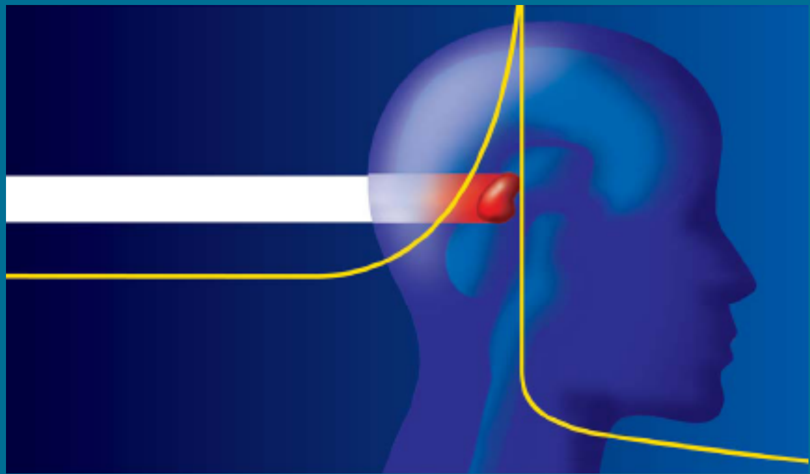
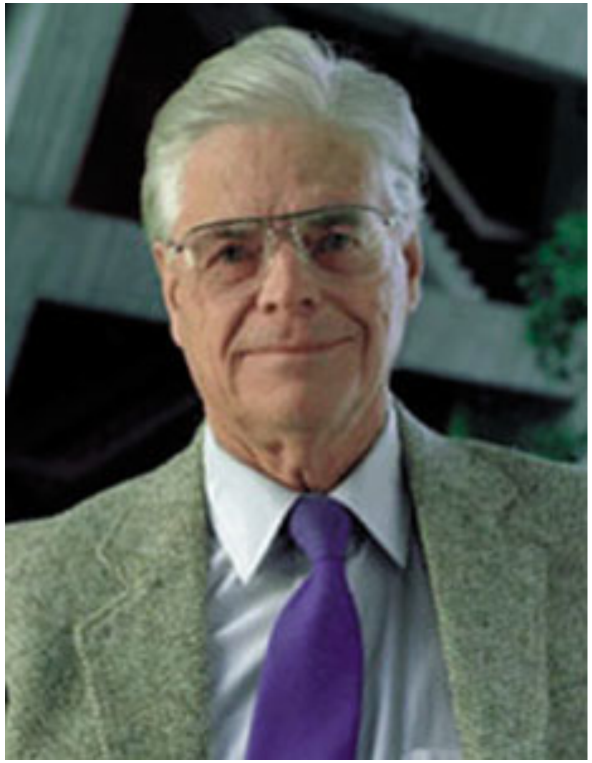
Autumn Lectures / Tbilisi / 2013

Tumor therapy with protons and light ions



21 October 2013 | Markus Büscher

Proton Beam Therapy – History



A Man - A Vision

In 1946 Harvard physicist
Robert Wilson (1914-2000) suggested*:

- **Protons can be used clinically**
- **Accelerators are available**
- **Maximum radiation dose can be placed into the tumor**
- **Proton therapy provides sparing of normal tissues**
- **Modulator wheels can spread narrow Bragg peak**

*Wilson, R.R. (1946), "Radiological use of fast protons," Radiology 47, 487.

Proton Beam Therapy – History

1946 R. Wilson suggests use of protons

1954 First treatment of pituitary tumors

1958 First use of protons as a neurosurgical tool

1967 First large-field proton treatments in Sweden

1974 Large-field fractionated proton treatments program begins at HCL, Cambridge, MA

1990 First hospital-based proton treatment center opens at Loma Linda University Medical Center

Proton Beam Therapy – Today

JÜLICH FORSCHUNGSZENTRUM

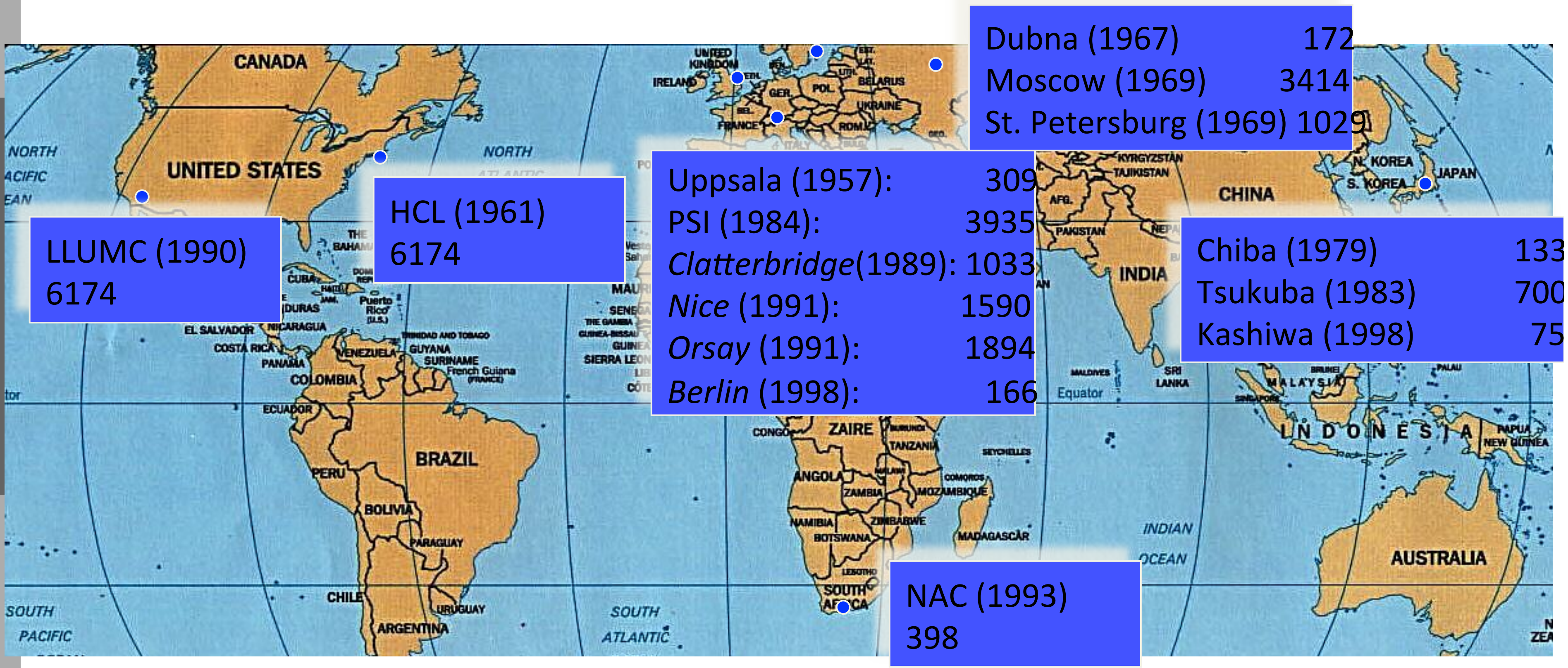
X-ray and Proton therapy are well established

Protons:

- 5,000 – 10,000 potential patients p.a. in Germany

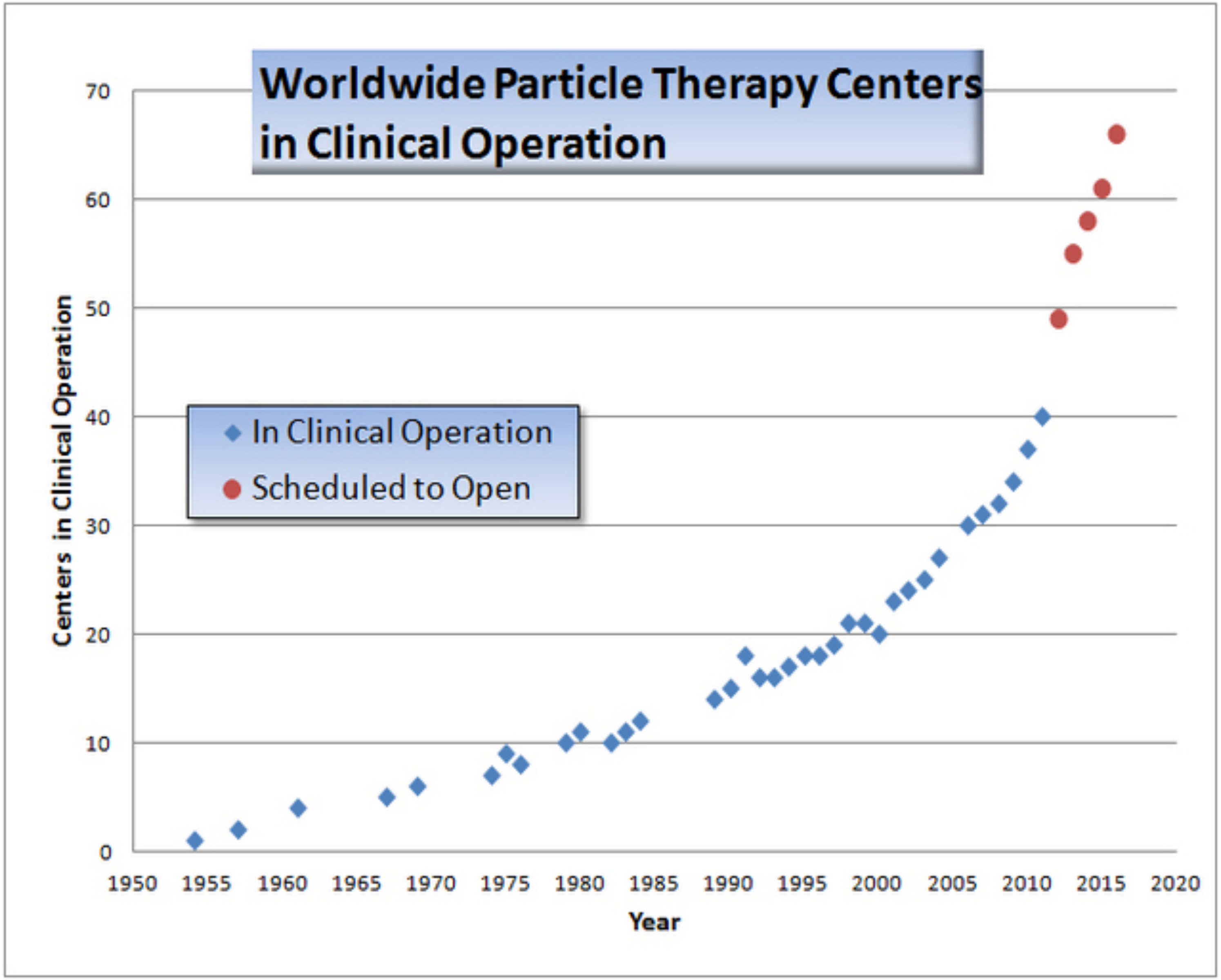
Proton Beam Therapy – Today

World wide: 39 therapy centers / 55.000 treatments p.a.



