Physics/Biology of Radiation Therapy

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Questions are welcome at any time

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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

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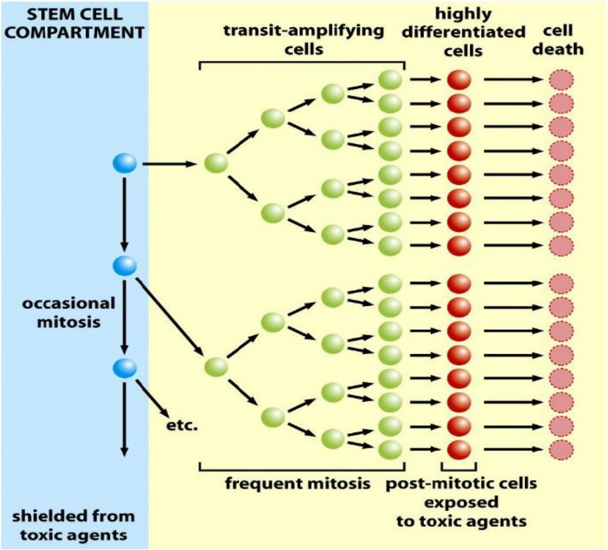
Some Biology…

Tissue organization and protection of the stem cell genome

stem cells can renew themselves through mitotic cell division and can differentiate into a diverse range of specialized cell types

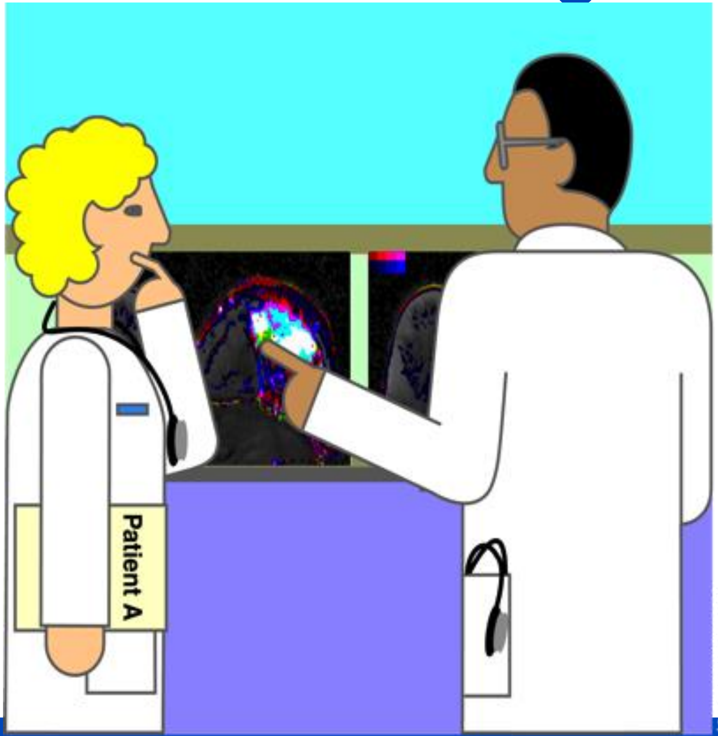
the two broad categories of mammalian stem cells are embryonic stem cells & adult stem cells



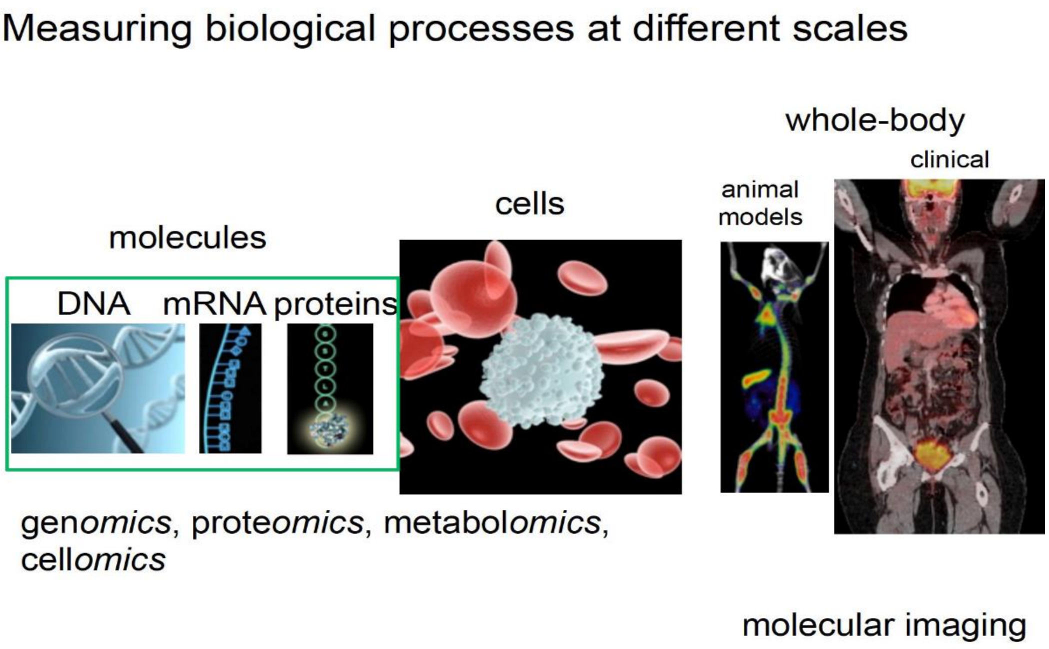
The Biology of Cancer (© Garland Science 2007)

Some Biology…

How is cancer diagnosed?



Patient Diagnostic Evaluation



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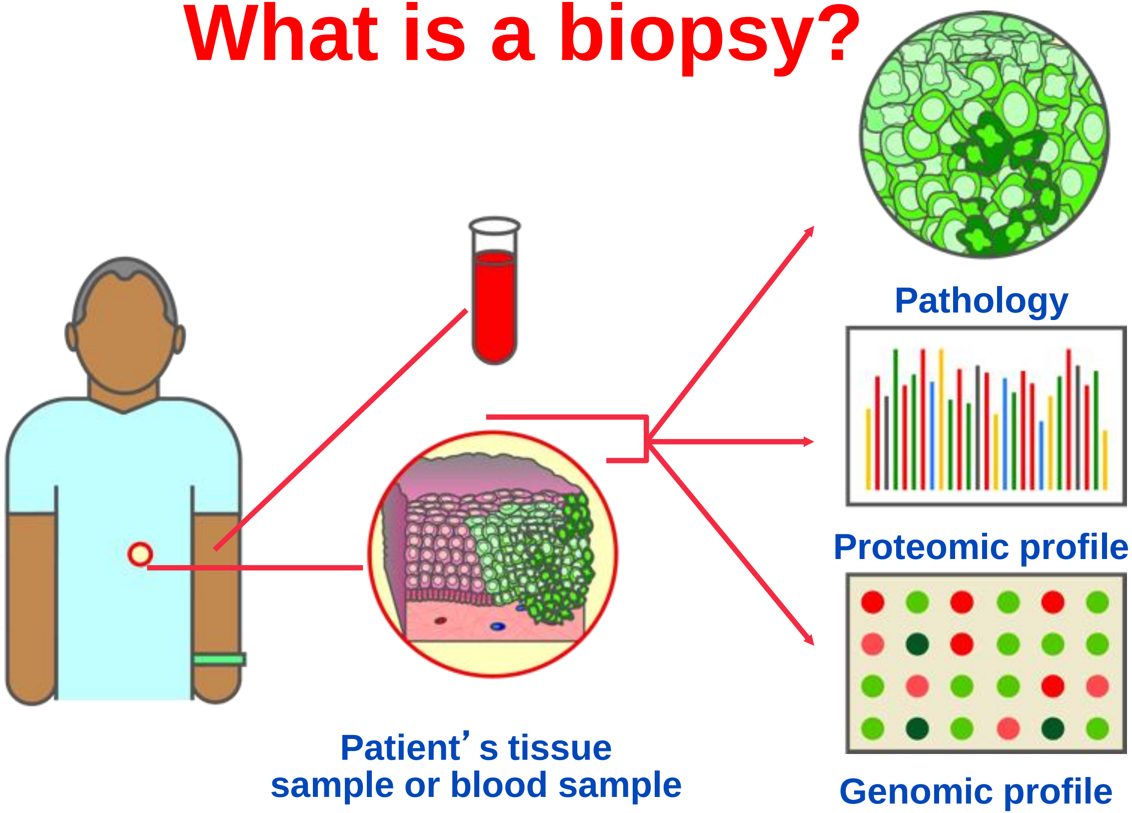
Let‘s start with Biology …

What is a biopsy?



