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with Efficient Ion Accelerator

Image it, then treat it: the basic principles behind cancer theranostics

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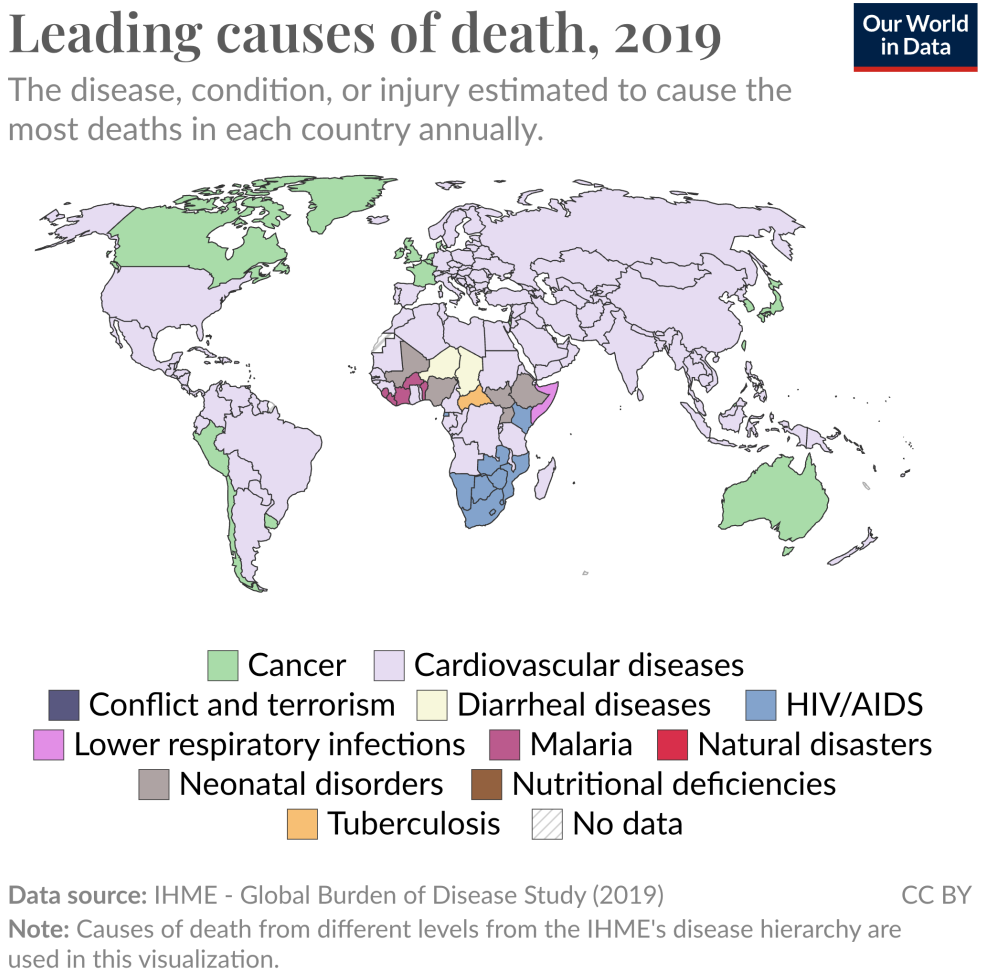
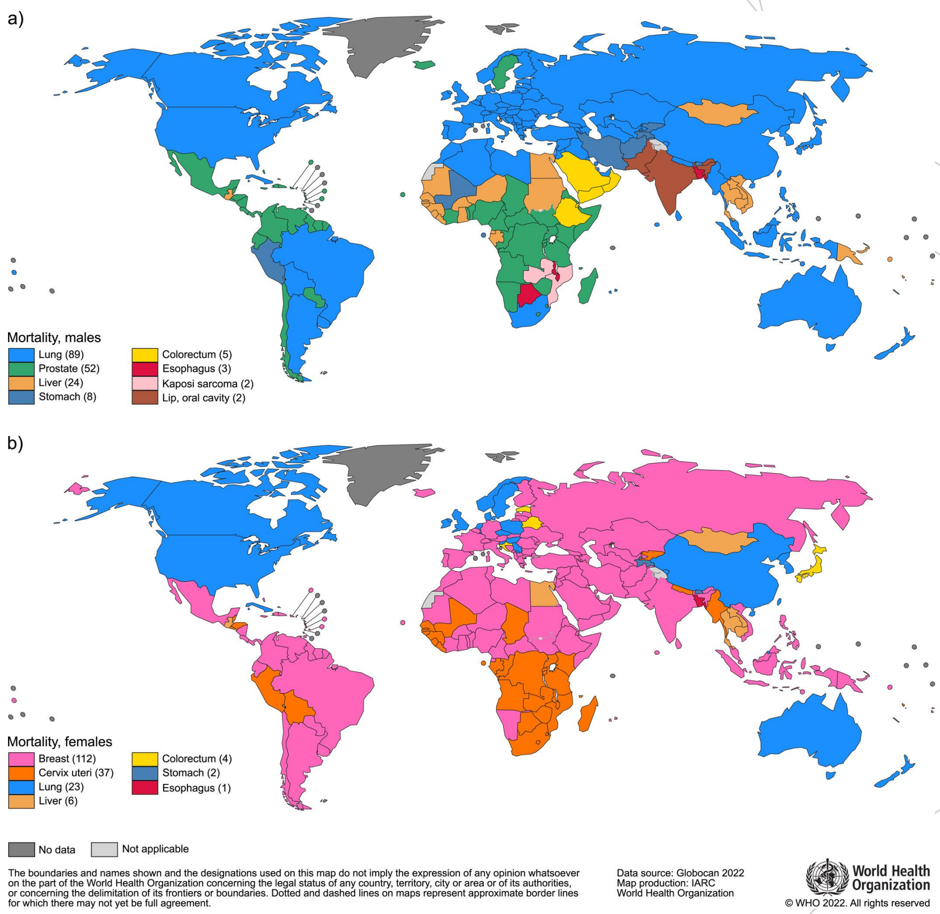
Overview

- Basics of cancer
- How do we fight cancer today – diagnosis & treatment?
- Radiation therapy (external / internal)
- Why radiation works?
- Theranostics