Next generation: Carbon ions

Proton Beam Therapy – Today

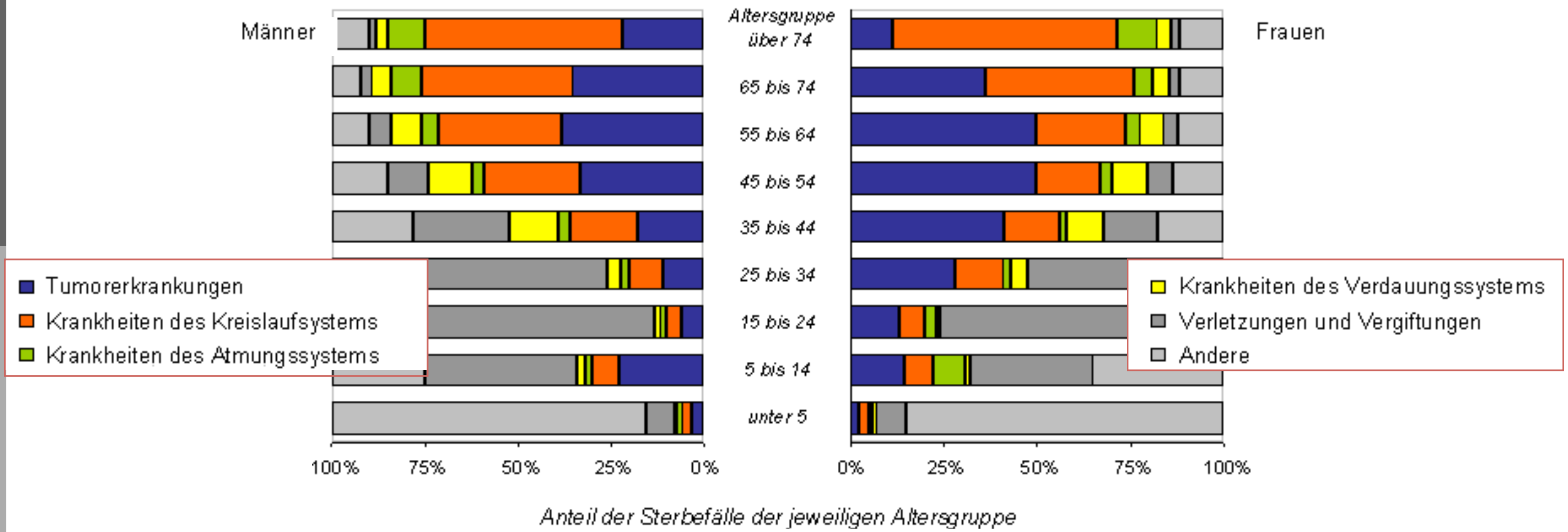


Proton Beam Therapy – Cancer

~486,000 incidences per year in Germany

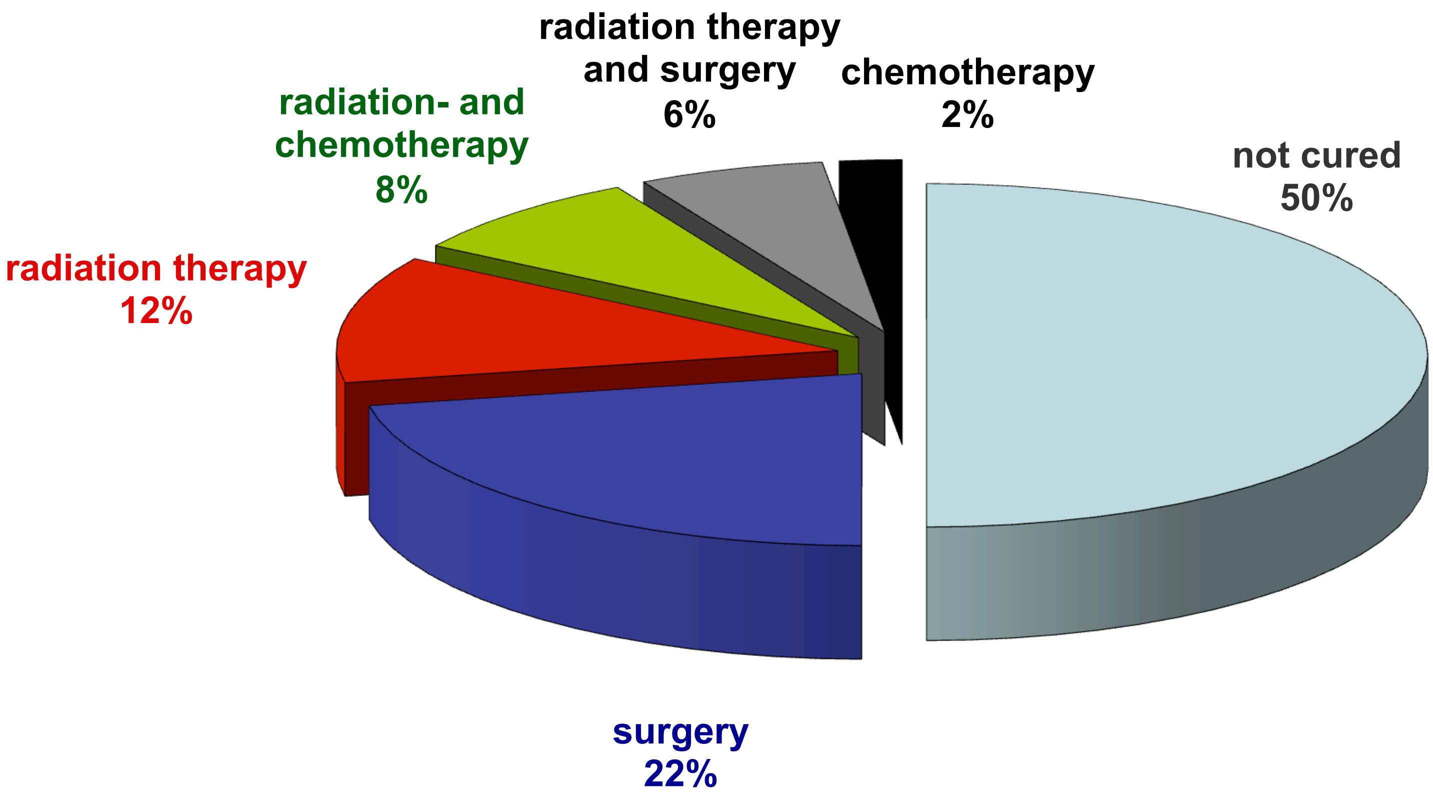
Every 3rd human gets a malignancy during her/his lifetime

Every 5th person dies of cancer



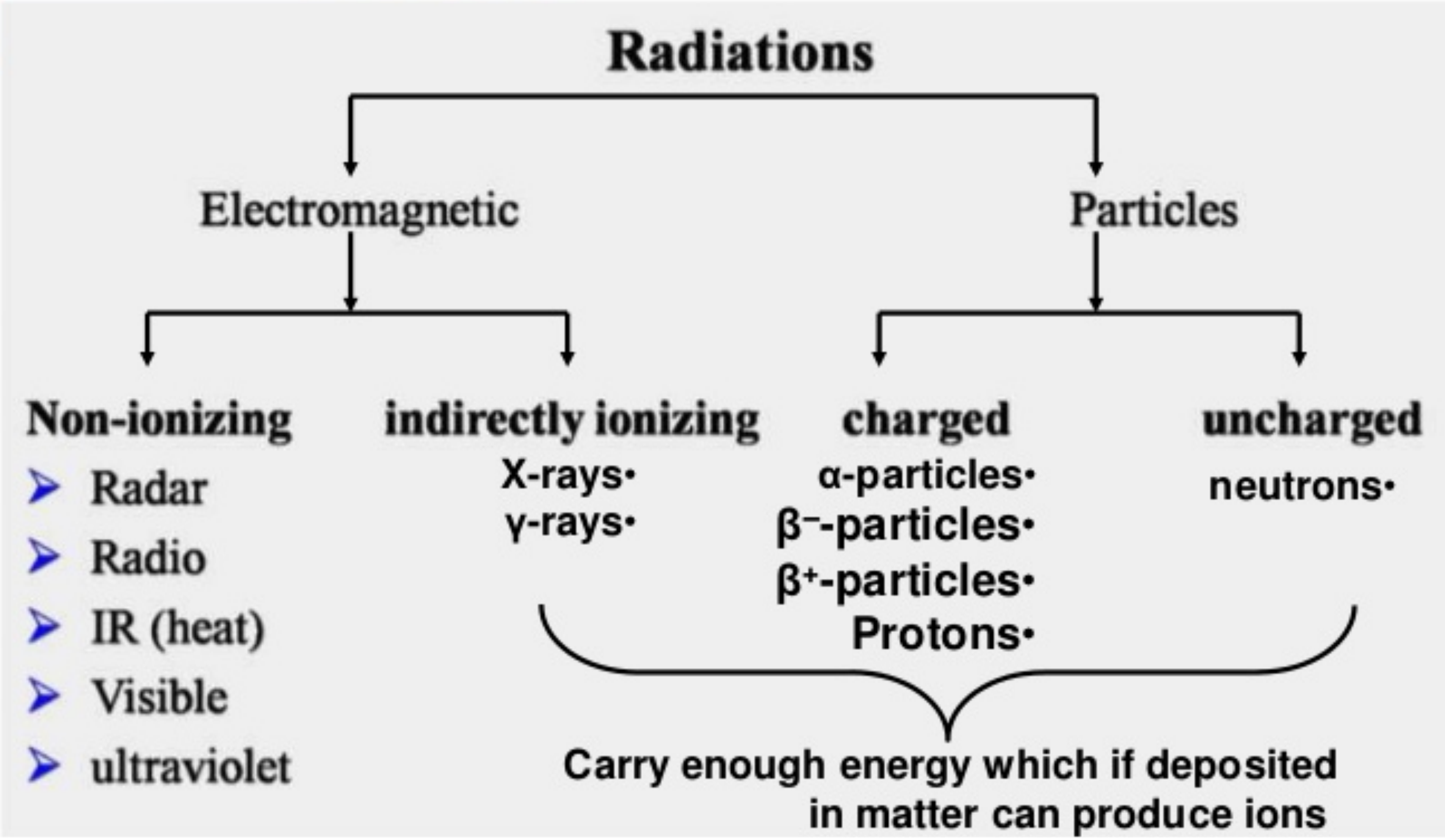
Proton Beam Therapy – Cancer

Treatments



taken from: Cancer Statistics Review, NIH 1992

Proton Beam Therapy – Radiation



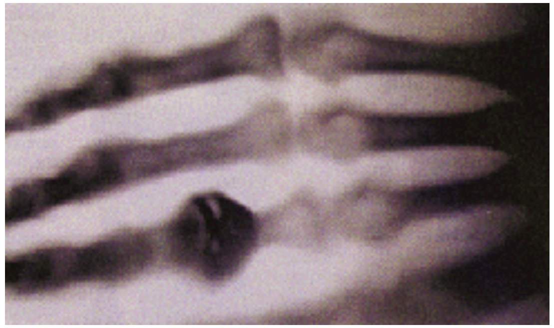
Mitglied der Helmholtz-Gemeinschaft

Proton Beam Therapy – Radiation

X rays: discovery 1895

Wilhelm Conrad Röntgen 1845 – 1923
Nobel price for physics 1901

First x-ray picture:
Mrs. Röntgen's hand



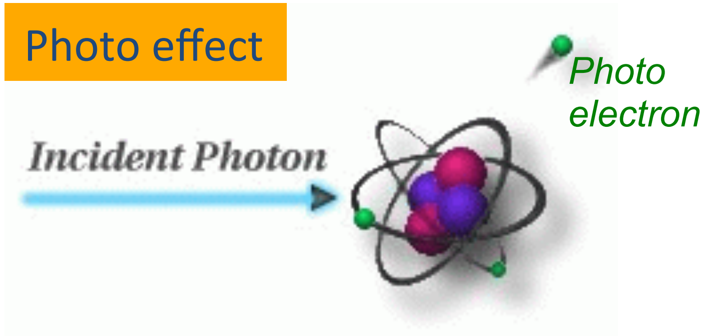
X rays interact with human tissue!

First successful treatment: 1899 (skin cancer)

Proton Beam Therapy – Radiation

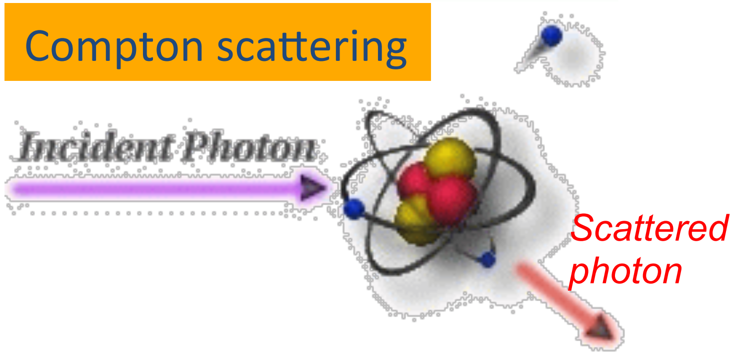
X rays: interaction with matter

Photo effect



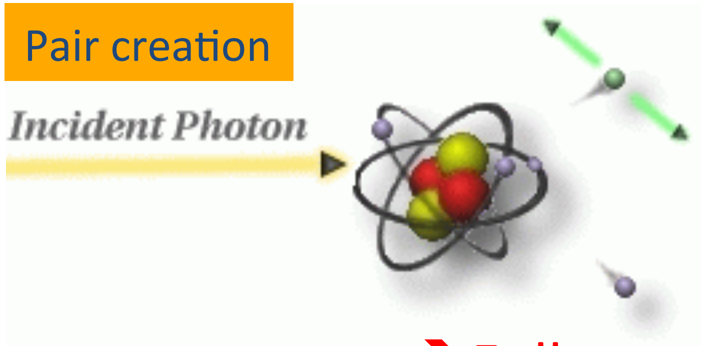
x-ray photon is absorbed, resulting in the ejection of electrons from the outer shell

Compton scattering



x-ray photon is deflected by an interaction with an electron. The electron gains energy and is ejected from its orbital position

Pair creation



electron and positron pair is created with the annihilation of the x-ray photon

➔Full energy deposit close to the point of absorption

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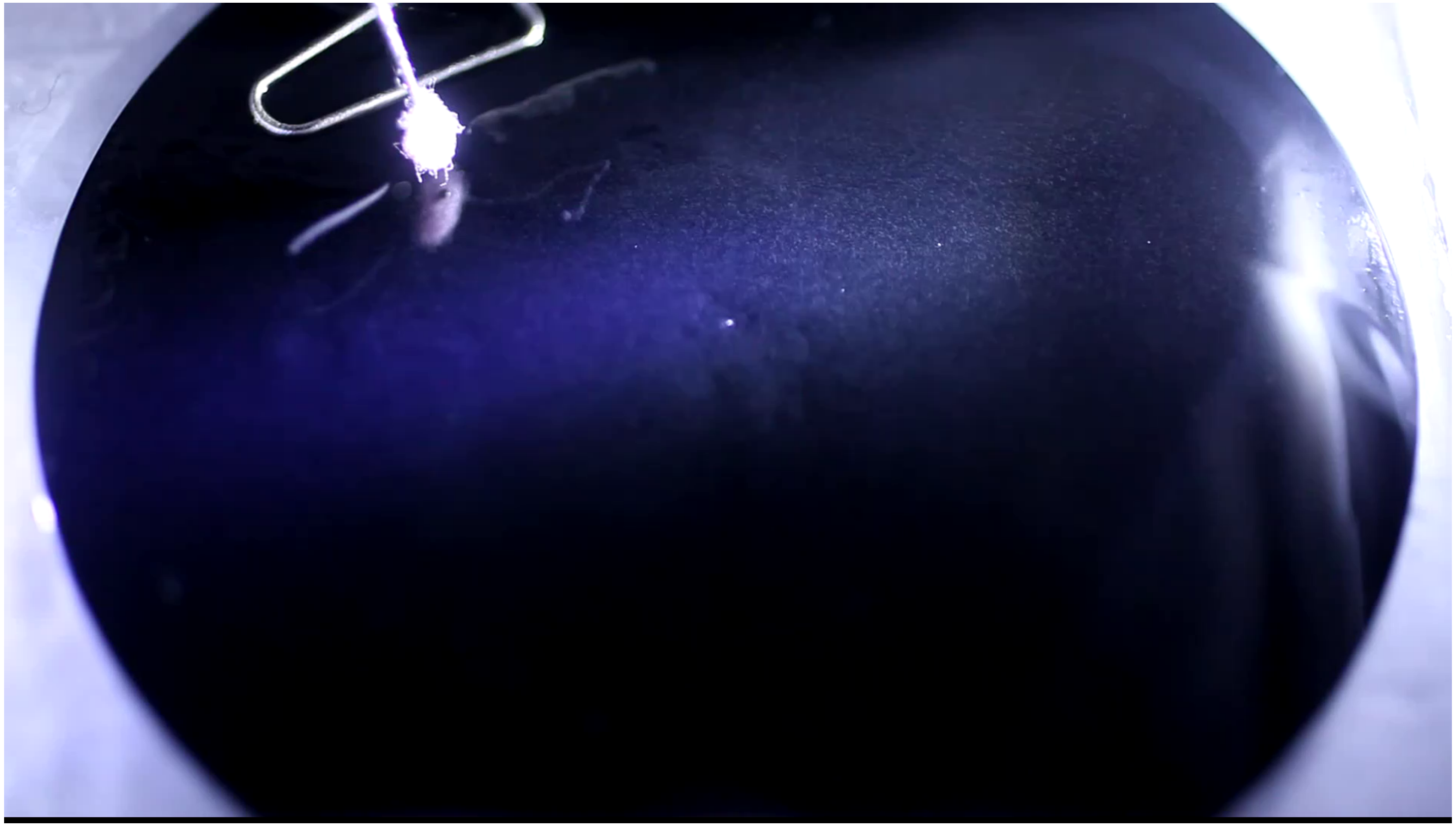
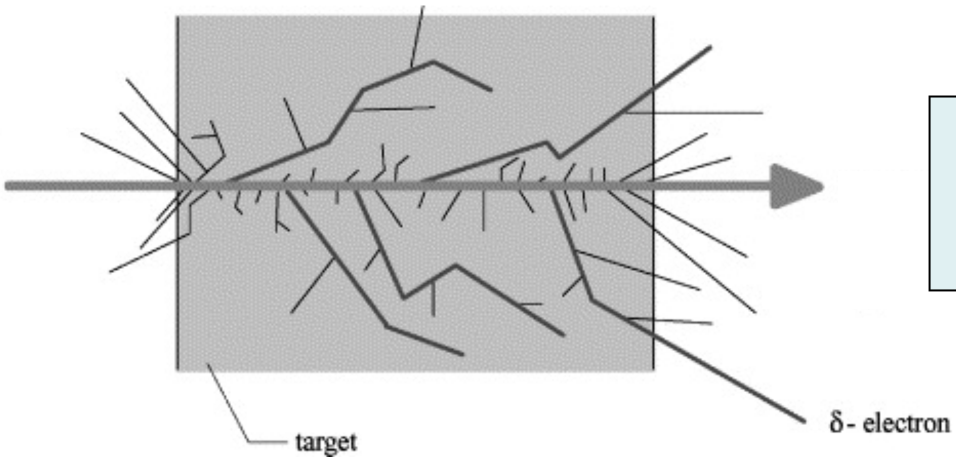
Proton Beam Therapy – Radiation