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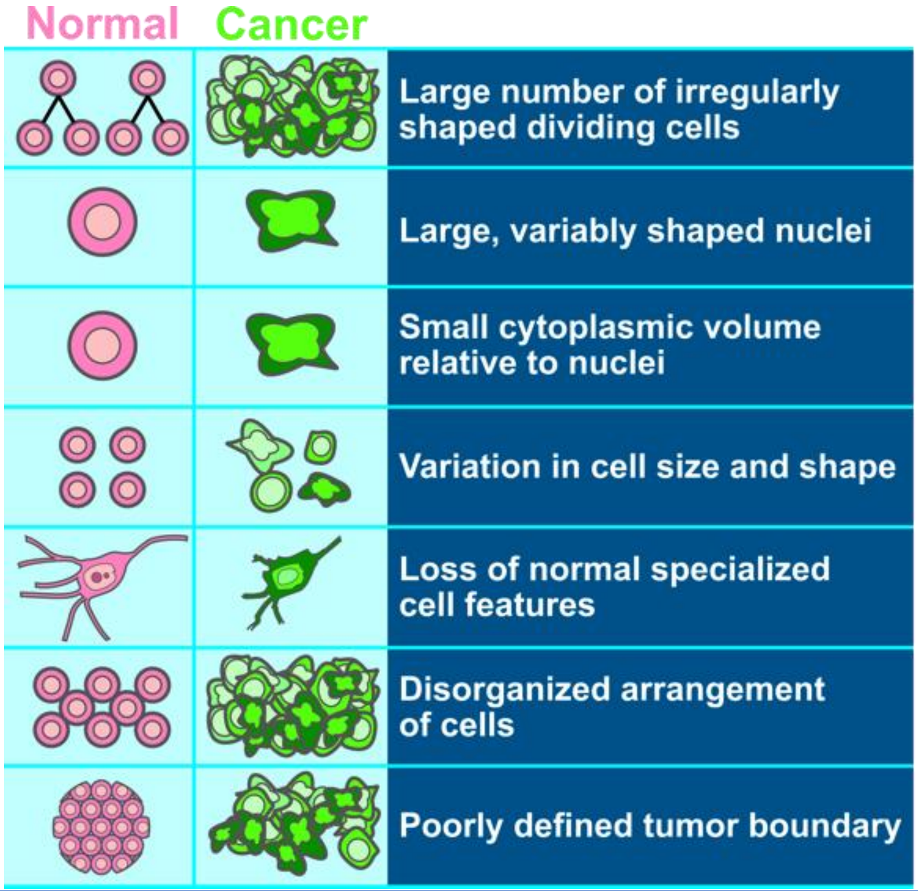
What does a pathologist look for in biopsy tissue?



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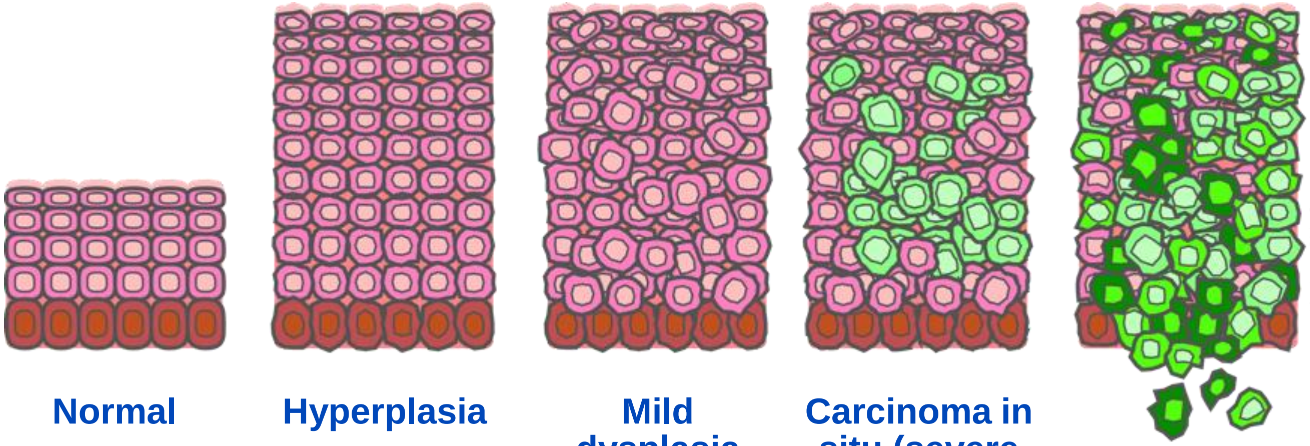
Some more Biology…

How does Cancer look like under the microscope?

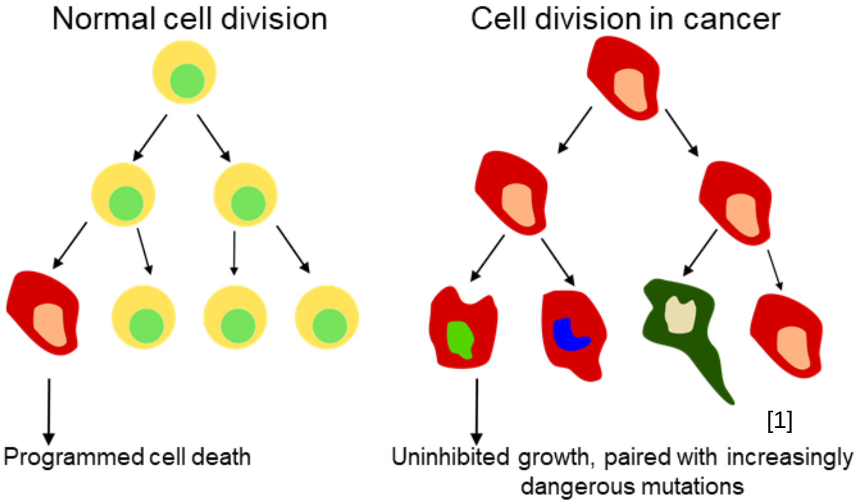


Normal | Hyperplasia | Mild dysplasia | Carcinoma in situ (severe dysplasia) | Cancer (invasive)

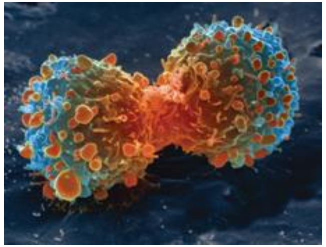
What is Cancer ?

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

healthy cells vs. cancer cells



Cancer cell of a lung tumor during cell proliferation



[2]

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.