Cancer burden



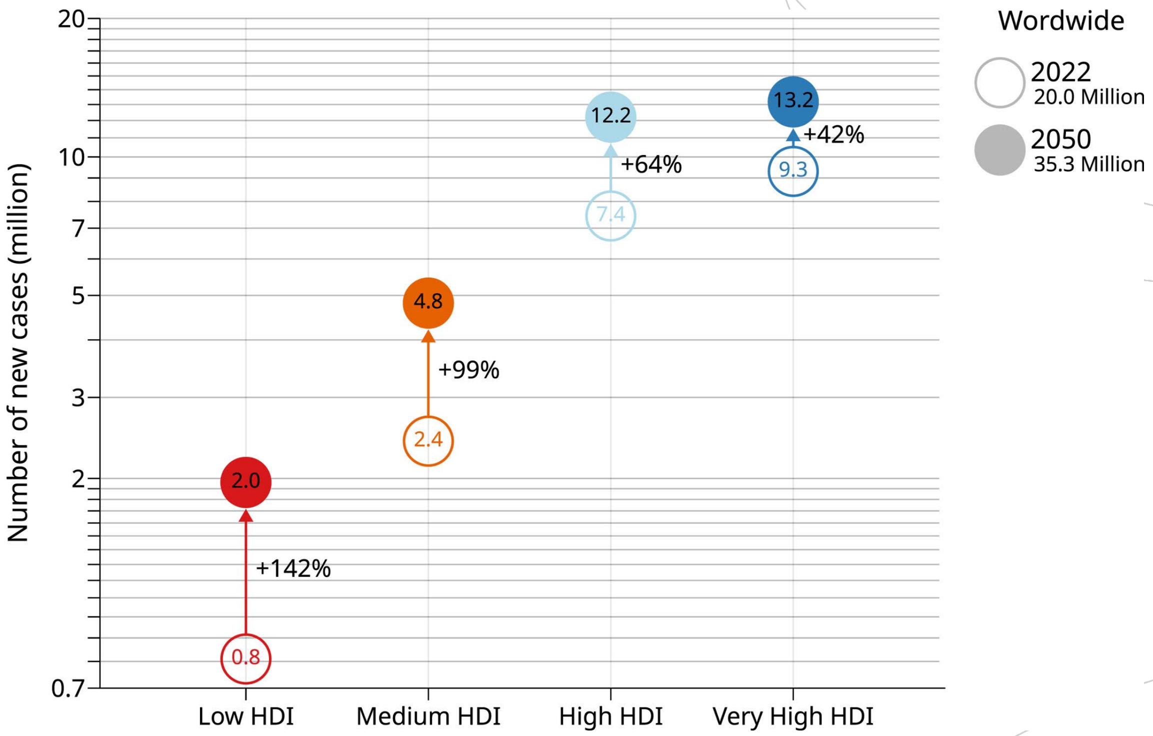


doi: 10.3322/caac.21834

Cancer burden

- **~20 million new cases / year globally** (incidence)
- **~10 million deaths / year**
- **Projected ~35 million cases by 2050**

- **Slovenia:**
  - **1 in 3 will develop cancer by age 75 (born 2022)**
  - **~19.000 new cases (~6.400 deaths) / year**
  - **> 130.000 living with a past cancer diagnosis**
  - **Prostate, lung, breast, colorectal, and skin melanoma**



doi: 10.3322/caac.21834; Register raka RS, OI Ljubljana - 2022

What is cancer?

Uncontrolled cell growth - and why treatment must remove cells manually

Uncontrolled growth

Rampant cell proliferation that does not stop when it should.

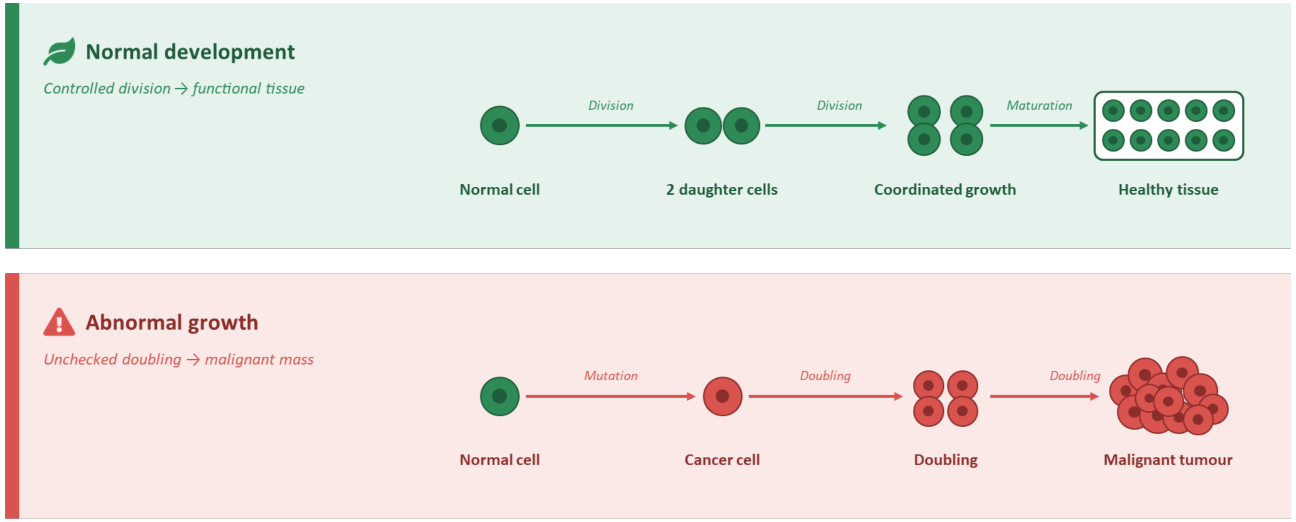
May metastasise

Cancer cells can detach and spread to distant parts of the body.

Over 100 types

Each is biologically distinct, with its own behaviour and treatment.

Healthy cells vs. cancer cells



Key idea: the same starting cell can follow either trajectory — the difference is whether the “stop dividing” signals are still intact.

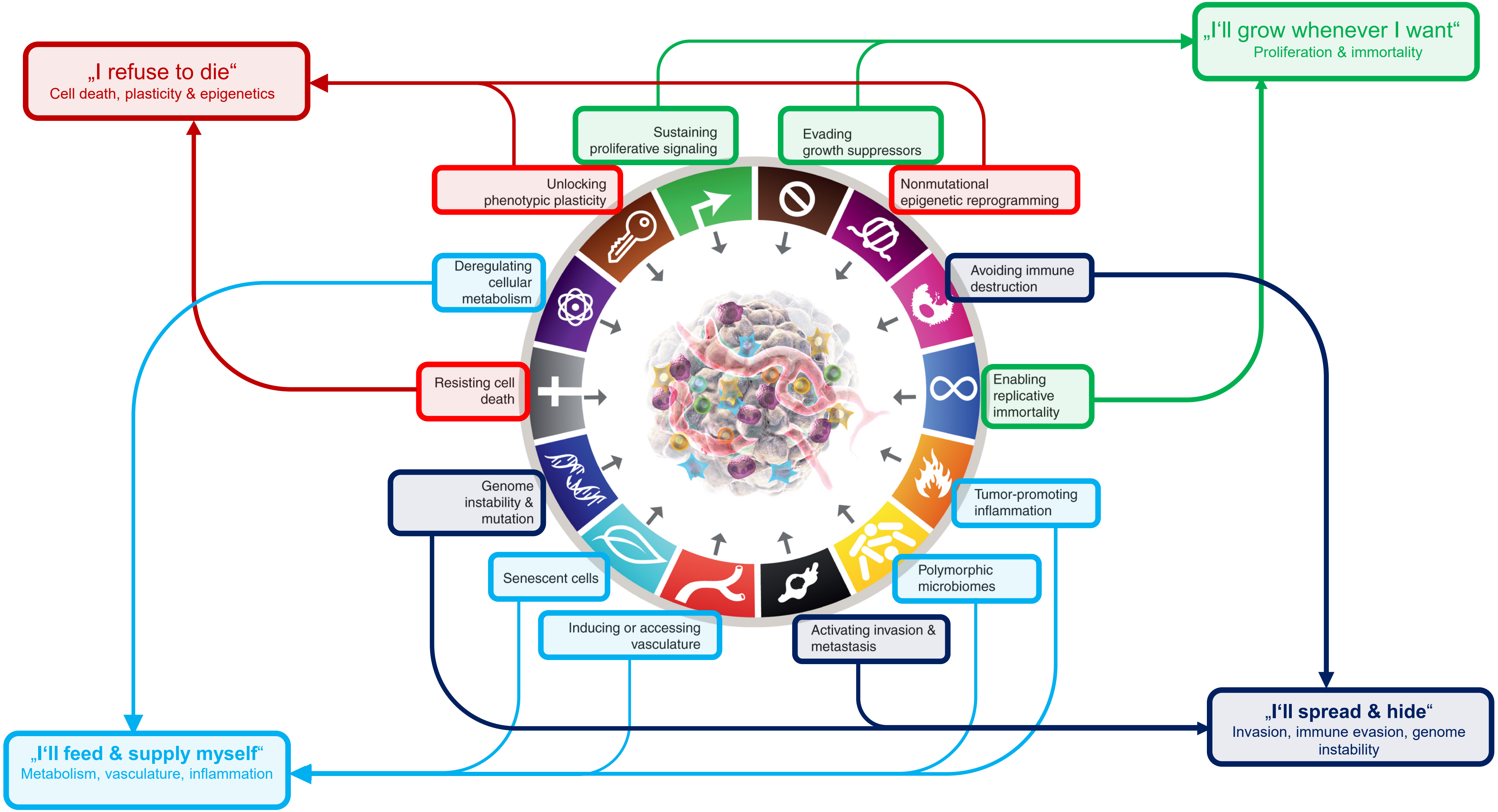
Theory of cancer formation

Random mutations disable apoptosis - the body’s built-in program for removing damaged cells.