Charged particles: continuous energy loss / tracks



Proton Beam Therapy – Radiation

Charged particles: continuous energy loss

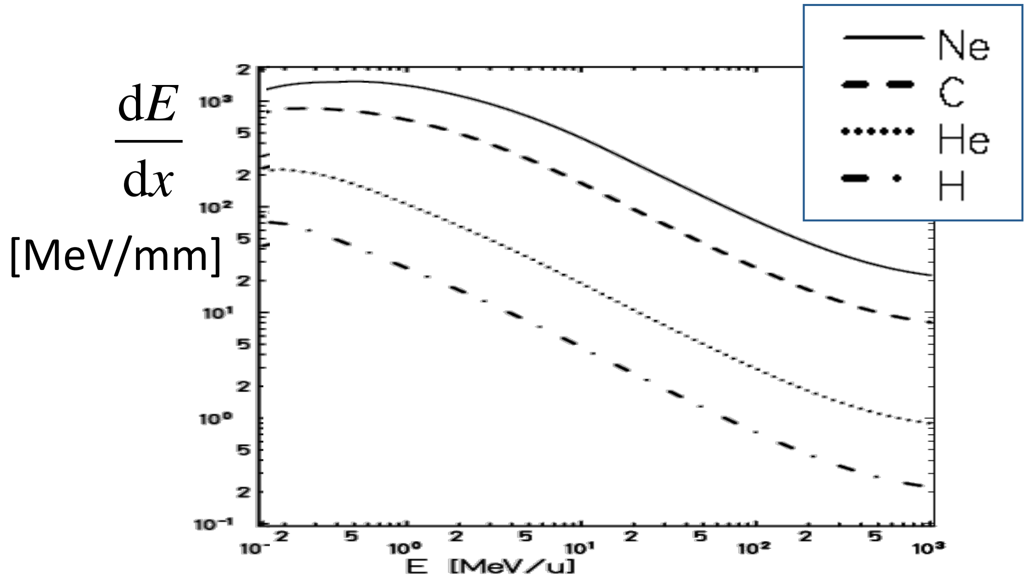


Energy loss through production of **δ elektrons** (ionization)

Bethe-Bloch formula

$$-\frac{\mathrm{d}E}{\mathrm{d}x} = \frac{4\pi e^4 N_a Z z_{eff}^2}{m_e v^2} \ln \frac{2mv^2}{I}$$

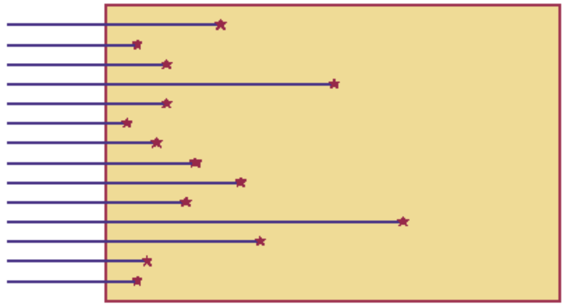
$$+ \text{relativistic terms}$$

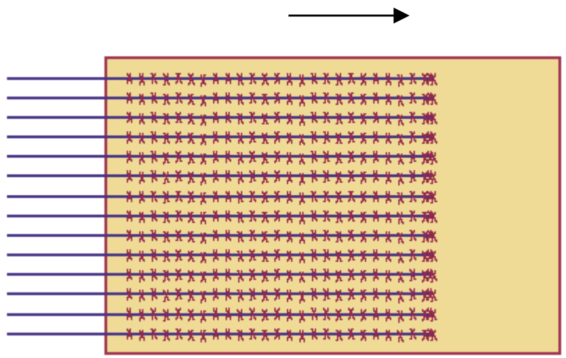


Proton Beam Therapy – Radiation

Photons

It cannot be predicted where a certain photon is absorbed
Energy is deposited close to the point of the first interaction





Charged particles

Continuous energy loss
Well defined range

→Which one is better for radiation therapy?
(energy deposit as function of penetration depth?)

Proton Beam Therapy – Energy deposit

The essentials of radiation therapy:

Biological effect of radiation mediated by ionization

Photons Charged particles

Higher ionization density (→dN/dx, dE/dx) means that more tumor cells are killed

Tumors can tolerate (at least) as much radiation as healthy tissue.
Dose must be to localized to the tumor!

Proton Beam Therapy – Energy deposit

Photons:

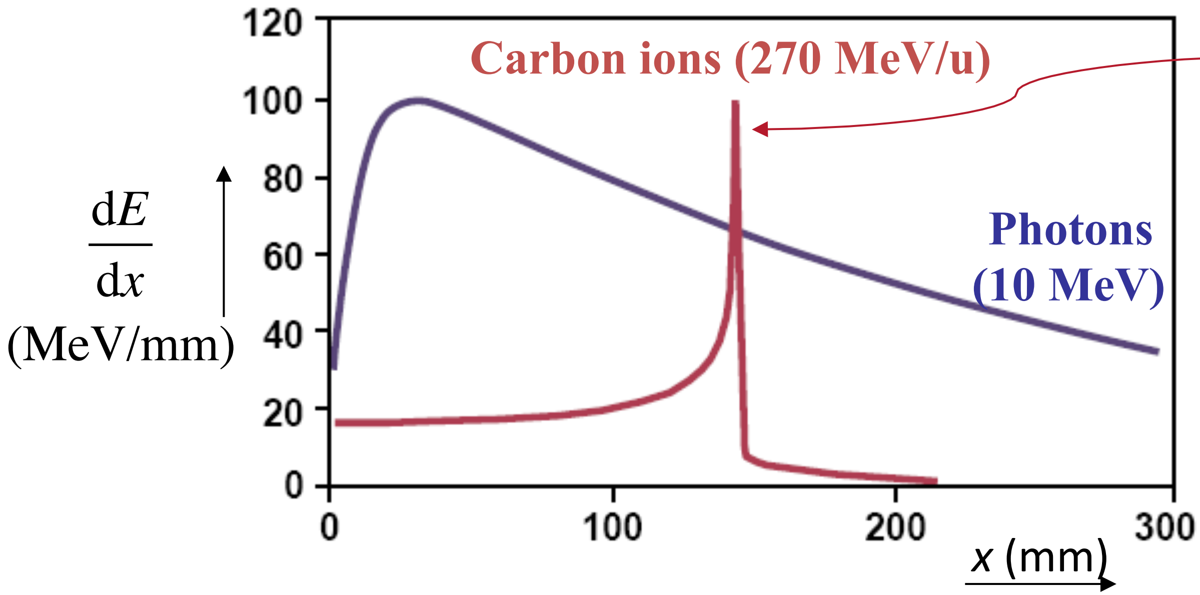
$$-\frac{\mathrm{d}N(x)}{\mathrm{d}x} \propto N(x) \Rightarrow \frac{\mathrm{d}N(x)}{\mathrm{d}x} \propto e^{-x}$$

Charged particles:

$$-\frac{\mathrm{d}E(x)}{\mathrm{d}x} \propto \frac{1}{v(x)^2}$$

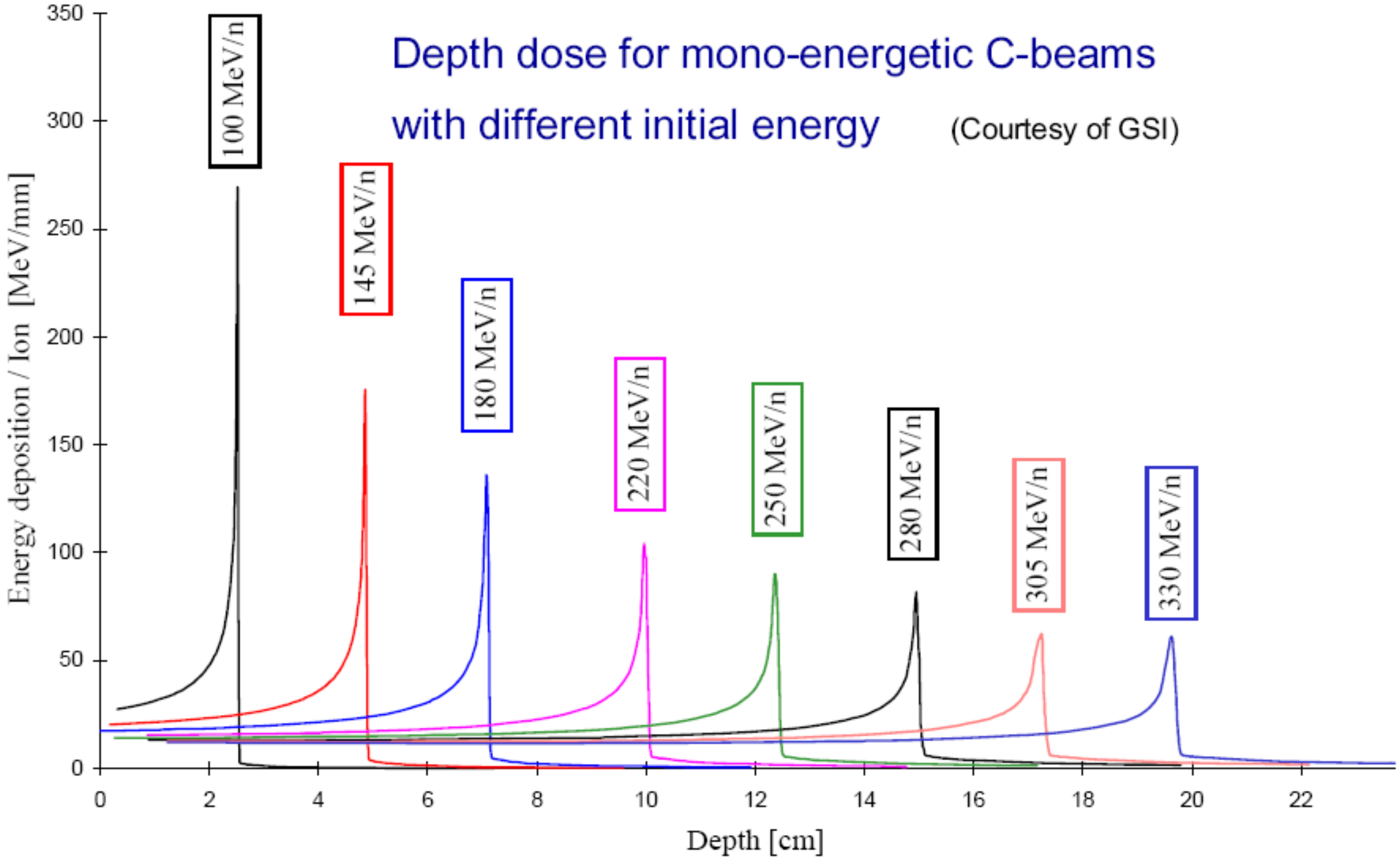
Maximum at end of track ($v \to 0$)

