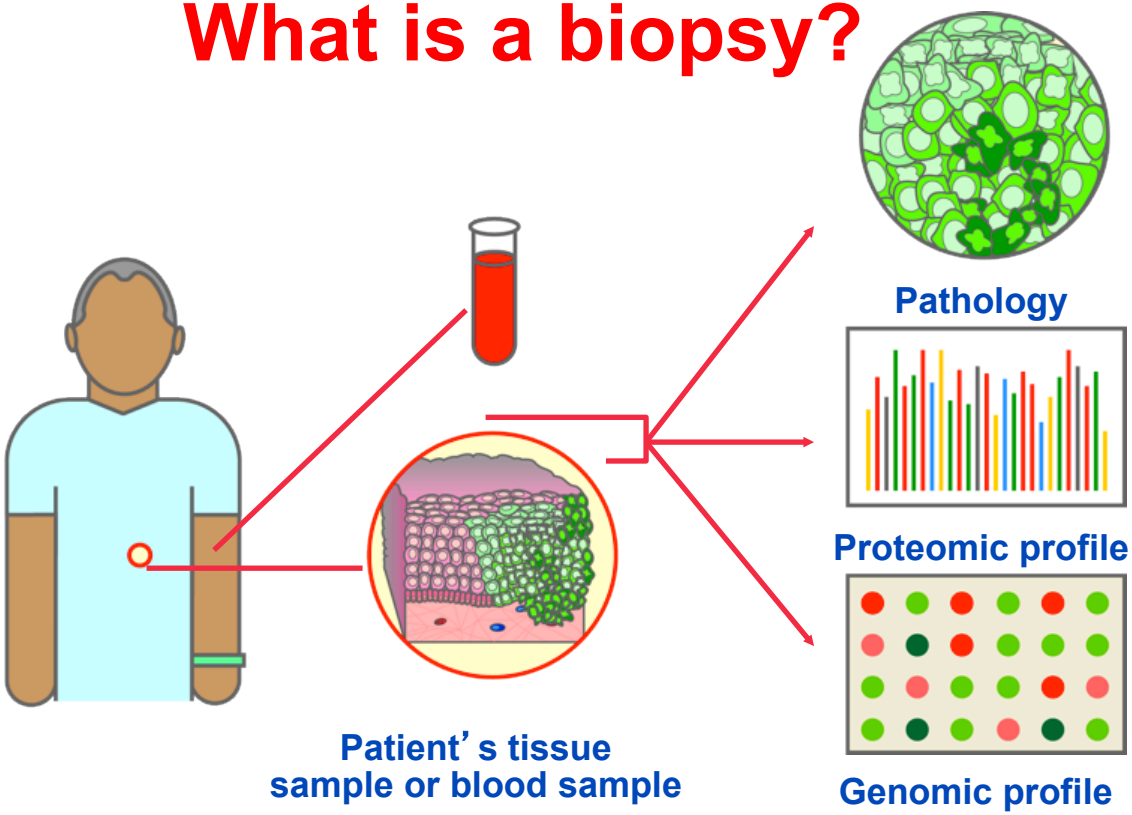
How to Treat Cancer ....
With minimal side-effects

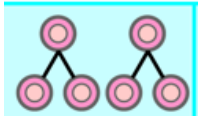
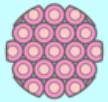
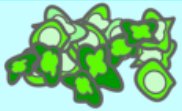
- Holy grail of oncology
- Identify characteristics that distinguish tumor cells from normal cells
- Design a Monotherapy that selectively ablates tumor cells

Let‘s start with Biology …

What is a biopsy?

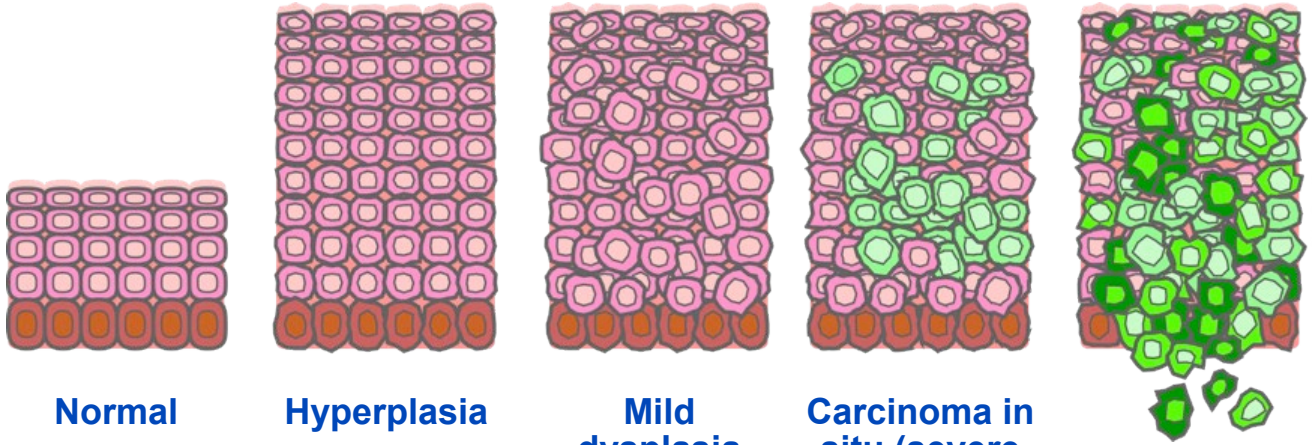


What does a pathologist look for in biopsy tissue?

Normal	Cancer	
		Large number of irregularly shaped dividing cells
		Large, variably shaped nuclei
		Small cytoplasmic volume relative to nuclei
		Variation in cell size and shape
		Loss of normal specialized cell features
		Disorganized arrangement of cells
		Poorly defined tumor boundary

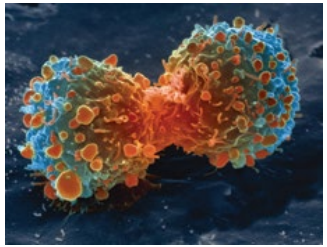
Some more Biology…

How does Cancer look like under the microscope?



What is Cancer ?

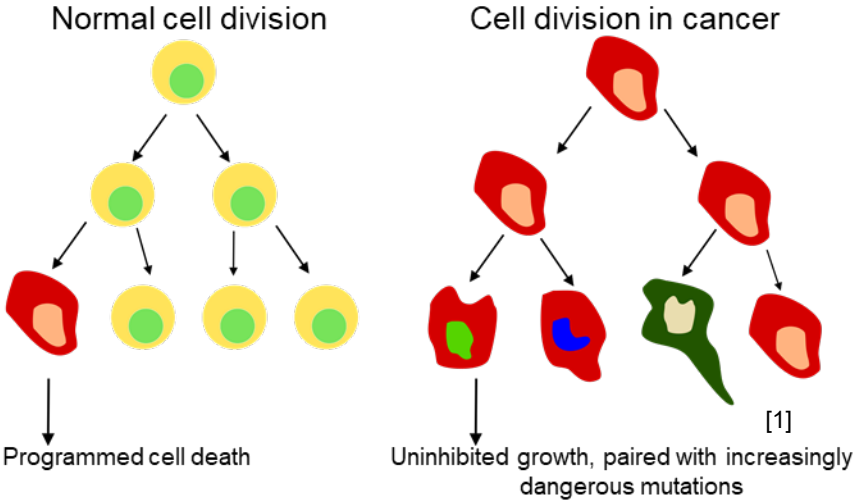
- is uncontrolled cell proliferation and cell rampant growth
- cancer may spread to other parts of the body
- over 100 different types, individual



Cancer cell of a lung tumor during cell proliferation

[2]

healthy cells vs. cancer cells



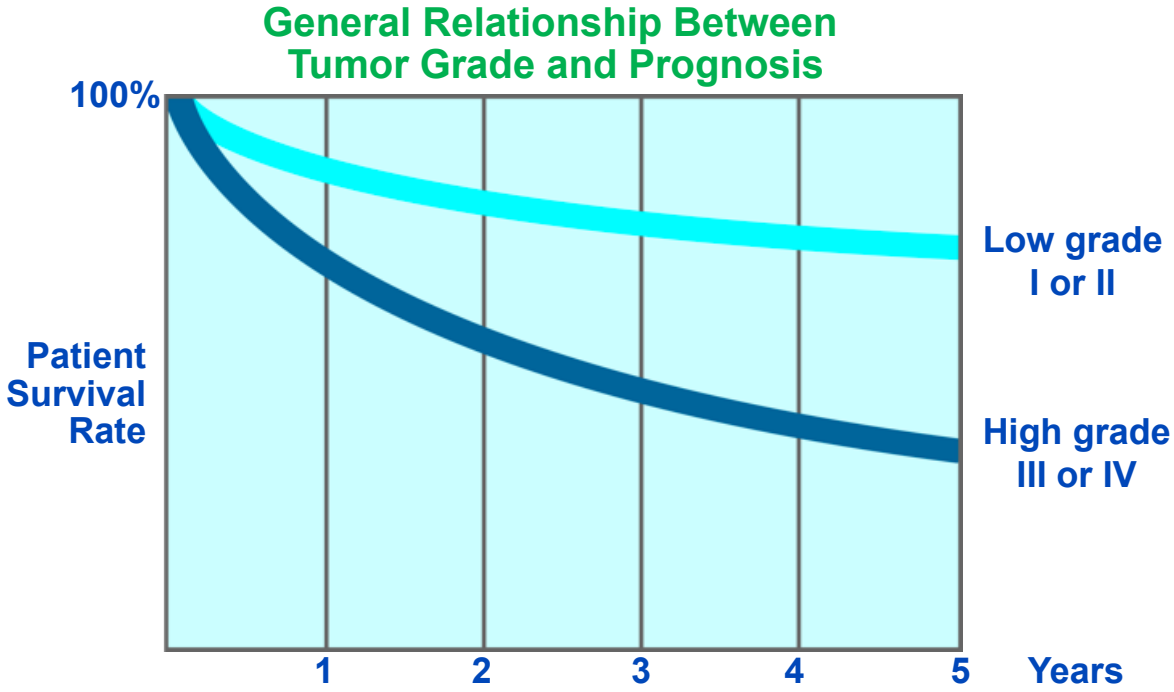
[1]