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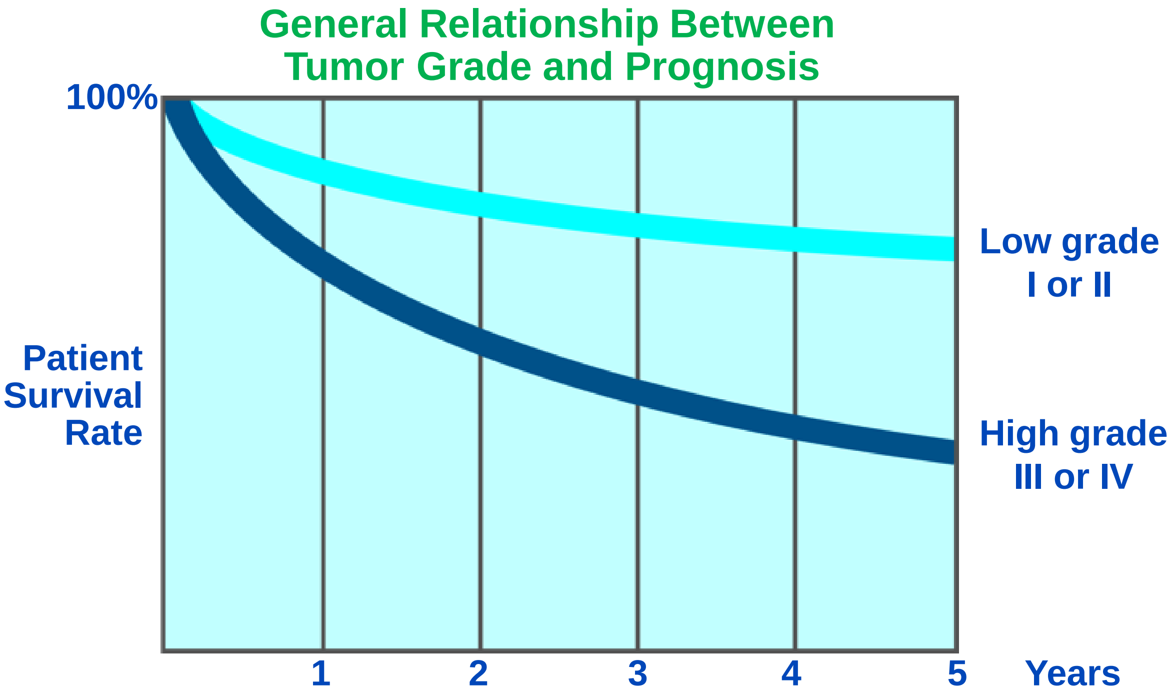
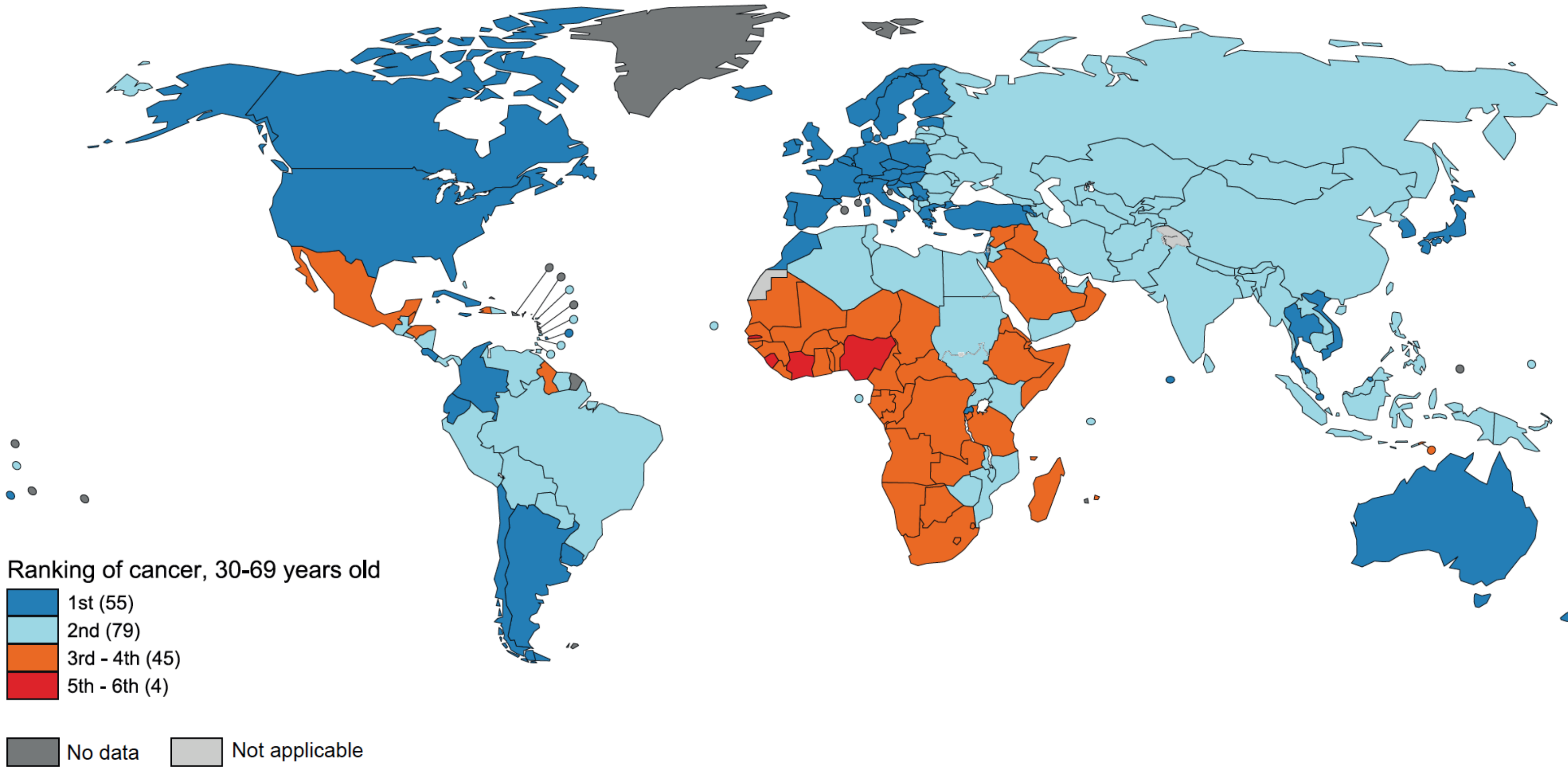
What is the relationship between tumor grade and patient survival?



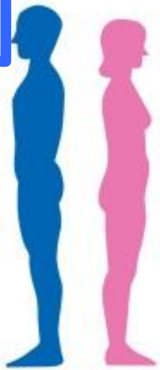
Cancer - incidence



[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

Males			Females		
Prostate	161,360	19%	Breast	252,710	30%
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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%**

Hallmark of Cancer

“Warburg Effect”

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Adequate oxygen

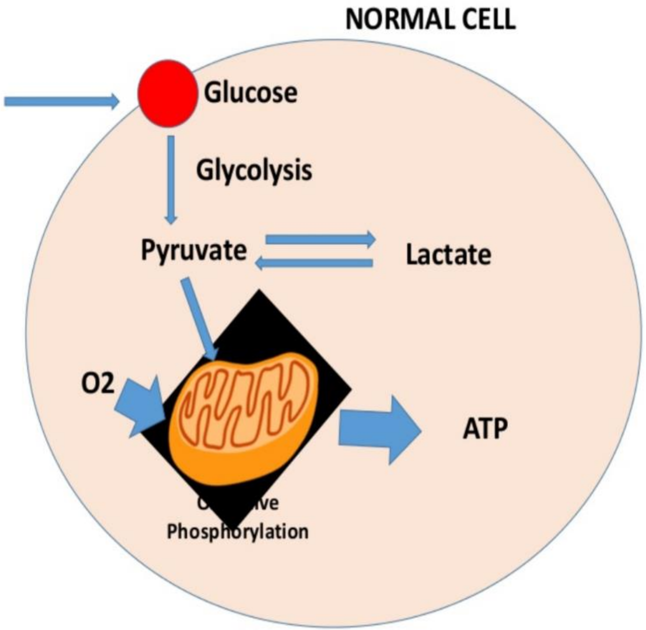
ATP is generated by Oxidative Phosphoryation

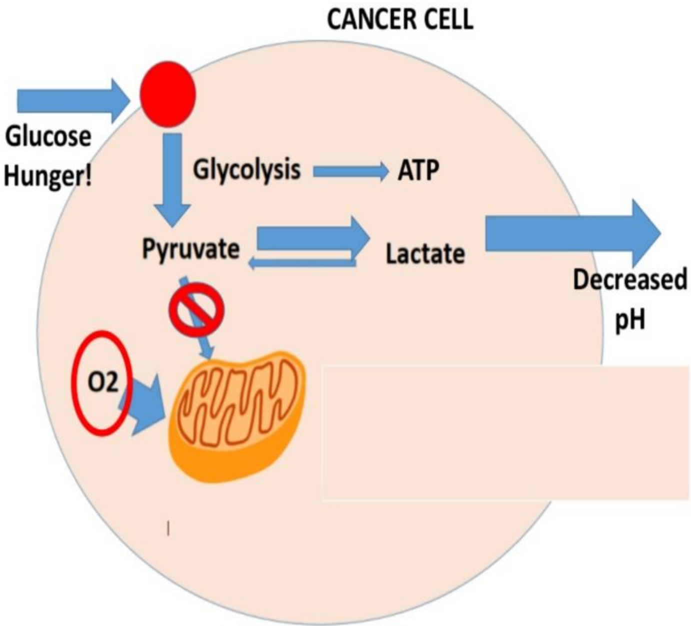
As Oxygen Decreases

Shift from Oxidative phosphorylation to **Glycolysis**

Anaerobic glycolysis

PASTEUR EFFECT





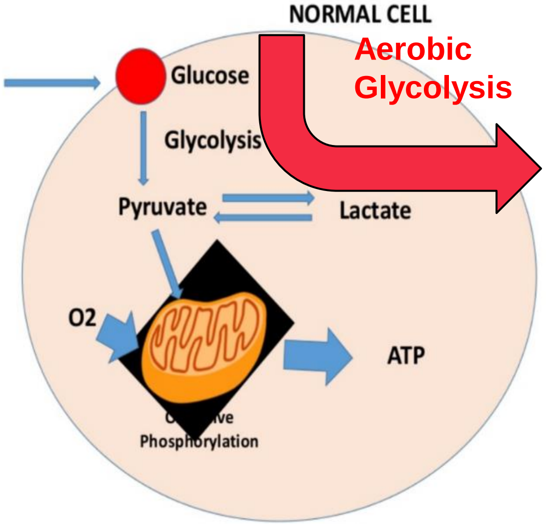
Otto Heinrich Warburg
German Physiologist

