

# Radiotherapy

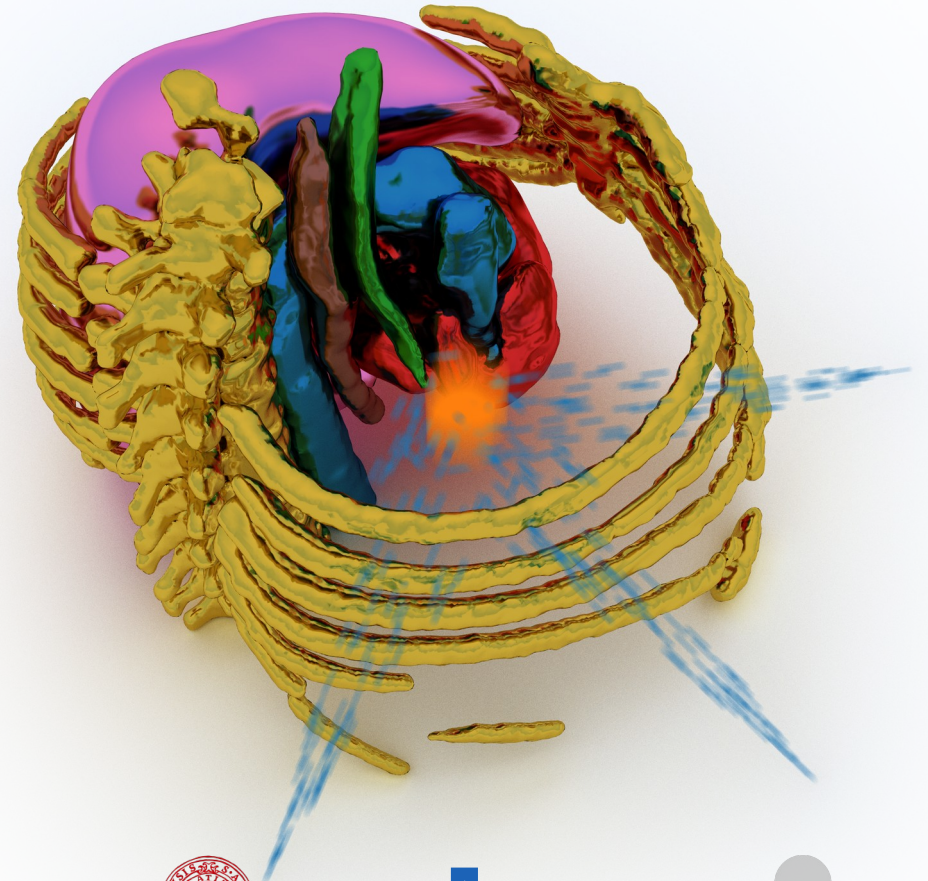
## *Past, present and future*

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Master's Programme in Medical  
Nuclide Techniques

2025-12-09



UPPSALA  
UNIVERSITET



AKADEMISKA  
SJUKHUSET

Skandion  
kliniken

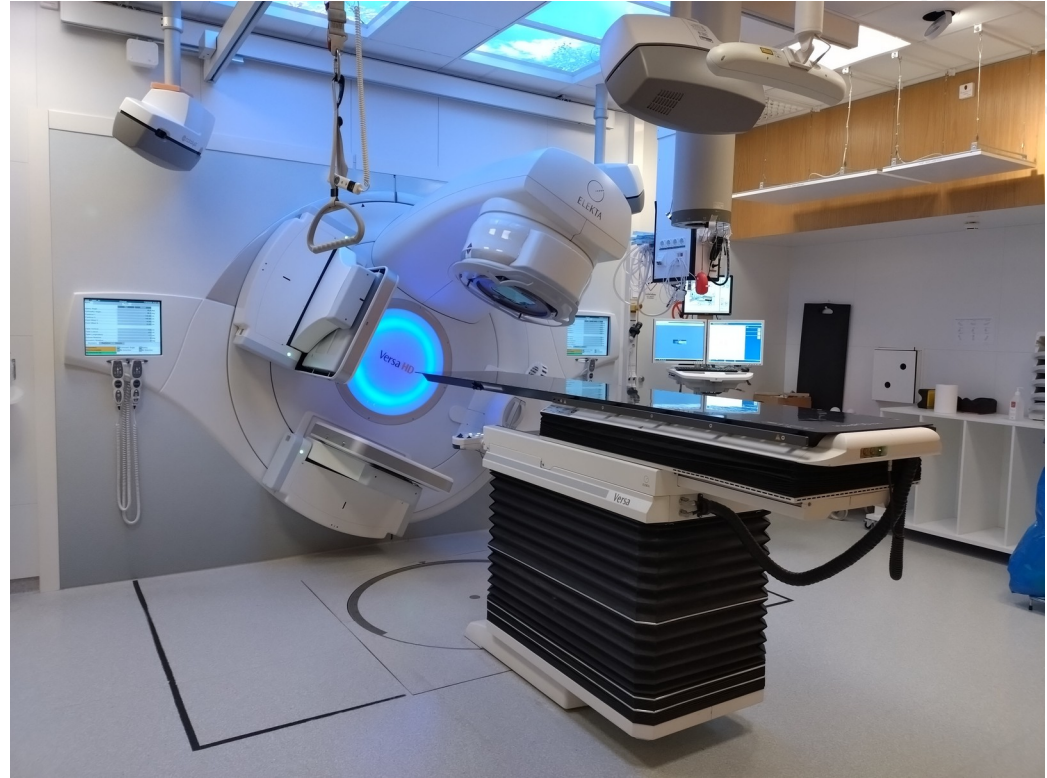
# External beam radiotherapy

Radiation source placed outside the body.

Is used to treat most anatomical sites.

Half of all cancer patients receive radiotherapy!

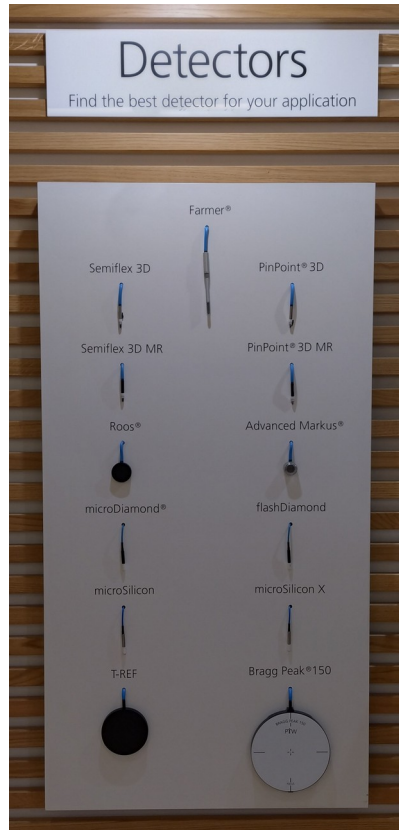
30% of all cured cancer is attributed to radiotherapy!  
(Cancerfonden)



# External beam radiotherapy: Detectors

Detectors are used for quality assurance in the clinic and for various purposes in research.

Important to validate output from machines before treatment!



*Delta4 phantom (ScandiDos)  
Adapted from:  
<https://delta4family.com/>*

# External beam radiotherapy: Overview

## 1. First hour

- Background and history
- Modern X-ray radiotherapy
- Brachytherapy and electron beam therapy



## 2. After the break

- Proton therapy
- Tech. developments
- Biological aspects



# **Part 1: Background and history**



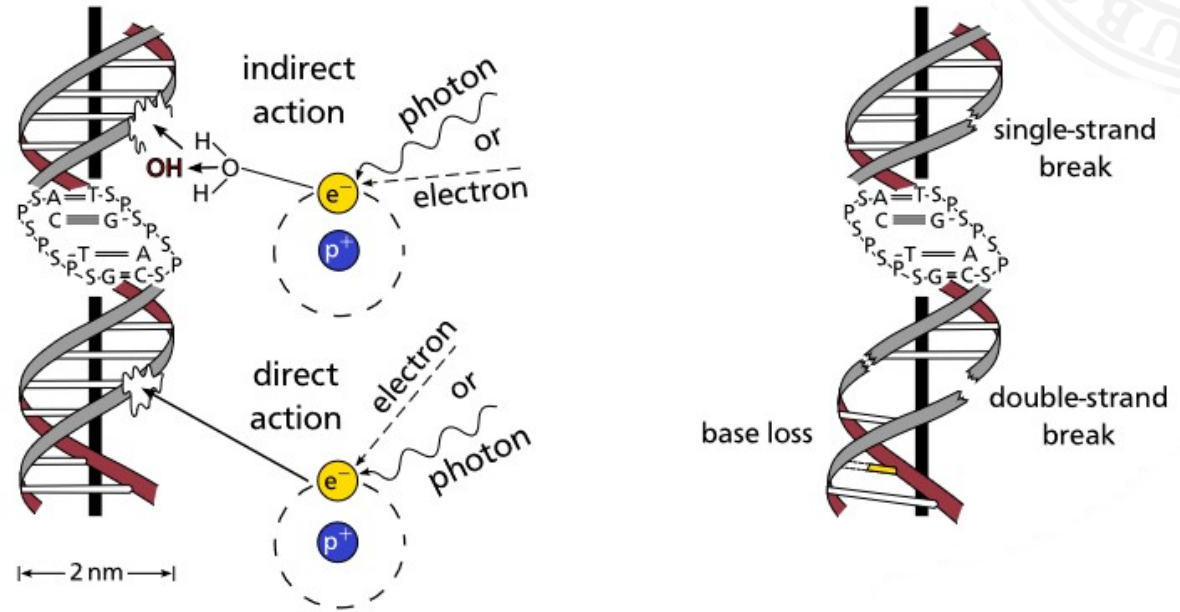
# Mechanism of effect

## Damage to the DNA

Ionizing radiation can cause severe damage, such as multiple **double-strand breaks**, that lead to cell death.

Radiation is measured in **Gray (Gy)**.

$$1 \text{ Gy} = \frac{1 \text{ Joule}}{1 \text{ Kg}}$$



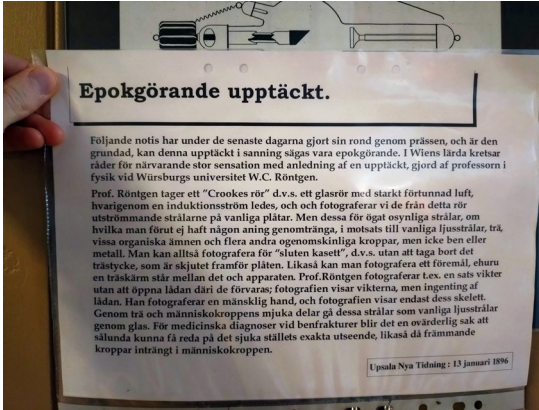
*Radiation can damage the DNA molecule through indirect or direct ionization. Adapted from Richter, 2012.*

# Discovery of x-rays (1890s)

X-rays discovered in **1895**.  
Started being used for  
treatments only shortly after.



*Hand mit Ringen (Hand with Rings) – Wilhelm Röntgen's first medical X-ray image, 1895. Adapted from Wikipedia.*



*Uppsala Nya Tidning 1896 January 13th*

*“The following has the past few days made its way through the press, and if, this discovery can in all truth be époque defining. In the academic circles of Vienna there is at this moment large sensation with regards to a discovery made by professor of physics at Würzburg university W.C. Röntgen.*

*...”*

- 1896-First therapeutic attempt to treat a local relapse of breast carcinoma by Emil Grubbe (Chicago)
- 1896 - First use of x-rays for stomach cancer by Victor Despeignes (Lyon)
- 1896 - Irradiation of a skin tumour in a 4-year-old by Léopold Freund (Vienna)

# Early history (1900s)



First reported successful treatment in the world, Sweden, skin cancer patient **1899**.

Radiumhemmet opened in **1910**, now part of Karolinska.



*X-ray treatment at Radiumhemmet, Stockholm, in the 1920s. Adapted from Wikipedia.*



*X-ray tubes formerly used at Uppsala University Hospital (Akademiska Sjukhuset).*

*Displayed at Medicinhistoriska Museet in Uppsala.*

# Medicinhistoriska museet



Free admission for  
students at UU!

Öppettider hösten 2025

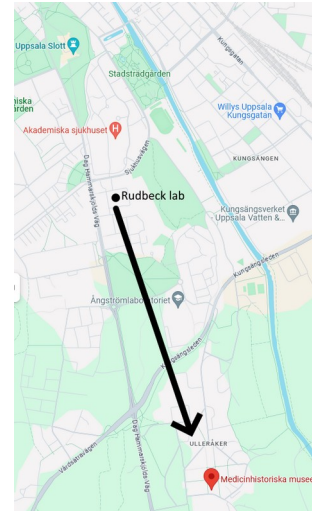
3 sept – 21 dec 2025

Tisdagar kl. 13–17

Torsdagar kl. 13–20

Söndagar kl 11–16

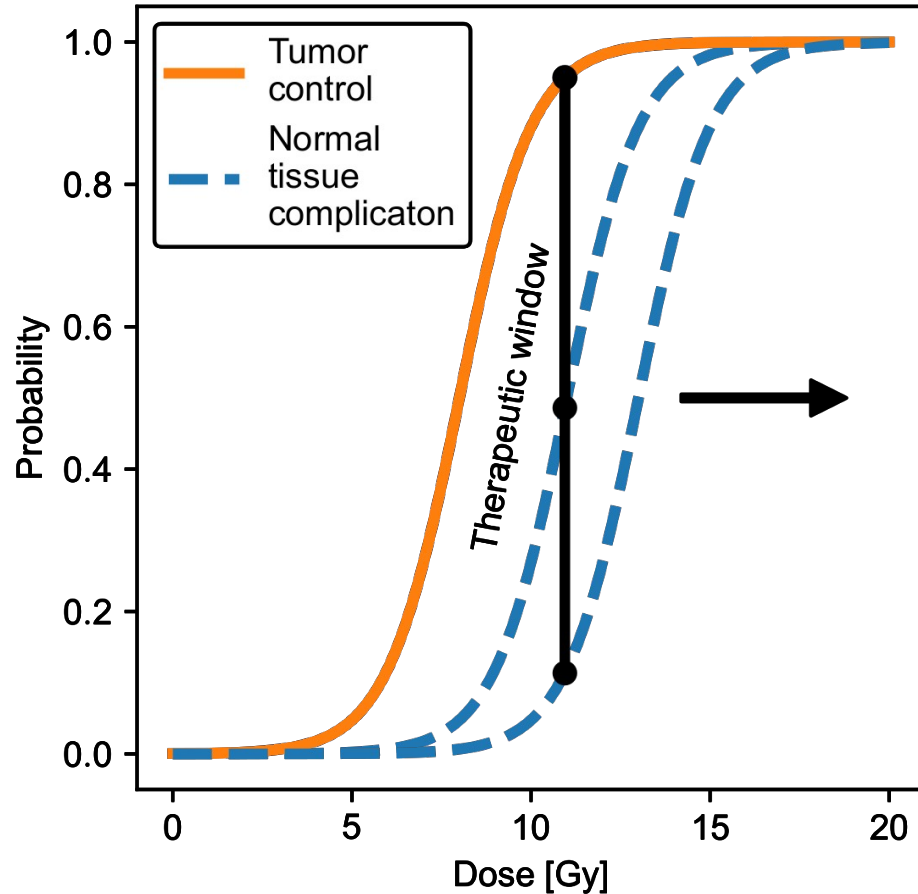
Möt T-celler och andra spännande strukturer i silver.  
Utställningen öppnar söndag den 7 december.



Karin Valegård, silverkonstnär och docent i molekylärbioologi, skapar smycken inspirerade av forskning. Regulatoriska T-celler och andra strukturer förknippas med 2025 års Nobelpris i medicin, kemi och fysik – dessutom har de vackra former och spännande strukturer som låter sig tolkas tredimensionellt.