Consequence

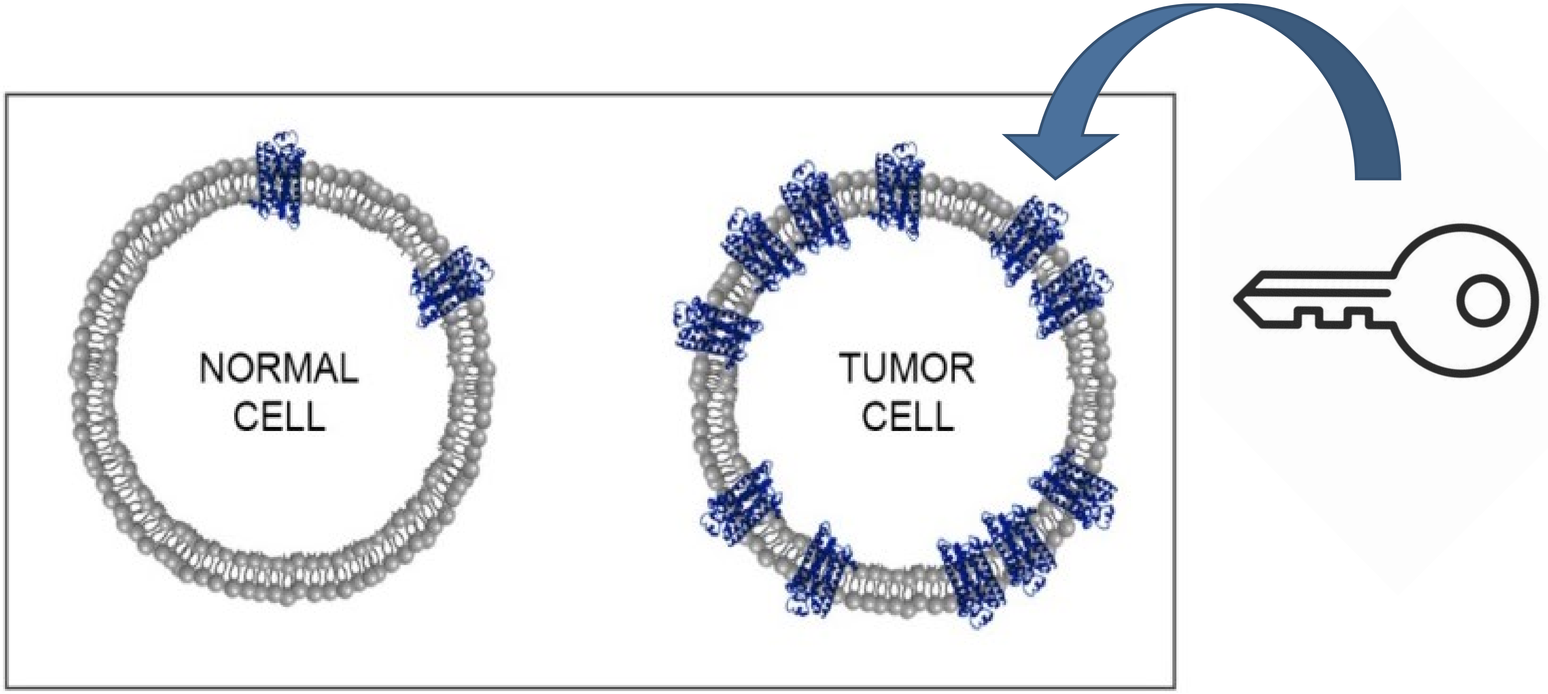
Cancer cells must be removed or killed “manually” through medical treatment.

Hallmarks of cancer



Cancer Discov. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059

From hallmark to target – receptor overexpression

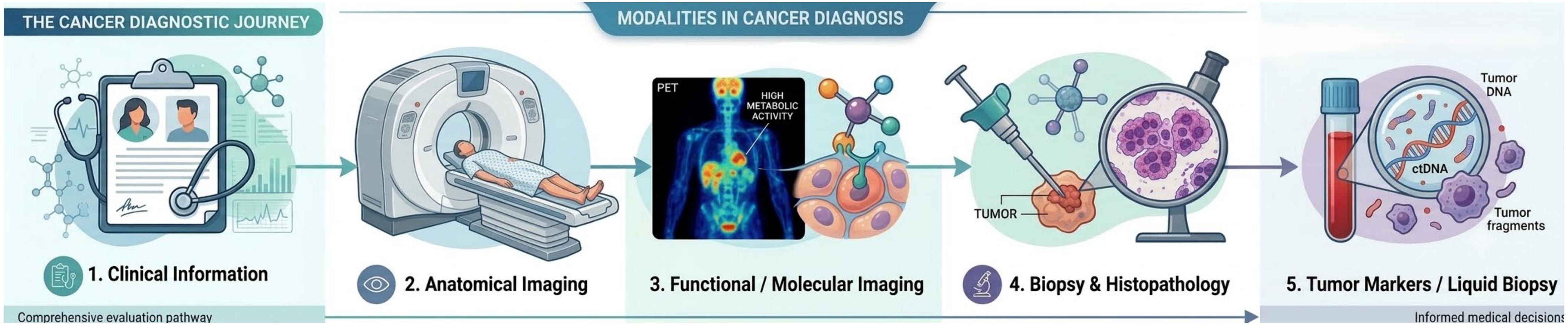


Mutation drives massive receptor overexpression.

Q: What if we could attach a radioactive atom to the molecule that SPECIFICALLY binds to that receptor?

How do we find it?

- By detecting these hallmarks with diagnostic toolbox:
  - Clinical information
  - Anatomical imaging (CT, MRI, ultrasound) - shows location and size
  - Functional / molecular imaging (PET, SPECT) - shows what the tumor is doing
  - Biopsy & histopathology - confirms what kind of cancer
  - Tumor markers / liquid biopsy - blood-based clues



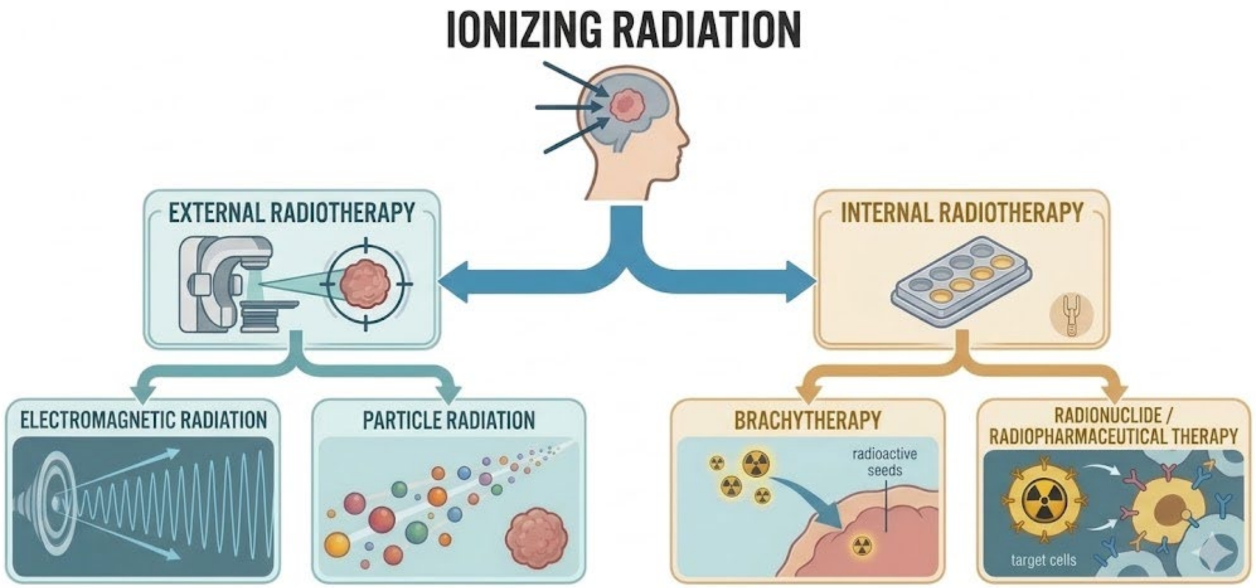
The treatment toolbox

Goals of treatment:

- **Cure** disease permanently
- **Control** the progress
- **Relieve** the pain, palliation, increase QoL

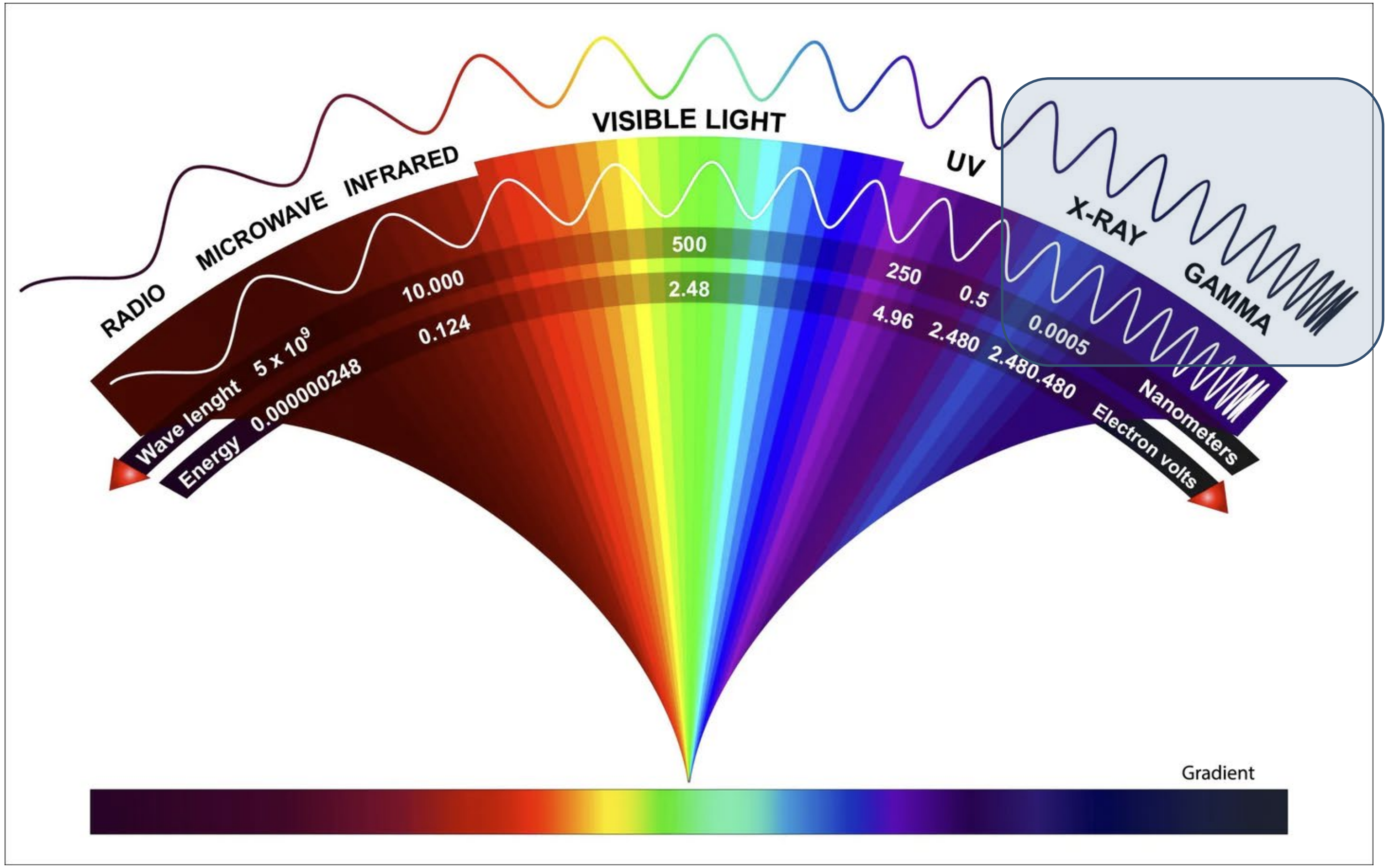
Radiation therapy

Radiation therapy, or radiotherapy, is a type of cancer treatment in which specialists kill cancerous cells in the body by exposing them to **ionizing radiation**, such as X-rays, gamma rays, high-energy electrons or heavy particles.



Natural radiation

Ionizing radiation = high enough E to ionize atoms and disrupt chemical bonds



Electromagnetic: photons

No mass, no charge

Gamma rays
Emitted from the nucleus; the basis of most diagnostic imaging.

X-rays
Produced by accelerating electrons; standard in radiology and external-beam therapy.

Natural radiation

Ionizing radiation = high enough E to ionize atoms and disrupt chemical bonds

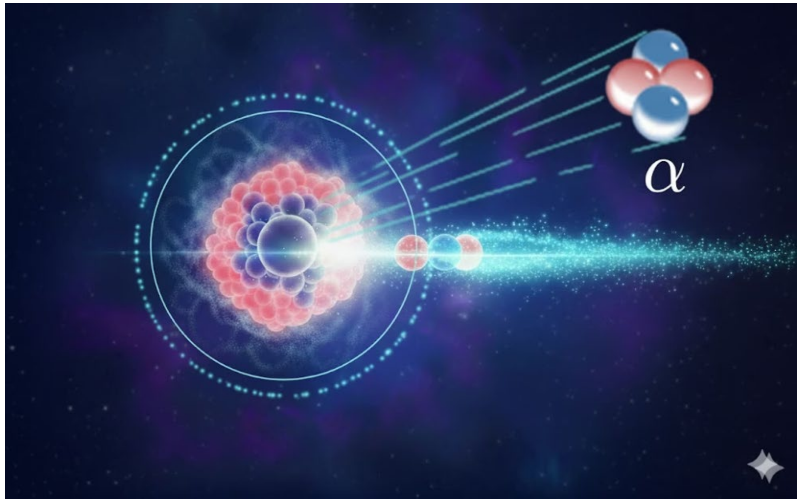
Particle radiation

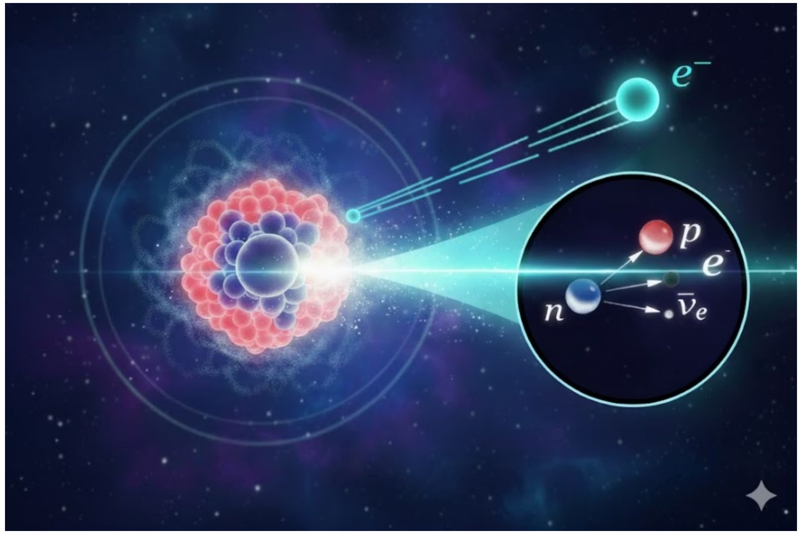
Mass and (usually) charge

Alpha (α)
Helium nuclei: 2 protons + 2 neutrons. Heavy, slow, very short range.