Observed that cancer cells had increased rates of glycolysis

Despite the availability of adequate oxygen levels

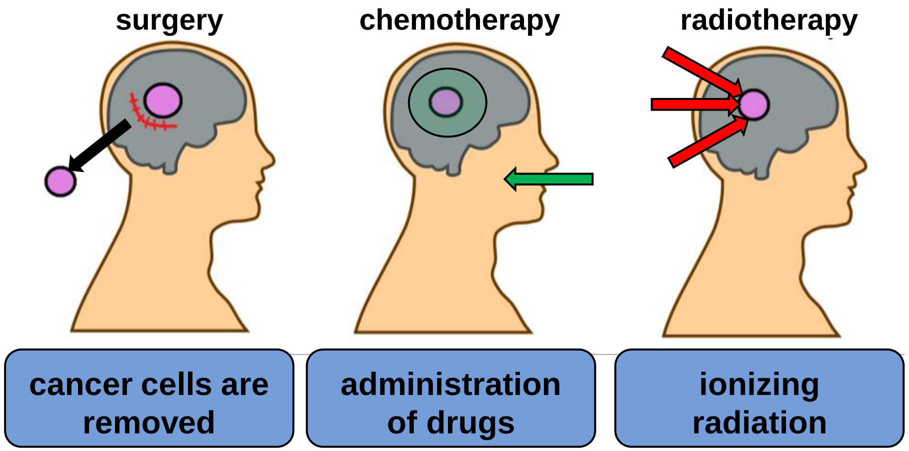
Aerobic glycolysis

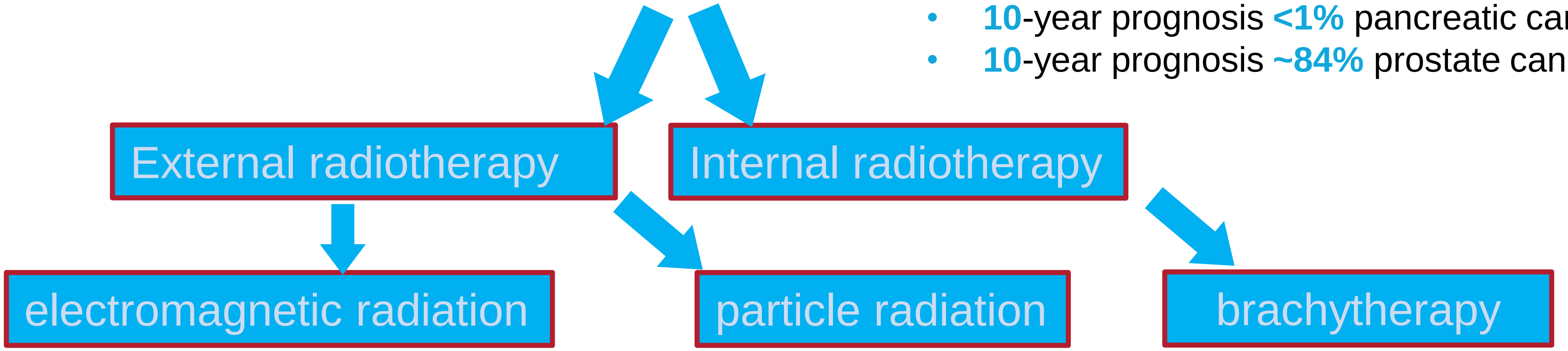
WARBURG EFFECT



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

[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

Radiation
From Small amounts
to
Large Amounts

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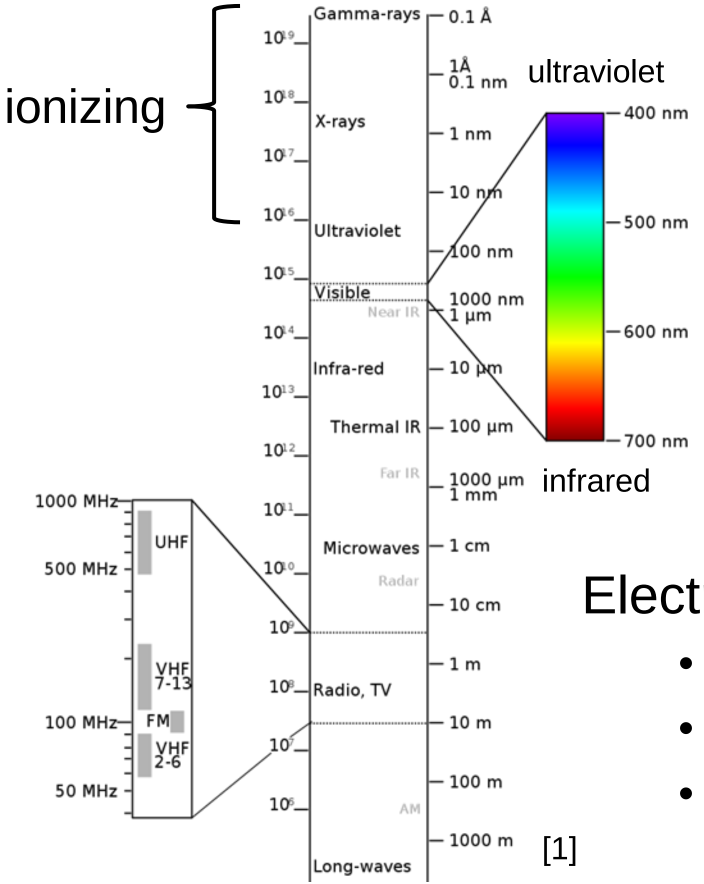
Natural radiation



Spectrum visible
to the
human eye (light)

Electromagnetic radiation - **Photons**

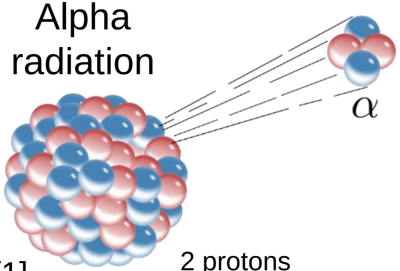
- Gamma rays
- X-rays
- But also: radio, light, microwaves, etc.

[1] !Original: PenubagVector: Victor Blacus (https://commons.wikimedia.org/wiki/File:Electromagnetic-Spectrum.svg), „Electromagnetic-Spectrum“, https://creativecommons.org/licenses/by-sa/3.0/legalcode

Natural radiation

- Particle radiation
  - Alpha radiation – helium nuclei
  - Beta radiation – electrons/positrons
  - Other nuclei/ions (e.g. cosmic radiation)

Alpha radiation

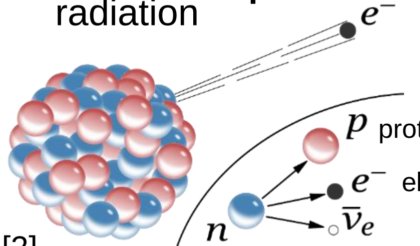


[1]

2 protons
+
2 neutrons

Beta radiation

β-



proton
electron
electron neutrino
neutron

[2]

Types of radioactive decay

Type	Nuclear equation	Representation	Change in mass/atomic numbers
Alpha decay	${}^{A}_{Z}X \quad {}^{4}_{2}He + {}^{A-4}_{Z-2}Y$		A: decrease by 4 Z: decrease by 2
Beta decay	${}^{A}_{Z}X \quad {}^{0}_{-1}e + {}^{A}_{Z+1}Y$		A: unchanged Z: increase by 1
Gamma decay	${}^{A}_{Z}X \quad {}^{0}_{0}\gamma + {}^{A}_{Z}Y$	γ Excited nuclear state	A: unchanged Z: unchanged
Positron emission	${}^{A}_{Z}X \quad {}^{0}_{+1}e + {}^{A}_{Y-1}Y$		A: unchanged Z: decrease by 1
Electron capture	${}^{A}_{Z}X \quad {}^{0}_{-1}e + {}^{A}_{Y-1}Y$	X-ray	A: unchanged Z: decrease by 1

[3]

[1] Inductiveload (https://commons.wikimedia.org/wiki/File:Alpha_Decay.svg), „Alpha Decay“, marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-self
[2] Inductiveload (https://commons.wikimedia.org/wiki/File:Beta-minus_Decay.svg), „Beta-minus Decay“, marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-self
[3] openstax CNX – Radioactive Decay. Accessed from https://cnx.org/contents/IbTLTDQM@1.6:RSq8dk2S@1/Radioactive-Decay on 12.02.2021