# Improving the therapeutic window



## Physical aspects

- Type of radiation
- Precision
- Accuracy

## Radiobiological aspects

1. Oxygenation
2. Radiosensitivity
3. Fractionation

# Fractionated treatments (1930s)

Treat with lower dose at several occasions to allow normal tissue repair (Coutard et al 1932).

## **Biological aspects**

4 R's of radiobiology

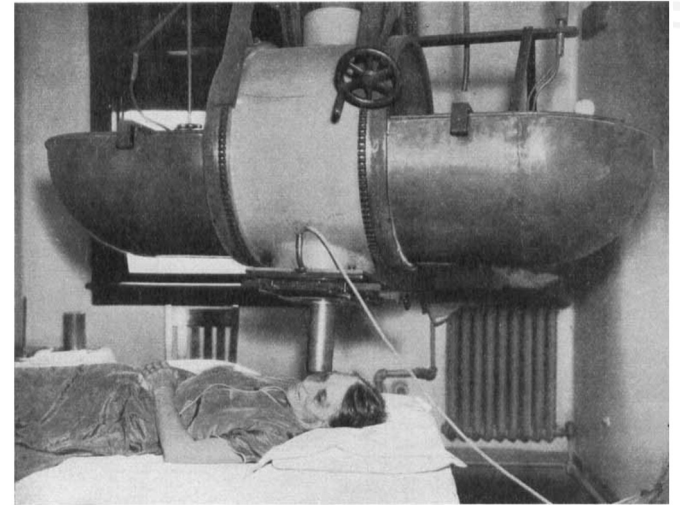
1. Repair
2. Redistribution
3. Reoxygenation
4. Repopulation

Standard fractionated treatments are still 2 Gy to the tumor in 30-40 fractions!



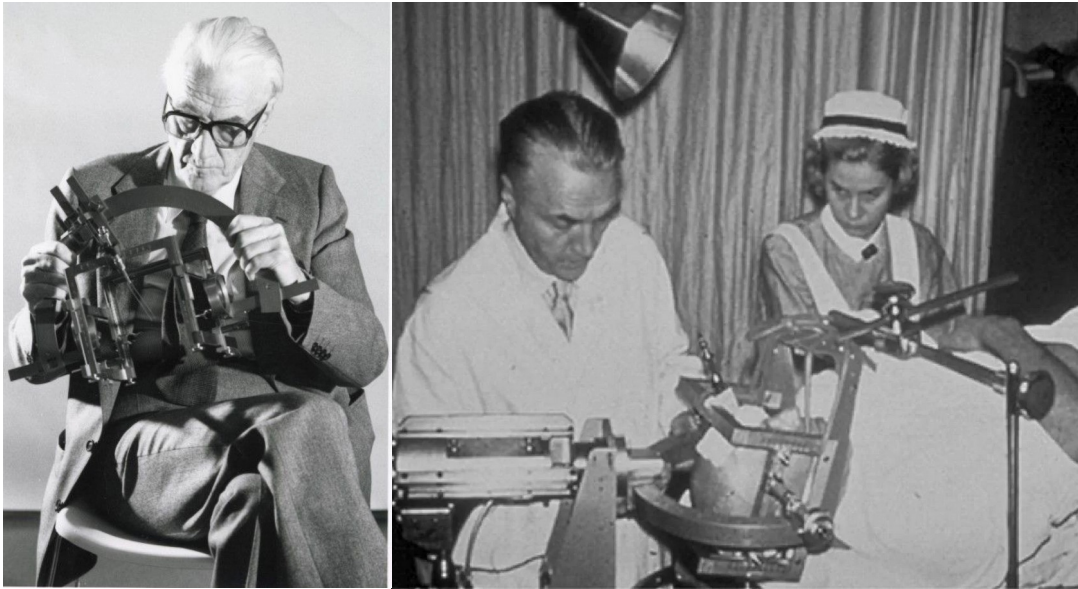
Sterilization of rams without excessive skin damage.

<https://radiologykey.com/time-dose-and-fractionation-in-radiotherapy/>



*Fractionated treatment with 700 kV x-ray source. Martin 1935.*

# Stereotactic radiosurgery (1950s-1960s)



*Stereotactic frame and proton therapy at The Svedberg lab in Uppsala.*

<https://www.elekta.com/company/about-us/story/>



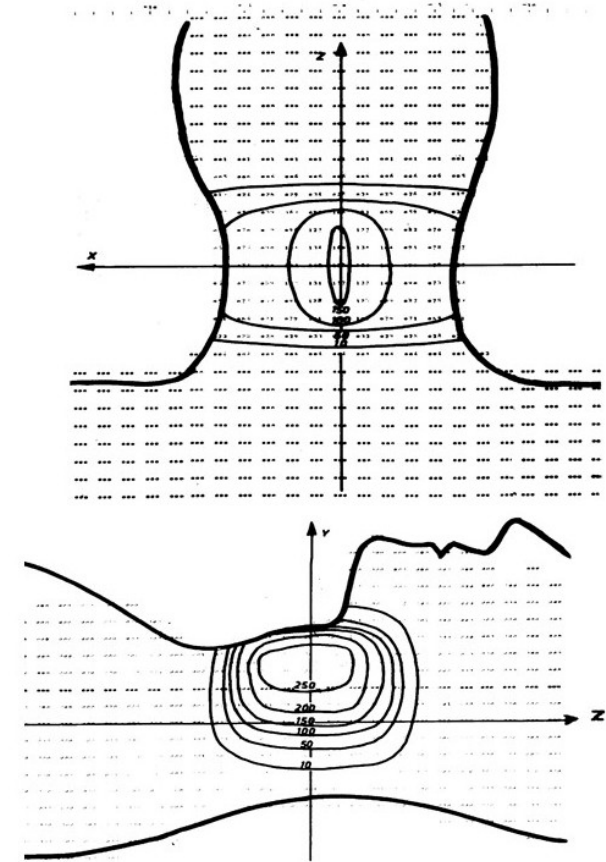
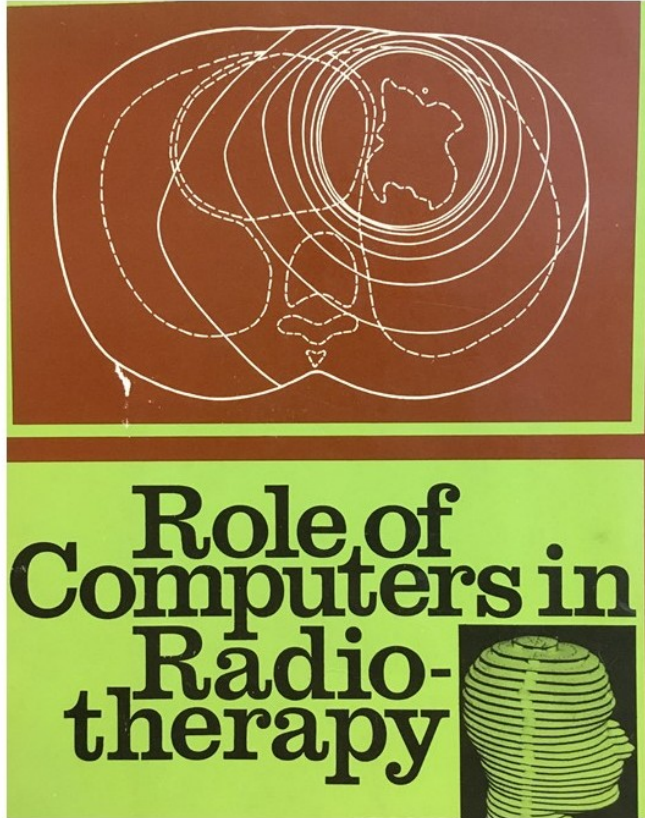
*Gamma knife (1960s).  
180 Cobolt-60 sources.*

# Computers in radiotherapy (1960s)

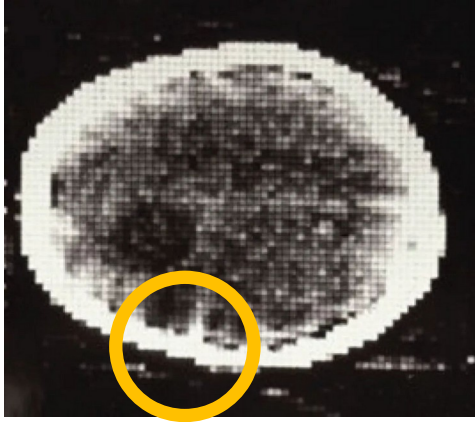
International Atomic Energy Agency in Vienna in 1965 and 1967 reported on the potential use of computers in RT.

3D dose distribution.  
3D virtual phantom.

Shown as anatomical slices, before introduction of the CT scanner!



# Computed Tomography (CT) imaging (1970s)

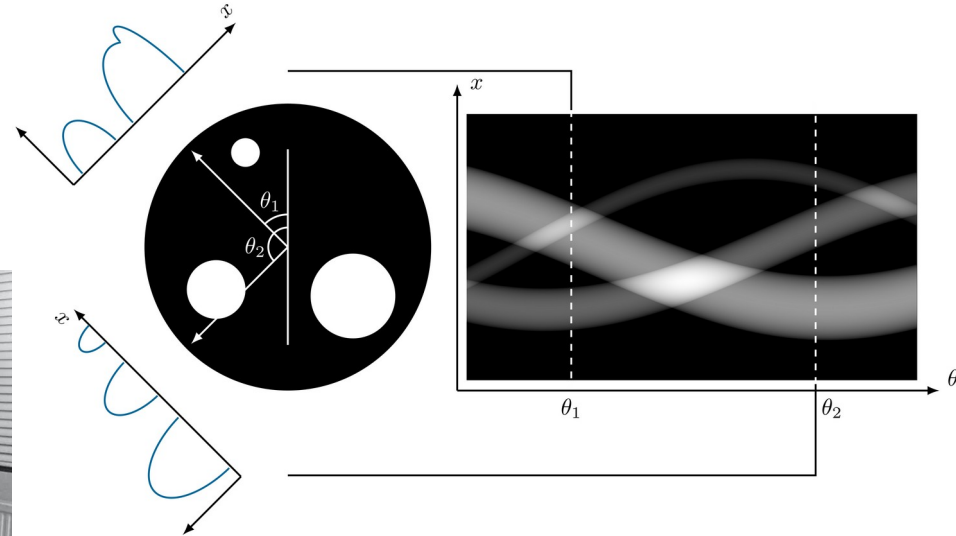


*First clinical CT (1971)*

First CT scanner in Europe outside of England installed at Karolinska hospital (neurosurgery) in 1975.



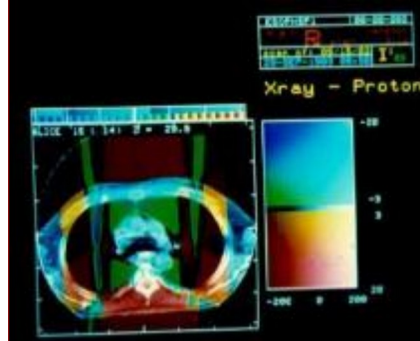
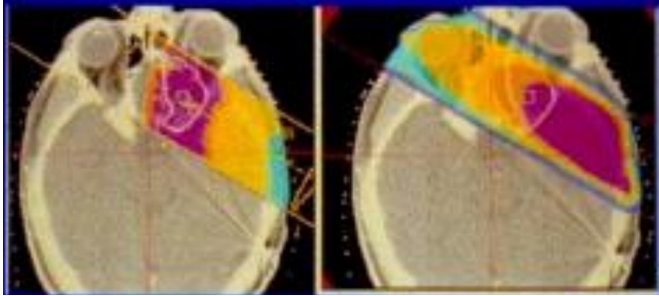
Nobel prize (1979)  
*Godfrey Hounsfield (1972)*



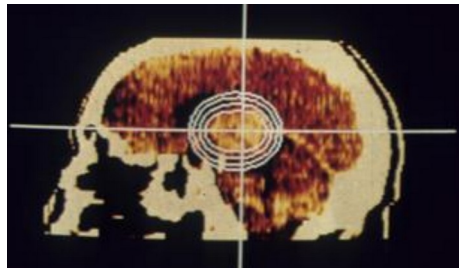
*Projections from 360 degree angles create a sinogram used for CT image reconstruction. Adapted from Häggmark 2021.*

# CT based treatment planning (1980s)

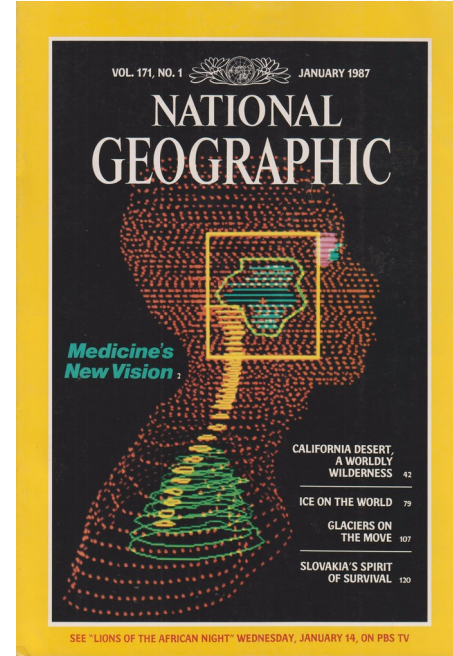
First CT at RT department of Karolinska in the late 1980s.  
Very slow! One image slice at the time.



*Early 1980s x-ray and proton therapy planning by Goitein et al 1985.*



*Early 1980s stereotactic radiosurgery planning by Hartmann et al 1985.*



## ***Medicine's New Vision (1987)***

*“Incredible machines that can peer into the human body as never before are helping physicians save lives. Veteran journalist Howard Sochurek describes these new technologies from firsthand experiences.”*

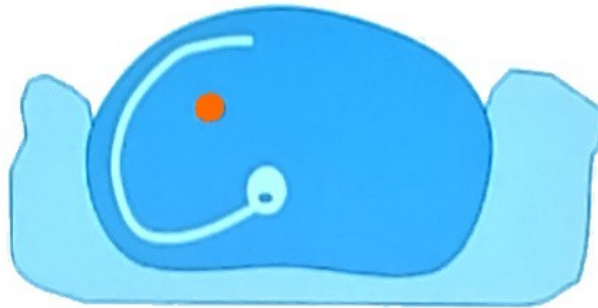
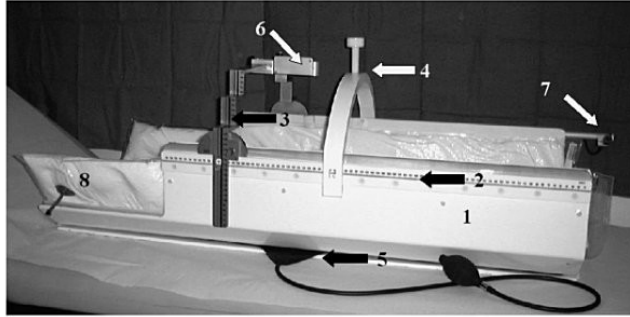
# Stereotactic body radiotherapy (1990s)

Reproducible  
precision RT of  
tumors in the thorax  
and abdomen.

High dose in few  
fractions.

Patient fixated with  
inflatable cushion in  
a stereotactic box.

Developed at  
Karolinska.  
(Lax et al 1994.)