Beta (β)
Fast electrons or positrons. Lighter, longer range than alpha.

Heavy ions
e.g. carbon nuclei; also reach us as cosmic radiation.





Penetration characteristics & radiation protection

Alpha (α) particles

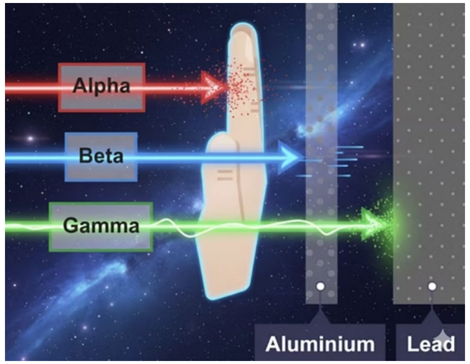
- **Range in air:** Up to 10 cm only
- **Shielding:** Paper sheet or human skin sufficient
- **Primary hazard:** Internal contamination through ingestion or inhalation
- **Penetration:** Minimal - cannot penetrate outer skin layer

Beta (β-) particles

- **Range in air:** 10 cm to 3 metres depending on energy
- **Shielding:** Perspex (acrylic) glass combined with lead backing
- **Primary hazard:** Both internal and external exposure risks
- **Penetration:** Moderate - can penetrate skin but stopped by thin metals

Gamma (γ) radiation

- **Range in air:** 3 to 100+ metres, highly penetrating
- **Shielding:** Dense materials - lead, tungsten, concrete barriers required
- **Primary hazard:** External exposure at considerable distances
- **Penetration:** Extensive - passes through most materials easily



„Artificial“ radiation

Unlike natural radioactive decay, artificial radiation is produced on demand, with a chosen isotope, at a chosen activity, for a chosen purpose.

External beam radiation therapy

Radiation source stays outside the patient — beams target the tumour through the body

Linear accelerator (LINAC)

Accelerates electrons to near light speed; electrons hit a tungsten target producing high-energy X-rays directed at the tumour. Workhorse of modern radiotherapy — present in virtually every cancer centre.

X-rays / electrons

Proton accelerator (cyclotron / synchrotron)

Accelerates protons; dose is deposited precisely at the Bragg peak, sparing tissue beyond the tumour. Used in specialised particle therapy centres.

Protons

Carbon ion accelerator (synchrotron)

Heaviest ion used clinically; highest LET, most localised biological damage. Facilities include HIT Heidelberg and MedAustron Vienna.

Carbon ions

Radiation source stays OUTSIDE the patient

Medical radionuclide production

Produces radioactive atoms that are attached to a carrier molecule and given to the patient

Nuclear reactor

Neutron bombardment of target material; produces neutron-rich, beta-emitting isotopes. Primary source of ^{177}Lu, ^{131}I, ^{99}Mo. High yield, but requires reactor infrastructure.

^{177}Lu ^{131}I ^{99}Mo

Particle accelerator (cyclotron / LINAC)

Proton or deuteron bombardment; produces proton-rich isotopes. Source of ^{18}F, ^{68}Ga, and other short-lived PET radionuclides.

^{18}F ^{68}Ga

Radionuclide generator

Long-lived parent decays to short-lived daughter, eluted on demand at the hospital pharmacy. Classic example: ^{99}Mo/^{99m}Tc generator. No on-site accelerator required.

^{99m}Tc generator

Radioactive source goes INSIDE the patient

Both approaches exploit the same physics — but external beam **aims radiation at the tumour from outside**, while radionuclide therapy **delivers it from within, one cell at a time.**

How does radiation kill a cell?

1 Energy deposited

Radiation transfers energy to the tissue it passes through

→

2 Ionisation

Electrons are knocked from atoms, creating reactive ions

→

3 DNA breaks (single / double)

Chemical bonds rupture; DNA strands are severed

→

4 Cell death

Unable to repair, the cell can no longer divide and dies

Tissue range: Up to 100 micrometres

Particle energy: 5–10 MeV (very high)

High LET radiation

Cytotoxic effect: Double-strand DNA breaks, oxygen-independent

Localised damage with maximum biological effect

Tissue range: Up to 12 milimeters

Particle energy: Up to 2 MeV (moderate)

Low to medium LET radiation

Single-strand DNA breaks, base modification

Cross-fire effect Can irradiate adjacent cells (therapeutic advantage or concern)

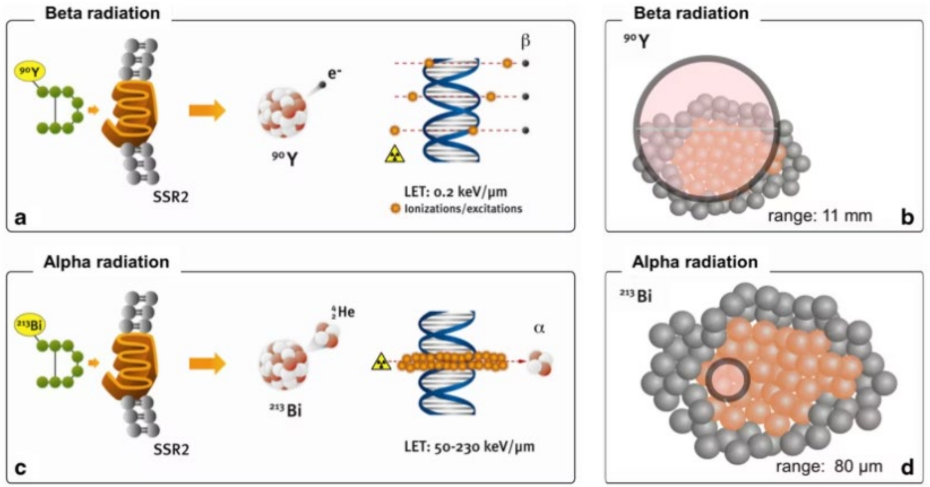
Tissue range: up to 30 cm

Photon energy: sub MeV

Low LET radiation

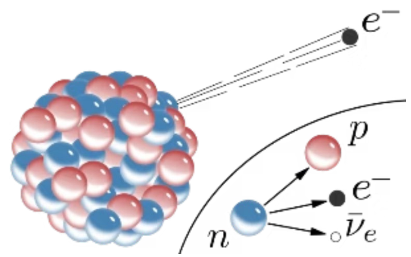
Low biological damage risk

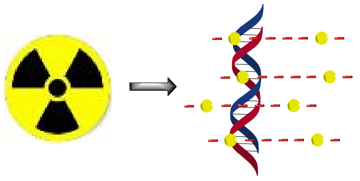
Penetrates deeply but causes less dense ionisation

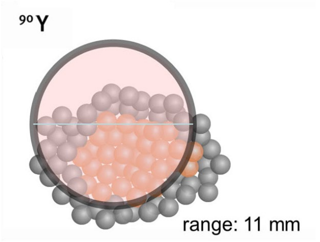


LET: Linear energy transfer: a measure of the energy an ionizing radiation transfers to a material (e.g. human tissue) per unit of distance traveled