Theory of cancer formation:

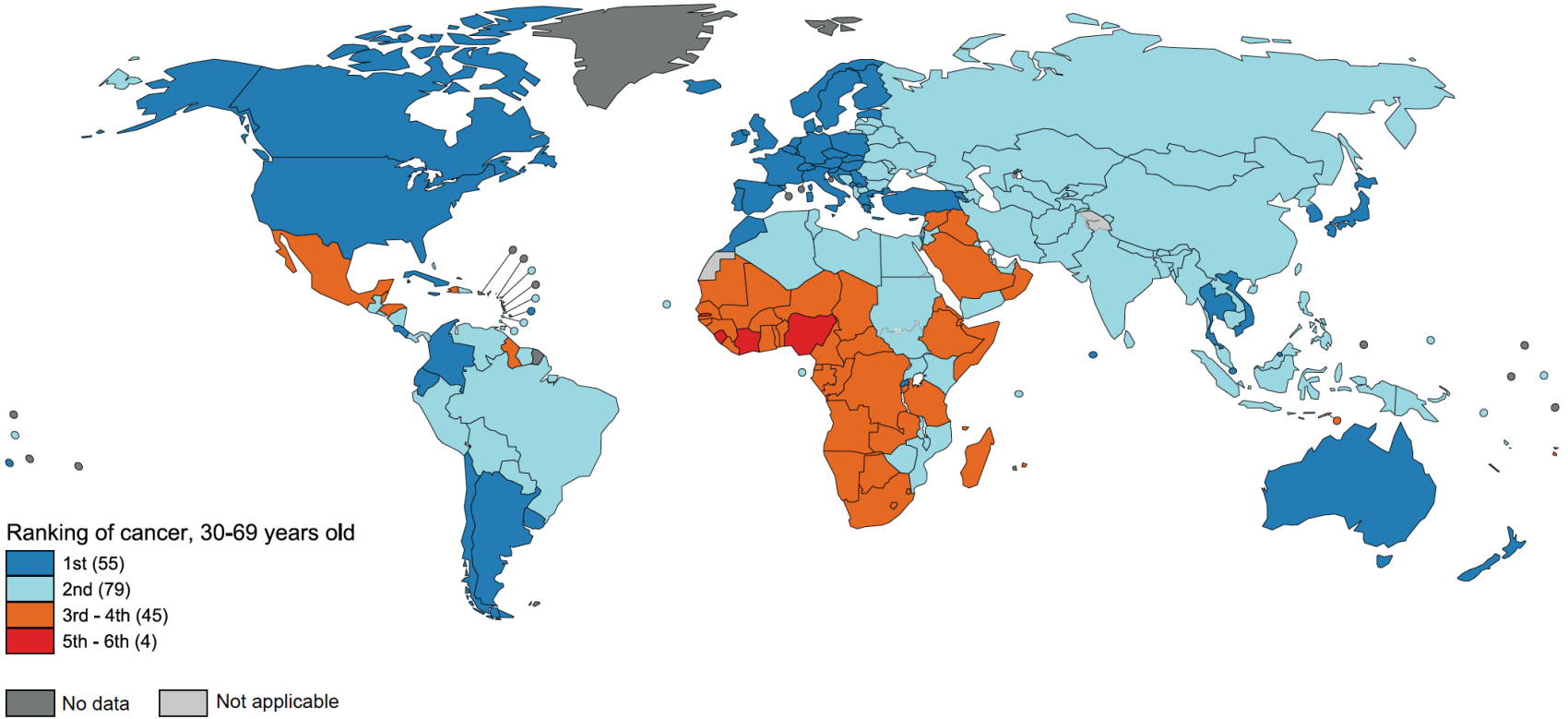
(random) mutation levers out i.a. programmed cell death
→ cells need to be removed / killed “manually” for treatment

[1] Garak76, Suhadi Jorhaa'ir (https://commons.wikimedia.org/wiki/File:Zellteilung_normal_im_Gegensatz_zu_Krebs.svg), „Zellteilung normal im Gegensatz zu Krebs“
[2] fineartamerica - Lung Cancer Cell Division. - Accessed from https://fineartamerica.com/featured/lung-cancer-cell-division-sem-steve-gschmeissner.html?product=metal-print on 12.02.2021. Lettering was adapted.

What is the relationship between tumor grade and patient survival?



Cancer - incidence



[1] Stewart, B. W. K. P., and Christopher P. Wild. "World cancer report 2014." (2014).
[2] Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries
[3] RKI, Report on cancer in Germany for 2013/2014, cancer registry data
[4] RKI, Report on cancer in Germany for 2015/2016, cancer registry data

2017 New Cancer Sites

Estimated New Cases

Males			Females		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**	**All Sites**	**852,630**	**100%**

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2017 Cancer Deaths

Estimated New Cases

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Estimated Deaths

	Males			Females	
Lung & bronchus	84,590	27%		Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%		Breast	40,610	14%
Prostate	26,730	8%		Colon & rectum	23,110	8%
Pancreas	22,300	7%		Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%		Ovary	14,080	5%
Leukemia	14,300	4%		Uterine corpus	10,920	4%
Esophagus	12,720	4%		Leukemia	10,200	4%
Urinary bladder	12,240	4%		Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%		Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%		Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**		**All Sites**	**282,500**	**100%**

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Hallmark of Cancer

“Warburg Effect”

Adequate oxygen

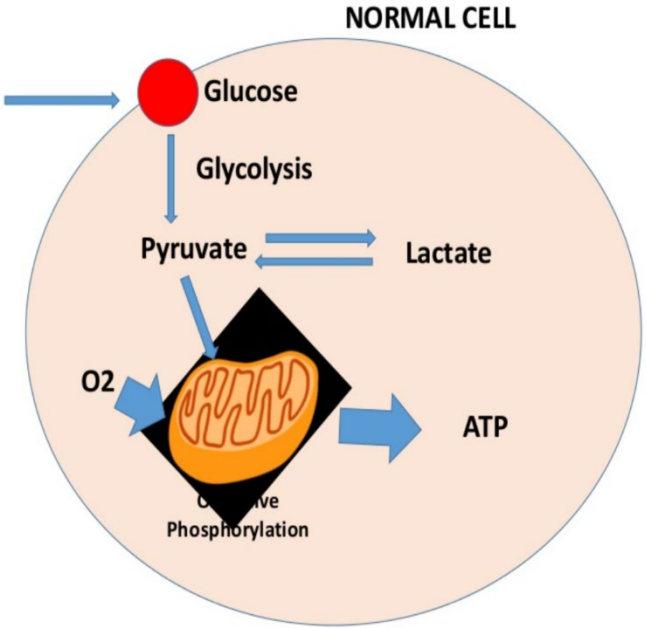
ATP is generated by Oxidative Phosphoryation

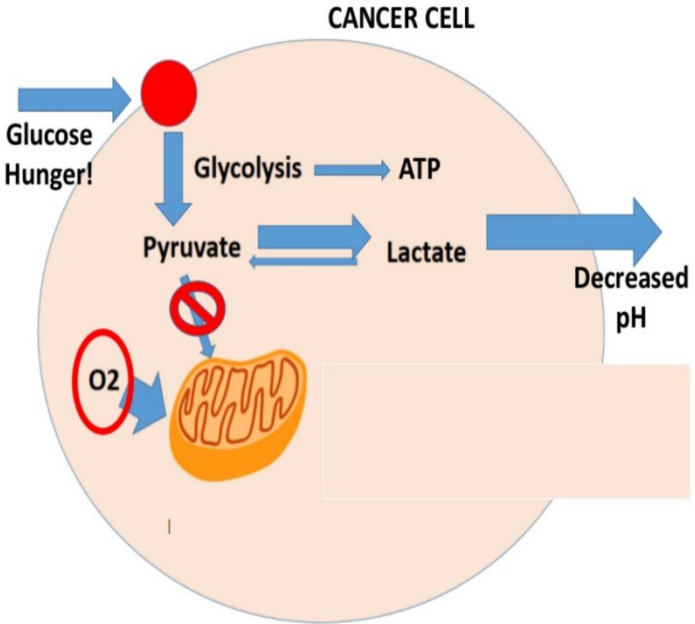
As Oxygen Decreases

Shift from Oxidative phosphorylation to **Glycolysis**

Anaerobic glycolysis

PASTEUR EFFECT





Early 20th Century

Otto Heinrich Warburg
German Physiologist

Observed that cancer cells had increased rates of glycolysis

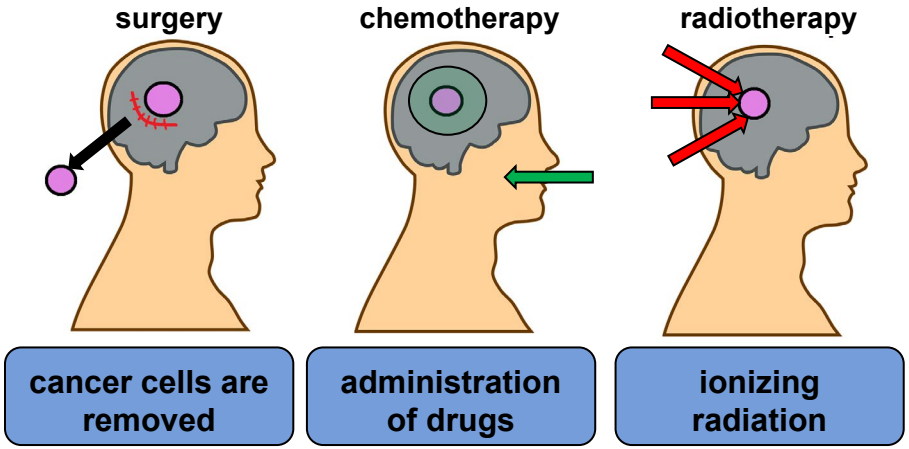
Despite the availability of adequate oxygen levels

Aerobic glycolysis

WARBURG EFFECT

Why do cancer cells activate glycolysis despite the presence of oxygen?