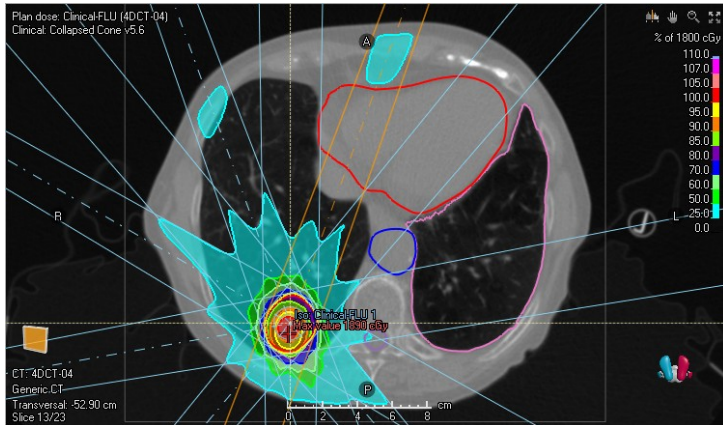
# **Part 2: Modern X-ray radiotherapy**



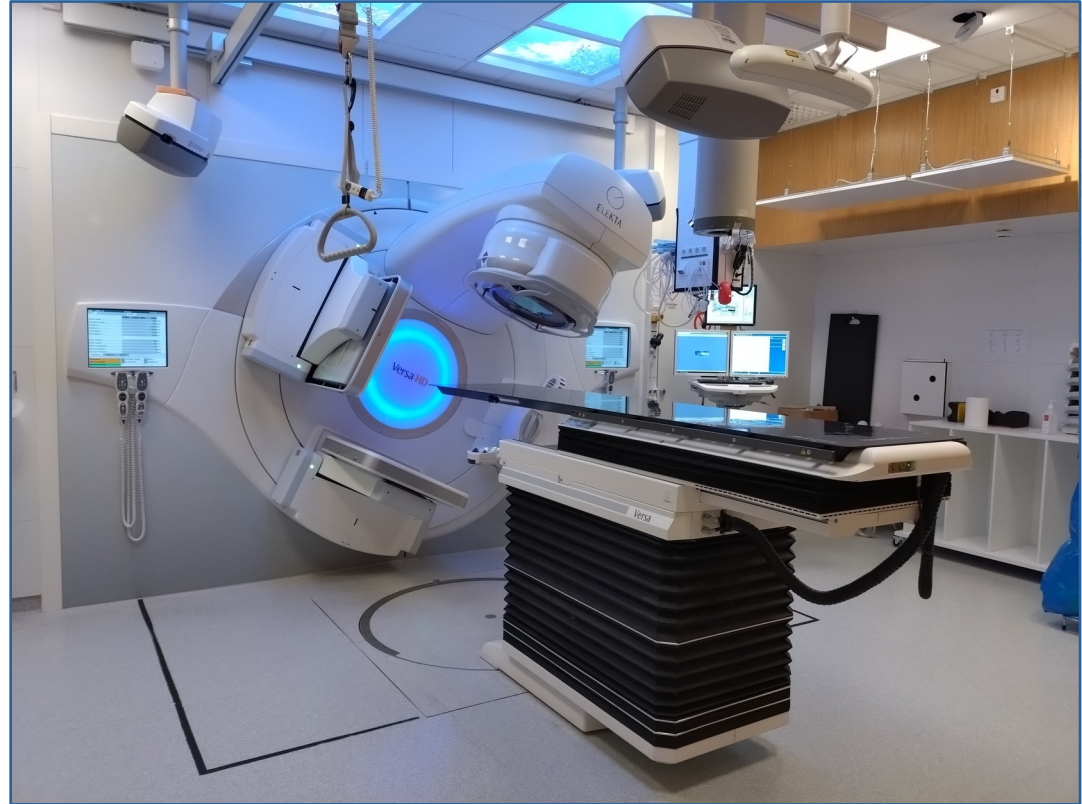
# Photon (X-ray) therapy

A high energy (6-18 MeV) photon beam is created by accelerating electrons that hit a heavy substrate and create X-rays.

The beam is shaped by collimators and the target is irradiated from several angles.

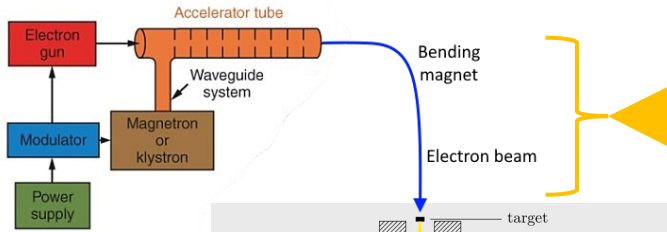


*Treatment plan dose distribution.*

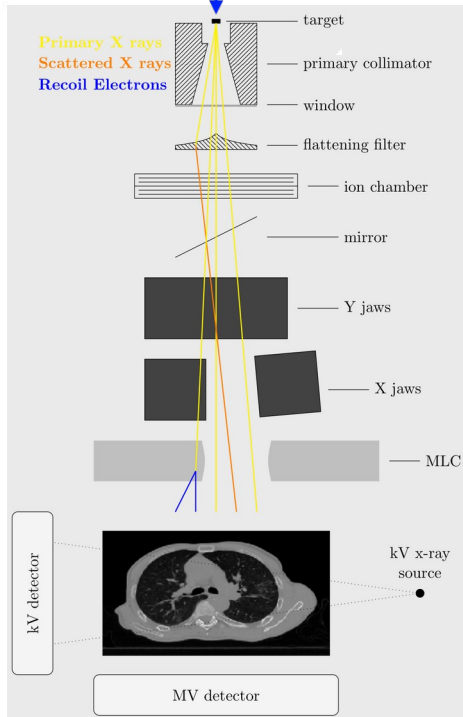


*Treatment room in Uppsala. The patient position can be adjusted by the table and the treatment head can rotate around the patient.*

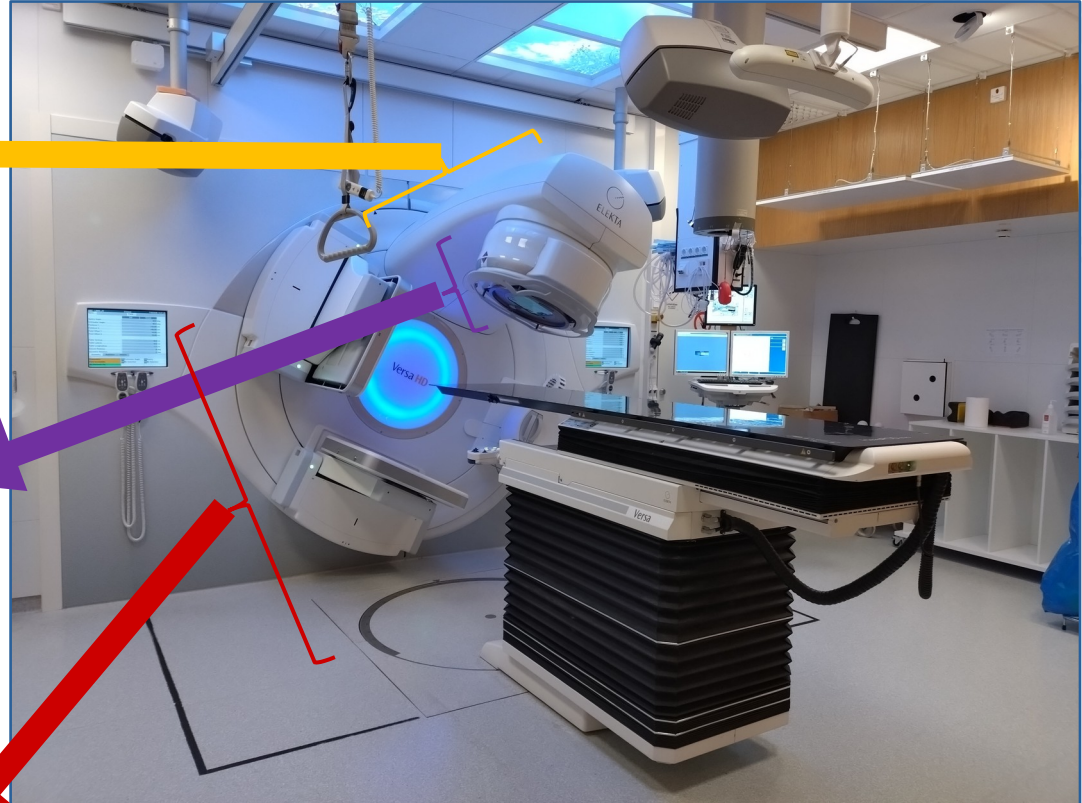
# Linear accelerator X-rays



*Adapted from Gibbons 2020.*



*Adapted from Battista 2019.*



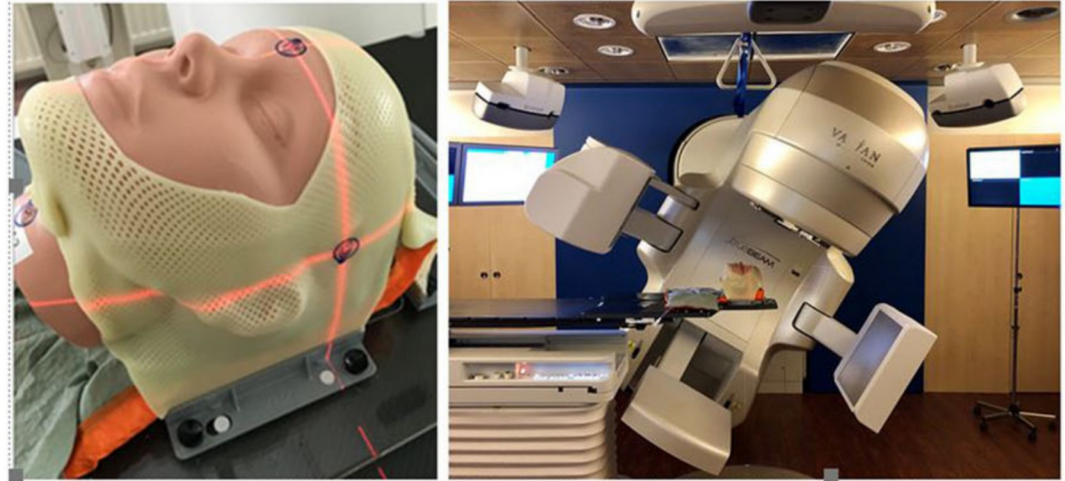
*Treatment room in Uppsala.*

How an X-ray linac works (8 minute video):  
<https://www.youtube.com/watch?v=jSgnWfbEx1A>

# Patient positioning

The patient has to be positioned correctly and consistently.

- **Immobilization:**
  - Inflatable cushions
  - Body frames
  - Face masks
- **Surface alignment:**
  - Laser + tattoos or markers
  - Surface scanning
- **Internal anatomy alignment:**
  - Portal imaging (2D projection, MV)
  - X-ray imaging (2D projection, kV)
  - Cone beam CT (CBCT) (3D image, kV)
  - Magnetic resonance (MR) (3D image)



*Patient positioning using laser surface scanning, face mask immobilization and CBCT.*

*Adapted from Freisleder et al 2020.*

# Target volume margins

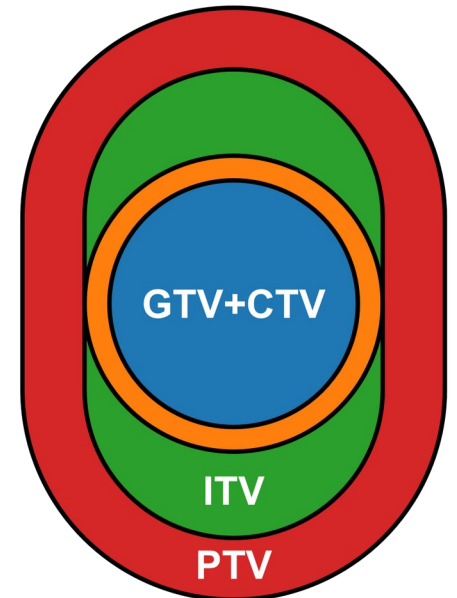
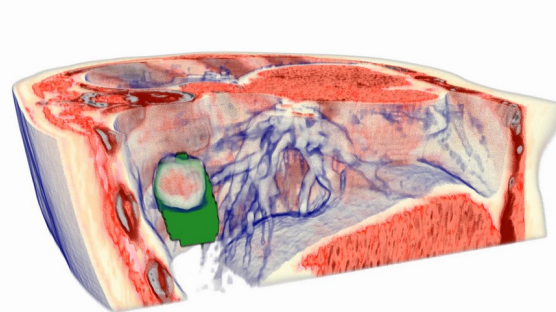
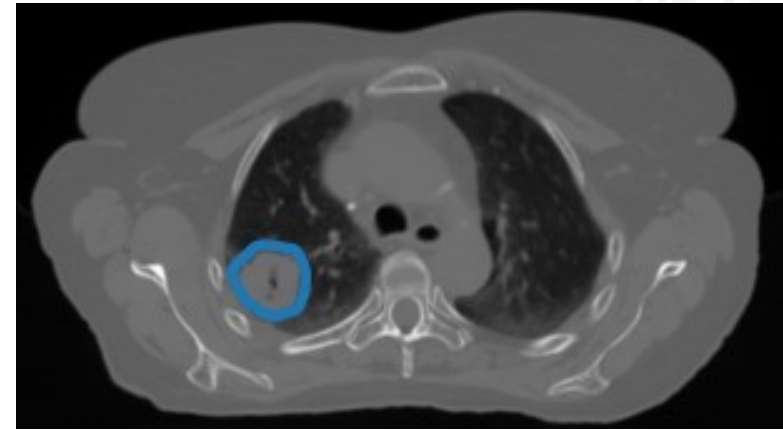
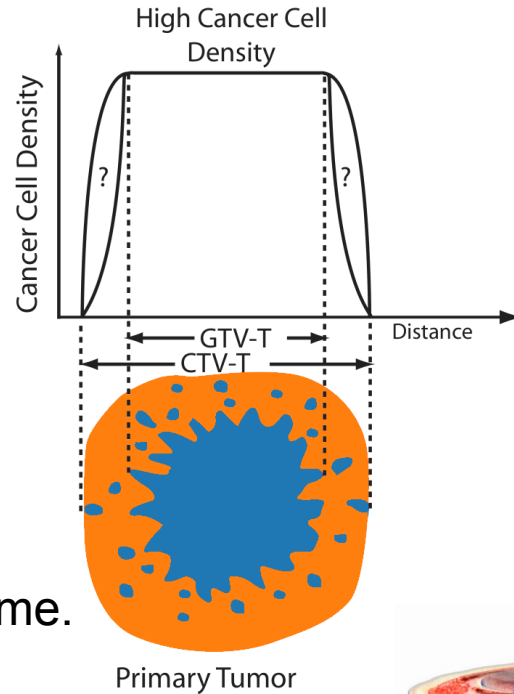
**GTV:** Gross tumor volume.  
Visible in CT.