Beta- radiation: The „rain“ effect



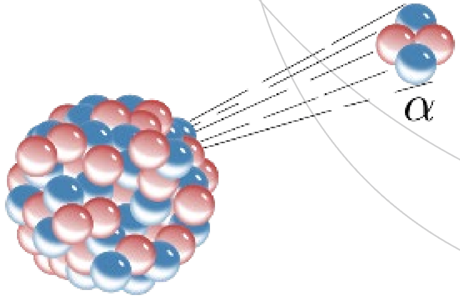


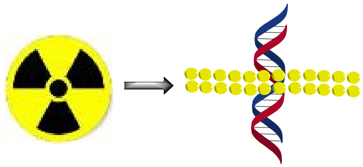


Key physical properties

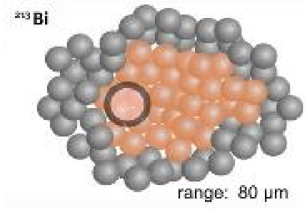
- Penetration depth: few mm in tissue
- Energy deposition: 0.2–2 keV/µm
- Ionisation density: sparse, distributed events
- Cellular effect: repairable DNA damage predominates
- Multiple „hits“ required for lethality (high activities, GBq range)

Alpha radiation: „The hammer effect“



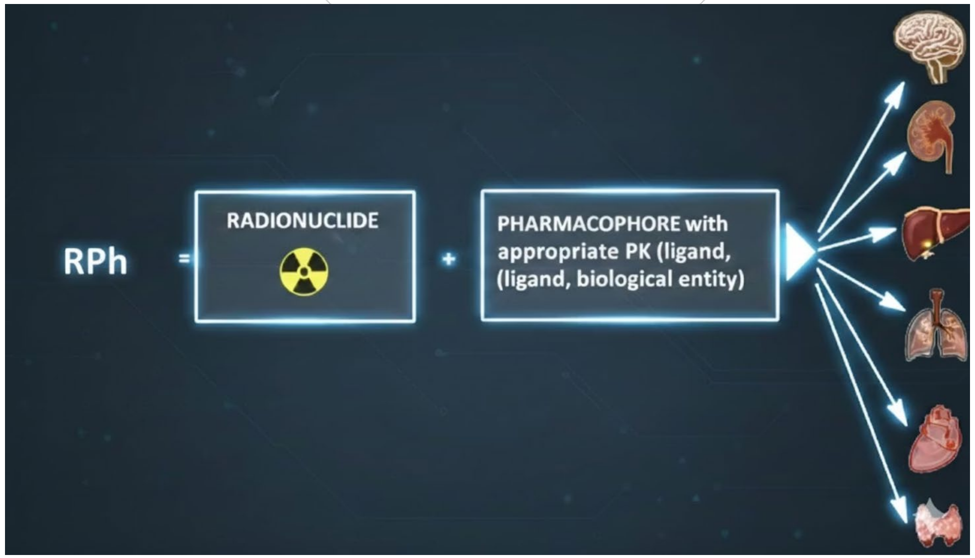


LET: 50-230 keV/μm
Domet: μm (^{213}Bi - 80 μm)
ionizations/excitations



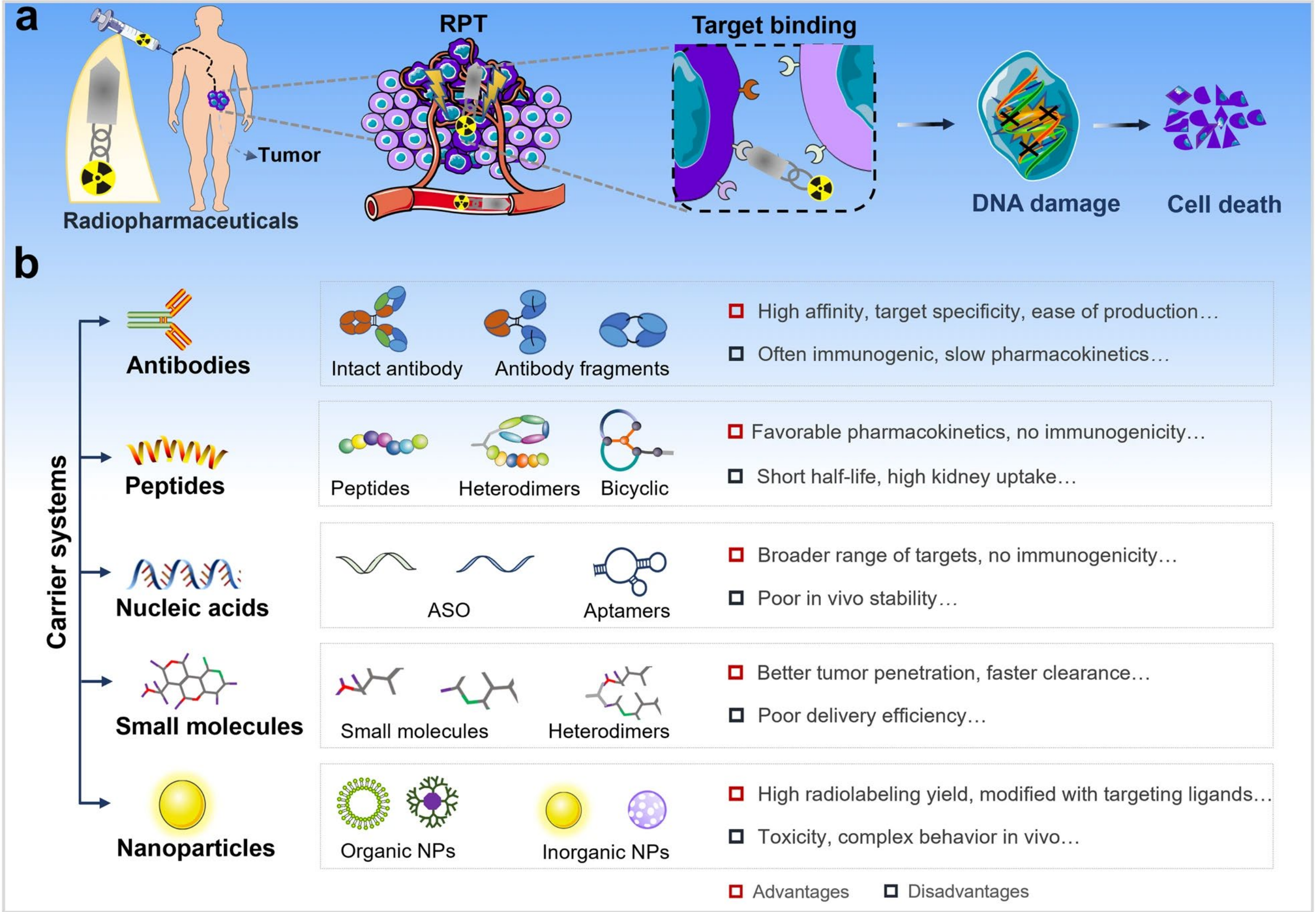
Radiopharmaceutical - definition

Radiopharmaceuticals combine **radioactive isotopes (radionuclides)** with **pharmaceutical carriers**, enabling visualisation of biological processes and targeted treatment of disease at the molecular level.