Radiation exposure in everyday life

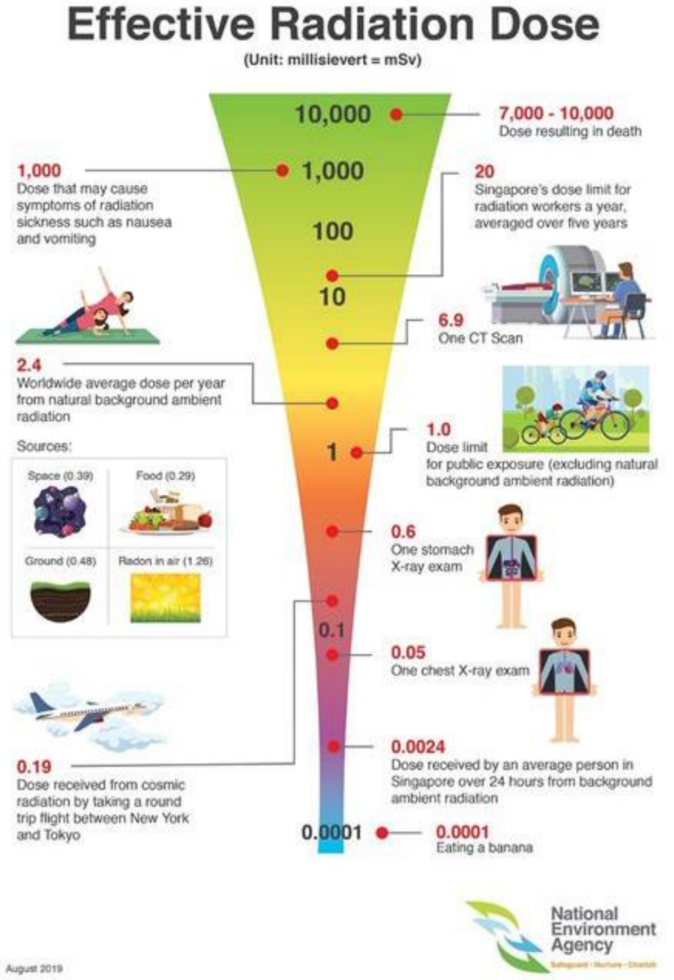
- Generally known: body dose

- 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:

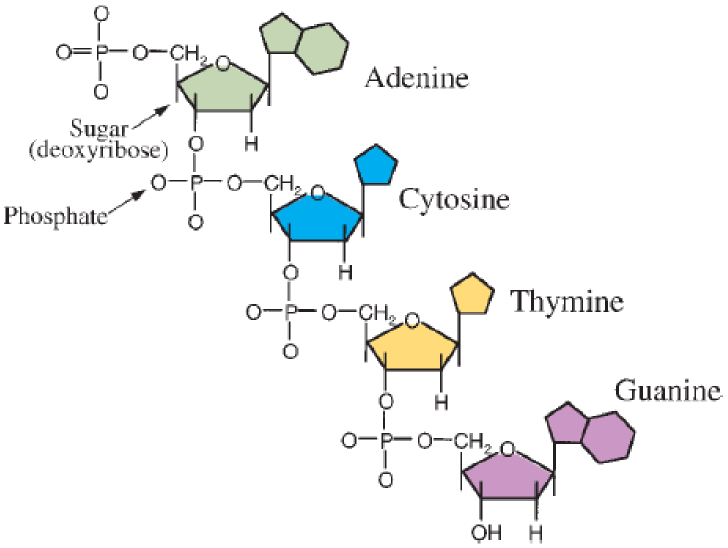
0.4 gram potassium consists to
0.01% of the radioactive potassium isotope K-40
1000 bananas in 8 hours → 0.1 mSv

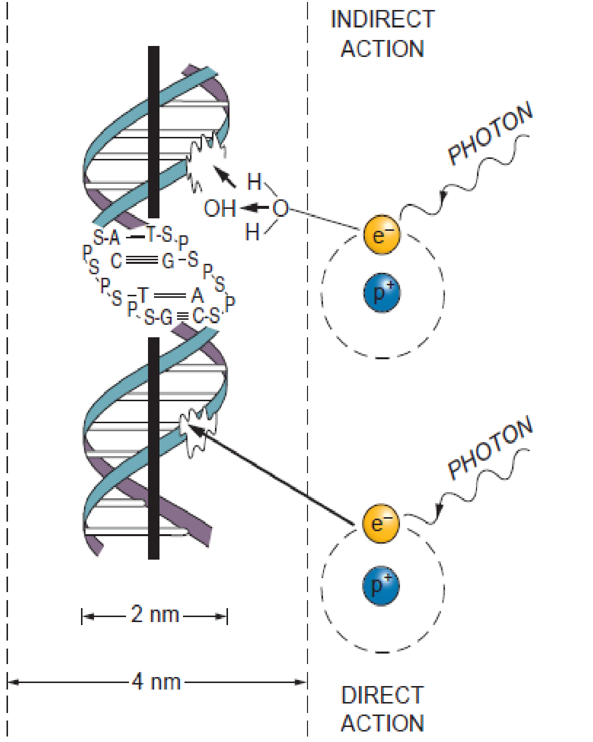
Average dose: 4 mSv per year



DIRECT AND INDIRECT ACTION

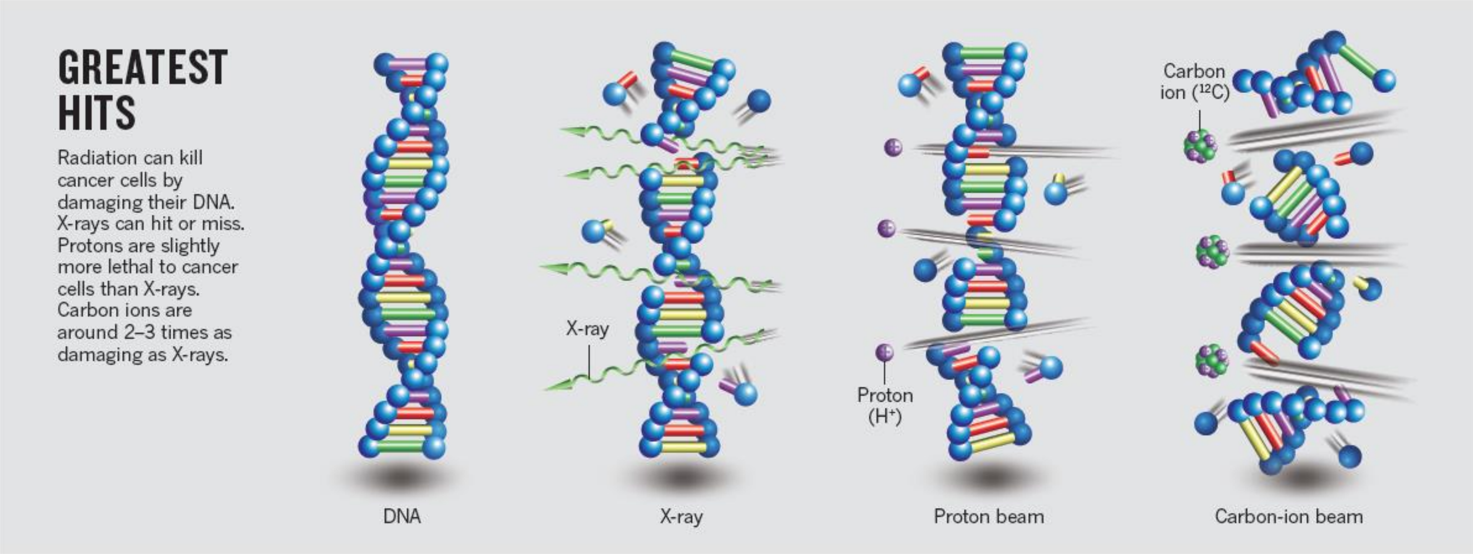
The biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA), which is the critical target, as described





Why bother with carbon ions?