**CTV:** Clinical target volume.  
Microscopic tumor spread.

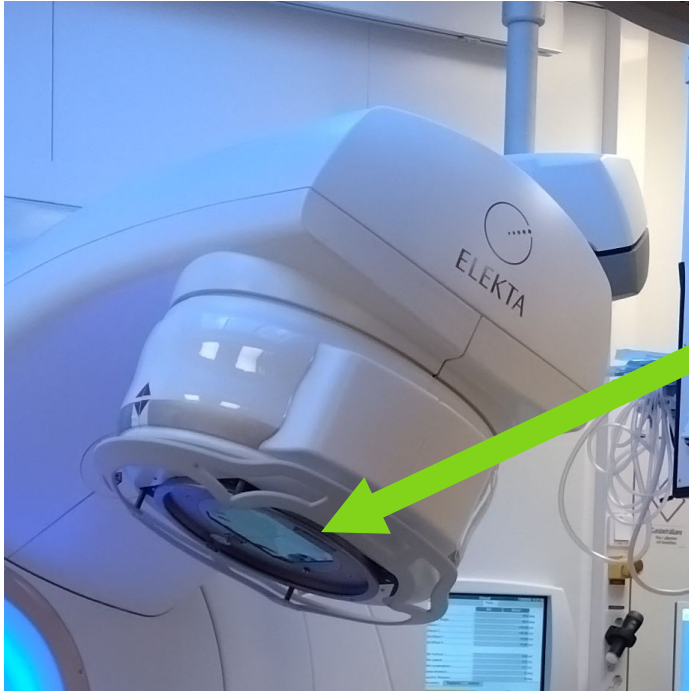
*Adapted from ICRU 71 (2004)*

**ITV:** Internal target volume.  
Motion encompassing.

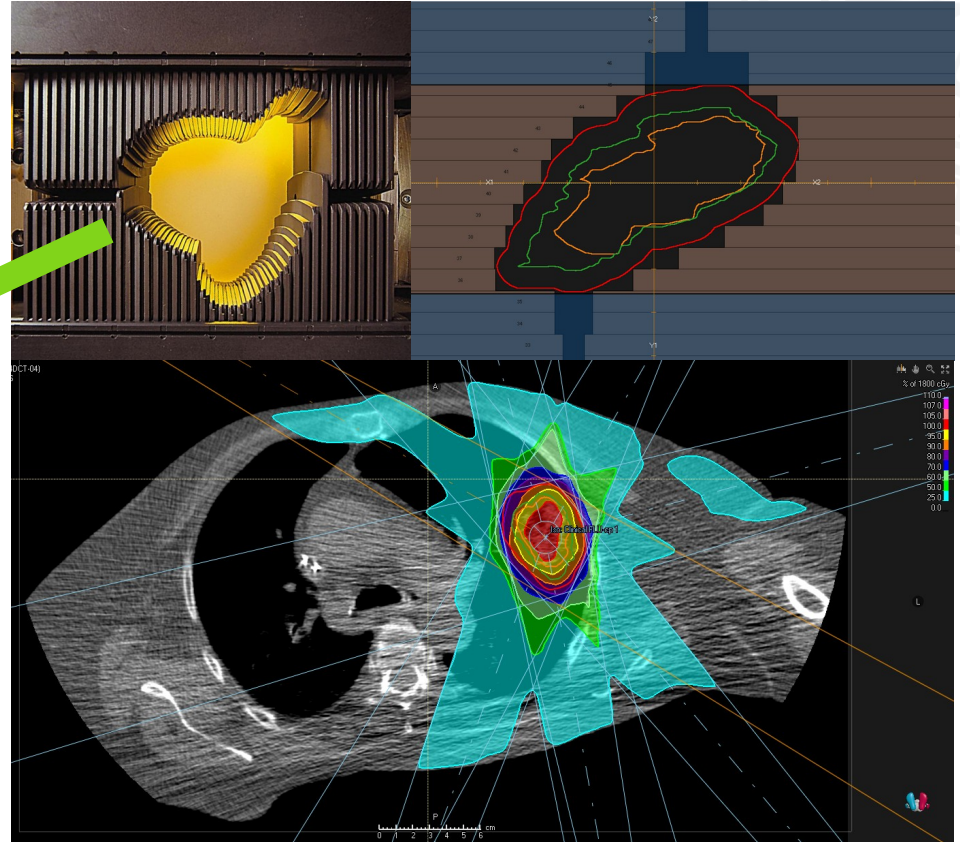
**PTV:** Planning target volume.  
Account for e.g. patient setup.



# Beam collimation



Multi leaf collimator (MLC) can be shaped to match the outline of the target (PTV) for 3D conformal treatments.



# Treatment planning

RayStation 11B - IonPG

Patient data management Patient modeling **Plan design** Plan optimization Plan evaluation QA preparation Treatment delivery

Plan setup 3D-CRT beam design Clinical-FLU-cp Clinical-FLU-cp Plan dose

1800 cGy x 1 fx = 1800 cGy  
Median dose (D50%)  
GTV  
Value: 1800 cGy

ROI material management  
ROI/POI details

Showing geometry status for: 4DCT-04

Name	Image set	Position	Machine	Fractions	Modality	Treatment technique
Clinical-FLU-cp	4DCT-04	HFS	RSL_InfinityAgl	1	Photons	3D-CRT

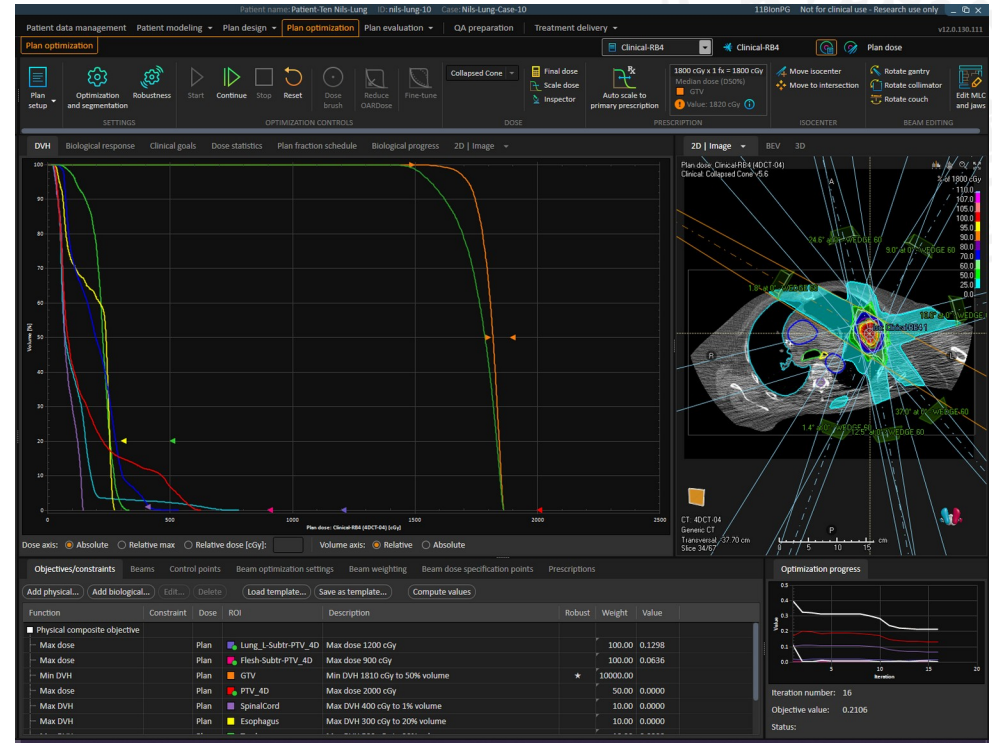
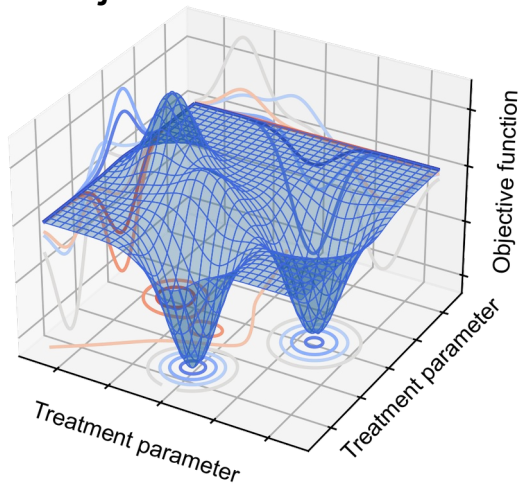
RayStation treatment planning system (TPS).

# Treatment plan optimization

Treatment planning system finds the optimal treatment parameters.

Trade-off between dose to the tumor and the dose to organs at risk according to user specification.

The specifications are summarized in a mathematical objective function which is minimized.



*Plan optimization in RayStation.*

**Part 3:  
Brachytherapy  
and  
electron beam  
therapy**



# Brachytherapy

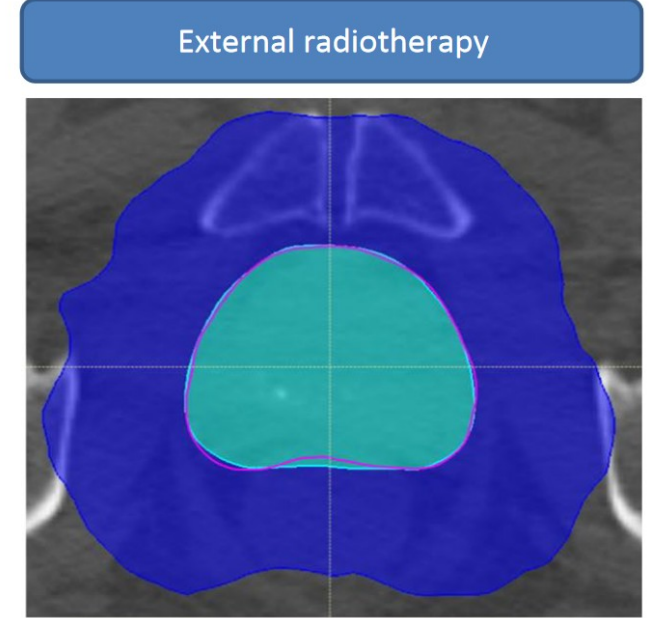
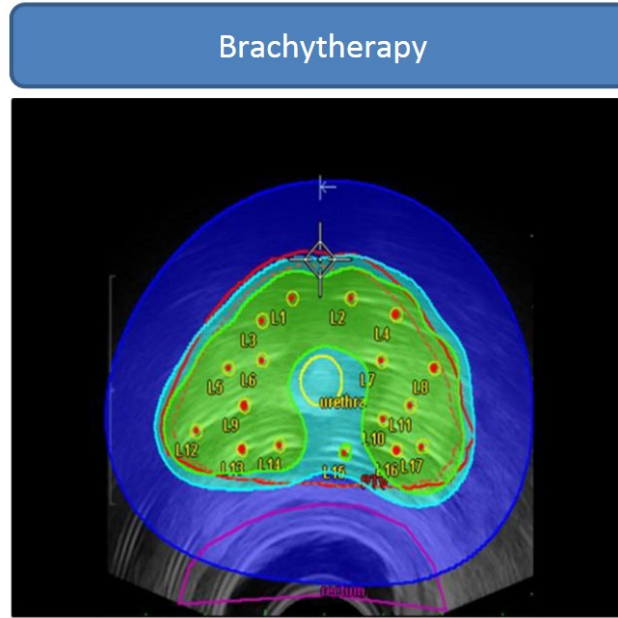
In external beam radiotherapy we always get an entrance dose.

Improve dose distribution by putting the **radiation source next to or inside the tumor!**

Can use:

- Implanted radioactive seeds that are placed inside the tumor. (lower dose rate).
- Needle with applicator (higher dose rate)

**It is an invasive intervention.**



*Brachytherapy boost to prostate target achieves a higher dose than the external radiotherapy with similar or lower dose to surrounding tissue.*

*Adapted from Chargari et al 2019.*

# Brachytherapy in Uppsala

Most treatments are palliative.

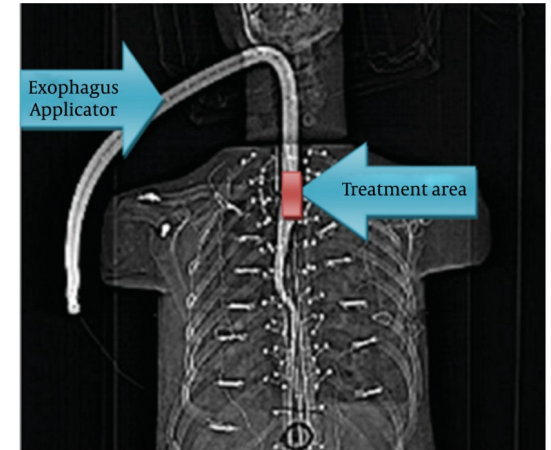
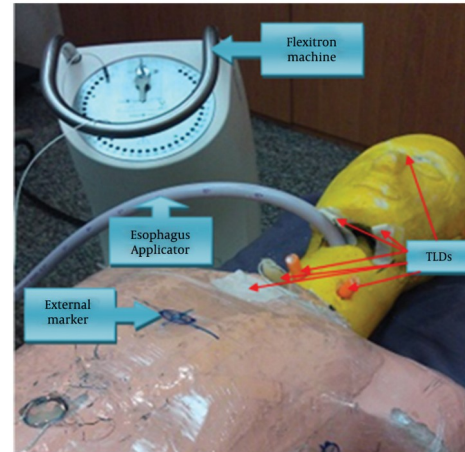
Cervix and prostate cancer are the most common (10-15 per year).  
High dose rate using needles and applicator with **Iridium 192** source.



*Cervix applicator.*

<https://www.elekta.com/products/brachytherapy/applicators>

Esophagus is less common.  
Palliative treatment, applied with catheter down the throat.



*Verification of esophageal brachytherapy delivery method.  
Adapted from Nikoofar et al 2015.*

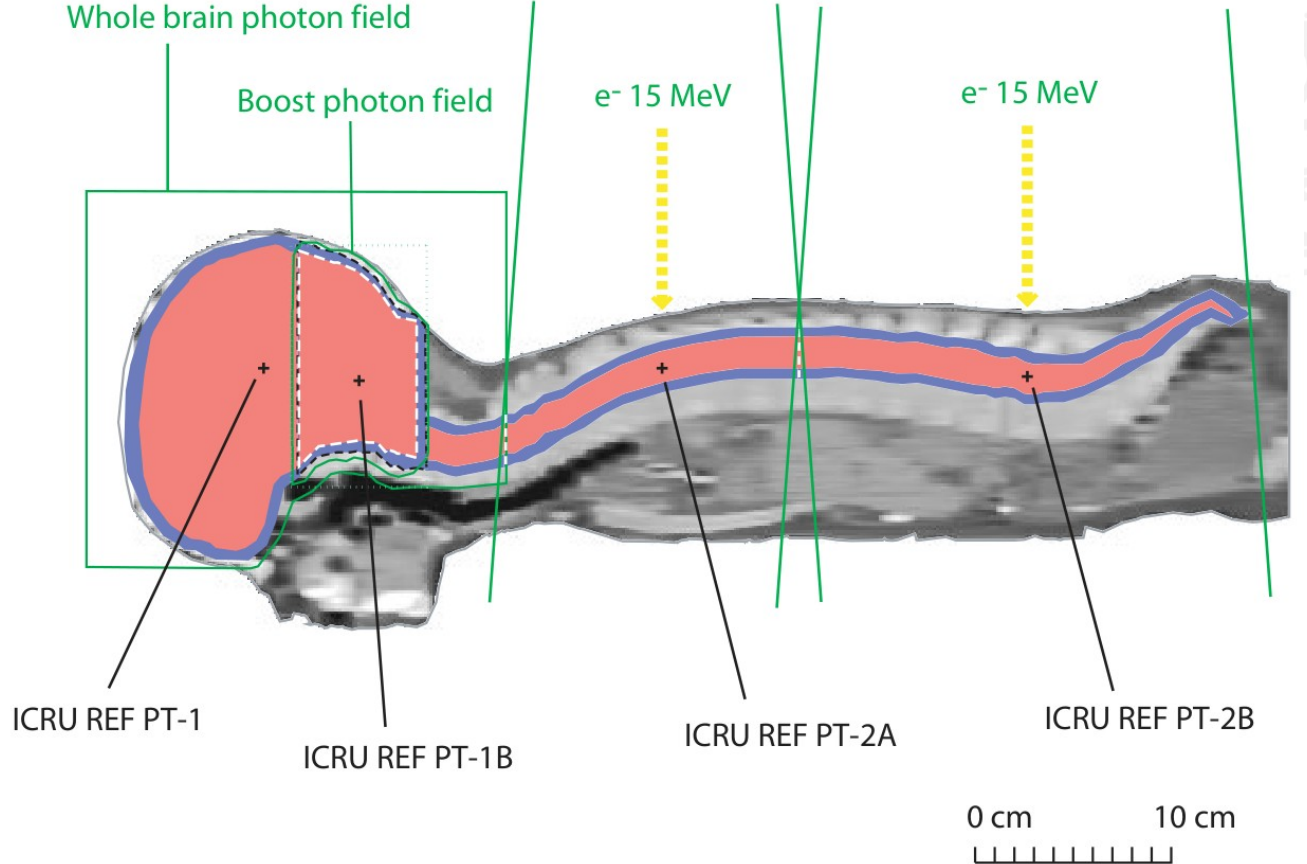
# Electron beam therapy

Short, finite, range of only a few centimeters.