Treatment options



Goal:

1. CURE leads survival
2. PALLIATIVE leads better quality of life

Chances of survival:

60% of all cancer patients survive more than **5** years [1]

- **10**-year prognosis **<1%** pancreatic cancer
- **10**-year prognosis **~84%** prostate cancer

External radiotherapy

Internal radiotherapy

electromagnetic radiation

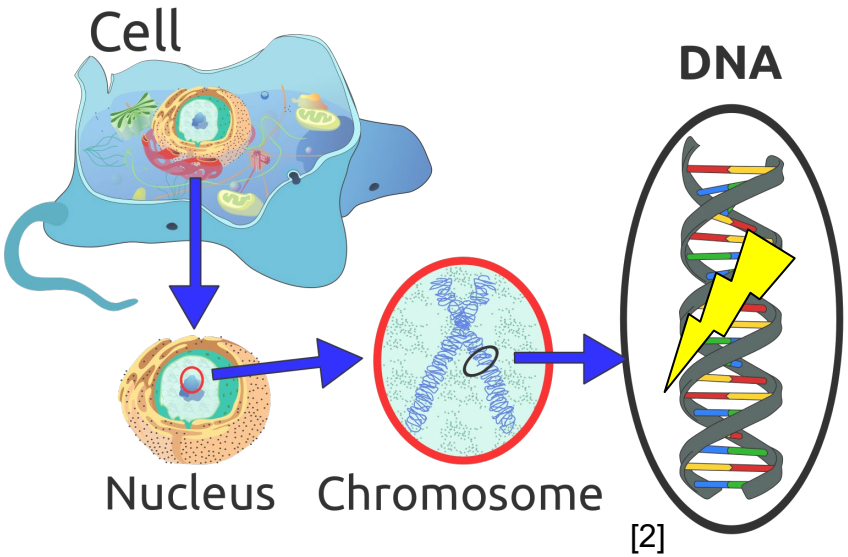
particle radiation

brachytherapy

[1] A joint publication of the Robert Koch Institute and the German Cancer Associations (Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V.), 11th issue, 2017, accessed on 20.11.2018

Radiotherapy - Biology

> 50% of all cancer patients receive radiotherapy [1]



[2]

Physical phase: 10^{-18} to 10^{-14} s

Elementary physical interactions between ionizing radiation and atom

Chemical phase: 1ms to ~ min

Reactive radicals react with molecules of the cell and change their chemical composition

Biological phase: after 1s to years

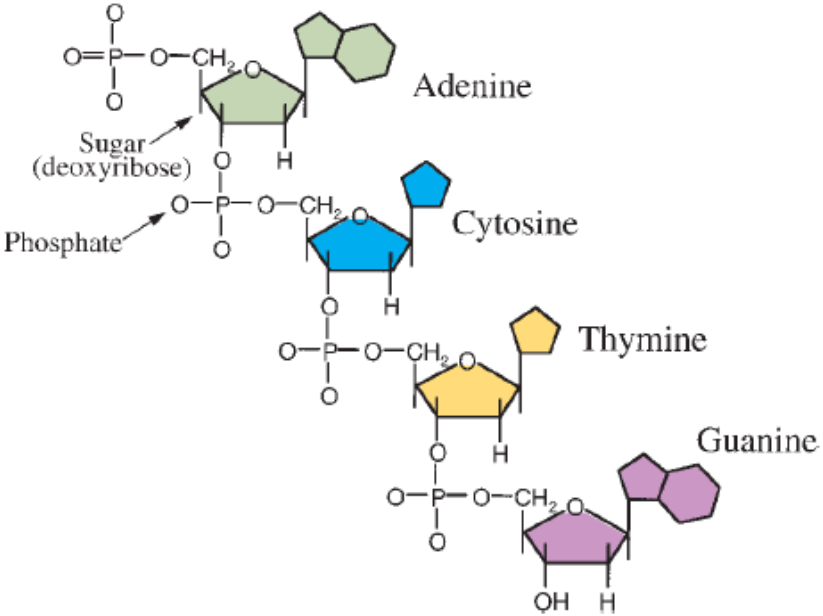
Cell death, loss of function of the organism

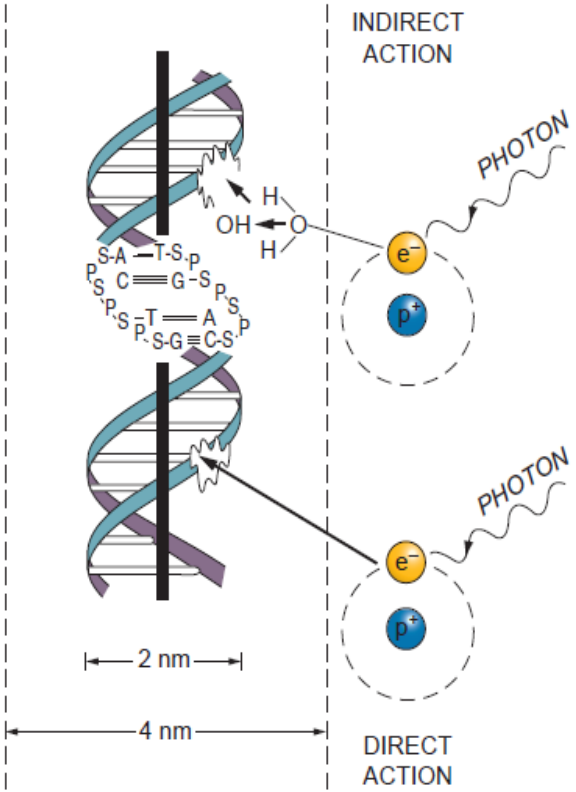
Serial organs: e.g. spinal cord
Parallel organs: e.g. lung

[1] Atun R. Jaffray et. al, Expanding global access to radiotherapy. Lancet Oncol., 2015
[2] Sponk, Tryphon, Magnus Manske, User:Dietzel65, LadyofHats (Mariana Ruiz), Radio89 (https://commons.wikimedia.org/wiki/File:Eukaryote_DNA-en.svg), „Eukaryote DNA-en“, https://creativecommons.org/licenses/by-sa/3.0/legalcode

DIRECT AND INDIRECT ACTION

The biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA), which is the critical target, as described





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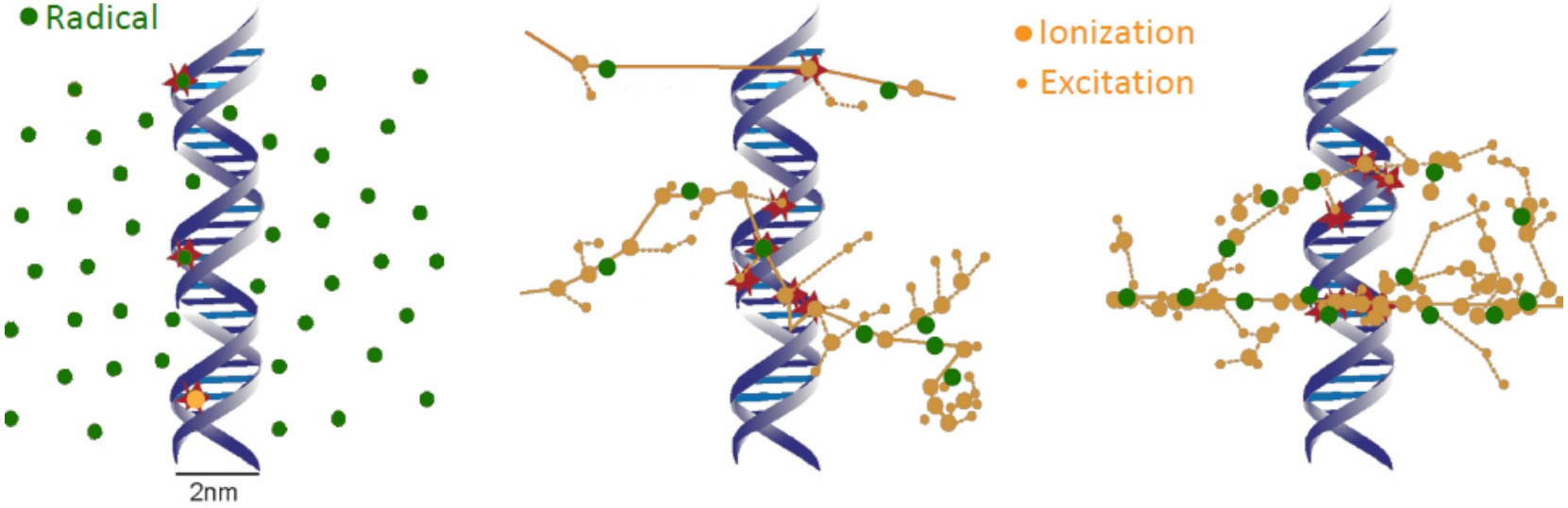


γ-radiation

Low LET radiation

High LET radiation

Low and homogeneous ionization density / radical production
→ Random distribution of indirect damage
→ Easier to repair by cell!