photons protons carbon ions

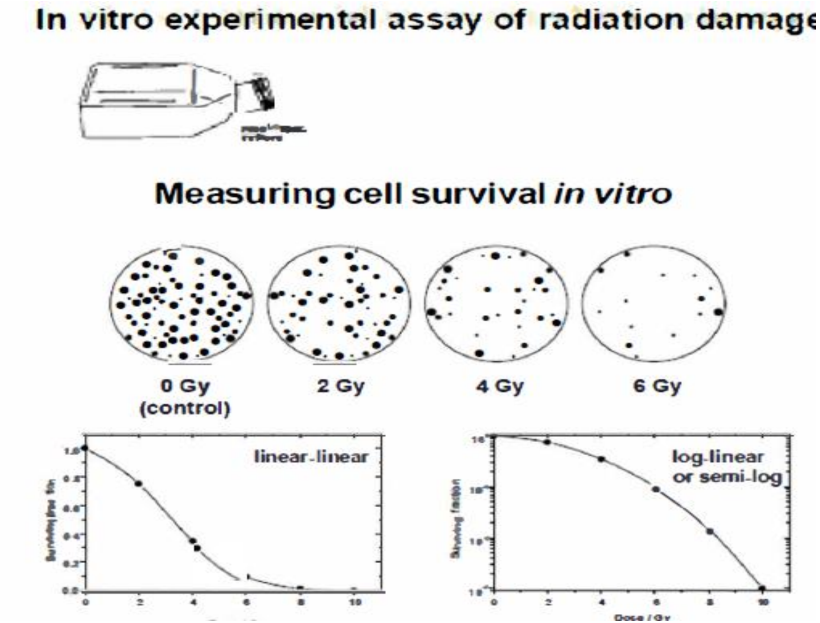


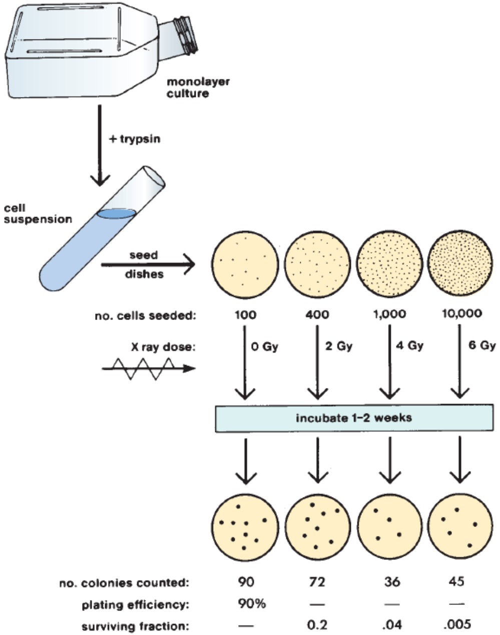
[1]

- 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.

GOLD STANDARD: Cell Survival Curves





- 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

INTRINSIC RADIOSENSITIVITY 117

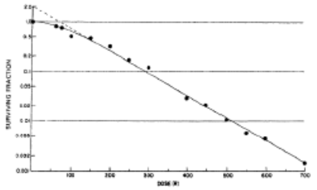


Figure 8.1. Radiation dose–response of human cancer cells in vitro. (Reproduced from Puck and Marcus, 1956, by copyright permission of The Rockefeller University Press.)

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

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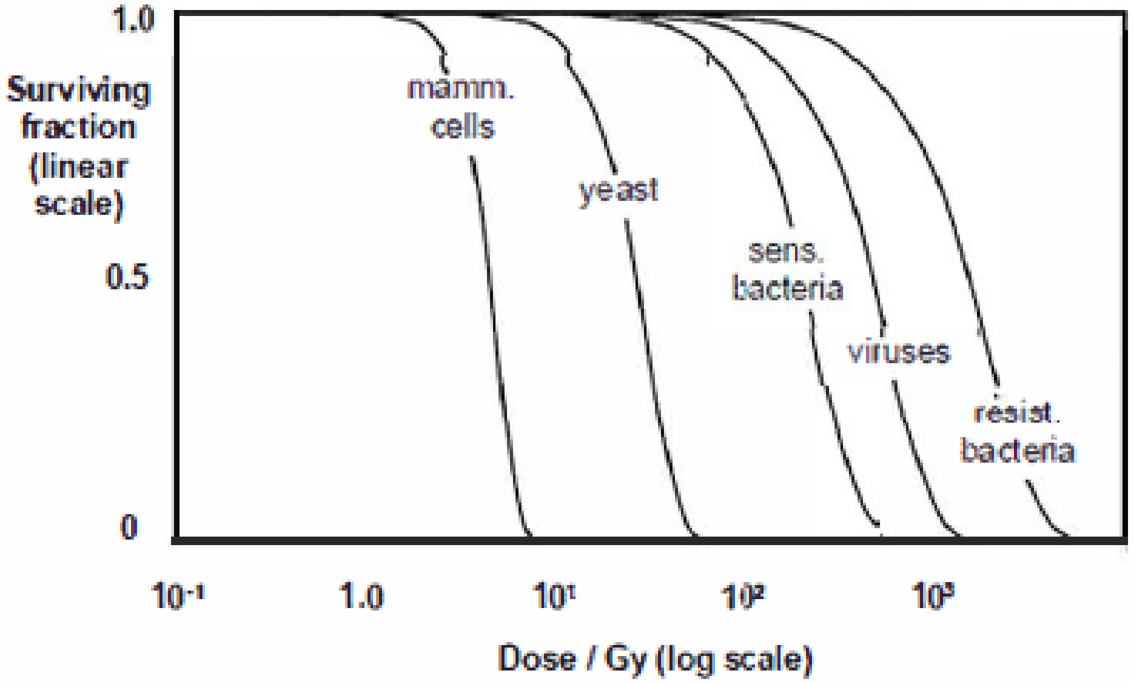
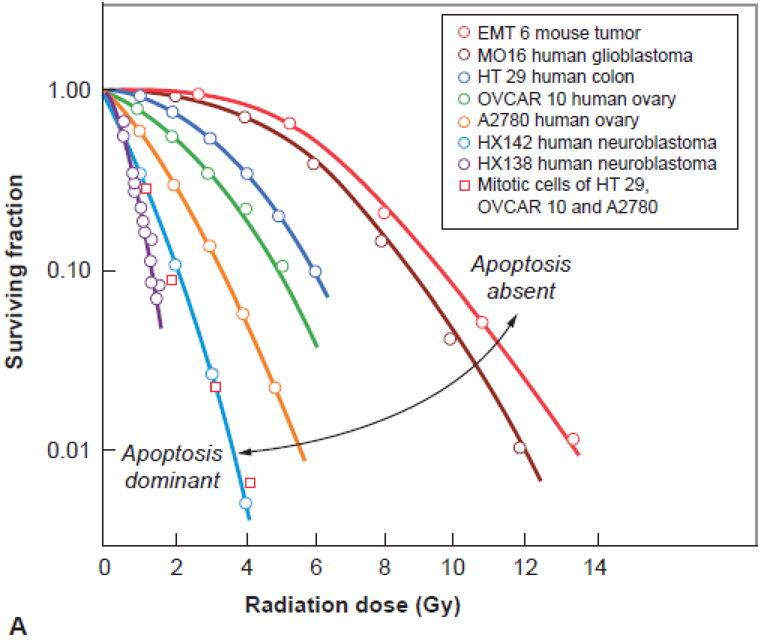
Cell Survival Curves

Survival and radiosensitivity in various systems



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



Linear Quadratic Model (LQM)

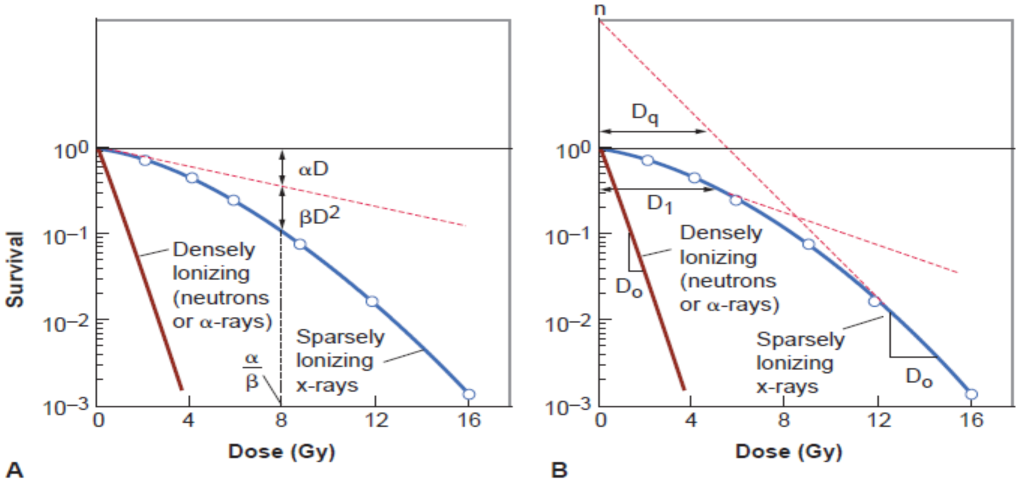
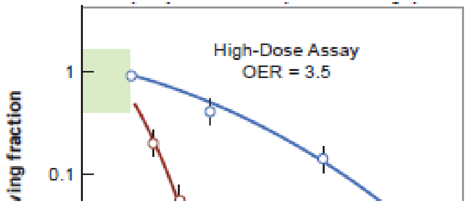
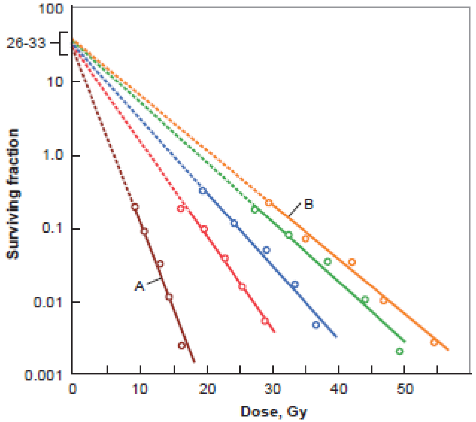