„Bragg Peak“



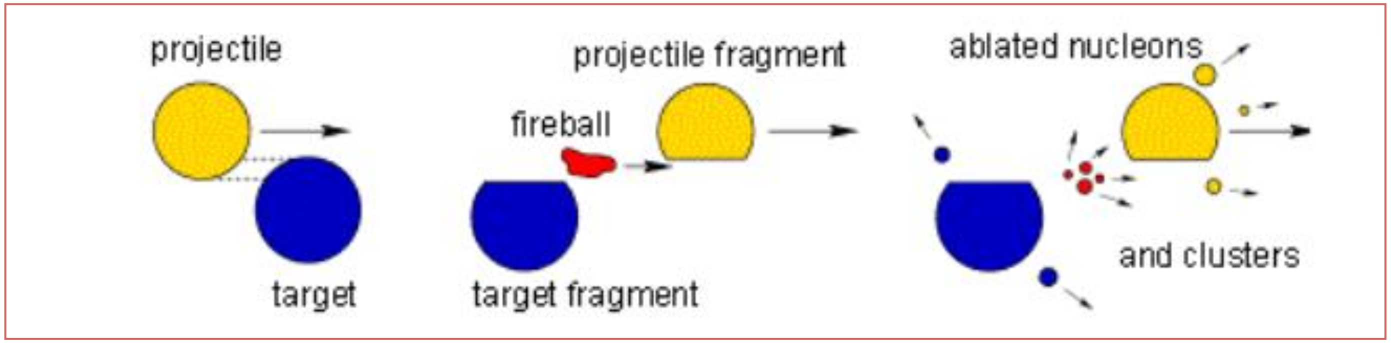
Proton Beam Therapy – Energy deposit

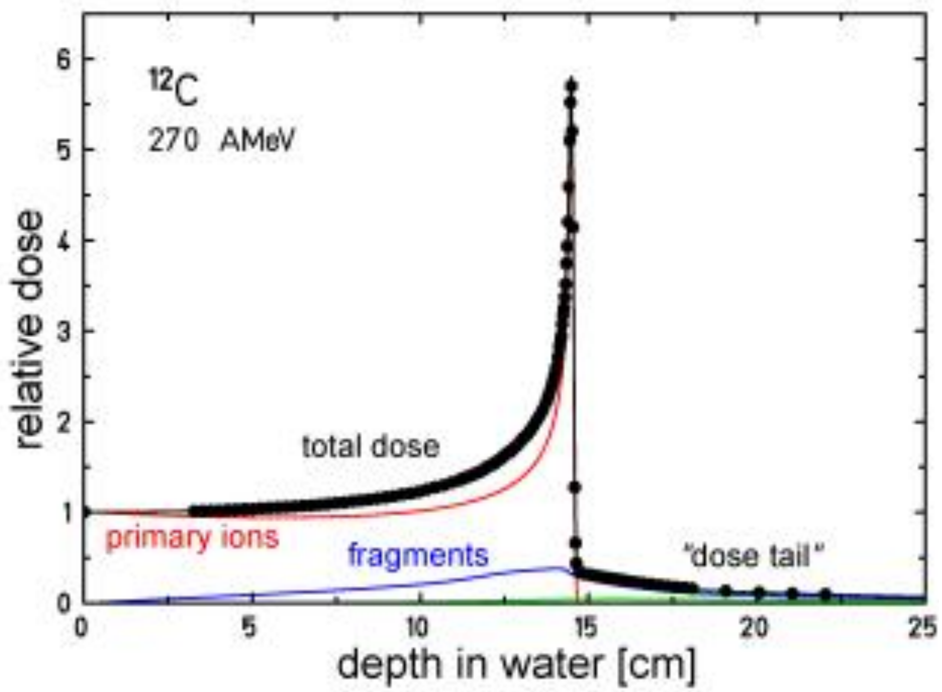
Energy dependence of the Bragg peak



Proton Beam Therapy – Energy deposit

Fragmentation: Nuclear reactions in the tissue

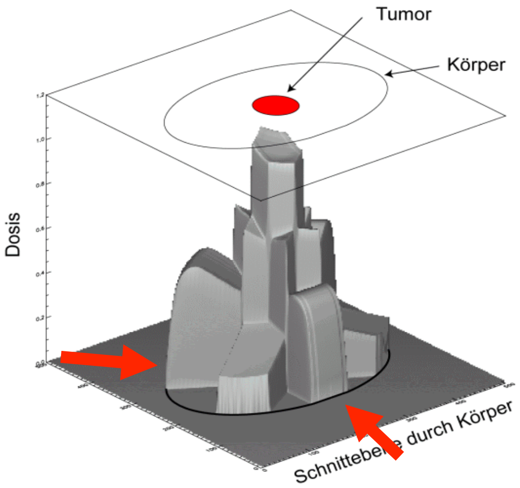


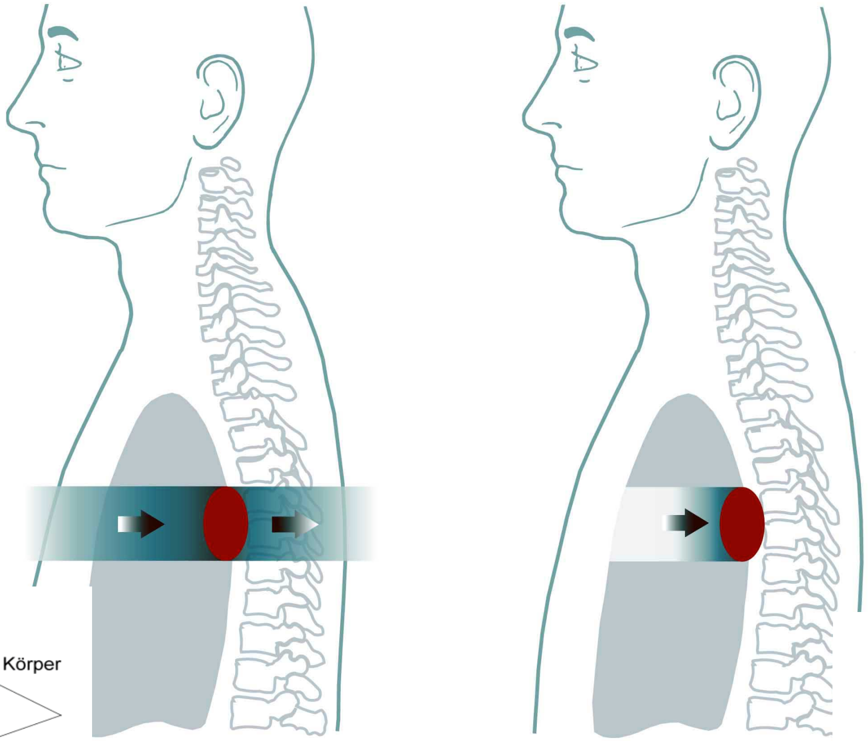


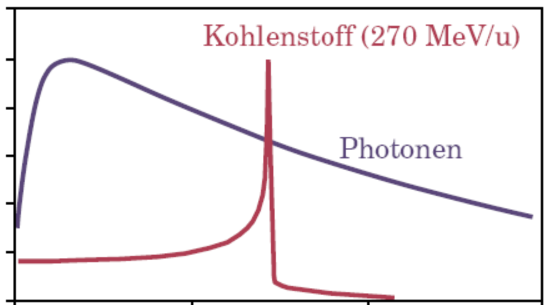
Proton Beam Therapy – Energy deposit

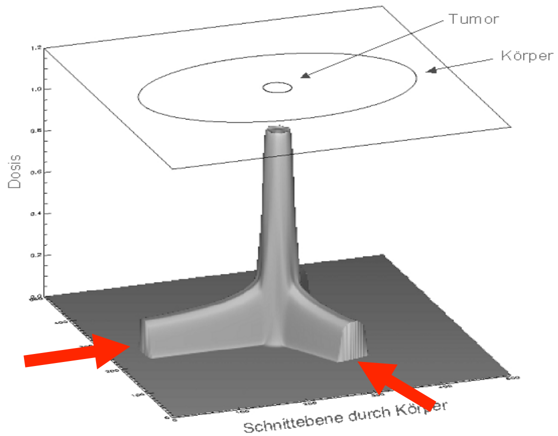
Photons

Charged particles



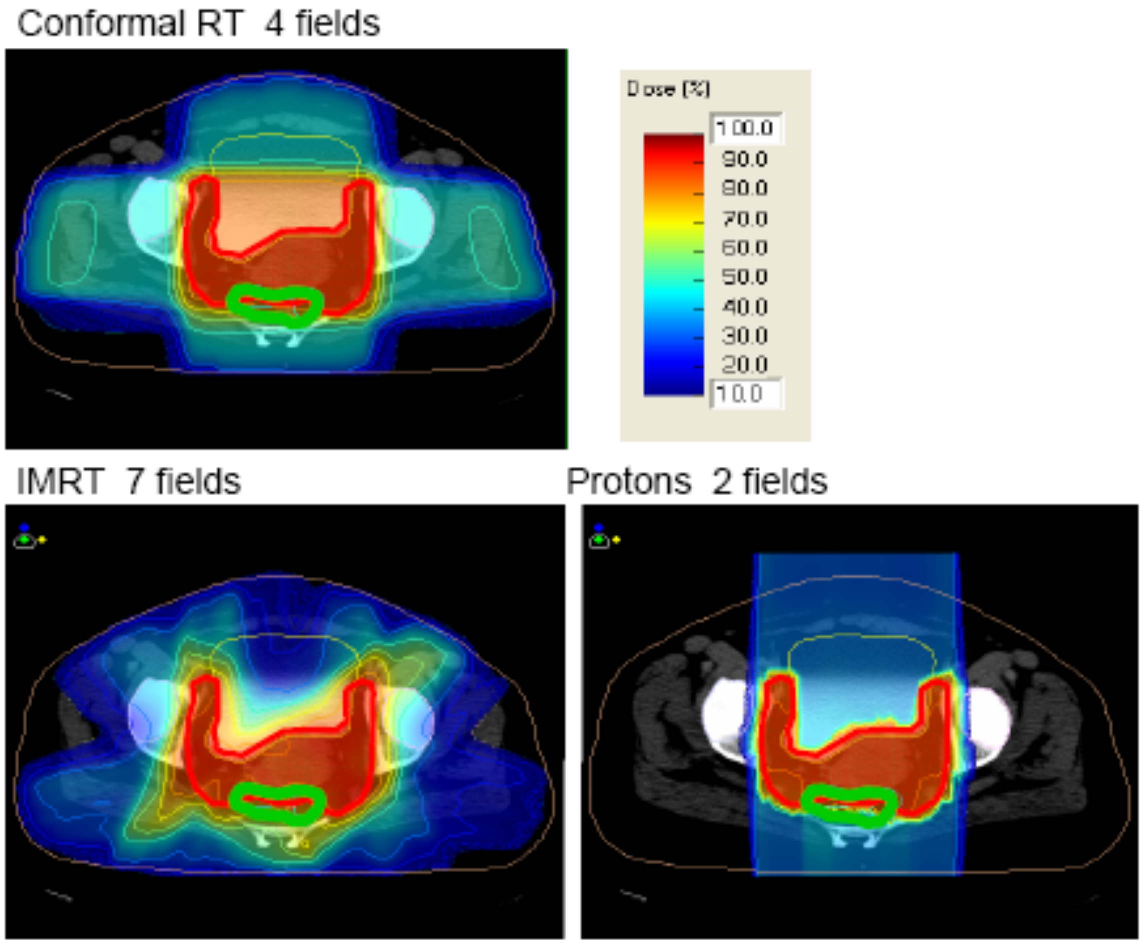






Proton Beam Therapy – Energy deposit

Simulation for irradiation at cervical



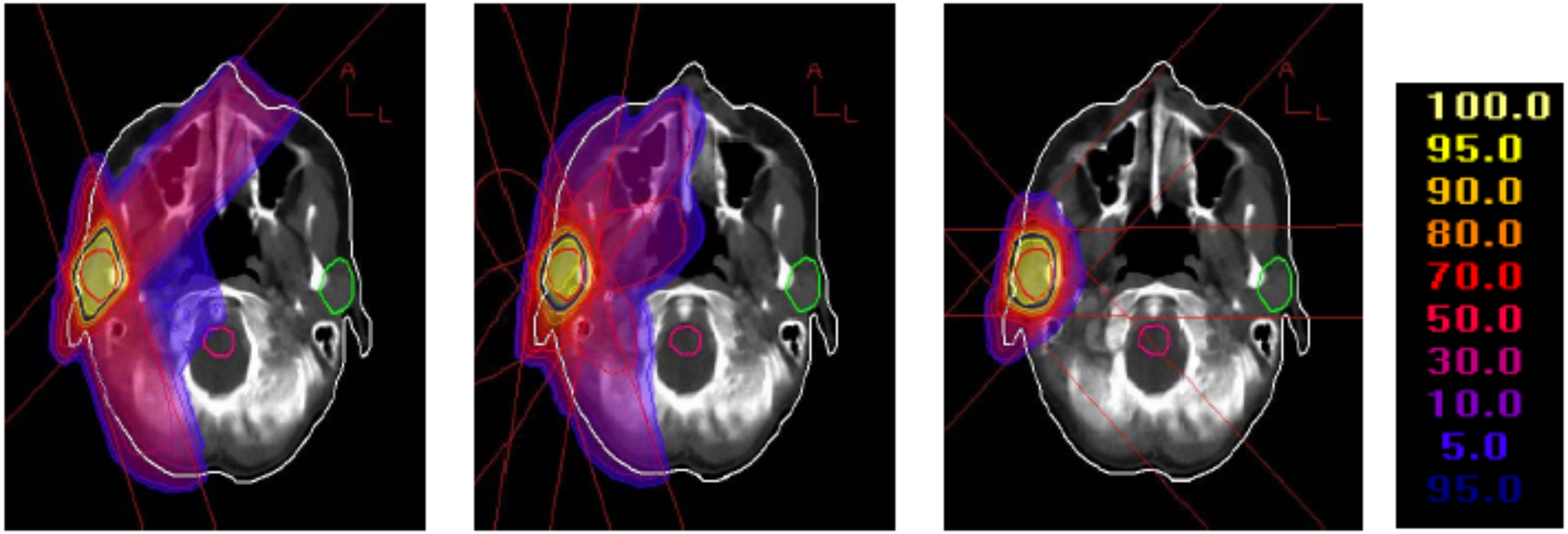
Universitätsklinik für Strahlentherapie-Radioonkologie, Innsbruck

Proton Beam Therapy – Energy deposit

Simulation for irradiation of brain

Photons | Protons

2 fields | 5 fields | 3 fields



Universitätsklinik für Strahlentherapie und Strahlenbiologie, AKH, Wien

Better dose distributions with Protons

Proton Beam Therapy – Units

JÜLICH FORSCHUNGSZENTRUM

Activity

Number of times each second a radioactive material decays and releases radiation

Dose (Absorbed)