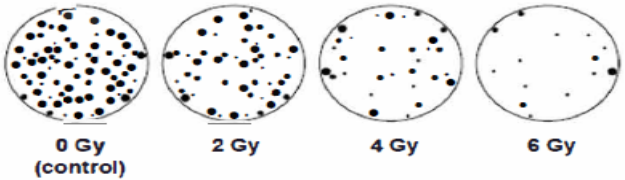
LET ↗

High and localized ionization density / (radical production)
→ Clustered/Complex DNA Damage
→ Very difficult to repair by cell!

3. Cell Survival Curves

In vitro experimental assay of radiation damage

Measuring cell survival *in vitro*



- Puck and Marcus (1955) developed a new method for the quantitative culture of mammalian cells. (HeLa cells, feeder cell technique)
- Elkind and Sutton (1960) proposed a model for repair of sublethal damage. In split-dose experiments, they measured recovery of survival as a function of the time interval between two doses

The first mammalian cell survival curve

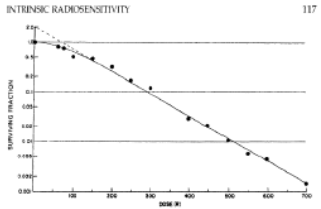
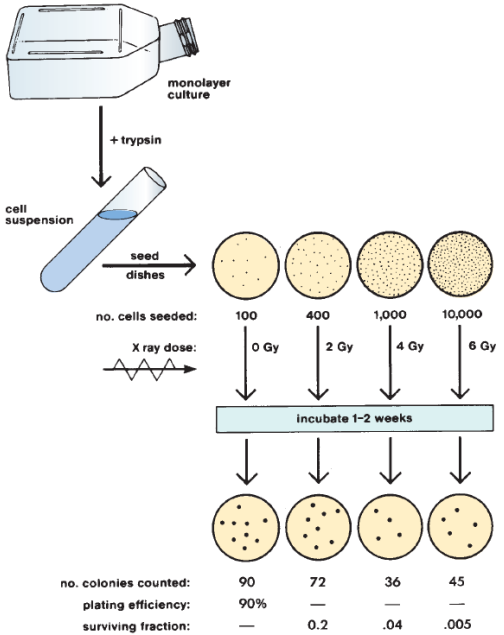


Figure 8.1. Radiation dose–response of human cancer cells *in vitro*. (Reproduced from Puck and Marcus, 1956, by copyright permission of The Rockefeller University Press.)



THREE POPULAR ESTABLISHED CELL-LINES

HeLa Cells (human cancer cells)

CHO Cells (Chinese hamster ovary cells)

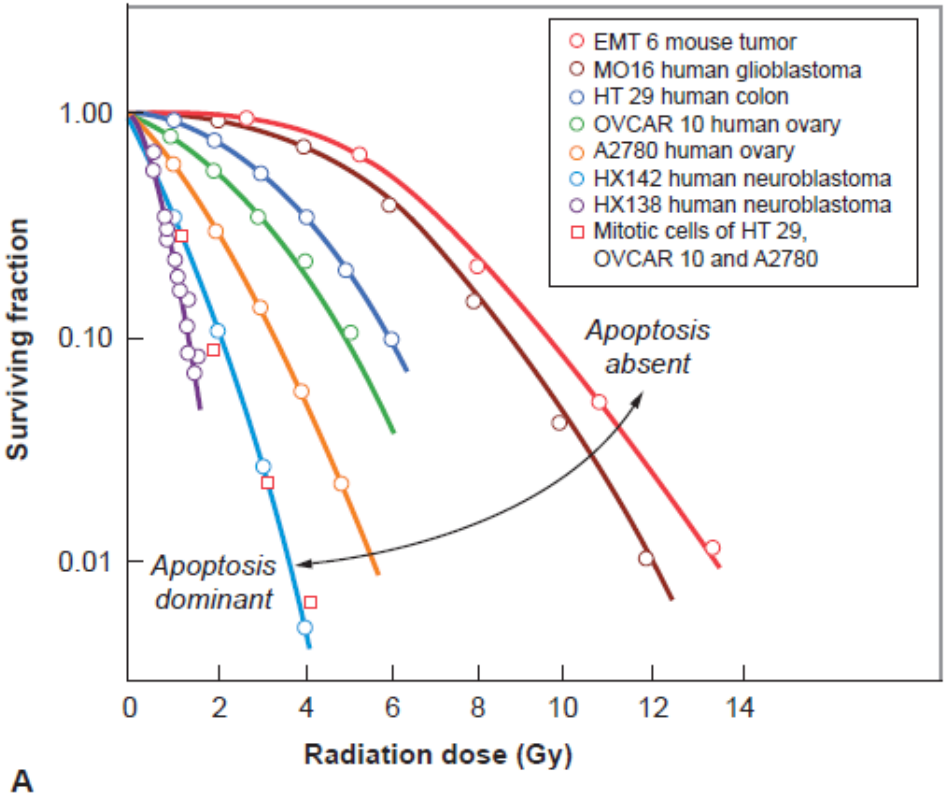
V79 Cells (Chinese hamster lung fibroblast cells)

Culturing Mammalian Cells

tissue → trypsin → single cell suspension → seeding →(medium+incubation) →crisis →established

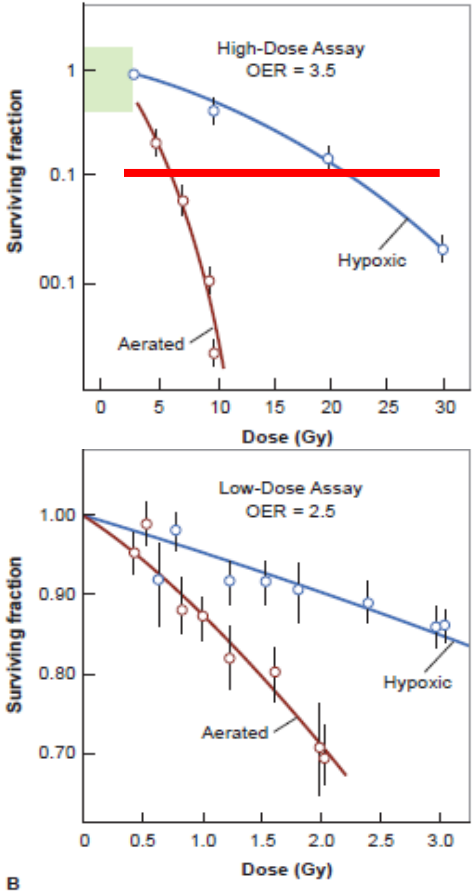
3. Cell Survival Curves

FIGURE 3.8 **A:** Compilation of survival curves for asynchronous cultures of several cell lines of human and rodent origin. Note the wide range of radiosensitivity (most notably the size of the shoulder) between mouse EMT6 cells, the most resistant, and two neuroblastoma cell lines of human origin (the most sensitive). The cell survival curve for mitotic cells is very steep, and there is little difference in radiosensitivity for cell lines that are very different in asynchronous culture. (Data compiled by Dr. J.D. Chapman, Fox Chase Cancer Center, Philadelphia.) **B:** DNA purified from various cell lines (survival curves shown in Fig. 3.8A) 18 hours after irradiation with 10 Gy and electrophoresed for 90 minutes at 6 V/cm. Note the broad variation in the amount of "laddering"—which is characteristic of an apoptotic



6. Oxygen Effect and Reoxygenation

FIGURE 6.1 Cells are much more sensitive to x-rays in the presence of molecular oxygen than in its absence

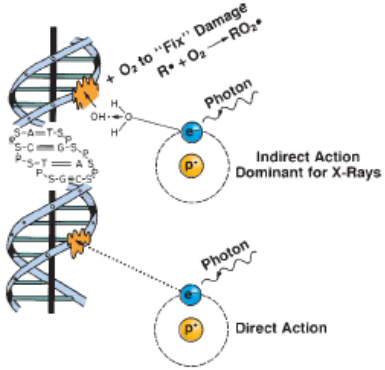


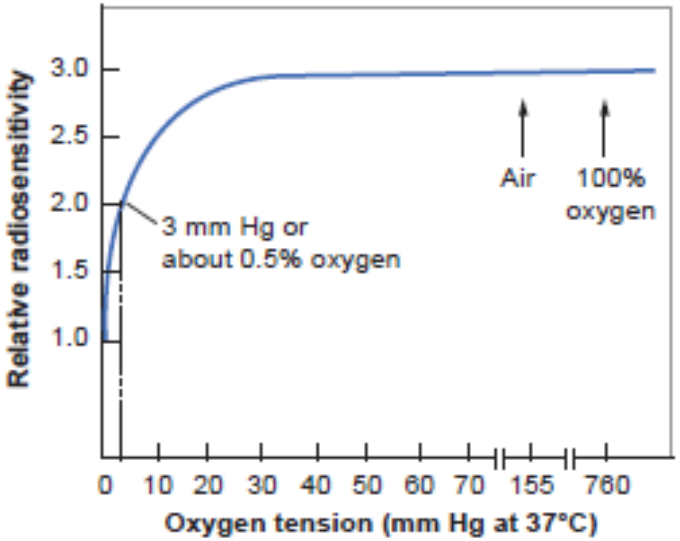
Oxygen is the best known and most general radiation sensitizer.