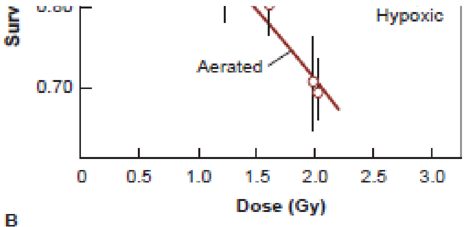
FIGURE 3.3 Shape of survival curve for mammalian cells exposed to radiation. The fraction of cells surviving is plotted on a logarithmic scale against dose on a linear scale. For α-particles or low-energy neutrons (said to be densely ionizing), the dose-response curve is a straight line from the origin (i.e., survival is an exponential function of dose). The survival curve can be described by just one parameter, the slope. For x- or γ-rays (said to be sparsely ionizing), the dose-response curve has an initial linear slope, followed by a shoulder; at higher doses, the curve tends to become straight again. **A:** The linear quadratic model. The experimental data are fitted to a linear-quadratic function. There are two components of cell killing: One is proportional to dose (αD); the other is proportional to the square of the dose (βD^2). The dose at which the linear and quadratic components are equal is the ratio α/β. The linear-quadratic curve bends continuously but is a good fit to experimental data for the first few decades of survival. **B:** The multitarget model. The curve is described by the initial slope (D_1), the final slope (D_0), and a parameter that represents the width of the shoulder, either n or D_q.

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





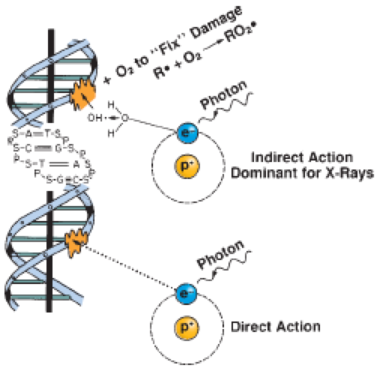


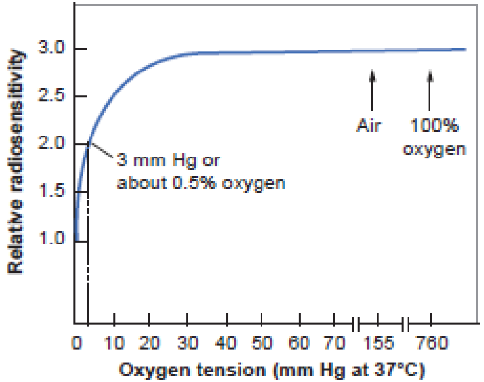
Oxygen is the best known and most general radiation sensitizer.

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

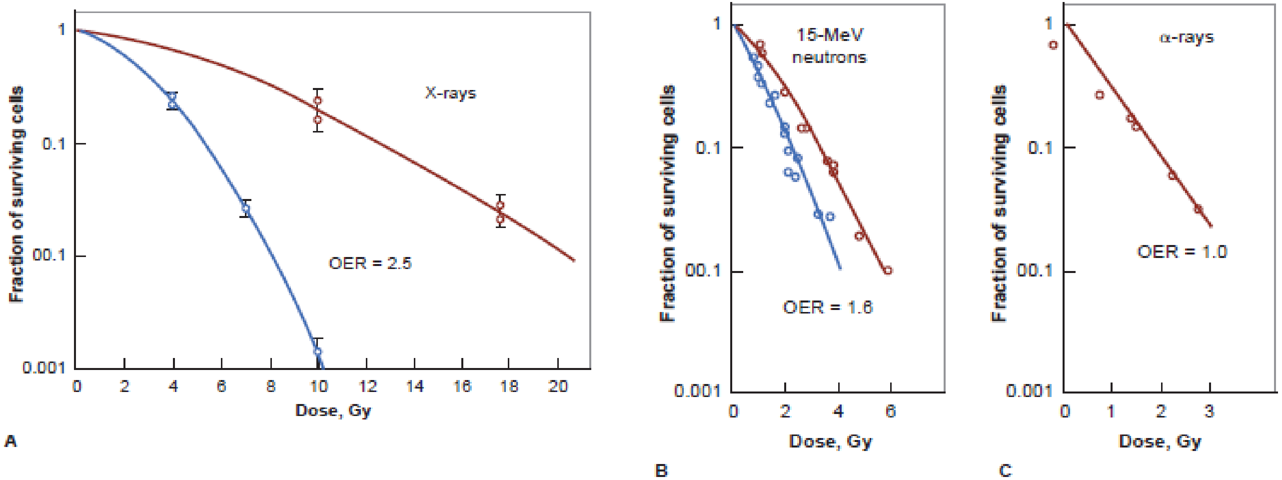
$$OER = \frac{Dose(hypoxia)}{Dose(oxygenated)}$$

Oxygen Fixation Hypothesis (OFH)





Oxygen Effect and LET Dependency



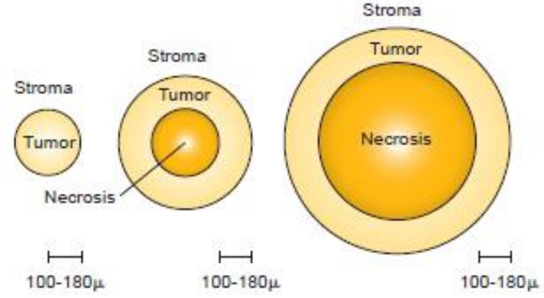
Response to Ionizing Radiation Depends on Radiation Quality

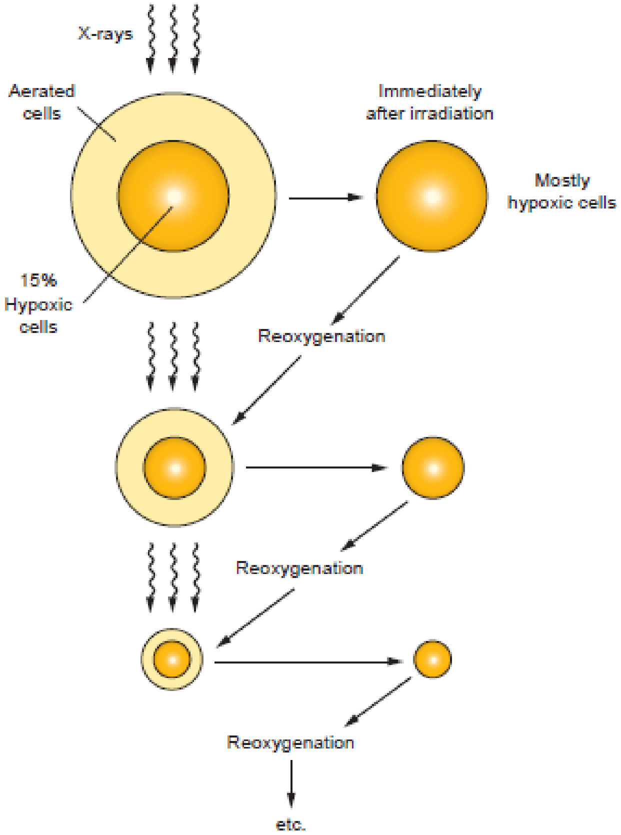
- LET, linear energy transfer = average energy imparted to a medium by a charged particle per unit track length (keV/μm)
  - Low LET: sparsely ionizing (x-rays, γ-rays)
  - High LET: densely ionizing (α-particles, heavy charged ions)

Typical LET Values

Radiation	LET (keV/μm)
Cobalt-60 γ-rays	0.2
250 kVp X-rays	2.0
10 MeV protons	4.7
150 MeV protons	0.5
14 MeV neutrons	12 (track average)
	100 (energy average)
290 MeV Carbon ions	12
2.5 MeV α-particles	166
2 GeV Iron ions	1,000