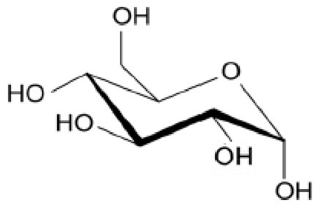
..Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

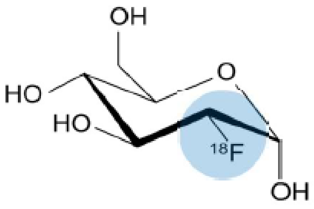
Carrier molecule (pharmacophore)

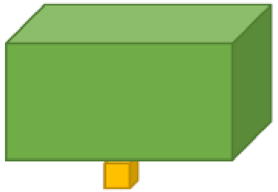


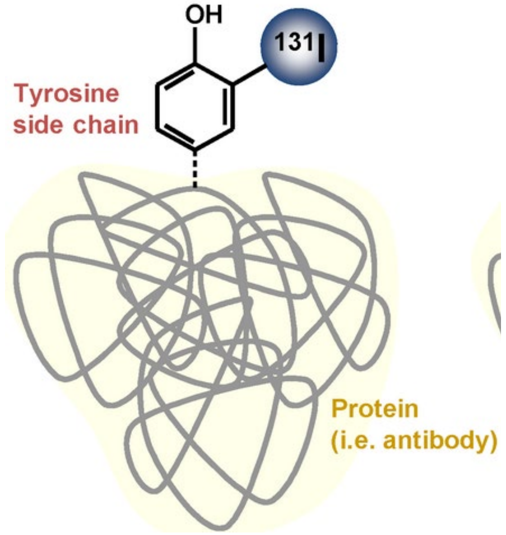
RN + Pharmacophore = Radiopharmaceutical

1. Direct chemical (covalent) radiolabelling (radiohalogens, such as fluorine-18, iodine-131) to the pharmacophore (e.g. glucose molecule, mAb):



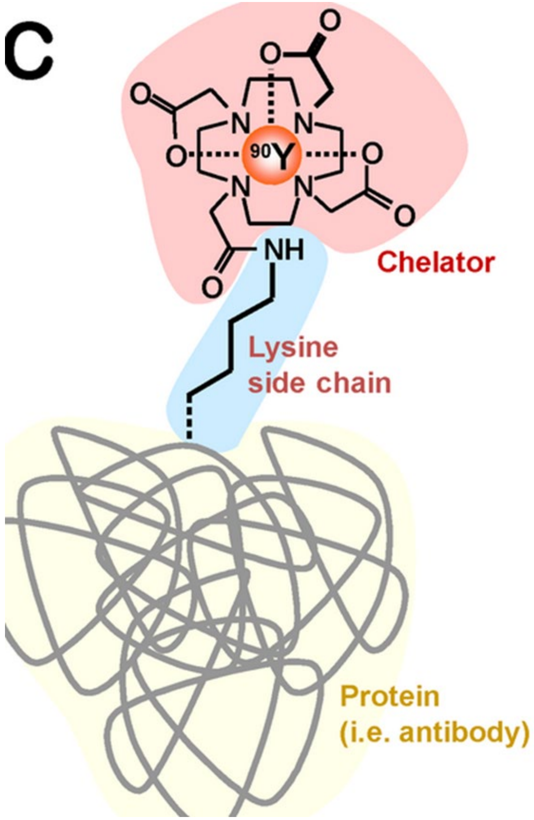






RN + Pharmacophore = Radiopharmaceutical

2. Chelator-mediated radiolabelling (radiometals, such as gallium-68, lutetium-177) to the pharmacophore (e.g. small molecules, peptides, mAb):



Radiopharmaceuticals

Diagnostic radiopharmaceuticals

Gamma emitters

Isotopes: ^{99m}Tc, ^{123}I, ^{111}In

Modality: SPECT/CT imaging

Single-photon emission computed tomography provides functional imaging with anatomical correlation for disease localisation.

Positron emitters

Isotopes: ^{18}F, ^{68}Ga

Modality: PET/CT imaging

Positron emission tomography offers superior resolution and quantification for metabolic and molecular imaging applications.

Therapeutic radiopharmaceuticals

Beta- emitters

Isotopes: ^{177}Lu, ^{90}Y, ^{131}I

Applications: PRRT, radioligand therapy, thyroid treatment

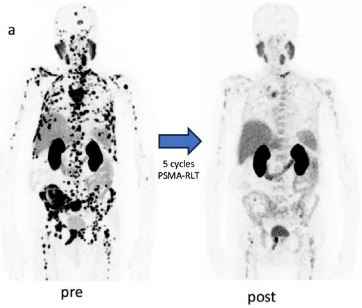
Medium-range therapeutic particles for targeted tumour destruction with manageable radiation safety requirements.

Alpha particle emitters

Isotopes: ^{223}Ra, ^{225}Ac, ^{212}Pb, ^{211}At

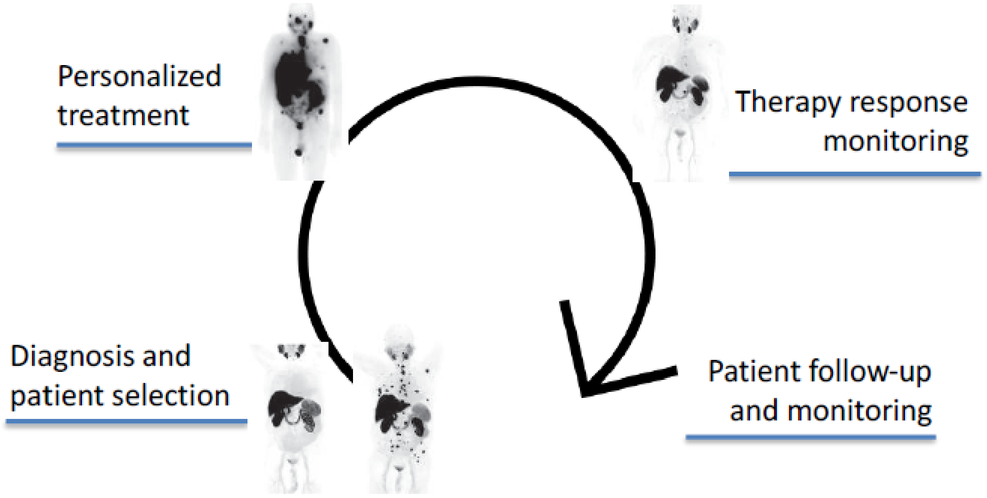
Applications: PRRT, radioligand therapy

High-LET therapy delivering potent cytotoxic effects with minimal range, ideal for micrometastatic disease.



Theranostics

- Diagnostic & therapy combined in a single molecule (single biological target).
- Combining nuclear medicine **imaging with radiopharmaceutical therapy**.
- **Improvement** of disease diagnosis, treatment, monitoring and follow-up.



Theranostics cycle

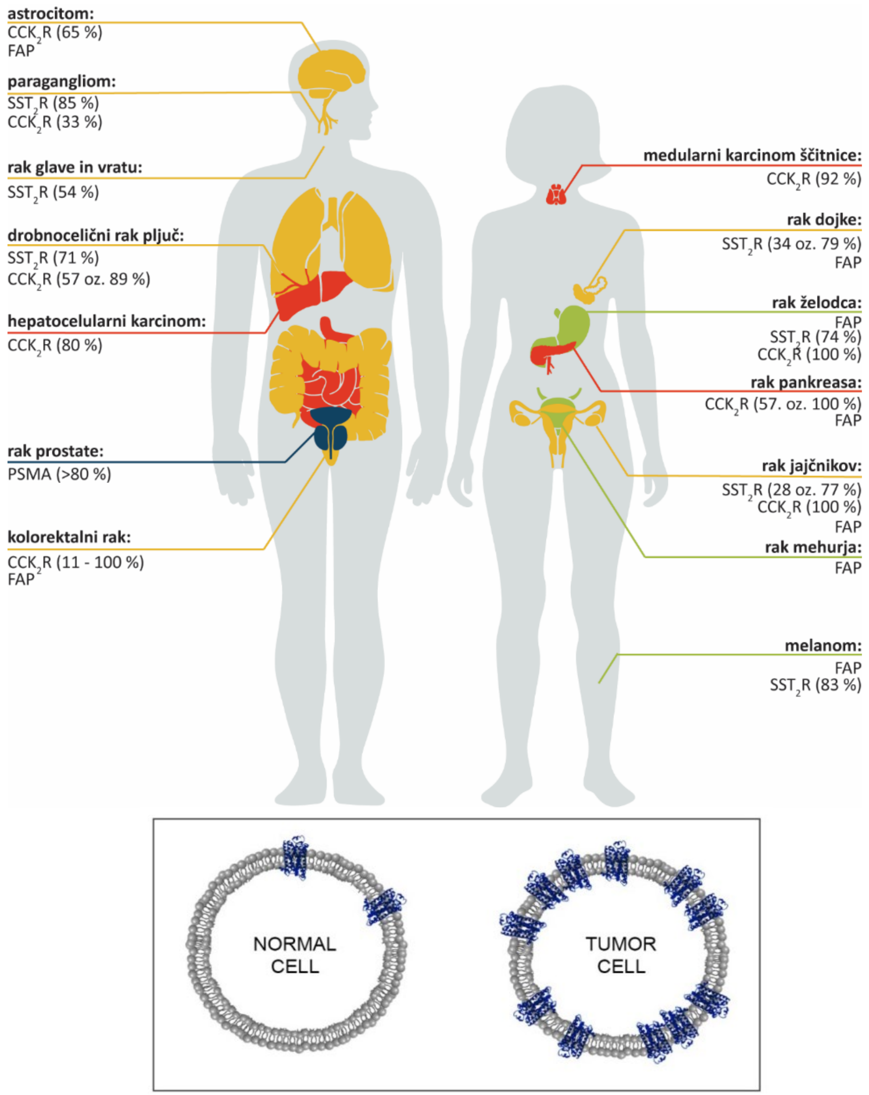
- Reduced risk of non-response ✓
- Reduced side effects ✓
- Minimized toxicity ✓