**Used to treat shallow targets.**

Can be delivered with same linear accelerator used for X-ray therapy.

Mostly superseded with proton therapy.



*Whole brain and spinal cord irradiation for treatment of medulloblastoma in a child.*

*Adapted from ICRU 71 (2004)*

# External beam radiotherapy

## 1. First hour

- Background and history
- Modern X-ray radiotherapy
- Brachytherapy and electron beam therapy

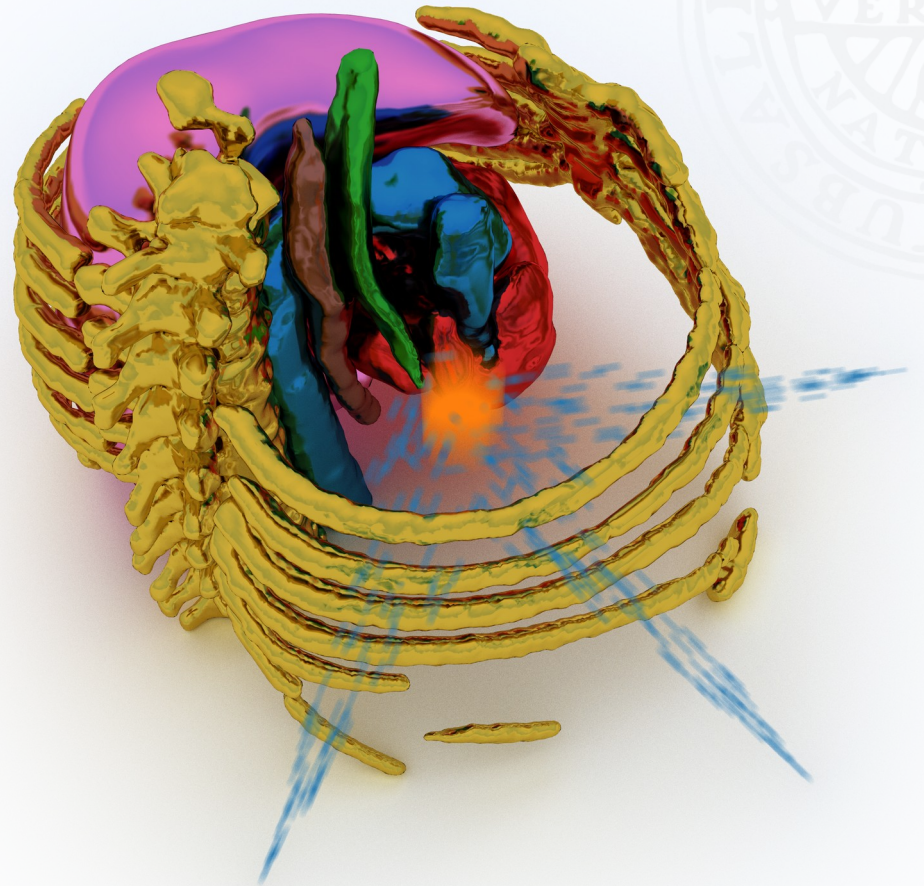


## 2. After the break

- Proton therapy
- Tech. developments
- Biological aspects

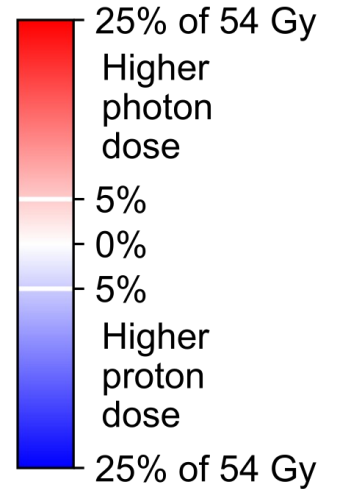
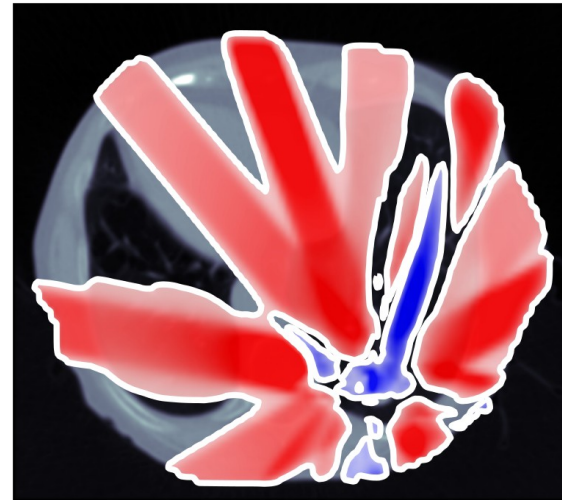
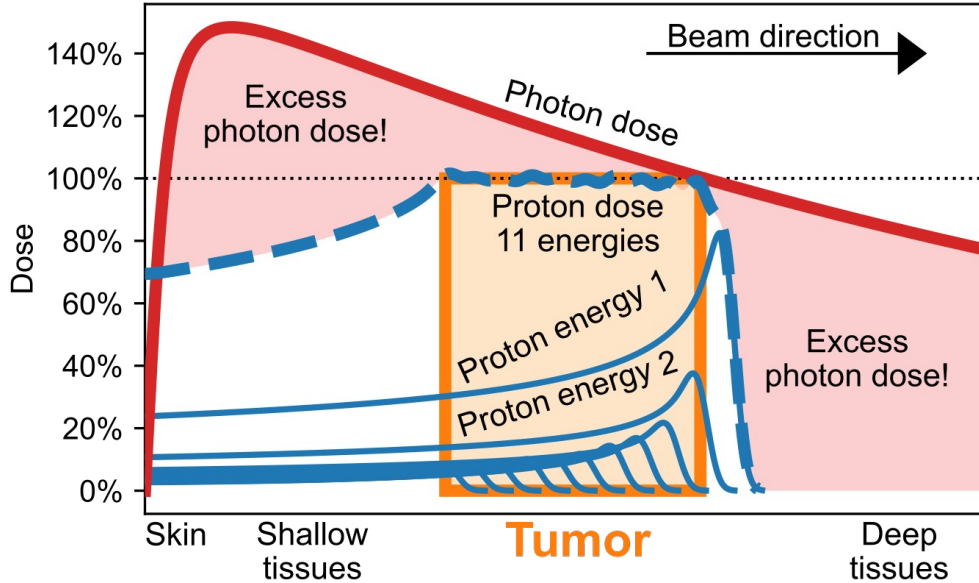


# Part 4: Proton therapy



# Proton therapy – Radiation that stops!

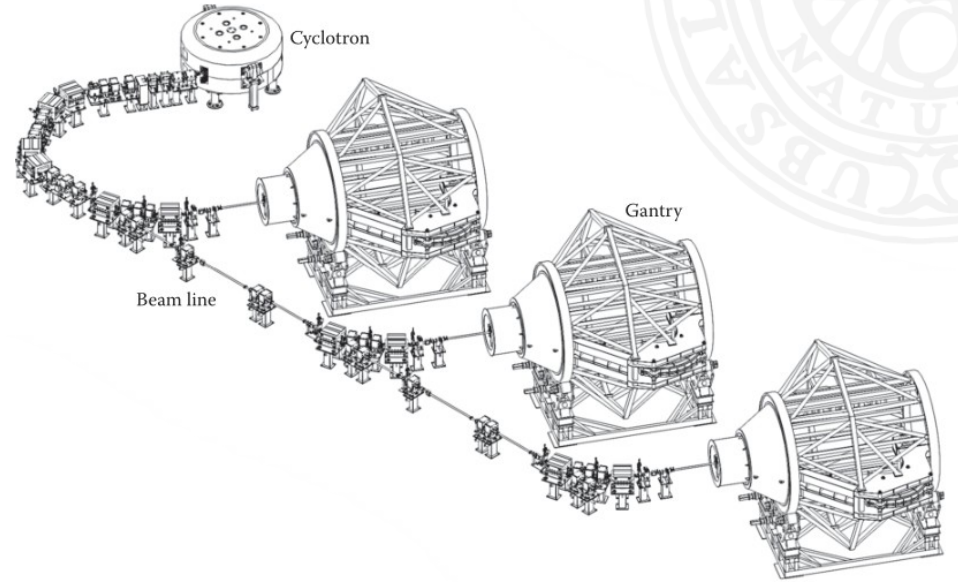
Charged particle radiation, such as a proton beam, have a **finite range**. The dose is the highest at the end of this range, at the **Bragg peak**. The range is energy dependent, a clinical energy of **230 MeV** have a range of **32 cm** in water.



# Proton therapy – In Uppsala

The **Skandion clinic** was built as a national proton therapy center.

The only clinic in Sweden and the first in the Nordics. Operational since 2015.

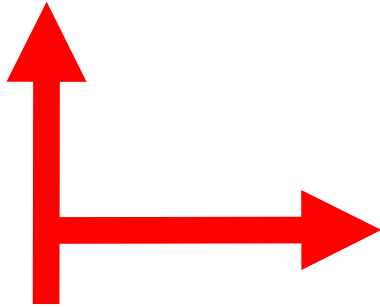
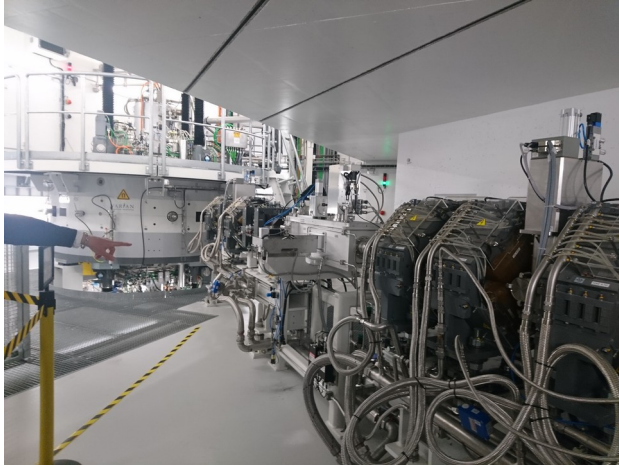


*The source of the proton beam is a 230 MeV cyclotron accelerator.*

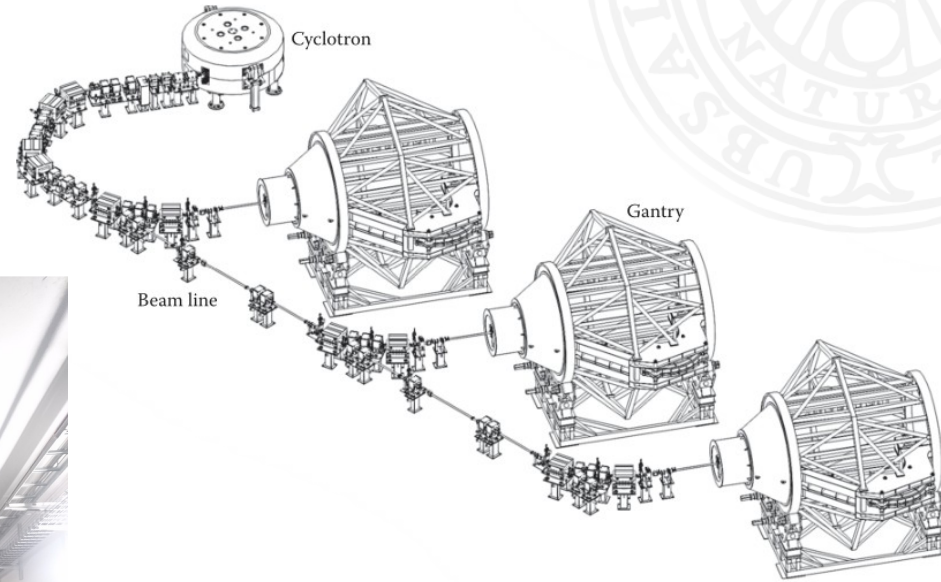
*Adapted from Tutorials in radiotherapy physics (2016), original source: IBA*

Second proton treatment in the world was in Uppsala in 1957! First was in Berkeley in 1954!

# Proton therapy – The beam



Cyclotron and beamline at the proton therapy center in Aarhus (Denmark).



*Beam is transported to patient by the beam line.  
Adapted from Tutorials in radiotherapy physics (2016),  
original source: IBA*

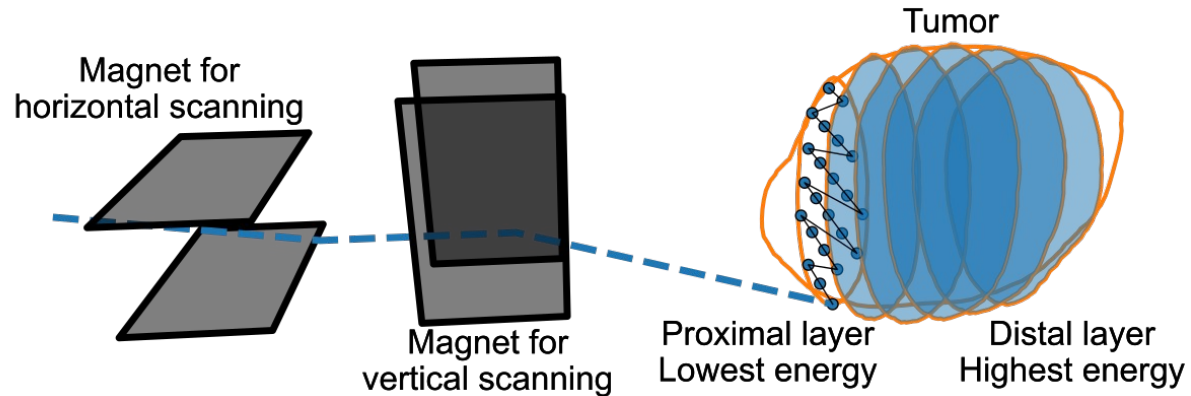
# Proton therapy – Delivering the dose



*Beam nozzle can be rotated around the patient.  
Treatment room at the Skandion clinic.*

By modulating the proton beam energy the range is adjusted.

The beam is steered horizontally and vertically by magnets.



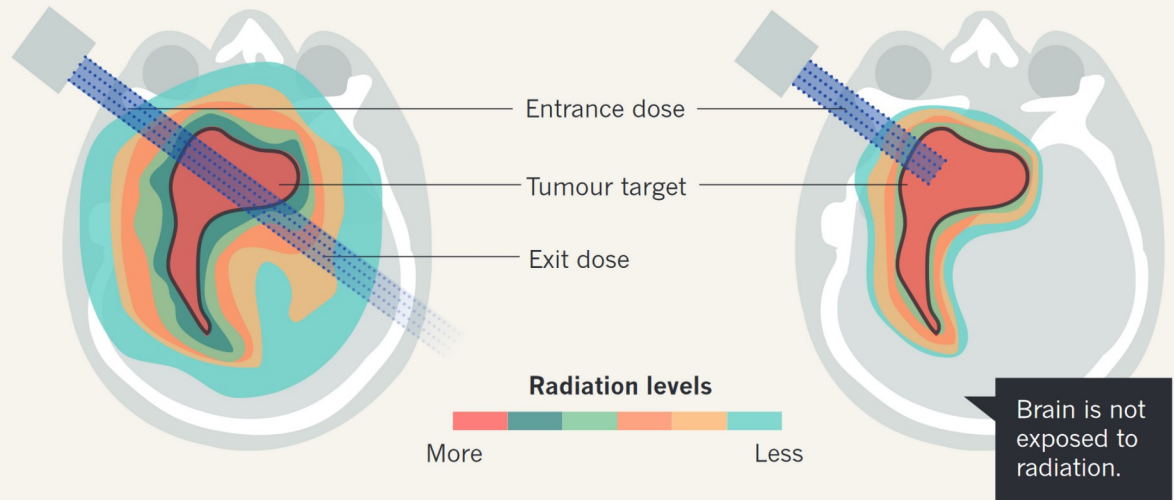
*A pencil beam scanning system can steer the beam to cover the tumor with dose.*

# Proton therapy – Reduced dose to healthy tissues

Best use case is for pediatric brain tumors.