Amount of radiation <u>energy</u> absorbed into a given mass of tissue

Dose (Equivalent)

Energy per unit mass times adjustments for the type of radiation involved (quality factor) and the <u>biological response</u> in the tissue (a weighting factor)

Equivalent dose converts dose into a measure of <u>risk</u>

Proton Beam Therapy – Units

Activity

1 decay/second = 1 Becquerel (Bq)

Dose (Absorbed)

1 Joule/kg = 1 Gray (Gy)

Dose (Equivalent)

1 Gray x quality factors = 1 Sievert (Sv)

Proton Beam Therapy – Units

Radiation Weighting Factors

Type and Energy Range		Weighting Factor
X and γ rays, electrons, positrons and muons		1
Neutrons	<10 keV	5
Neutrons	10 keV to 100 keV	10
Neutrons	100 keV to 2 MeV	20
Neutrons	2 MeV to 20 MeV	10
Neutrons	>20 MeV	5
Protons, other than recoil protons and energy >2 MeV		2
Alpha particles, fission fragments, nonrelativistic heavy nuclei		20

Proton Beam Therapy – Units

Tissue Weighting Factors

0.01	0.05	0.12	0.20
Bone surface	Bladder	Bone Marrow	Gonads
Skin	Breast	Colon	
	Liver	Lung	
	Esophagus	Stomach	
	Thyroid		
	Remainder		

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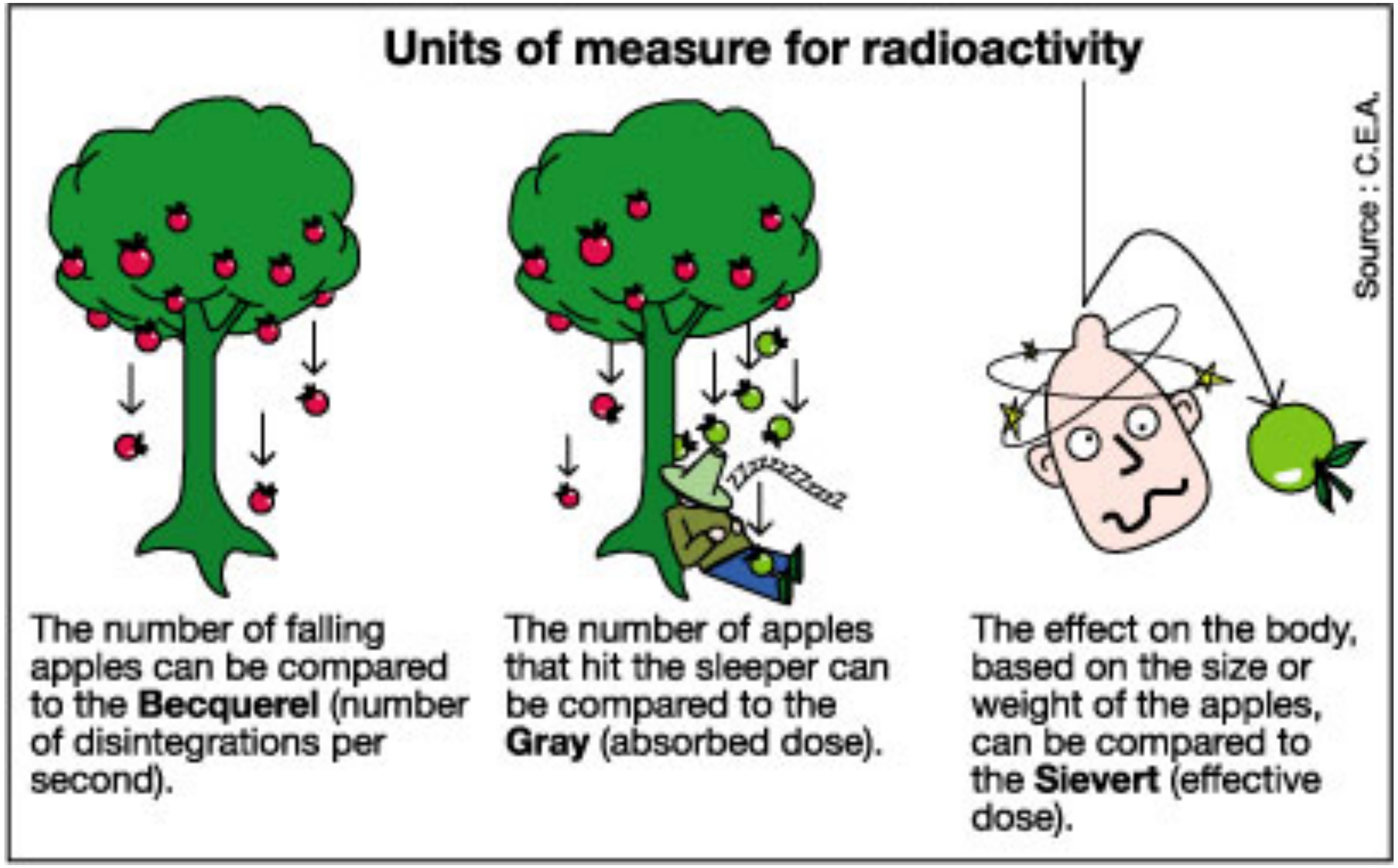
Proton Beam Therapy – Units



Proton Beam Therapy – Units

Typical doses

course of therapy	60 Gy (6000 cGy = 6000 rads)
whole body LD_{50}	4.5 Gy (450 cGy = 450 rads)
rad. worker limit (annual)	0.05 Sv (50 mSv = 5 rems) *
non-rad. worker (annual)	0.005 Sv (5 mSv = 0.5 rems)
general public limit (annual)	0.0005 Sv (0.5 mSv = 0.05 rems)
natural background (annual)	~0.003 Sv (3 mSv = 0.3 rems)
diagnostic chest x-ray	~0.00007 Sv (70 μSv = 7 mrem)
5 hour jet flight	~0.00003 Sv (30 μSv = 3 mrem)
dental x-ray	~0.00002 Sv (20 μSv = 2 mrem)

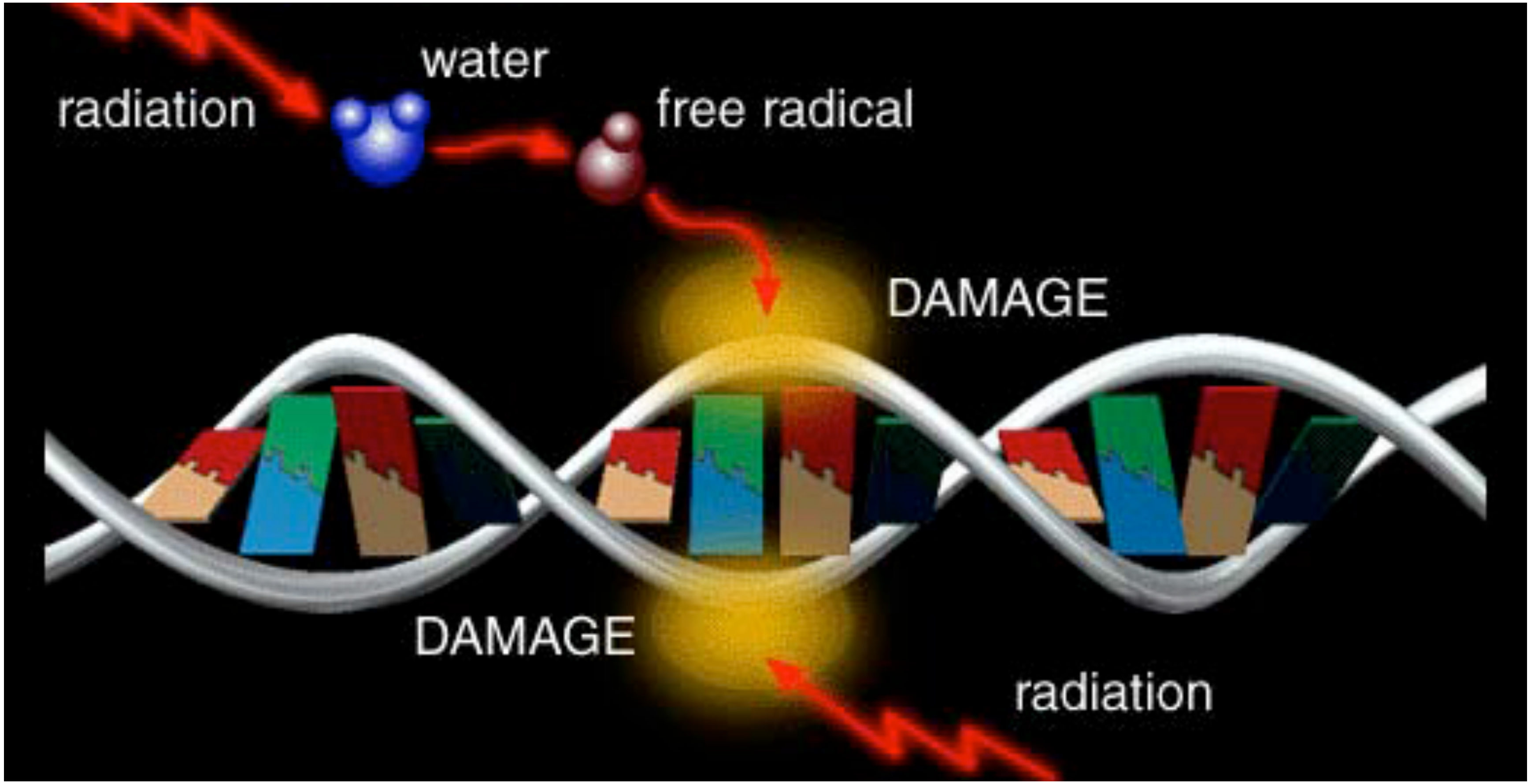
Proton Beam Therapy – Units

Lethal dose: 4.5 Gy (LD_{50}) for a man of 70 kg

Energy absorbed = 4.5 Gy x 70 kg ≈ 300 J

Thermal energy content of a sip of hot coffee if derived in the form of X-rays can be lethal

Proton Beam Therapy – Biological effects



Proton Beam Therapy – Biological effects

DNA <u>double-strand breaks</u> increase biological effectiveness

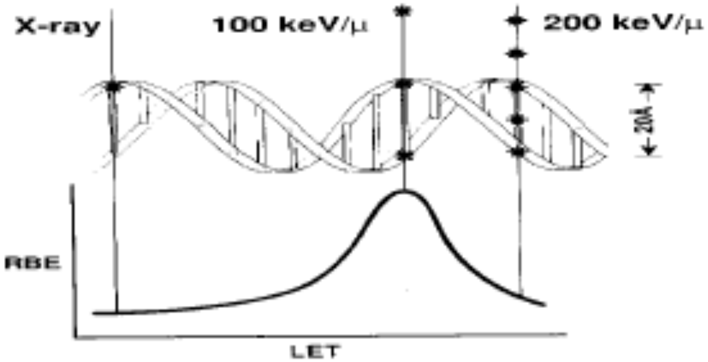
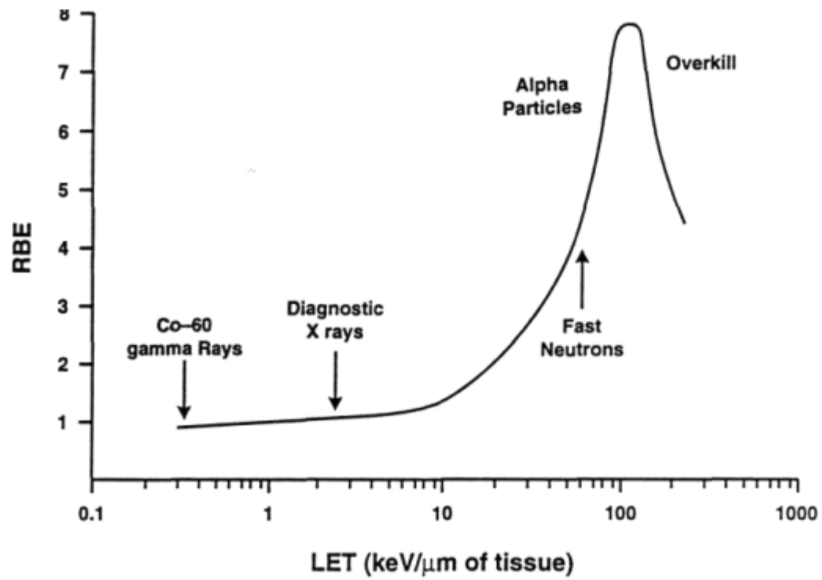
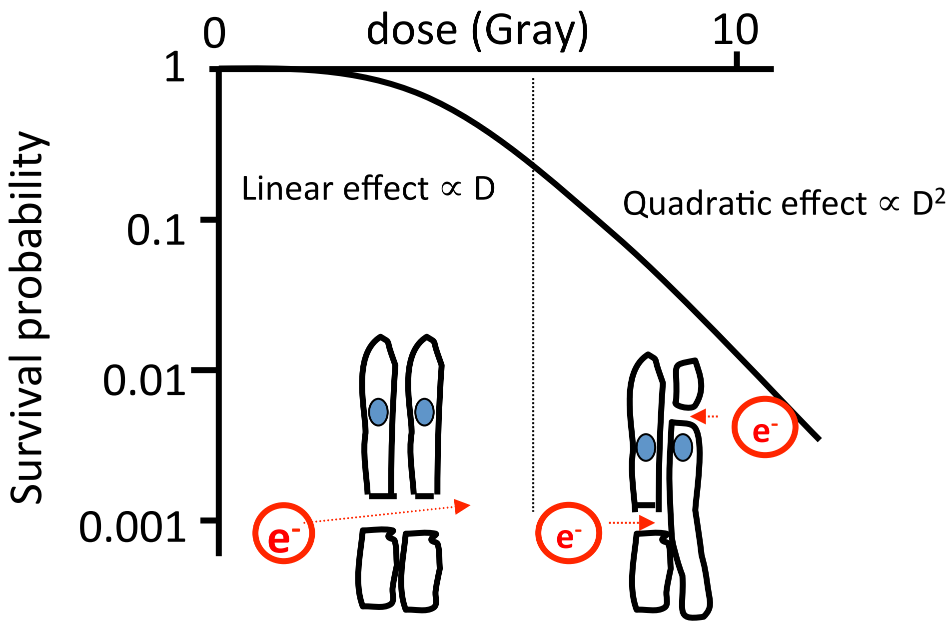


Figure 9-7. Diagram illustrating why radiation with an LET of 100 keV/µm has the greatest RBE for cell killing, mutagenesis, or oncogenic transformation. For this LET, the average separation between ionizing events coincides with the diameter of the DNA double helix (ie, about 20 Å [2 nm]). Radiation of this quality is most likely to produce a double-strand break from one track for a given absorbed dose.