Elvas F.: ESMIT, 2025

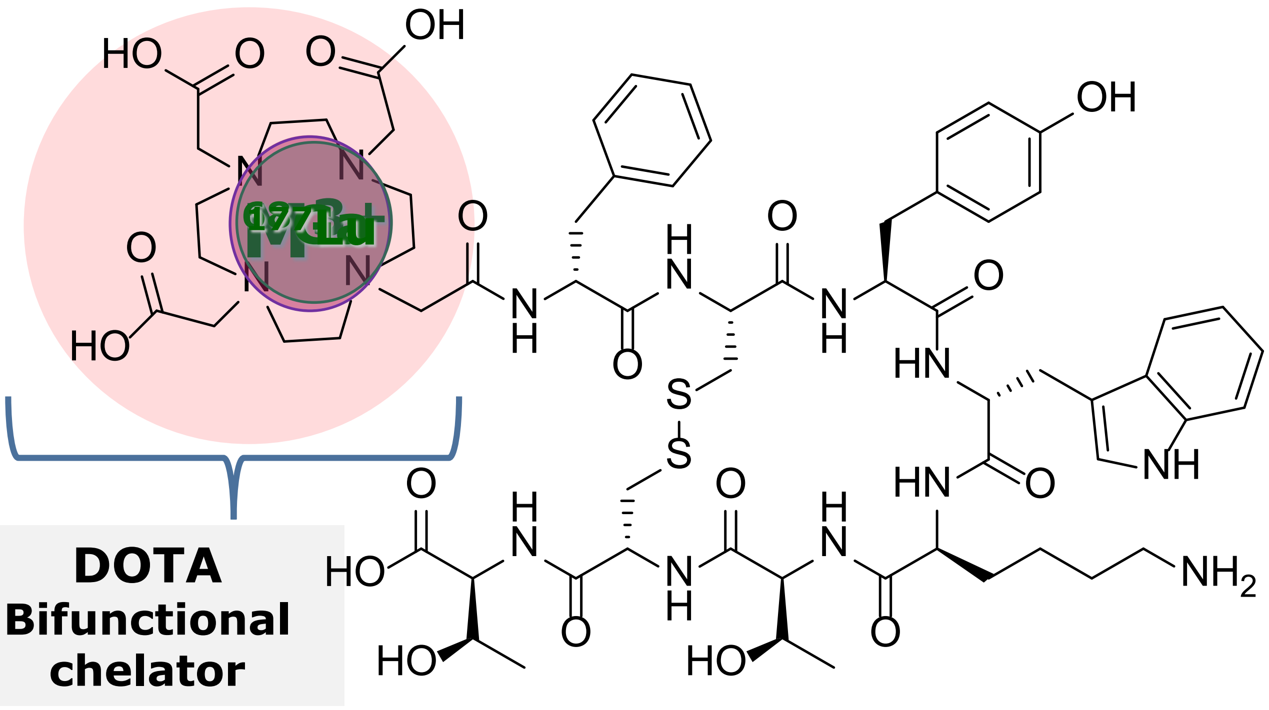
Theranostics - examples

Neuroendocrine tumors (GEP-NET):
- overexpression of somatostatin receptors (SSTR)

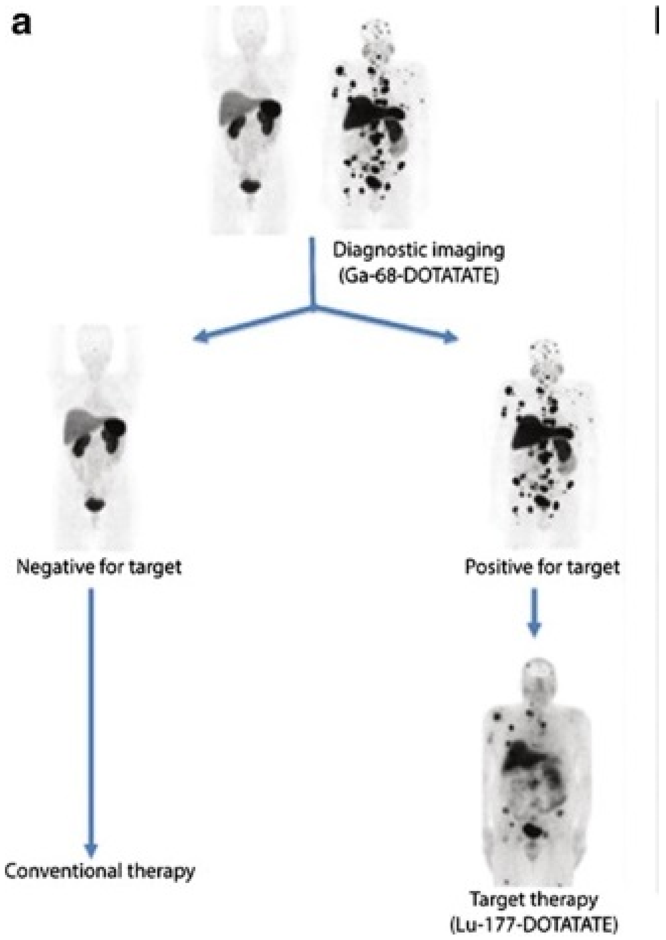
Prostate cancer:
- overexpression of PSMA (Prostate Specific Membrane Antigene)



Theranostics - SSTR



DOTA
Bifunctional chelator



Sathekge M., CME August 2013 Vol. 31 No. 8

Theranostics - PSMA

Key takeaways

- Cancer cells cannot undergo programmed cell death and must therefore be removed or killed through medical intervention.
- Ionizing radiation kills cells by breaking DNA strands; the biological effect depends on radiation type, LET, and delivered dose.
- Alpha particles cause dense, localised DNA damage; beta particles act over a longer range, irradiating adjacent cells through the cross-fire effect.
- Radiopharmaceuticals combine a radionuclide with a carrier molecule that navigates to the tumour, delivering radiation from within.
- Theranostics pairs a diagnostic radionuclide (e.g. ^{68}Ga) with a therapeutic one (e.g. ^{177}Lu) on the same carrier, confirming target expression before committing to therapy and enabling personalised, response-adapted treatment.
- Clinically validated theranostic targets include somatostatin receptors in neuroendocrine tumours ([^{177}Lu]Lu-DOTATATE) and PSMA in prostate cancer ([^{177}Lu]Lu-PSMA-617).

Thanks for your attention.

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