## CLINICAL BENEFITS

Beams of protons can be more tightly focused than beams of X-rays, killing cancer cells while sparing more of the surrounding tissue. This is beneficial for isolated tumours near sensitive parts of the body, such as the spinal cord and brain.



### CONVENTIONAL RADIATION THERAPY

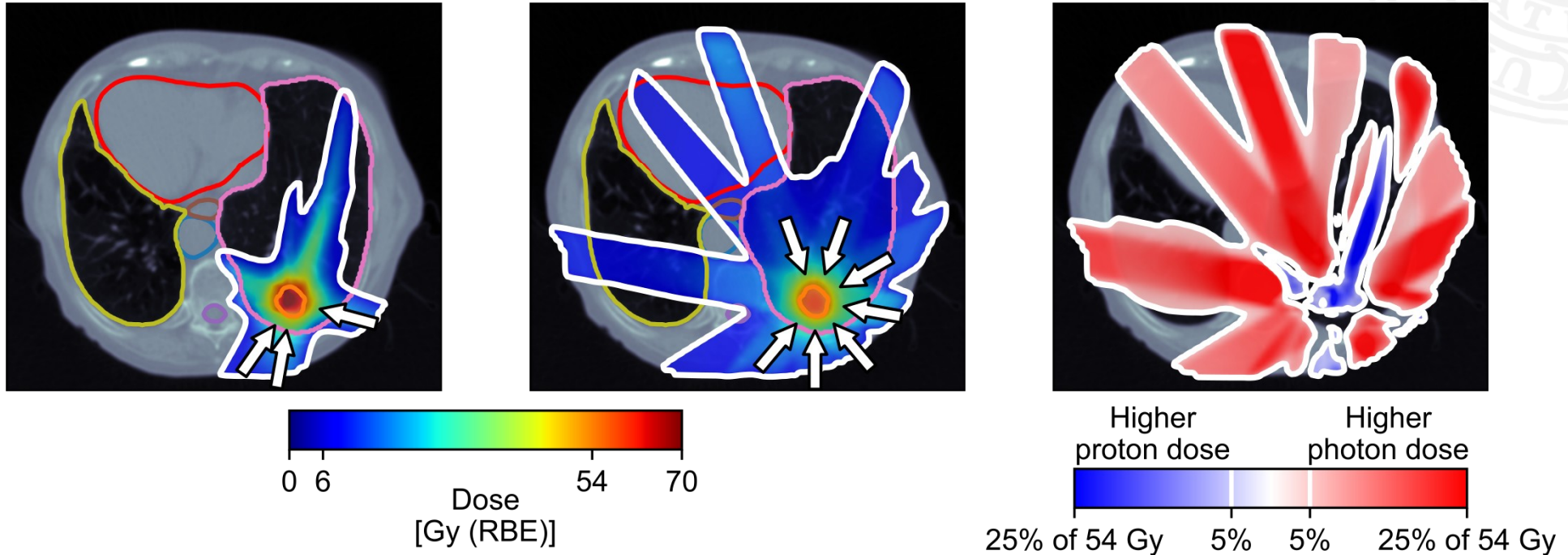
Beam passes through the patient, resulting in healthy cells being damaged by the beam.

### PROTON THERAPY

Protons can be tuned to stop at the depth of the tumour and release their energy. Fewer healthy cells are exposed.

*Adapted from Bortfeld et al (2017).*

# Proton therapy – Reduced dose to healthy tissues



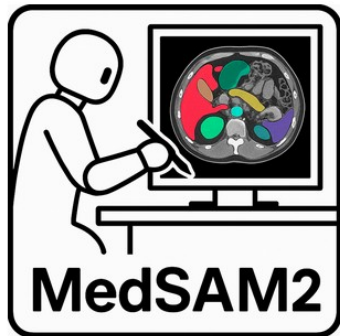
The cost of the improved dose distribution is that **proton therapy is more sensitive** to radiological and geometrical uncertainties due to patient positioning and anatomical changes.

# **Part 5: Technological developments**

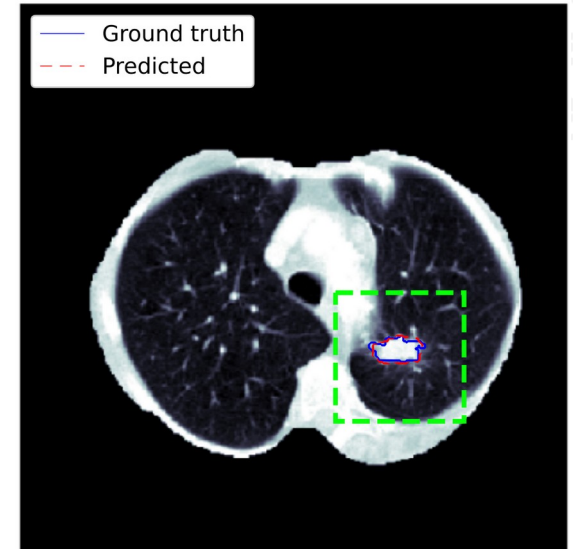
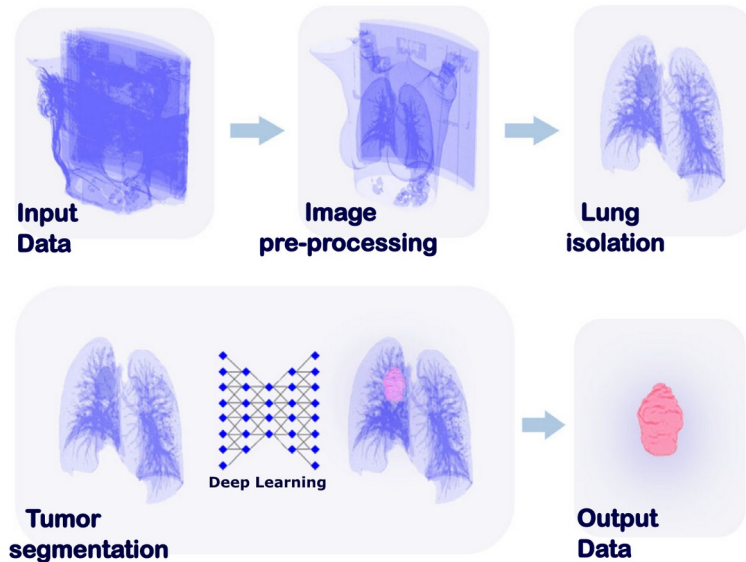


# AI for structure delineation

- Commercial tools used at Akademiska since ~2021.
- Used for basically all curative treatments.
- The contours are corrected by a radiologist.



Segment Anything in 3D Medical Images and Videos



*Automatic segmentation of lung tumor.  
Adapted from Primokov et al 2022.*

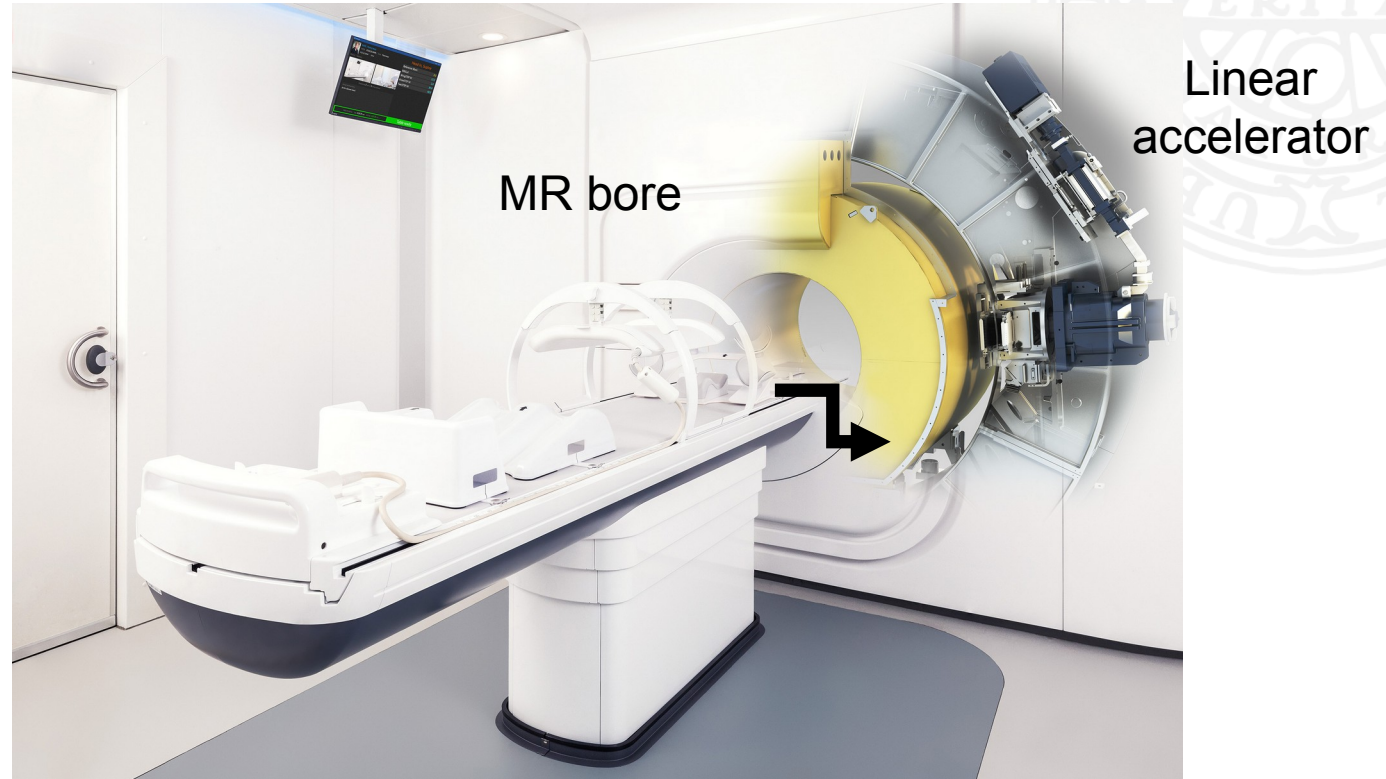
# MR-linac

Integrated magnetic resonance (MR) imaging and linear accelerator for X-ray radiotherapy.

Allows for improved patient positioning and motion monitoring.

Installed at Uppsala University Hospital since 2019.

Currently the only one in Sweden.



*Elekta Unity MR-Linac.*

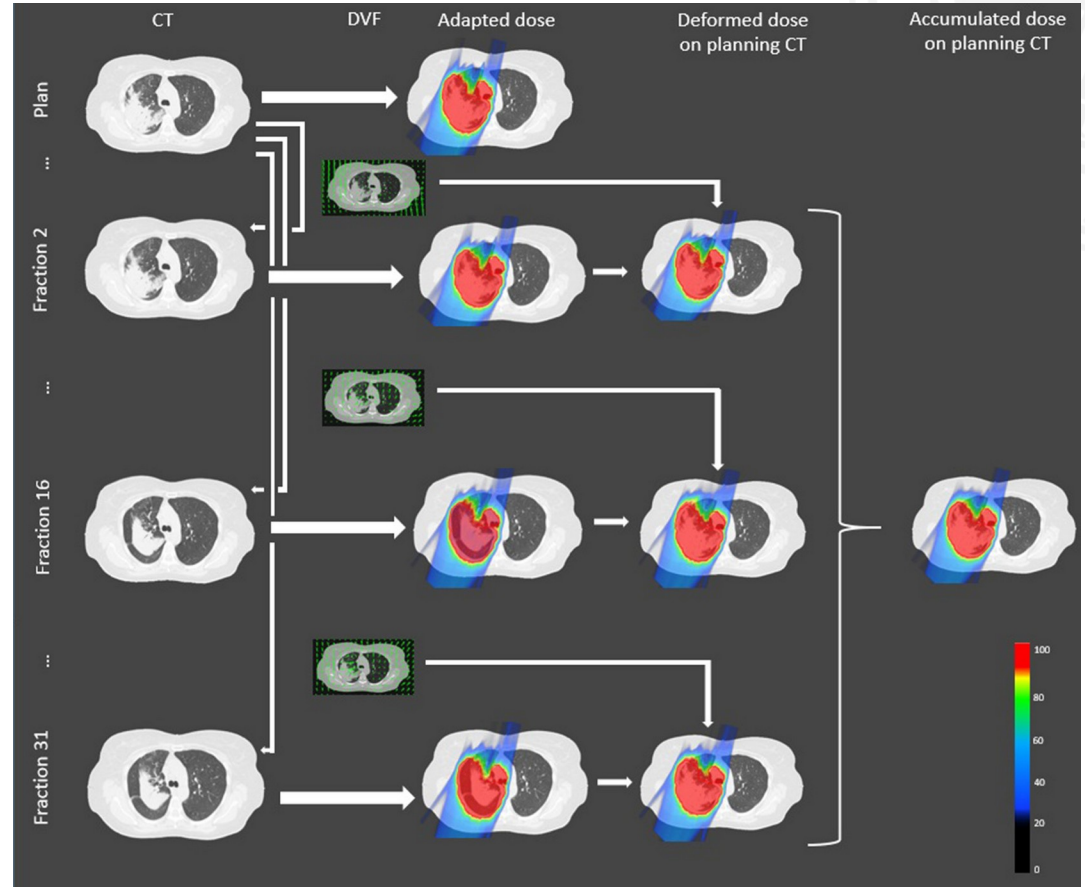
*<https://www.elekta.com/products/radiation-therapy/unity/>*

# Adaptive radiotherapy

Treatments can be given in fractions over the course of several weeks.

During this time anatomical changes can take place.

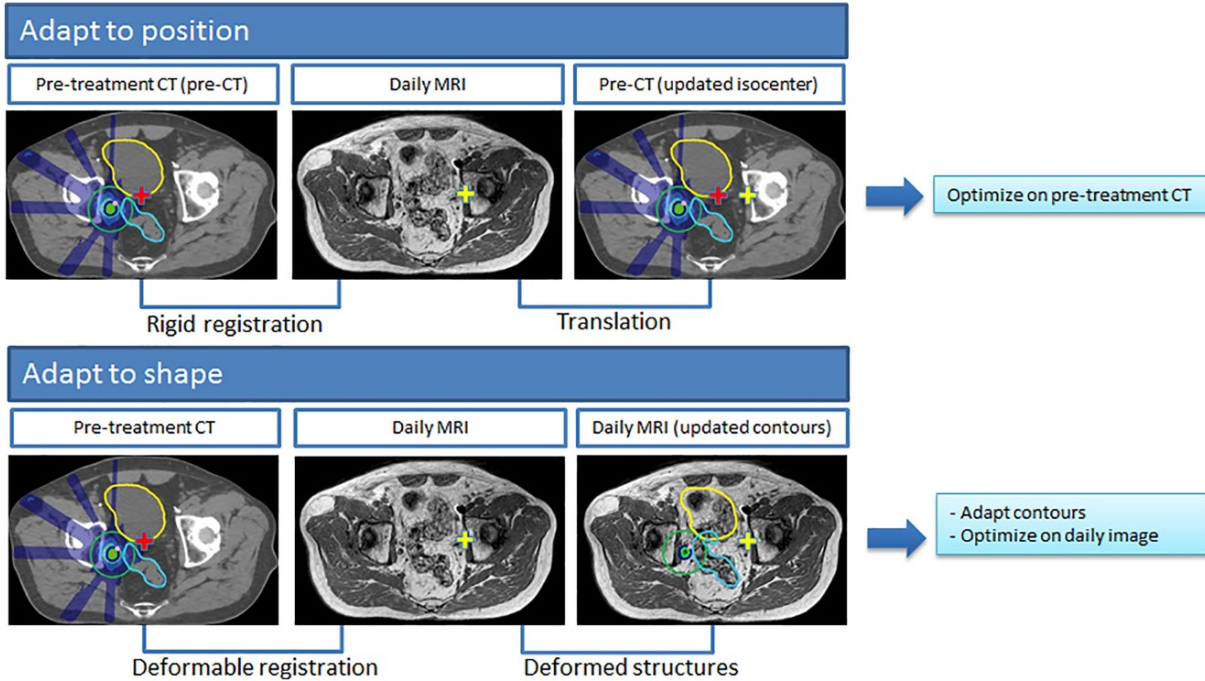
Treatments can be improved by imaging the patient at more occasions during this time period and adapting the plan!