Proton Beam Therapy – Biological effects



$$\text{effect} \propto \alpha \cdot D + \beta \cdot D^2$$

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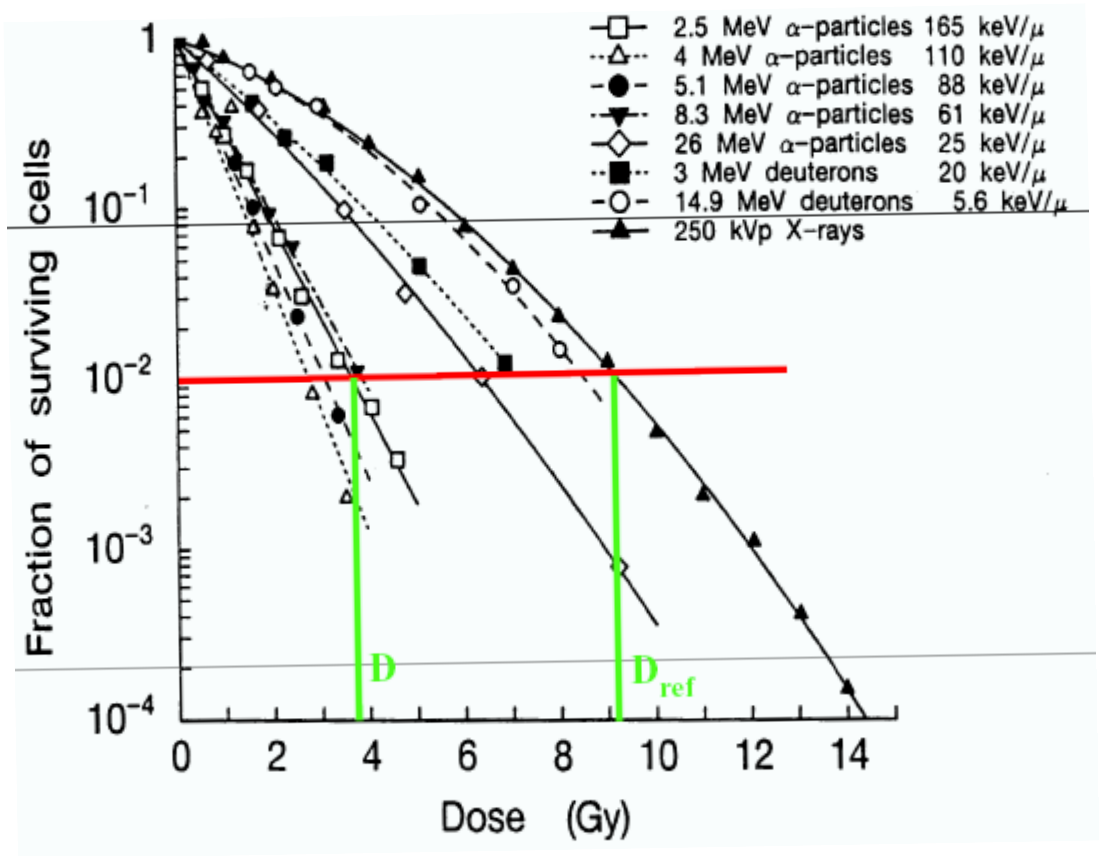
Proton Beam Therapy – Biological effects

JÜLICH FORSCHUNGSZENTRUM

Relative biological effectiveness (RBE)

$$RBE = \frac{\text{Dose of reference radiation with effekt } X}{\text{Dose of radiation of interest with effekt } X}$$



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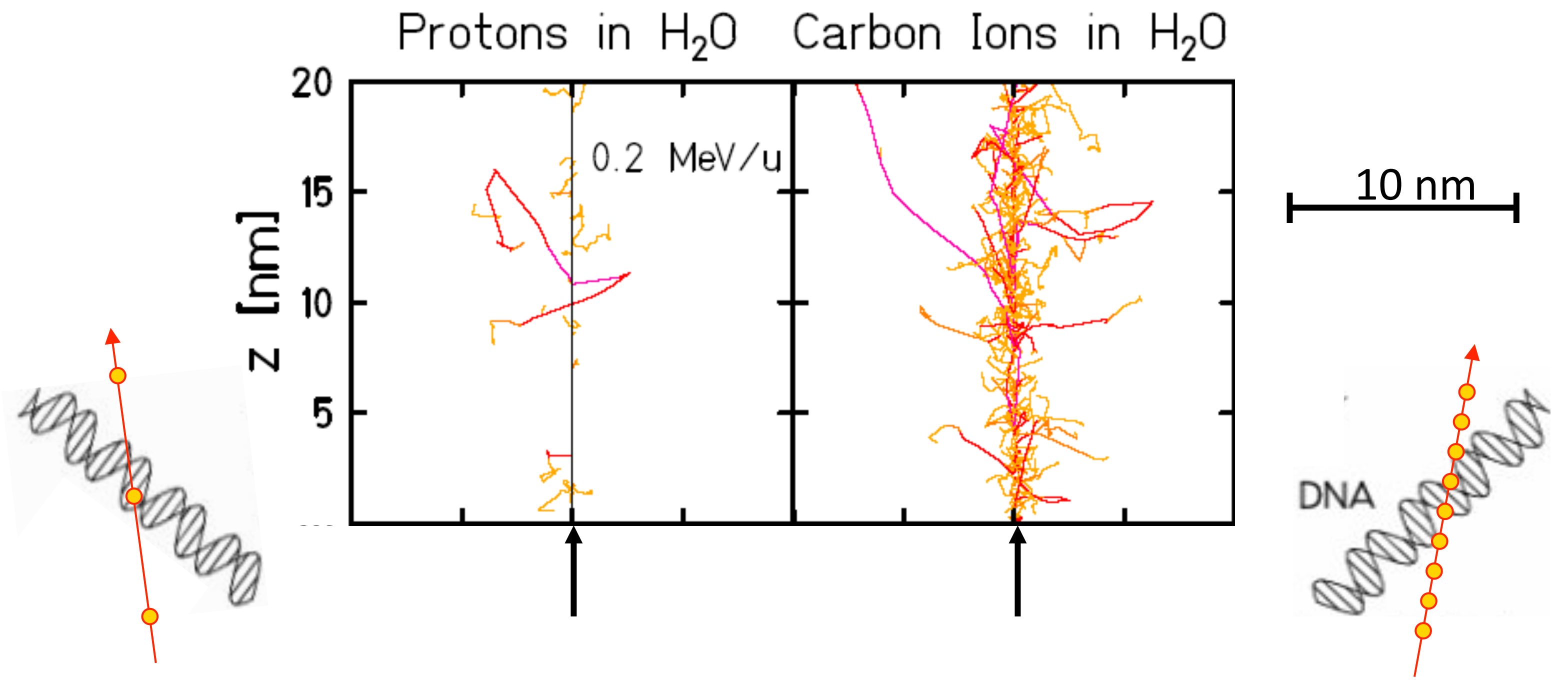
Proton Beam Therapy – Protons vs. Ions

Increased biological effectiveness

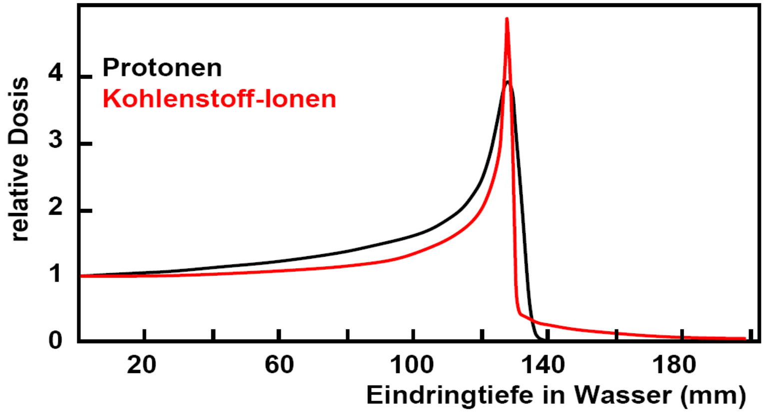
Energy loss through production of **δ elektrons** (simulation)