$$\text{OER} = \frac{\text{Dose(hypoxia)}}{\text{Dose(oxygenated)}}$$

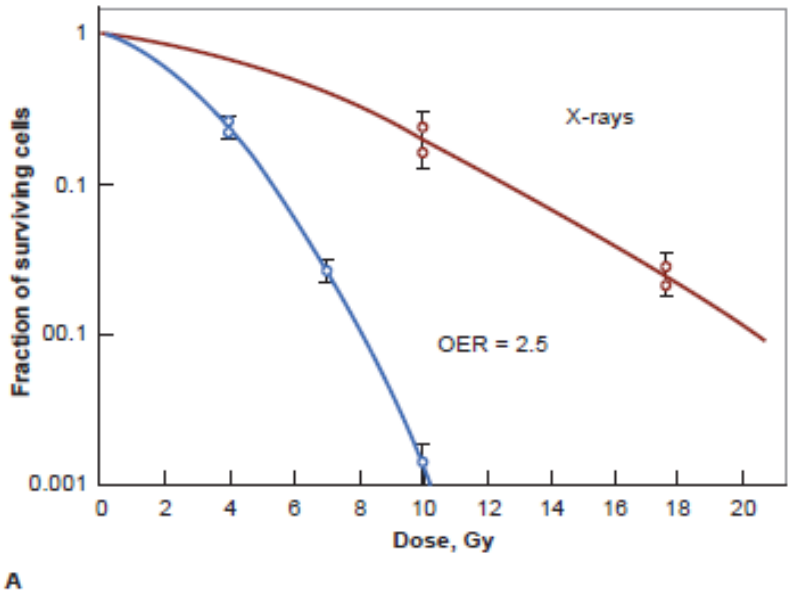
OER usually about 3 at high radiation doses, but can be lower at low doses.

Oxygen Fixation Hypothesis (OFH)

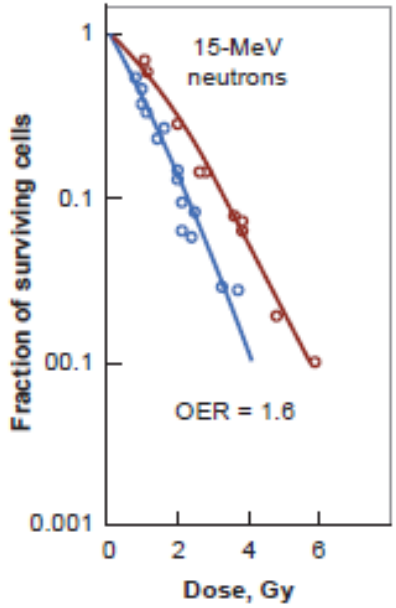




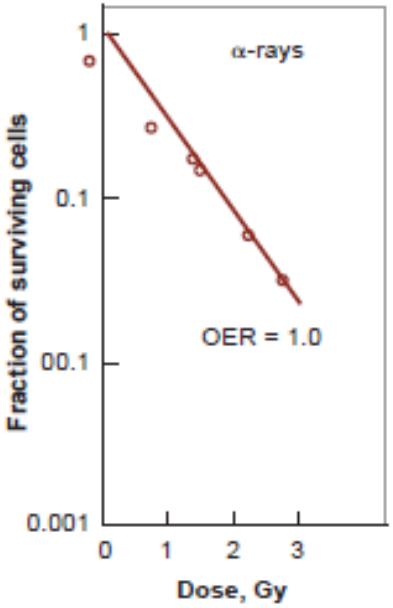
6. Oxygen Effect and LET Dependency



A

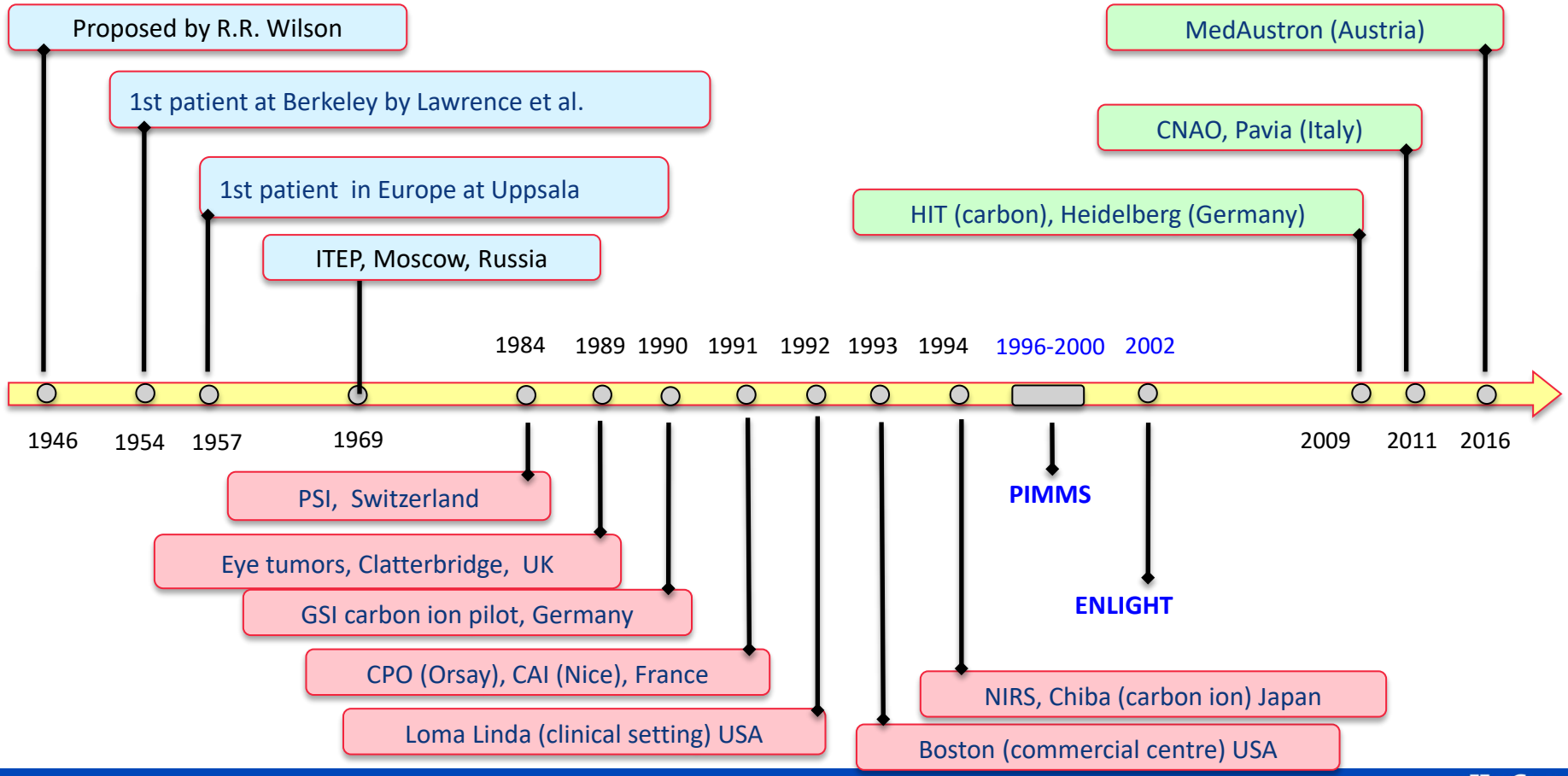


B

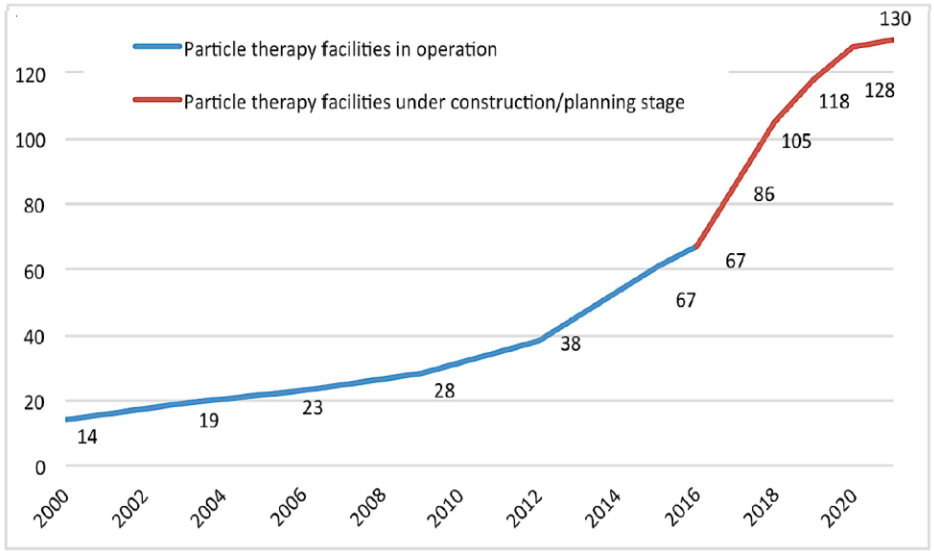


C

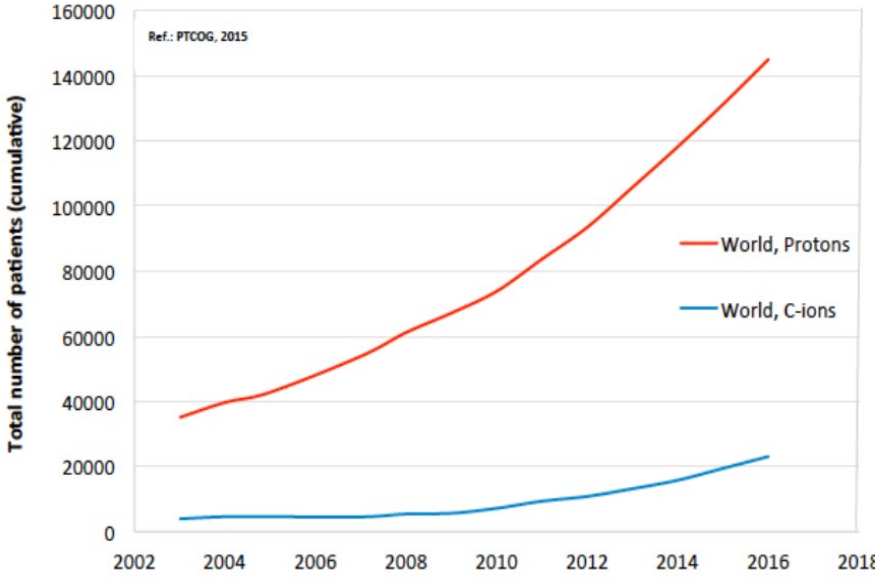
History of particle therapy



Increase of ion therapy facilites



[1]