*Tumor shrinkage during course of treatment.  
Adapted from Albertini et al 2020.*

# Adaptive radiotherapy for MR-linac

The integrated imaging makes the MR-Linac suitable for adaptive radiotherapy!

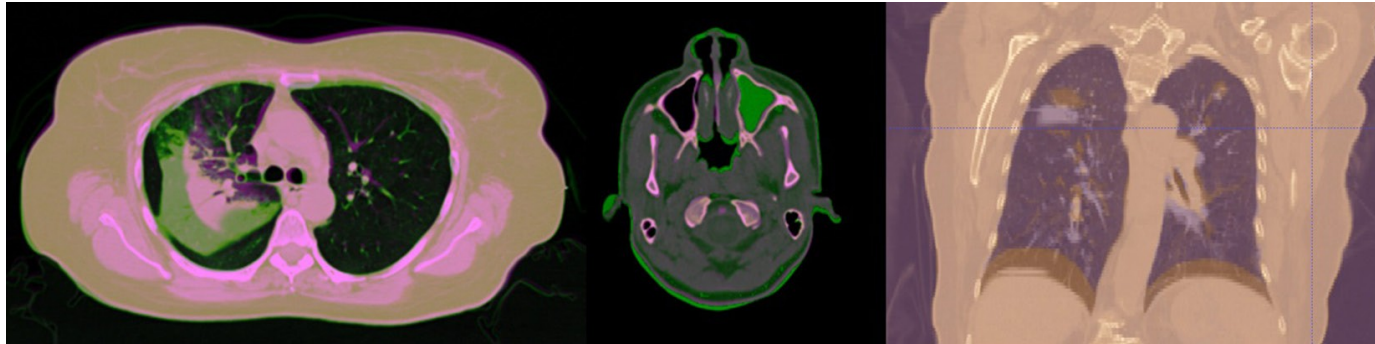


*Adapt to position and/or to anatomy.  
Adapted from Winkel et al 2019.*

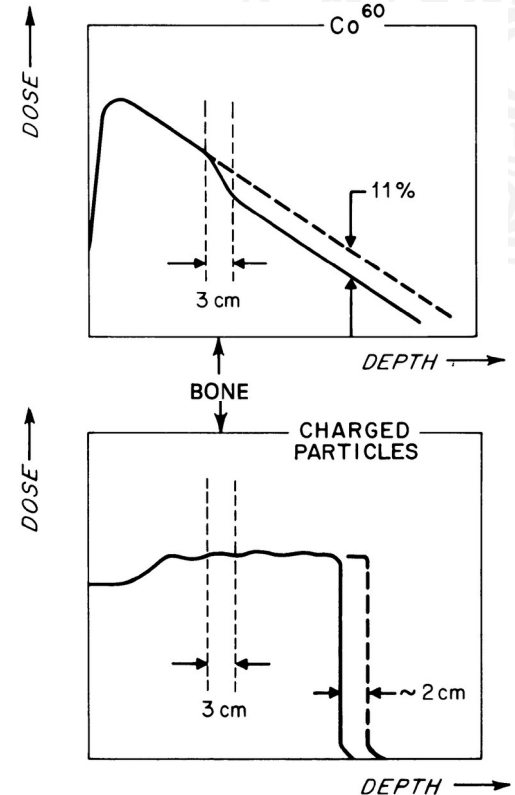
# Adaptive radiotherapy for proton therapy

Adapting the plan to daily anatomy is even more crucial for proton therapy!

Might cause complete miss since range is affected!



*Anatomical changes. Lung tumor shrinkage, nasal filling and respiratory motion. Adapted from Albertini 2020.*



*A change in density corresponds to change in intensity for a photon beam and range for a proton beam. Adapted from Orton et al 1982.*

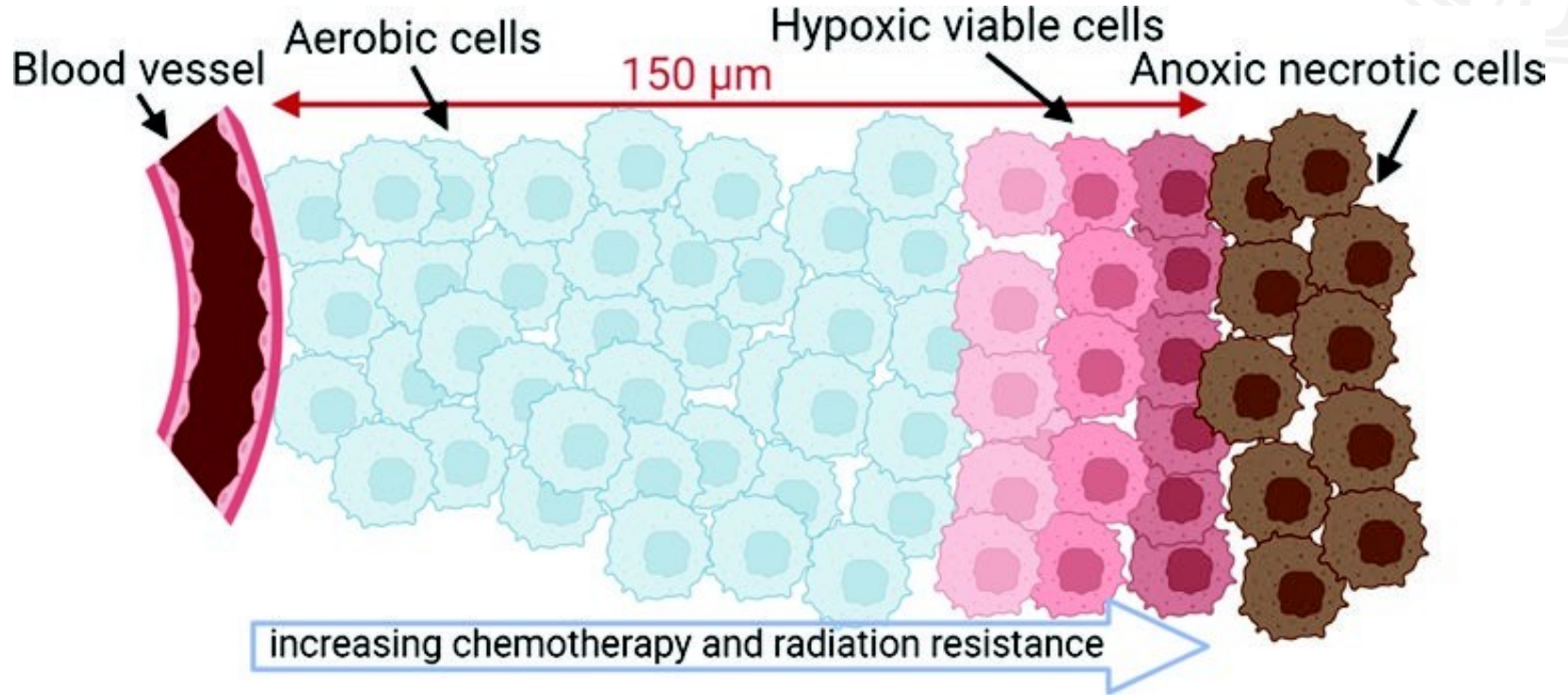


# **Part 6:**

# **Biological aspects**

# Adapt to biology: Hypoxia

Hypoxic cancer cells can be up to **three times** as resistant to radiation damage as aerobic cancer cells!  
Oxygen fixates the DNA radiation damage.

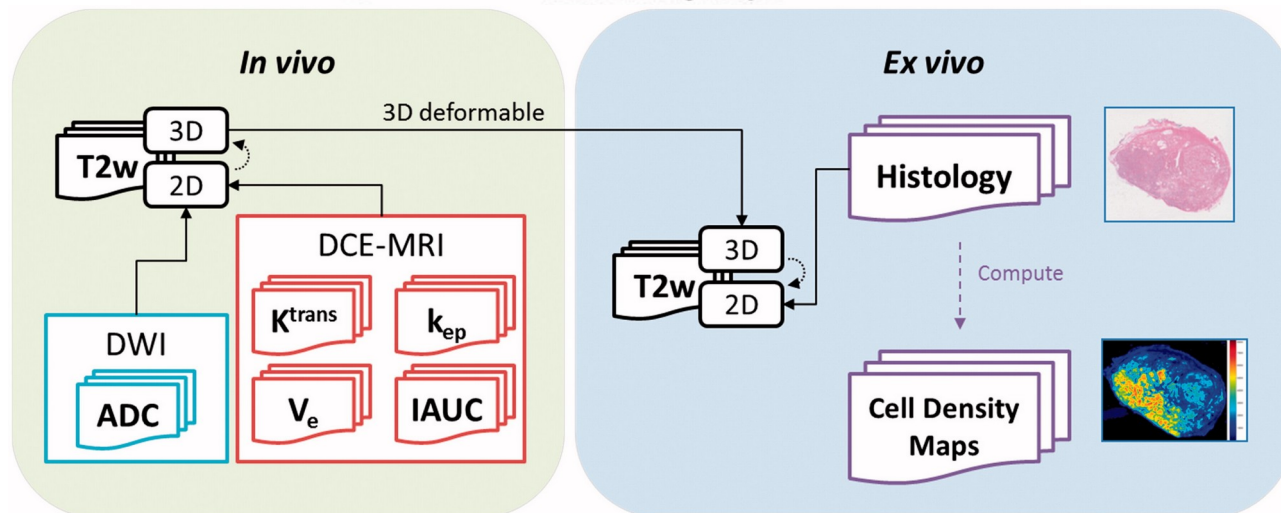
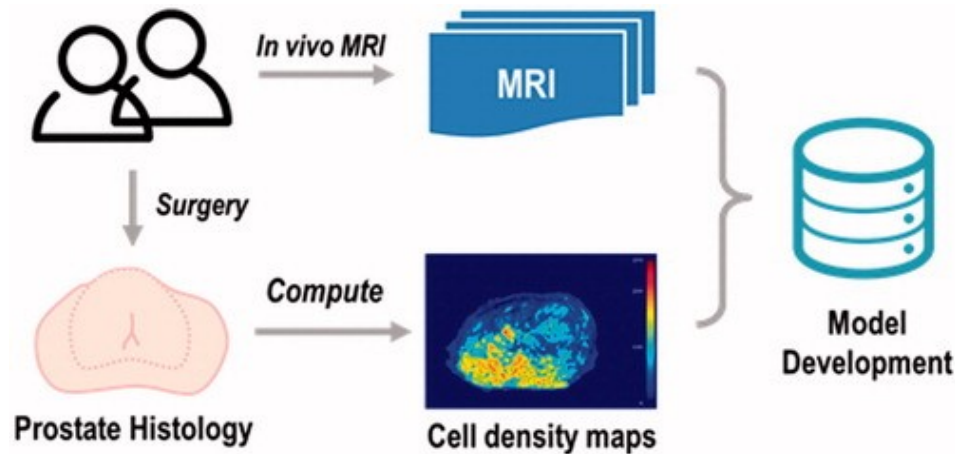


*Adapted from Baatout et al 2023.*

# Adapt to biology: Cell density

Disease grading is a prognostic factor and can be used to personalize the treatment.

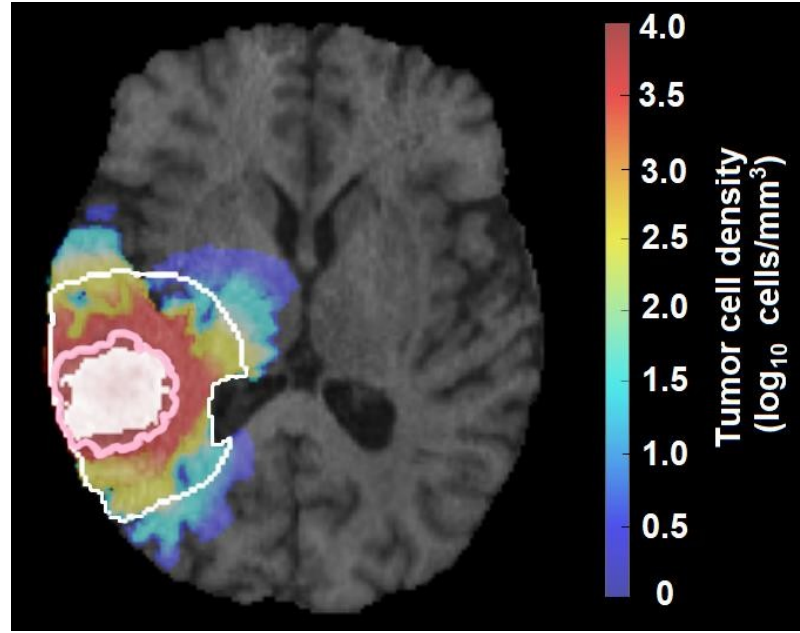
Can be estimated for prostate cancer using functional imaging of the cell density.



*Adapted from Sun et al 2018.*



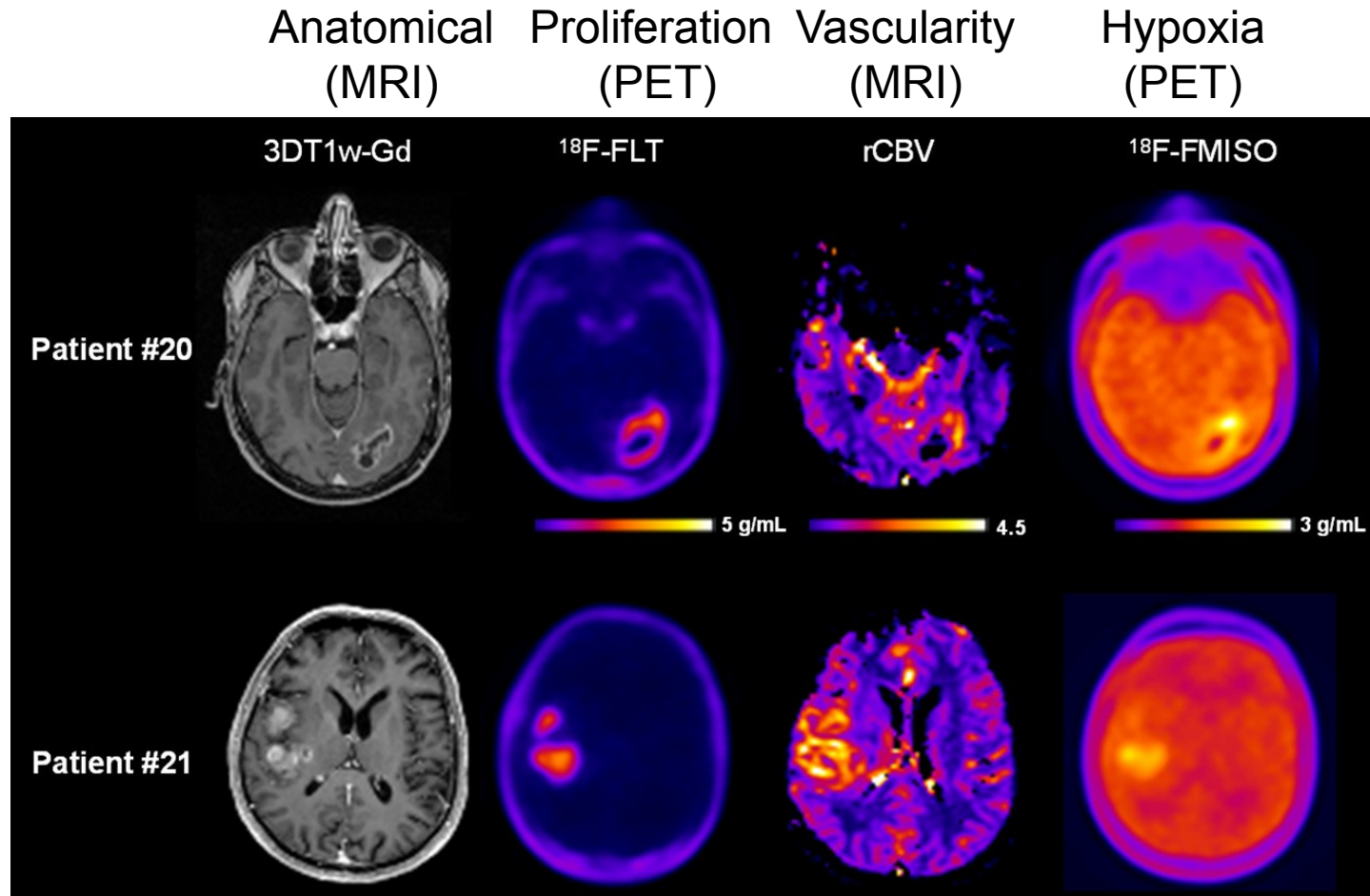
# Adapt to biology: Proliferation



*By simulating cell infiltration the proliferative tumor can be found to extend beyond the clinical target volume indicated in white.  
Adapted from Häger 2023.*