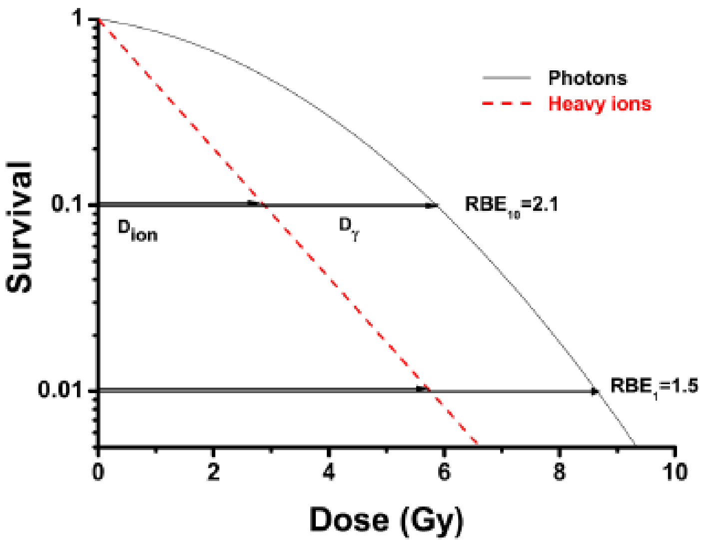
Process of Reoxygenation





Linear Energy Transfer (LET) and RBE

Radiation Type/Quality –Relative Biological Effectiveness (RBE)

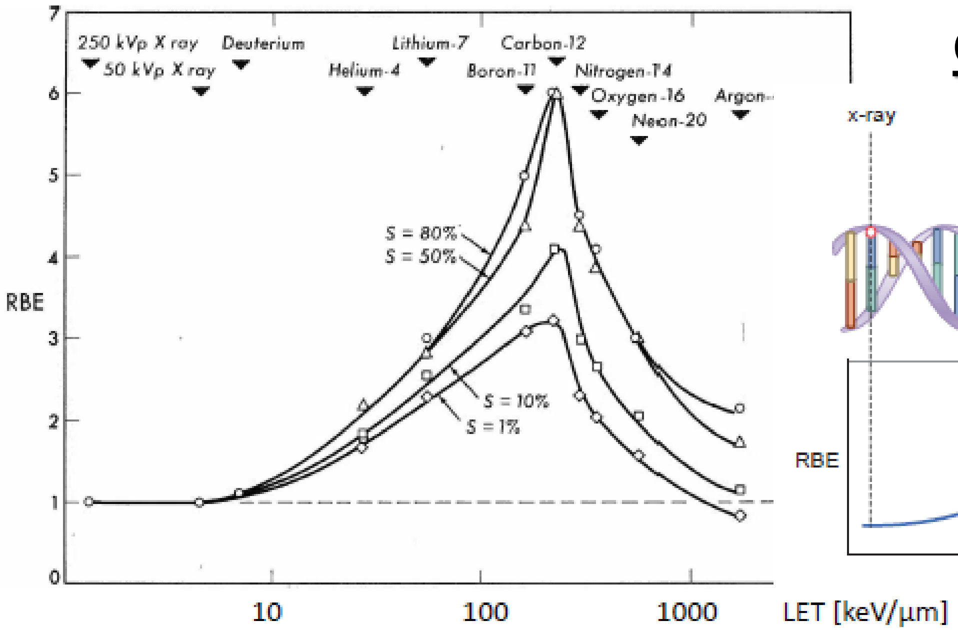


$$RBE = \frac{D_{ref}}{D_{particle}}\Big|_{iso-effect}$$

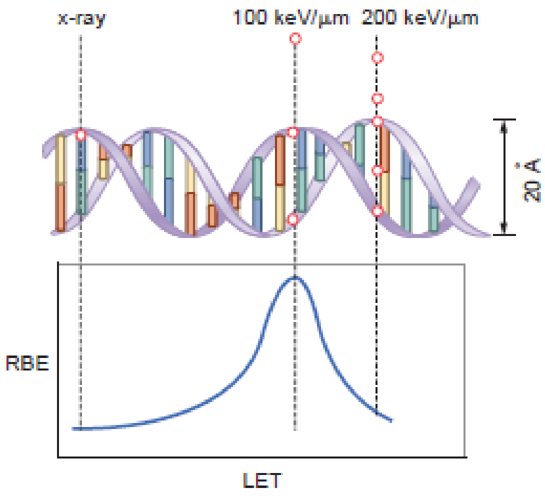
- RBE depends on:
  - Dose
  - Particle Type
  - Cell Line
  - Biological Endpoint
  - LET (Reminder: $LET_{\Delta} = \frac{dE}{dl}_{\Delta}$)

Linear Energy Transfer (LET) and RBE

Quantitative LET-dependency of RBE



Overkill Effect

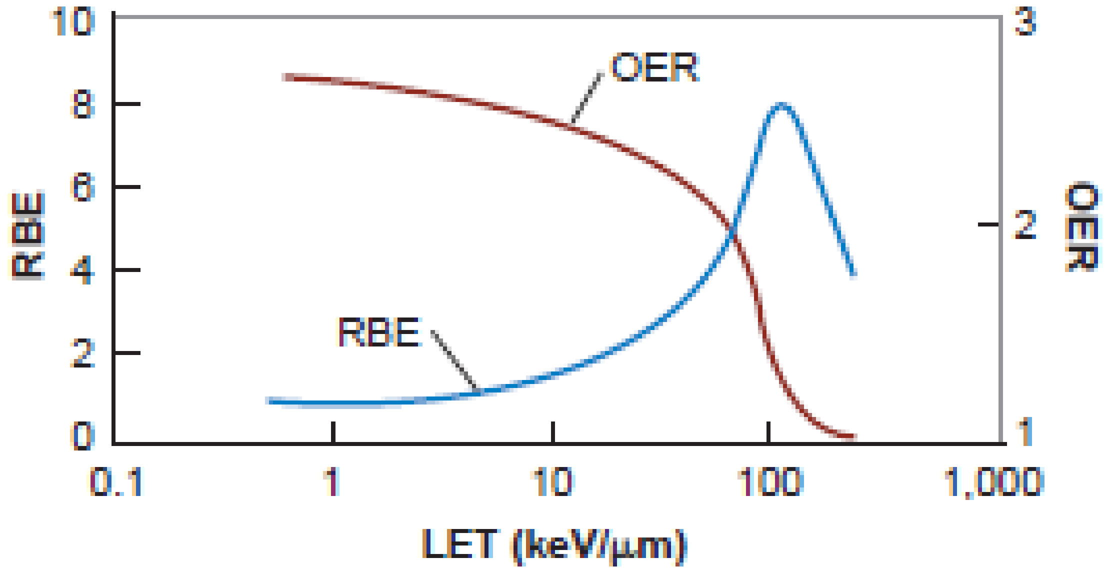


RBE drops after peak due to „Overkill-Effect"

Reminder: $RBE = \frac{D_{ref}}{D_{particle}}\Big|_{iso-effect}$

Linear Energy Transfer (LET), RBE and OER

OER Dependency on LET



Summary

- cancer diseases are characterized by uncontrolled growth of mutated cells
- radiation transfers energy to the tissue in form of elementary physical interactions
  → radiation dose
- energy release ionizes the tissue
  - → breaks down chemical bounds or forms new ones
  - → DNA damage
  - → cell death
- by artificially generating radiation, we can combat cancer cells in a targeted manner
- not without risk for the healthy tissue

  → but high conformity when applying particle beams

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- **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]

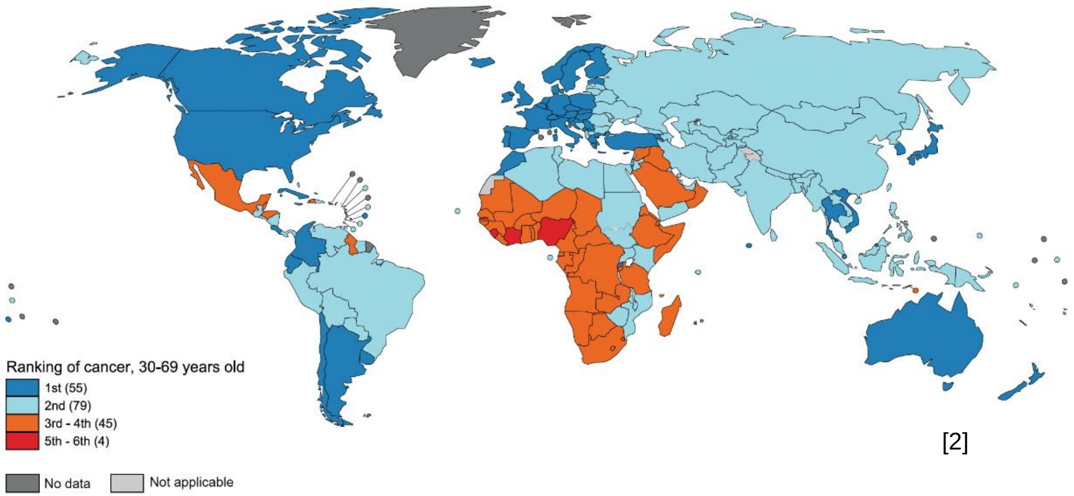
8 million deaths due to cancer in **2012** [1]

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