[2]

Currently: 112 facilities in operation worldwide
37 facilities under construction
29 facilities in planning stage

>200 000 patients were treated
<1% compared to radiotherapy with photons

[1] PTCOG – Facilities in Operation. Accessed from https://www.ptcog.ch/index.php/facilities-in-operation
[2] PTCOG – Patient statistics. Accessed from https://www.ptcog.ch/index.php/patient-statistics

Let's start from the beginning…

What about everyday life radiation?

Radiation exposure in everyday life

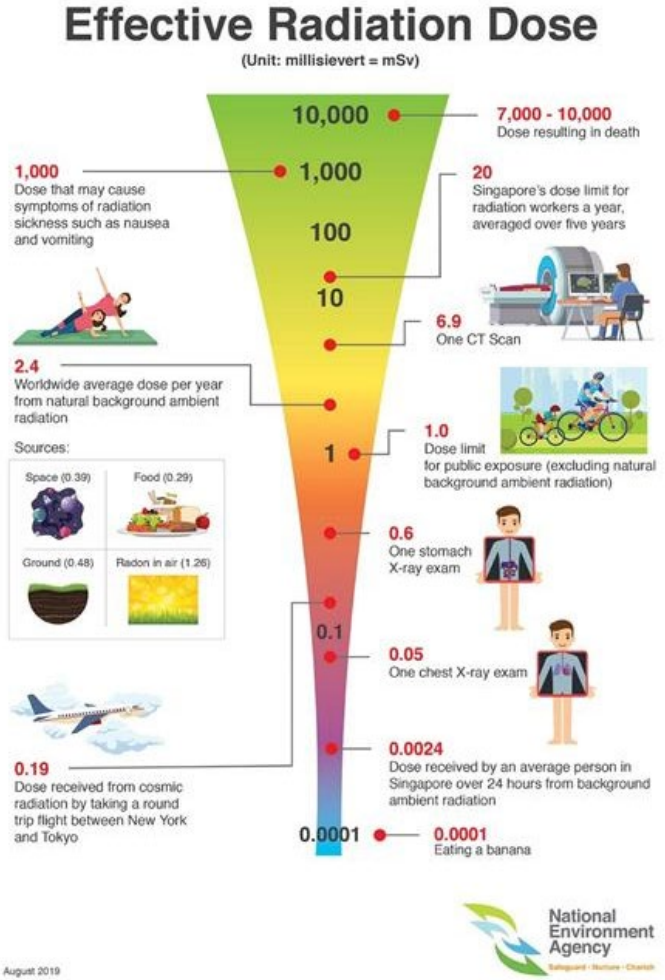
- Generally known: body dose

- given and measured in Sievert
- considers the sensitivity of the respective organ and radiation type
- cosmic and terrestrial radiation
- medical and technical applications
- diverse loads (e.g. flight travels)

Banana equivalent dose:

0.4 gram potassium consists to
0.01% of the radioactive potassium isotope K-40
1000 bananas in 8 hours → 0.1 mSv

Average dose: 4 mSv per year



Dose in radiotherapy

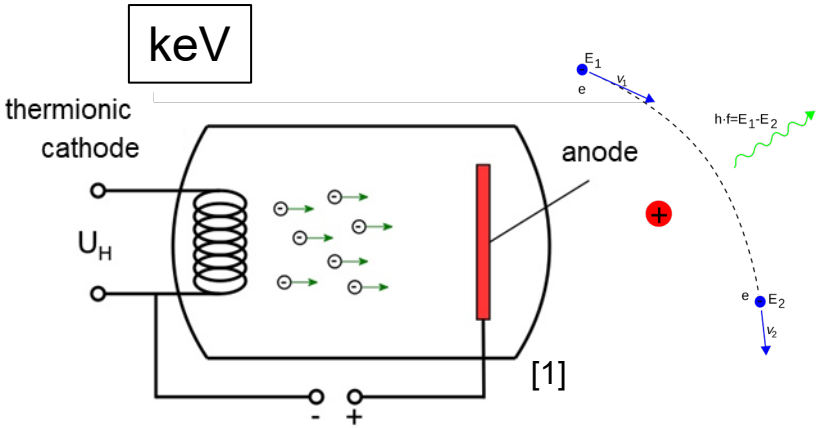
- We need local information in radiotherapy (we do not irradiate everything)
- Absorbed dose (its biological effect is not considered):
  - energy absorption ΔE per mass element $\Delta m = \rho \Delta V$

$$D = \frac{\Delta E}{\Delta m} = \frac{1}{\rho}\frac{\Delta E}{\Delta \mathrm{V}}$$

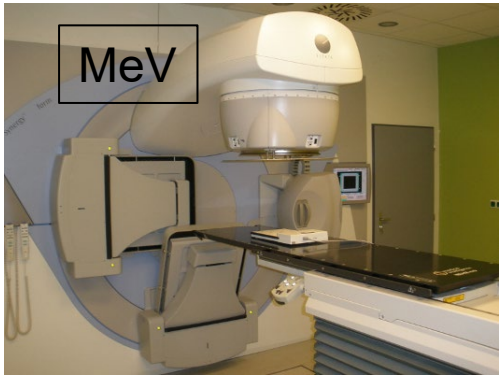
- High energy release ionizes atoms and breaks down chemical bounds or forms new ones
  → damage to DNA → cell death
  → but to achieve that, radiation has to be artificially created and applied in a targeted manner

Generation of high-energy photons

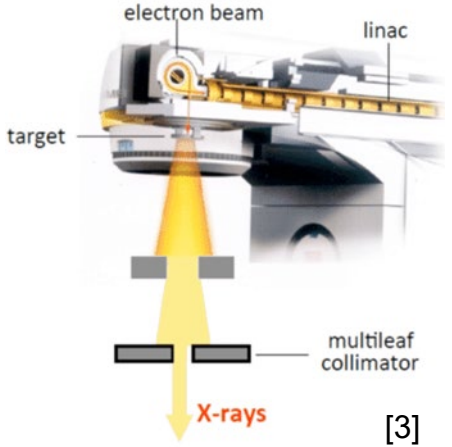
- photons are massless, have no electric charge and travel always at the speed of light
- No “acceleration, but frequency dependent energy”
- But: We can accelerate electrons!



[1]



[2]



[3]

tungsten target
→ bremsstrahlung

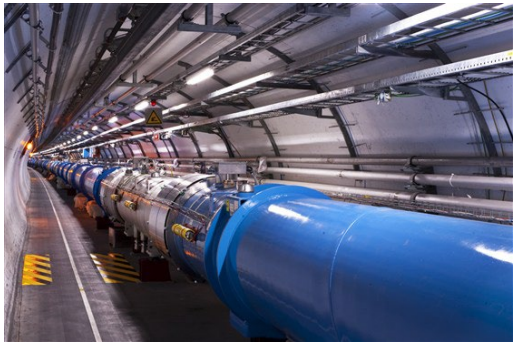
→ electrons loose energy due to bremsstrahlung → **high-energy photons**

[1] Physikunterricht-Online.de – Elektronen im elektrischen Feld. Accessed from https://physikunterricht-online.de/jahrgang-11/elektronen-im-elektrischen-feld/ on 12.02.2021, lettering was adapted
[2] Mouzi (https://commons.wikimedia.org/wiki/File:Linac.jpg), „Linac“, https://creativecommons.org/licenses/by-sa/3.0/legalcode
[3] ResearchGate – Figure – The linac (a), the magnets that deflect the electron beam by 270°.
Accessed from https://www.researchgate.net/figure/The-linac-a-the-magnets-that-deflect-the-electron-beam-by-270-the-target-and-the_fig3_335972529 on 12.02.2021

Particle accelerator

How do we generate high energy protons or ions?