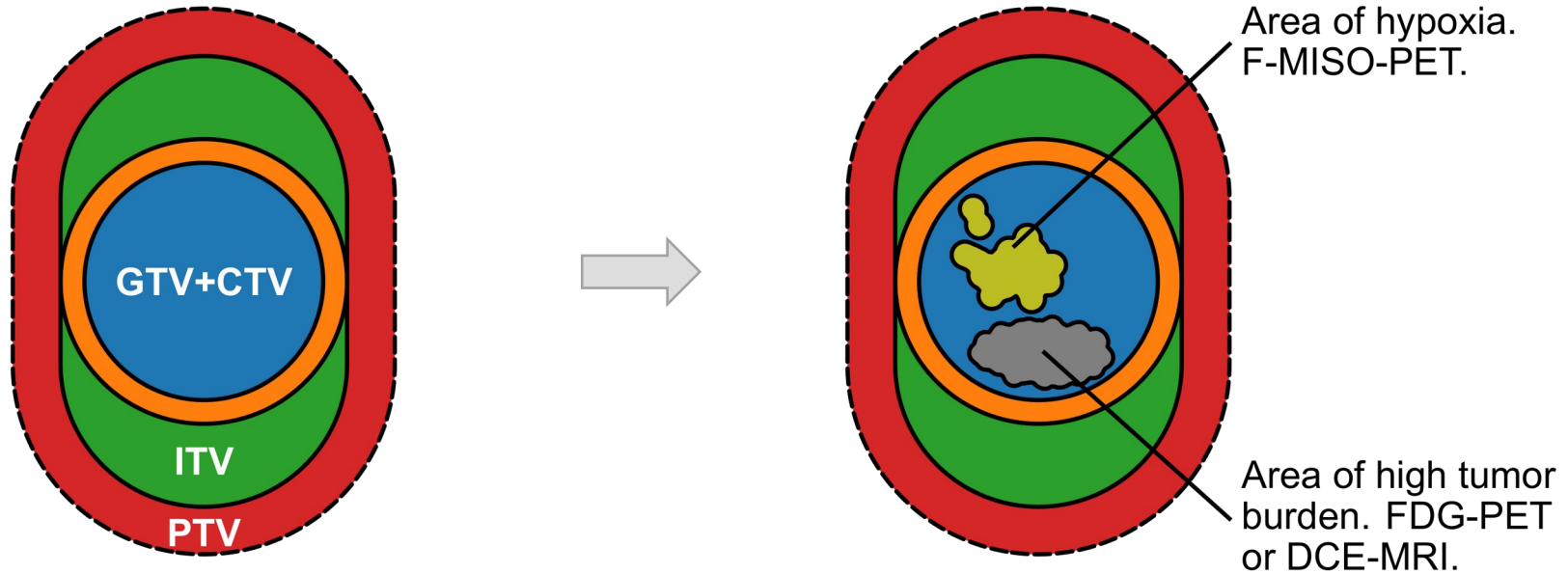
# Adapt to biology: PET and MRI



*Adapted from Collet et al 2021*

# Adapt to biology: Biological target volume (BTV)

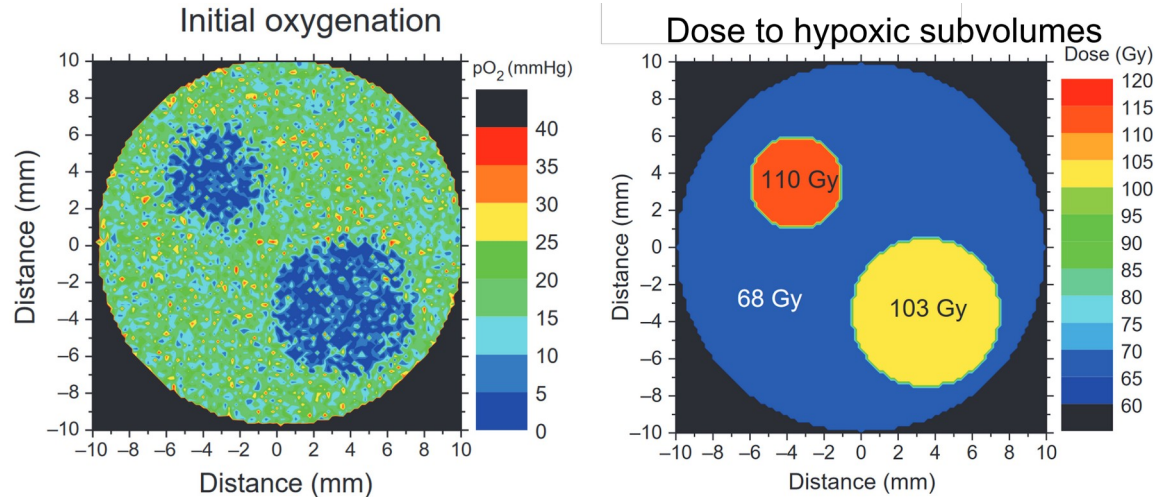
Identify sub-target areas using functional imaging such as PET or MR.



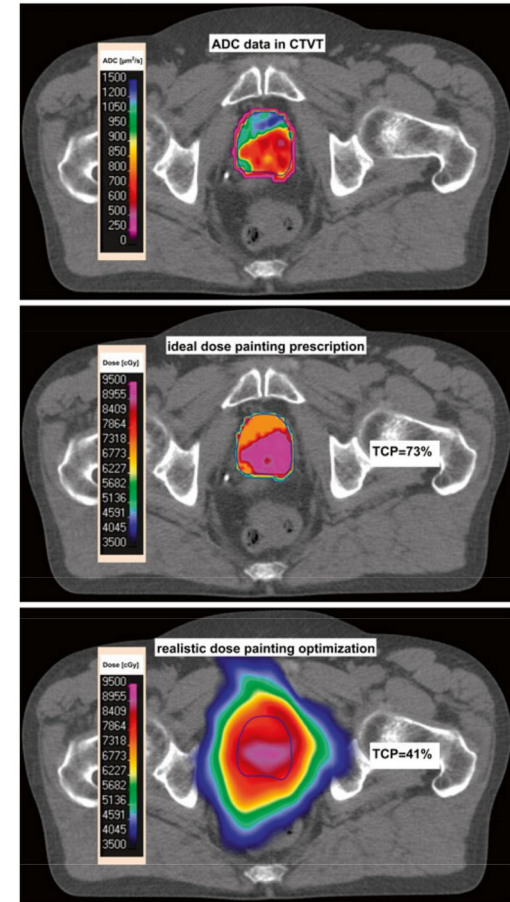
*Inspired by Beaton et al 2019.*

# Adapt to biology: Dose painting

Escalate the dose locally according to hypoxia or cell density.



*Hypoxia dose painting.  
Adapted from Toma-Dasu et al  
2009.*

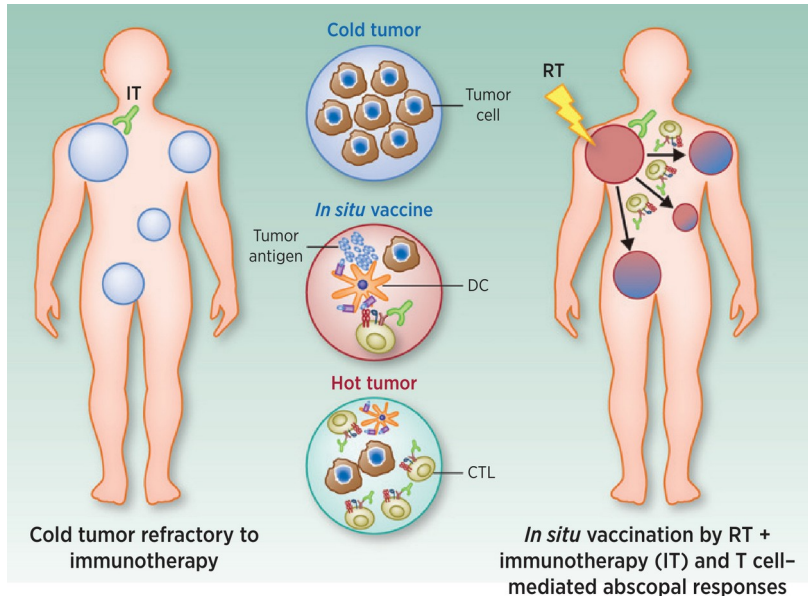


*Apparent diffusion coefficient (ADC)  
based cell density dose painting.  
Adapted from Grönlund 2019.*

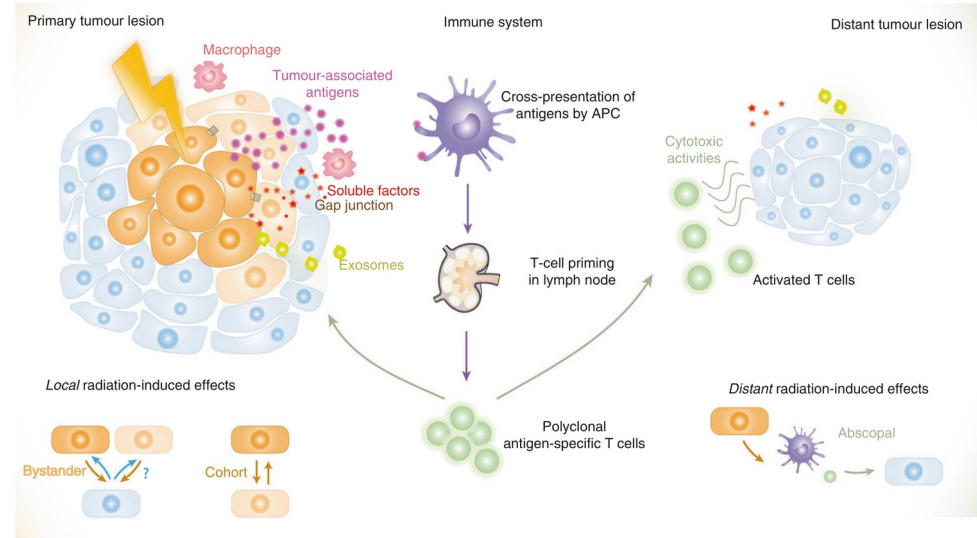
# Immune activation and systemic response

Radiotherapy of one tumor can cause immune activation that leads to shrinking of other tumors (Abscopal effect).

Sparing of circulating lymphocytes with e.g. FLASH could have effects on immune therapy.



*Adapted from Whiteside et al 2016.*

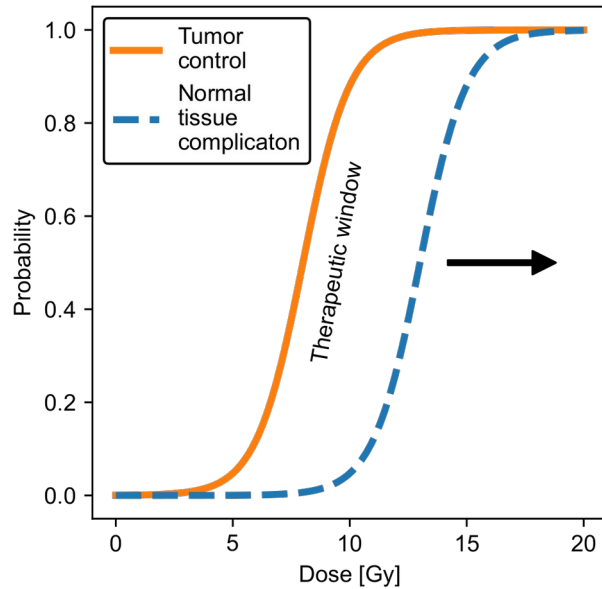


***Radiation induced immune response.  
Adapted from Daguinet et al 2020.***



# **Take home messages**

# Conclusions



1 in 3 people will develop a cancer.

1 in 2 of all cancer patients receive radiotherapy.

Even small improvements could have a big impact!

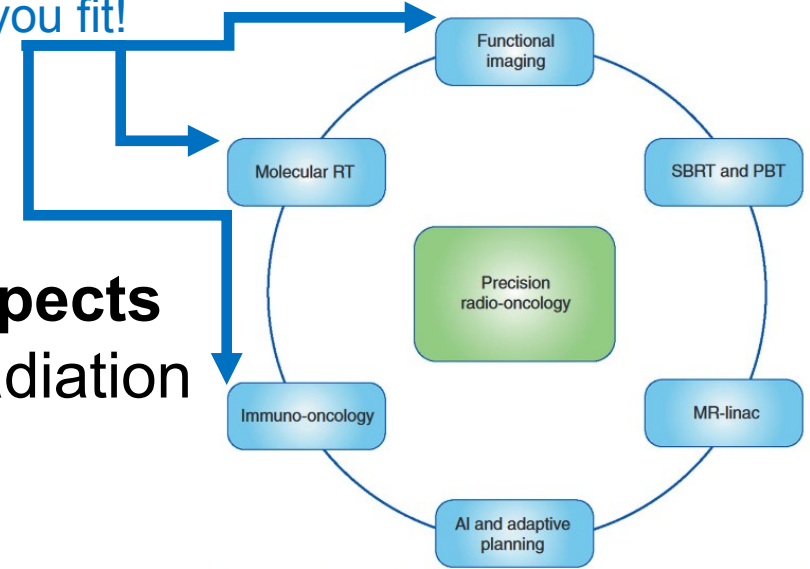
This is where you fit!

## Physical aspects

- Type of radiation
- Precision
- Accuracy

## Biological aspects

- Oxygenation
- Radiosensitivity
- Fractionation



**Fig. 4 The future of precision radiation oncology.** The future of precision radiation oncology will incorporate advanced radiotherapy techniques with functional imaging that will allow for biological dose optimisation. Novel biologically targeted radio-pharmaceuticals will enable selective delivery of internal radiation, termed molecular radiotherapy. Immune modulators will be used in combination with different radiotherapy techniques in the field of immuno radio-oncology to take advantage of the synergy between these two modalities of treatment. Artificial intelligence (AI) will assist with the adaptive planning process, allowing a new radiation plan to be created, based on imaging obtained on the day of treatment. SBRT stereotactic body radiotherapy, PBT proton beam therapy, CT computerised tomography, MR Linac magnetic resonance linear accelerator

*Adapted from Beaton et al 2019.*

# Links

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<https://www.smithsonianmag.com/innovation/fifty-years-ago-the-first-ct-scan-let-doctors-see-inside-a-living-skull-180978792/>

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