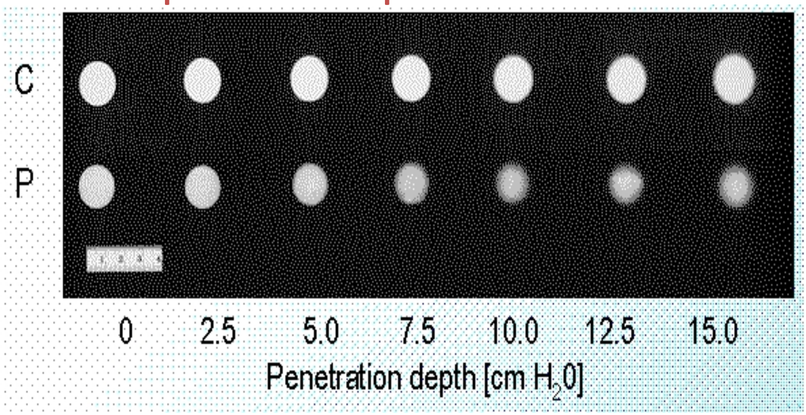
Proton Beam Therapy – Protons vs. Ions

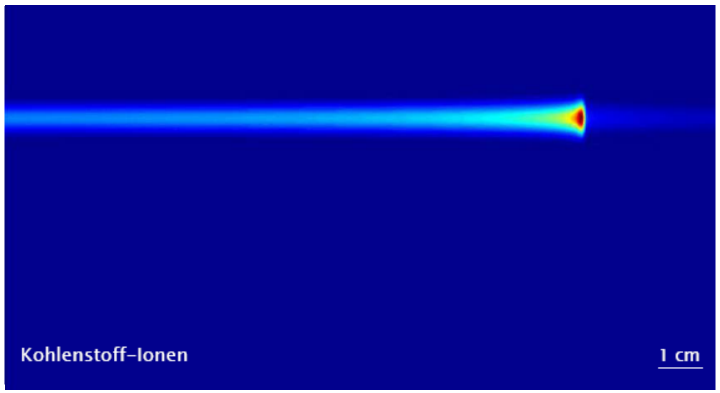
Extremely localized energy loss

Longitudinally
narrower Bragg-Peak



Transversally
sharper beam profile

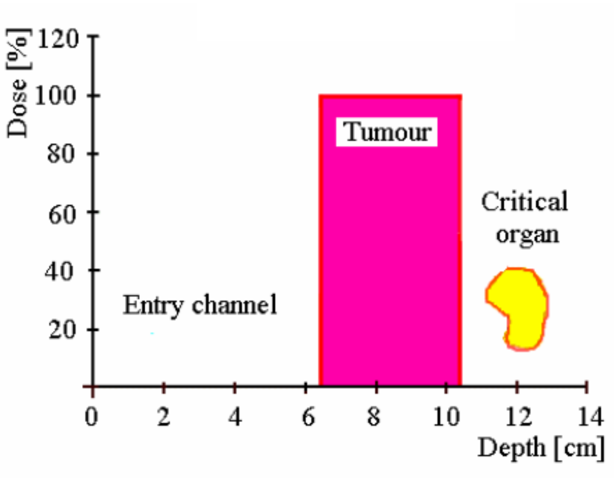




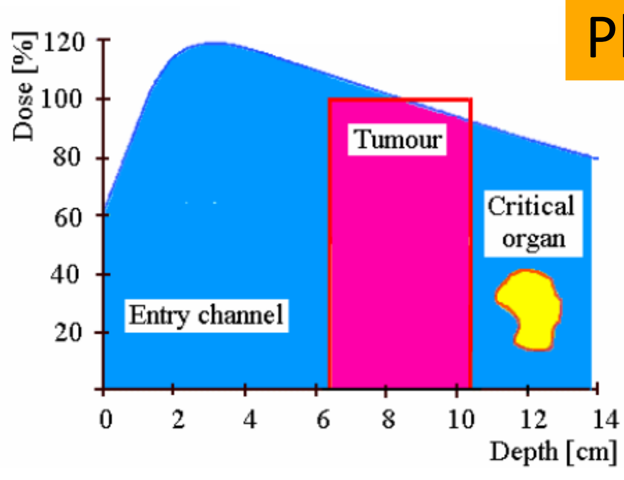
Proton Beam Therapy – Protons vs. Ions

Dose distributions

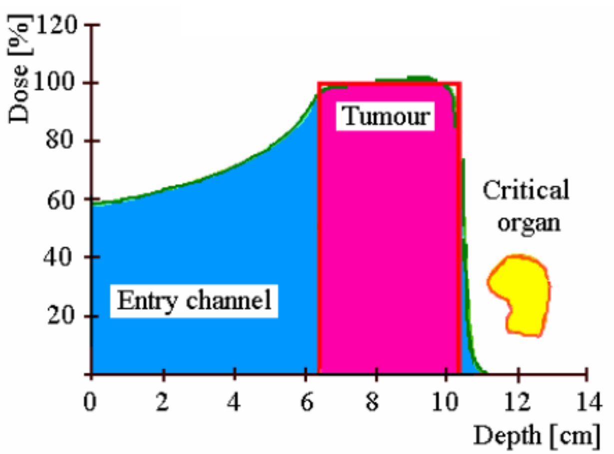
Ideal



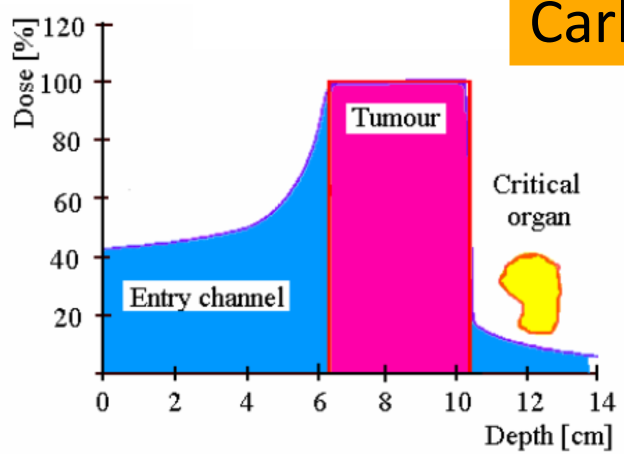
Photons



Protons



Carbon

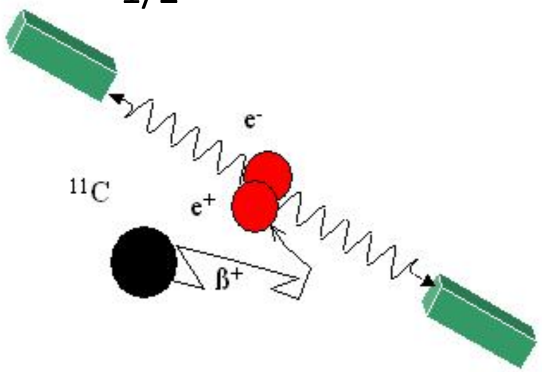


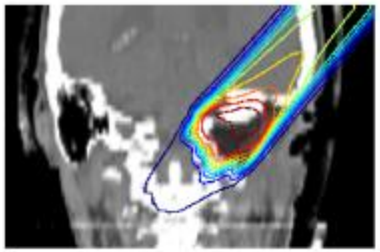
Proton Beam Therapy – Protons vs. Ions

PET Diagnostics

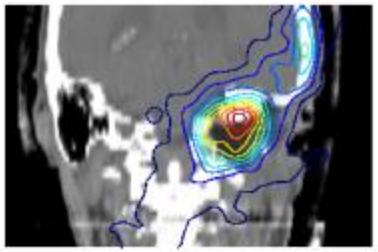
Fragmentation of ^{12}C $\longrightarrow$ Positron emitting isotopes

^{11}C ($T_{1/2}$ = 20 min), ^{10}C ($T_{1/2}$ = 19 s), …

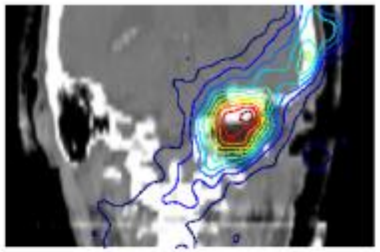




planned physical dose distribution



PET measured positron emitters

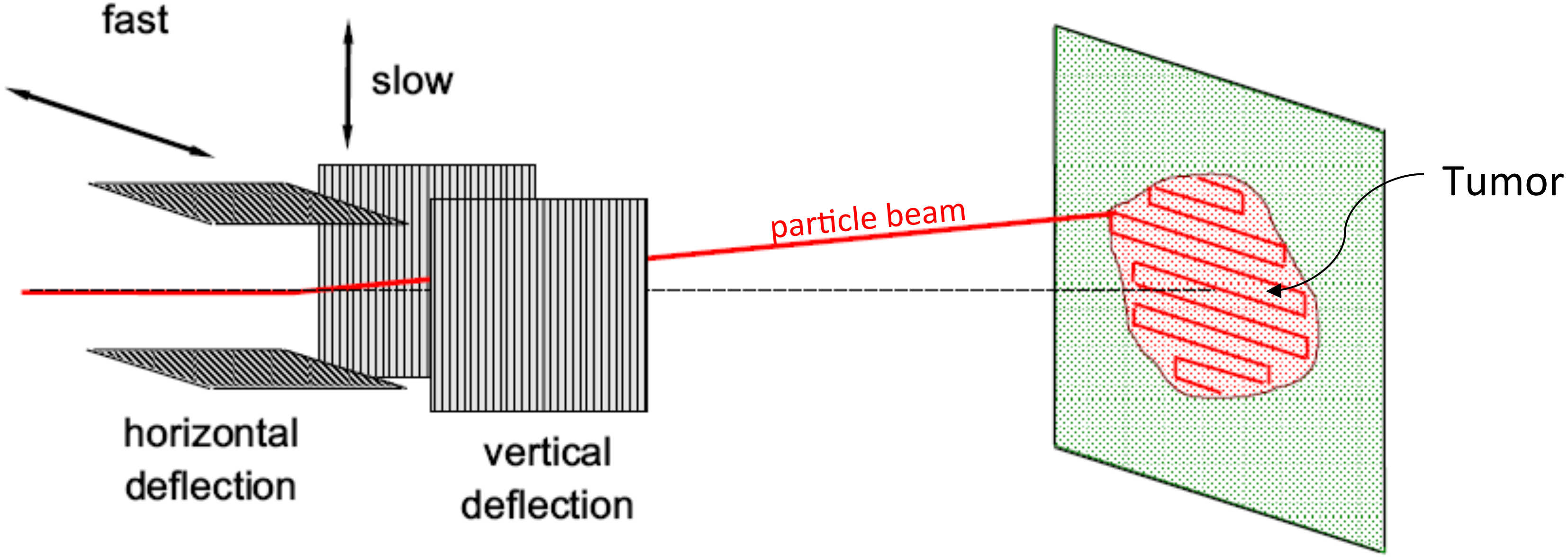


PET simulated positron emitters

Lateral resolution ca. 2.5 mm

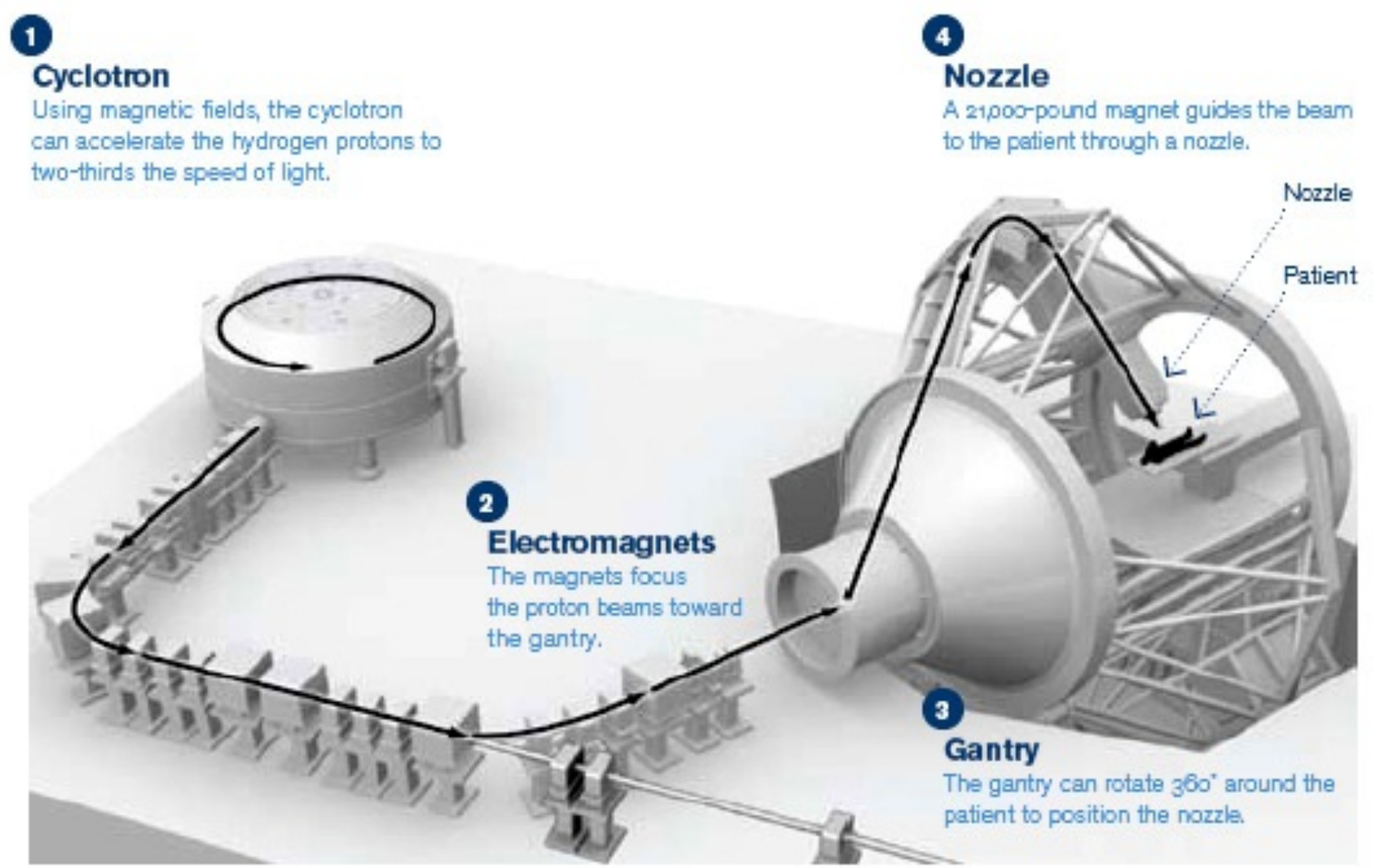
Proton Beam Therapy – 3d treatment

2d scanning & energy variation = 3d



Proton Beam Therapy – 3d treatment

Gantries: allow for irradiation from all sides



The Israel Proton Therapy Initiative

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Proton Beam Therapy – 3d treatment

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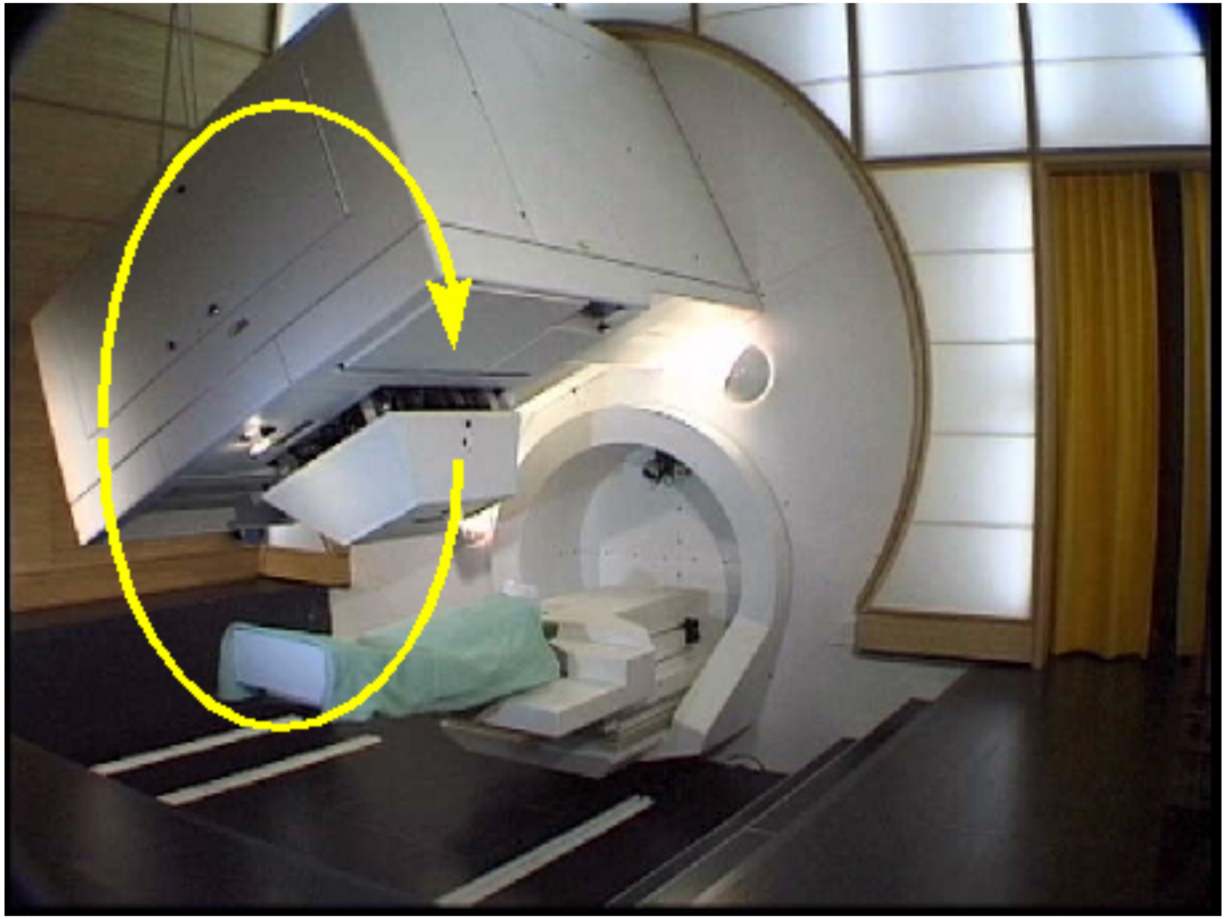
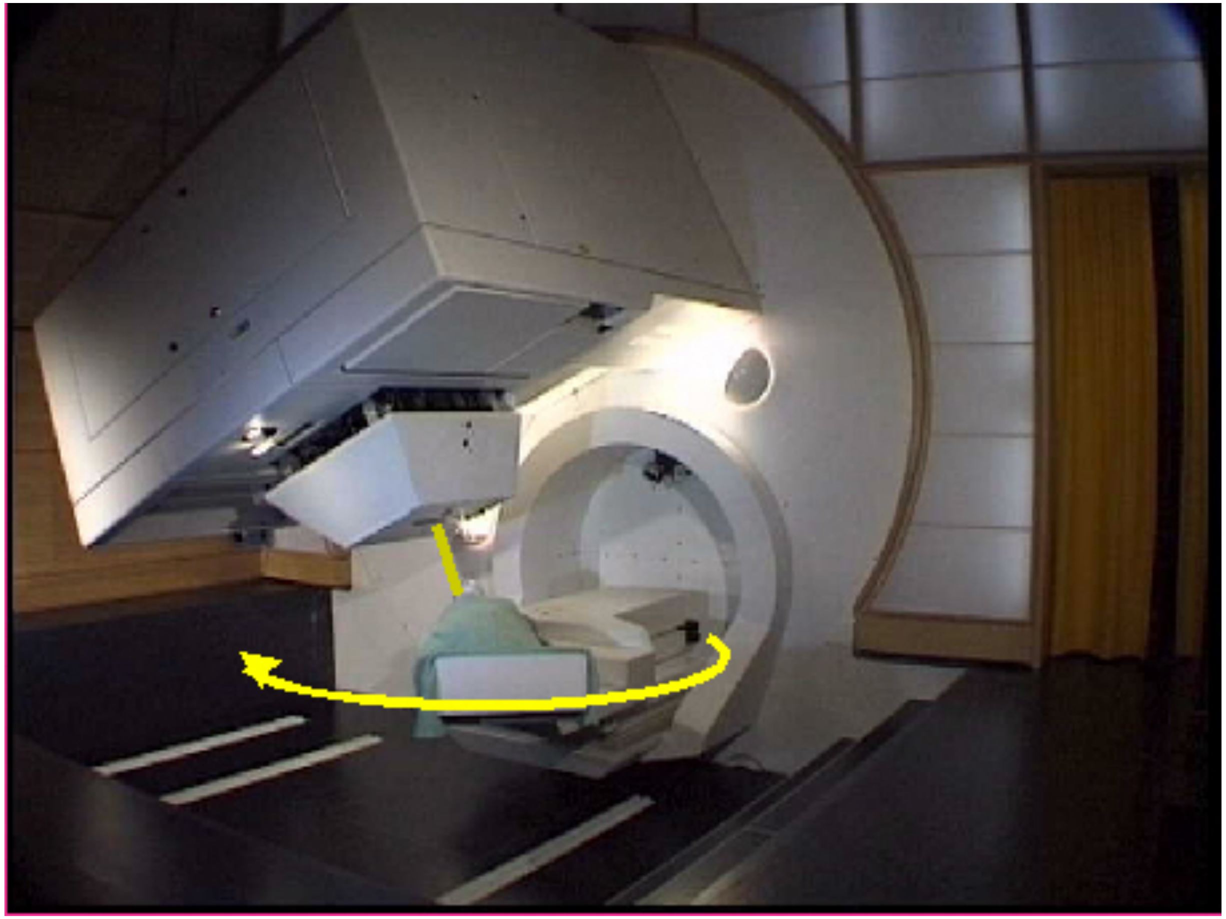
Gantry at PSI Villigen (Switzerland)