- acceleration due to electric fields
- linear or circular accelerator (depending on the required energy)
- e.g. Large Hadron Collider LHC (CERN)



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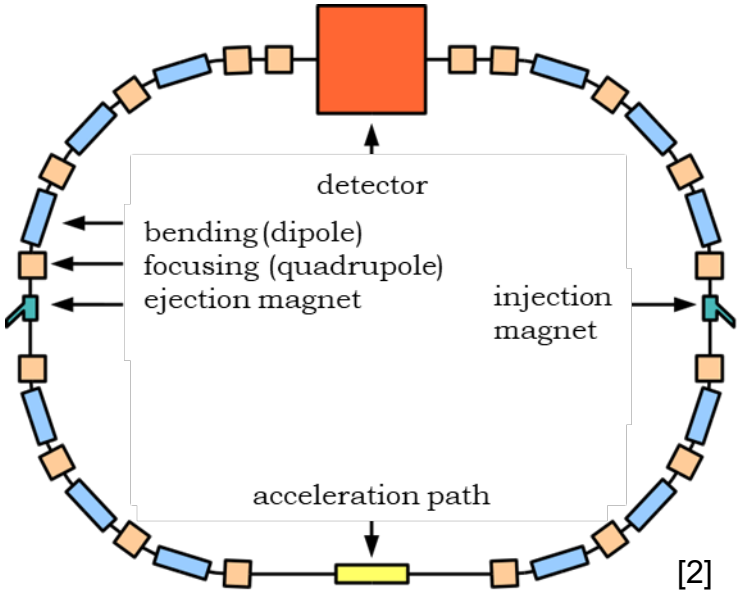
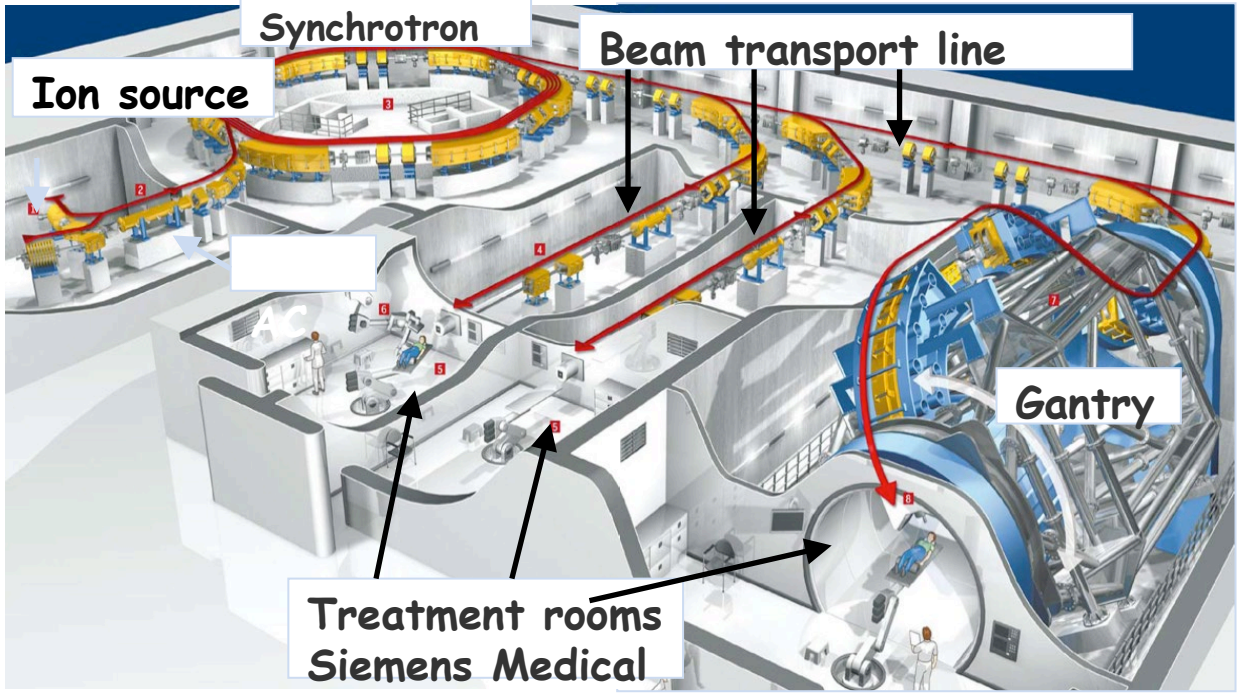


[2]

[1] Maximilien Brice (https://commons.wikimedia.org/wiki/File:CERN_LHC.jpg), https://creativecommons.org/licenses/by-sa/4.0/legalcode
[2 No machine-readable author provided. Florian DO assumed (based on copyright claims). (https://commons.wikimedia.org/wiki/File:Storage_ring_de.svg), „Storage ring de“, lettering was adapted, https://creativecommons.org/licenses/by-sa/3.0/legalcode

Large accelerators are necessary

- Heidelberg Ion-Beam Therapy Center (HIT)

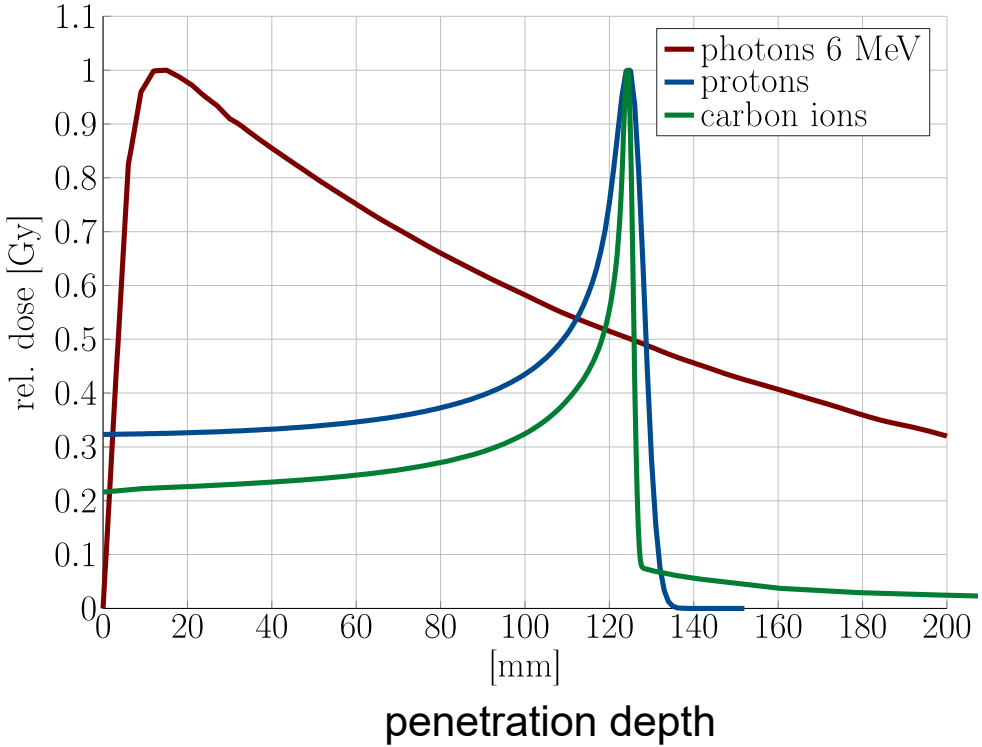


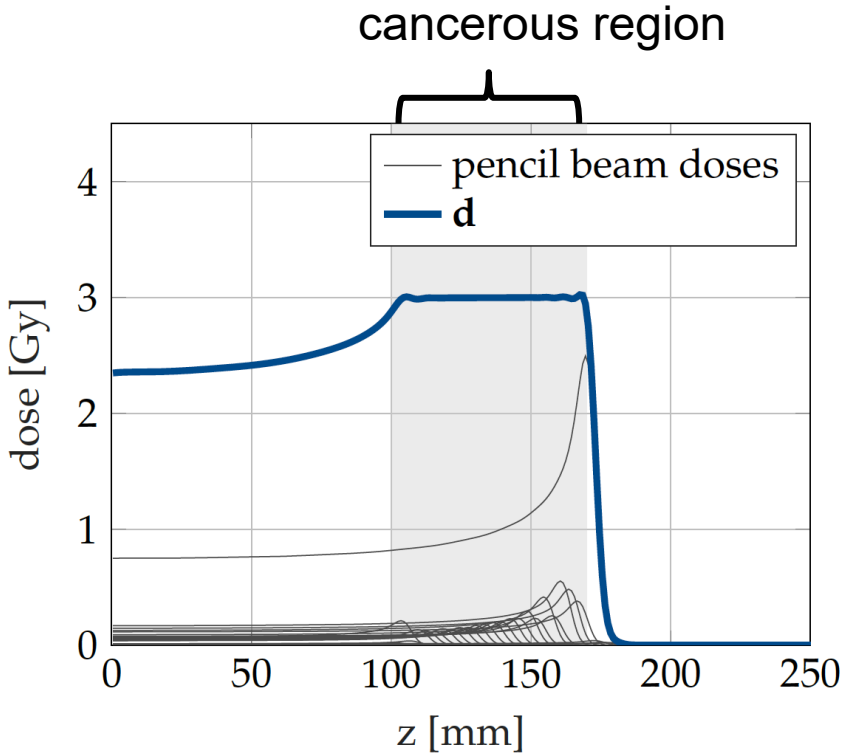
[1]

- First carbon facility with a gantry
- First patient treatment in 2009

[1] Universitätsklinikum Heidelberg – HIT Broschüre - HIT Ionentherapieanlage. Accessed from https://www.klinikum.uni-heidelberg.de/fileadmin/hit/dokumente/HIT_Broschuere.pdf on 12.02.2021

Why bother with particle therapy?