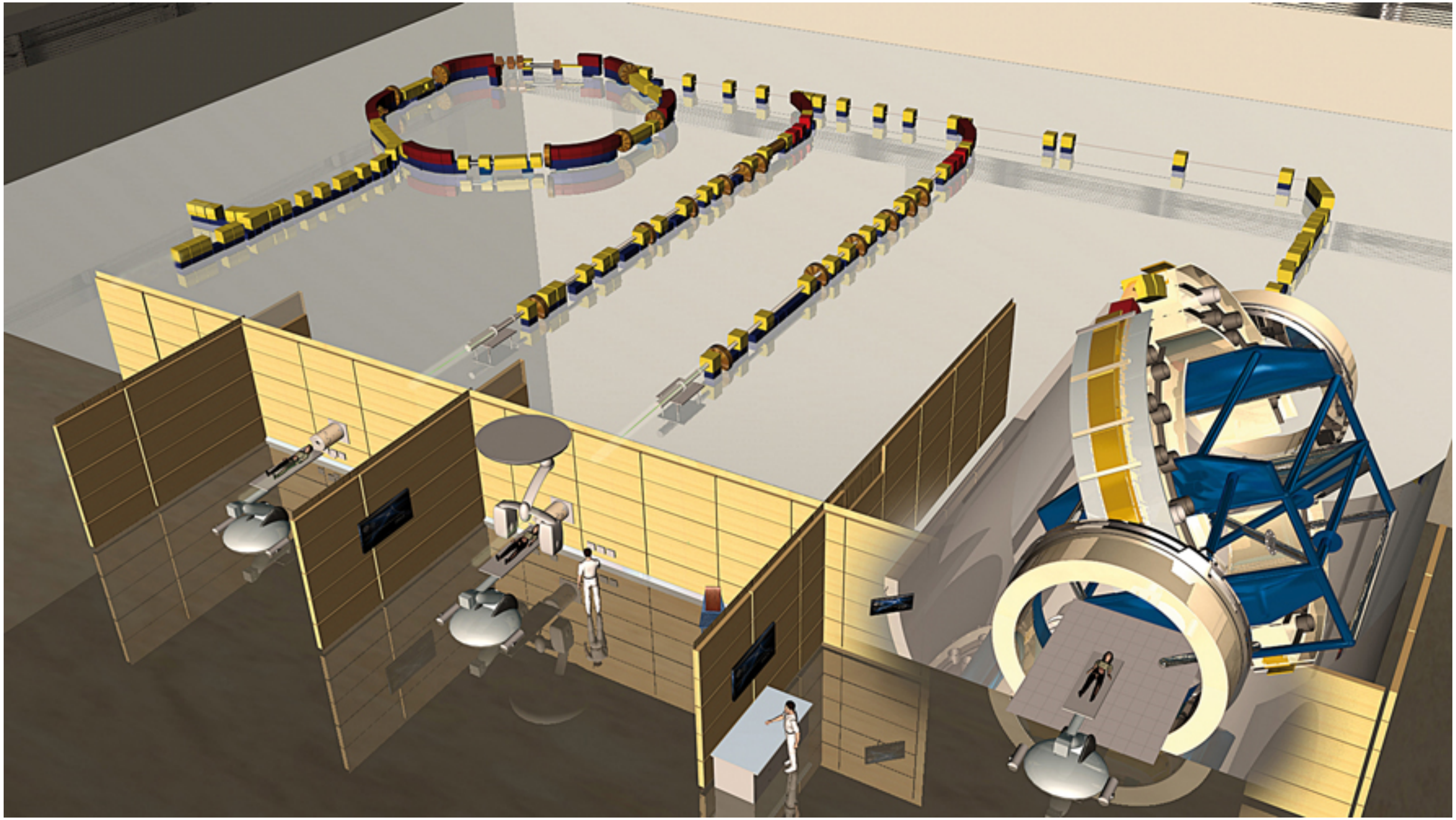
Proton Beam Therapy – 3d treatment

Gantry at PSI Villigen (Switzerland)



Proton Beam Therapy – Facilities

HIT (Heidelberg)



Proton Beam Therapy – Facilities

JÜLICH
FORSCHUNGSZENTRUM

HIT (Heidelberg)

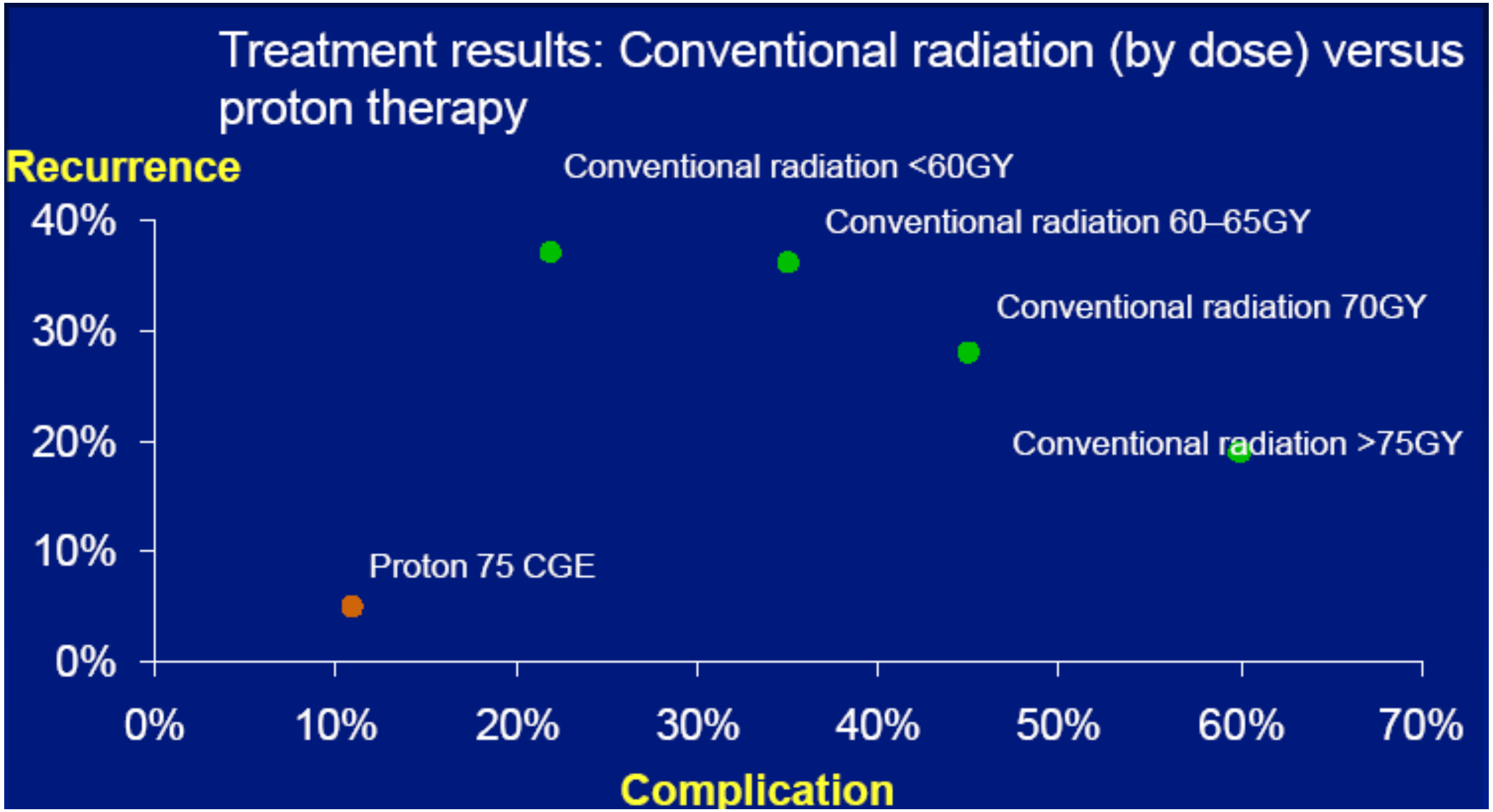
Proton Beam Therapy – Treatment

Research facility at GSI Darmstadt (1997 – 2008)

- over 180 patients (07/2003)
- approx. 70 % ^{12}C, 30 % ^{12}C + photons
- 350 days of clinical operation
- typical parameters:
  - approx. 20 fractions per patient
  - 2-4 fields per fraction
  - 3-3,5 Gye per fraction
  - tumor volums: 50-3200 cm^3
  - 1000-45000 points per tumor
  - 2-12 min. per field
- no in-field recurrance (2 out-of-field)
- only very mild side effects
- partially accepted as currative method

Proton Beam Therapy – Treatment

Treatment of prostate cancer at Loma Linda University Medical Center (USA)



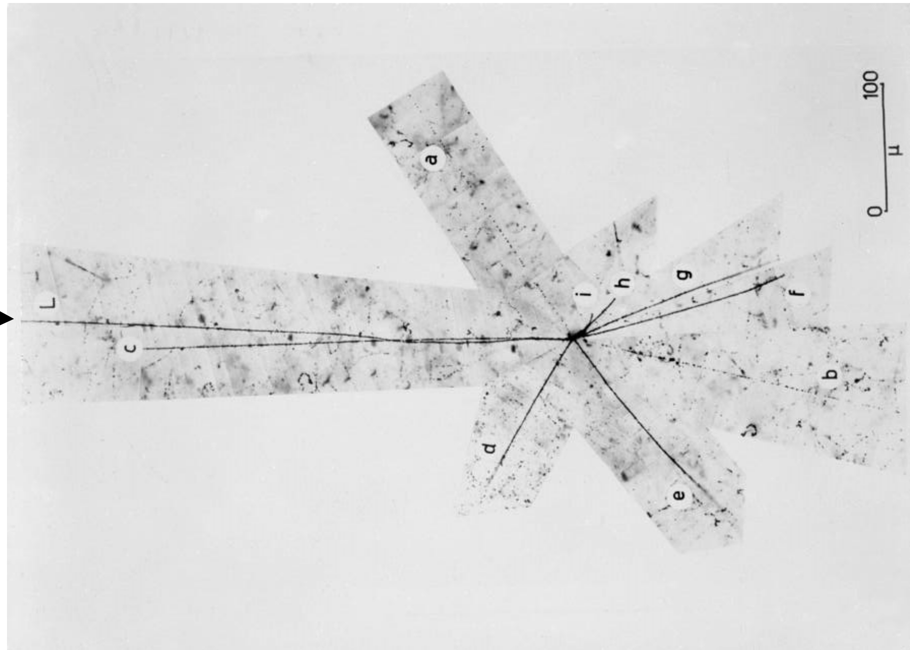
No double blind studies yet!

Proton Beam Therapy – The future

Irradiation with Antiprotons???

In principle, Antiprotons deliver an energy of $E = 2m_p c^2 \sim 2000$ MeV besides their kinetic energy (~100 MeV)

$\bar{p}$ →



First observation of a Proton-Antiproton annihilation (1955)

Proton Beam Therapy – The future

Laser-induced particle acceleration