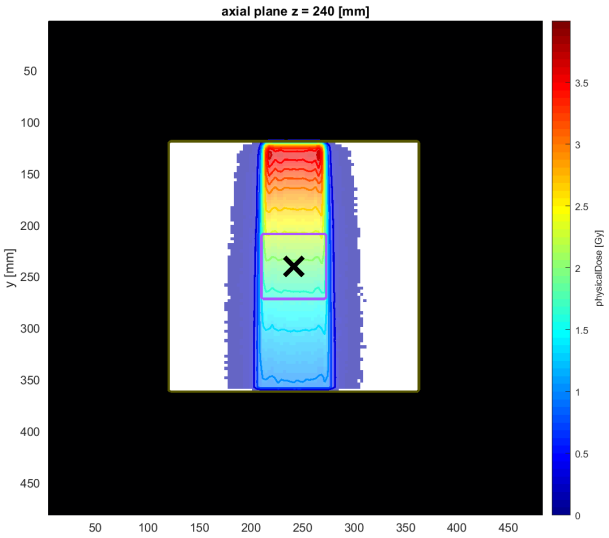




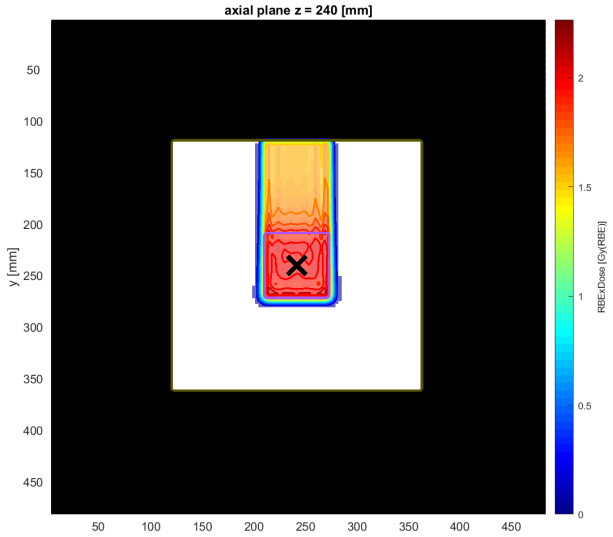
Why bother with particle therapy?

- We always risk damaging healthy tissue “on the way”...

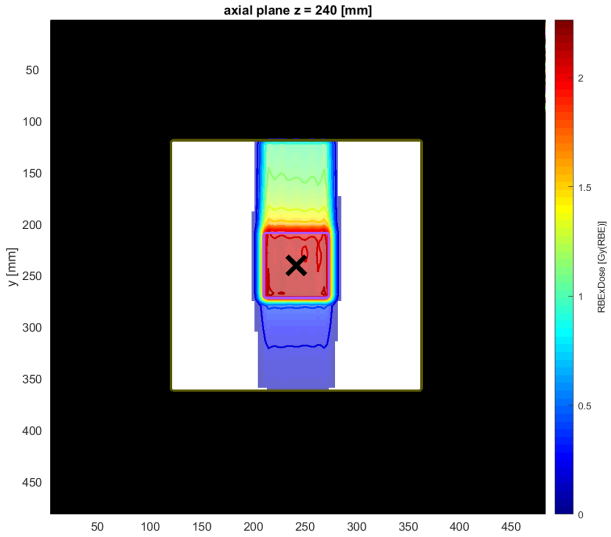
photons



protons



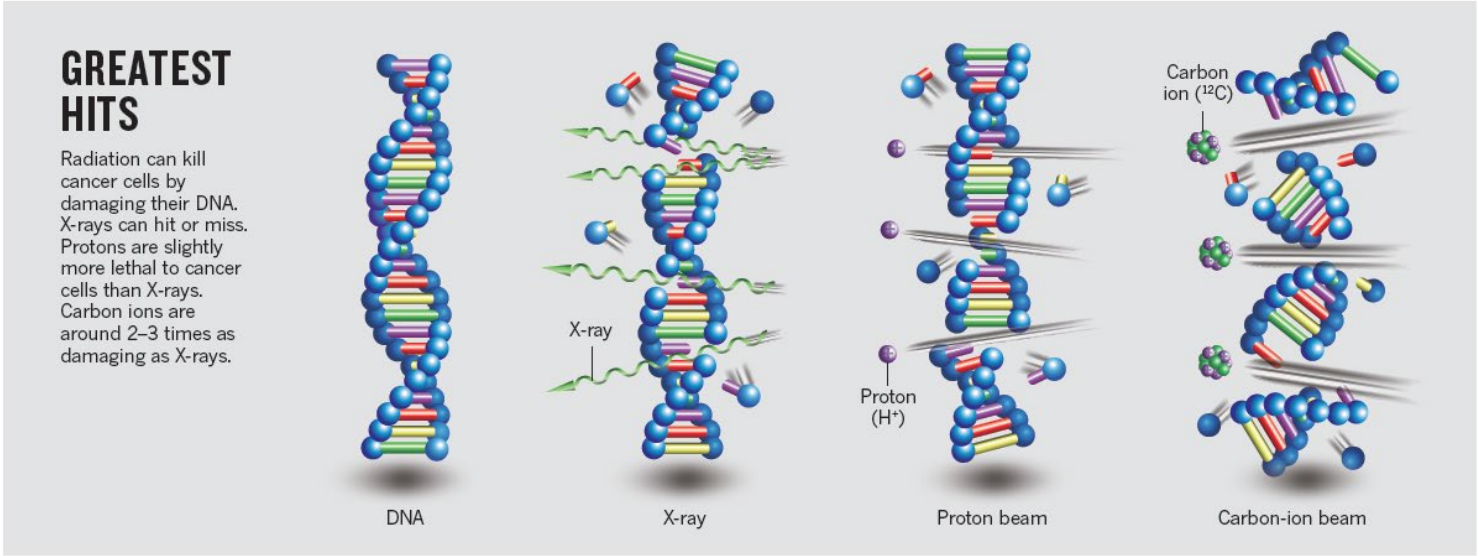
carbon ions



.... but it looks quite good for a particle beam ☺

Why bother with carbon ions?

photons protons carbon ions



[1]

- Energy release is **localized** to a varying extent. ^{12}C is 12 times heavier than p^+
- Heavy ions generate locally more severe damage → more difficult to repair

[1] Marx, V. (2014, April 4). Sharp shooters. 508. Nature, p. 137.

Open Issues from Clinical/Research Perspective

- 1-Need for better functional imaging (MRI/PET) of cancer to understand radioresistance part.
- 2-Toxicity is a limiting factor in how we treat cancer, limiting our ability to cure, new technologies such as FLASH, SFRT etc could help.
- 3-Cost of technology, is to high and complexity to difficult to adopt in 3rd world countries
- 4-Training of medical physicists can taking 5 years, in a clinical environment, virtual reality can optimize and reduce this
- 5-Patient data analysis is not easy due to all the data protection issues limit our ability to learn from current patient data.

- **Questions?**

[1]

[1] Gage Skidmore from Peoria, AZ, United States of America (https://commons.wikimedia.org/wiki/File:Captain_Jack_Sparrow_(5763467649).jpg), „Captain Jack Sparrow (5763467649)“, https://creativecommons.org/licenses/by-sa/2.0/legalcode

Cancer - incidence

Cancer incidence worldwide

14 million new cases of cancer in **2012** [1]

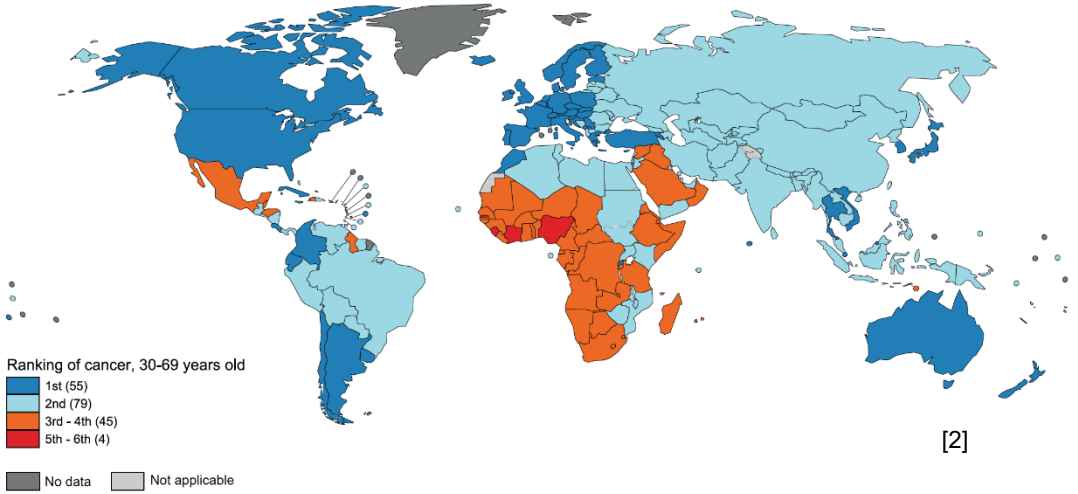
8 million deaths due to cancer in **2012** [1]

19 million new cases of cancer in **2020** [2]

10 million deaths due to cancer in **2020** [2]

2.3 million deaths **linked to corona**

28.4 million new cases of cancer in **2040** [2]
How many deaths in 2040?



[2]

Dark blue: Cancer is the leading cause of premature death

Cancer incidence national

- **500 000** new cases of cancer in Germany every year [3,4], 2.5 times the population of Mainz
- rising tendency due, among other things, to demographic developments

[1] Stewart, B. W. K. P., and Christopher P. Wild. "World cancer report 2014." (2014).
[2] Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries
[3] RKI, Report on cancer in Germany for 2013/2014, cancer registry data
[4] RKI, Report on cancer in Germany for 2015/2016, cancer registry data