RADIOBIOLOGY OF PULSED PARTICLE BEAMS

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SZÉCHENYI 2020
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OUTLINE

1. *Radiobiology – some basics*
2. *The time factor in conventional radiotherapy*
3. *Current developments in clinical dose delivery*

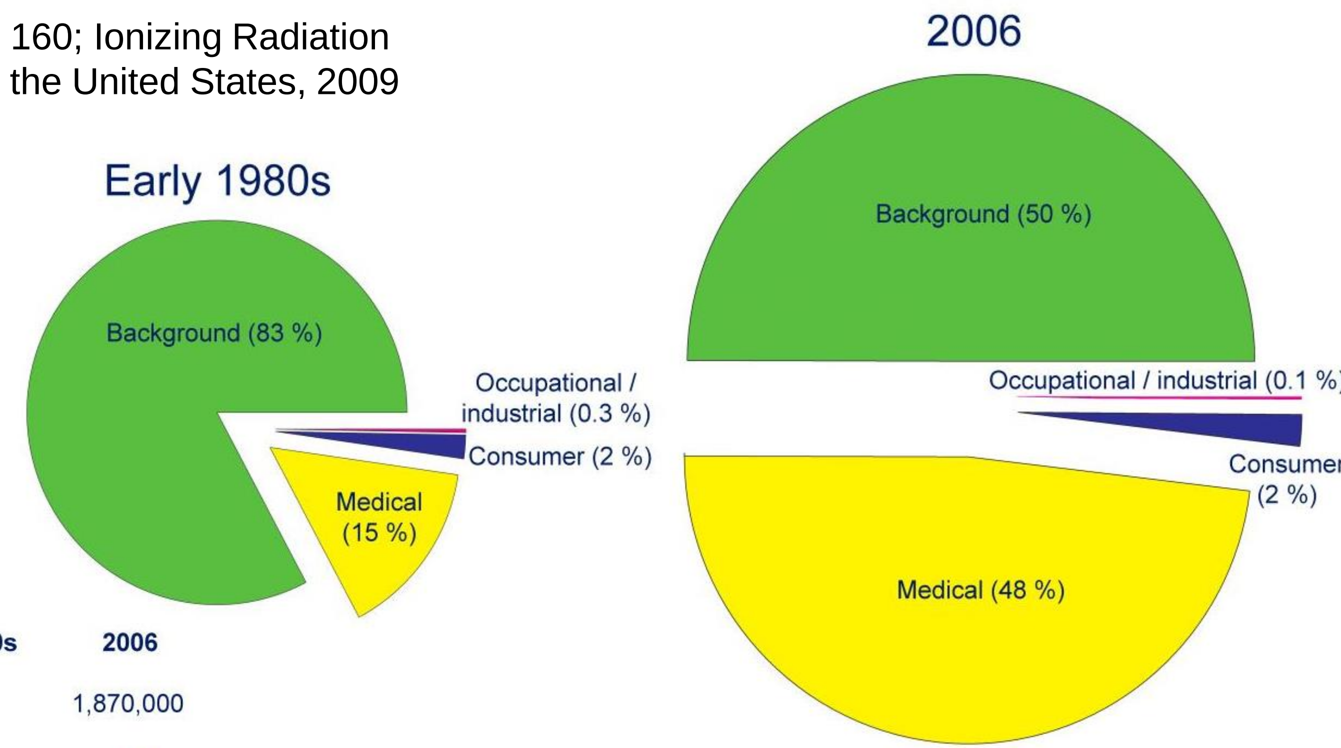
Introduction: Radiobiology – some basics

- Definitions
- Timescale of radiation action
  - Physical phase: Ionisation, LET
  - Chemical/biochemical reactions: Water radiolysis, indirect and direct DNA interaction
  - Biological effects: Consequences and quantification of radiation damage
  - Clinical effects

1. Definition of radiation biology

Radiobiology = interdisciplinary field aiming on the investigation of the interaction of (non)ionizing radiation on living things

UNSCEAR NCRP Report No. 160; Ionizing Radiation Exposure to the Population of the United States, 2009



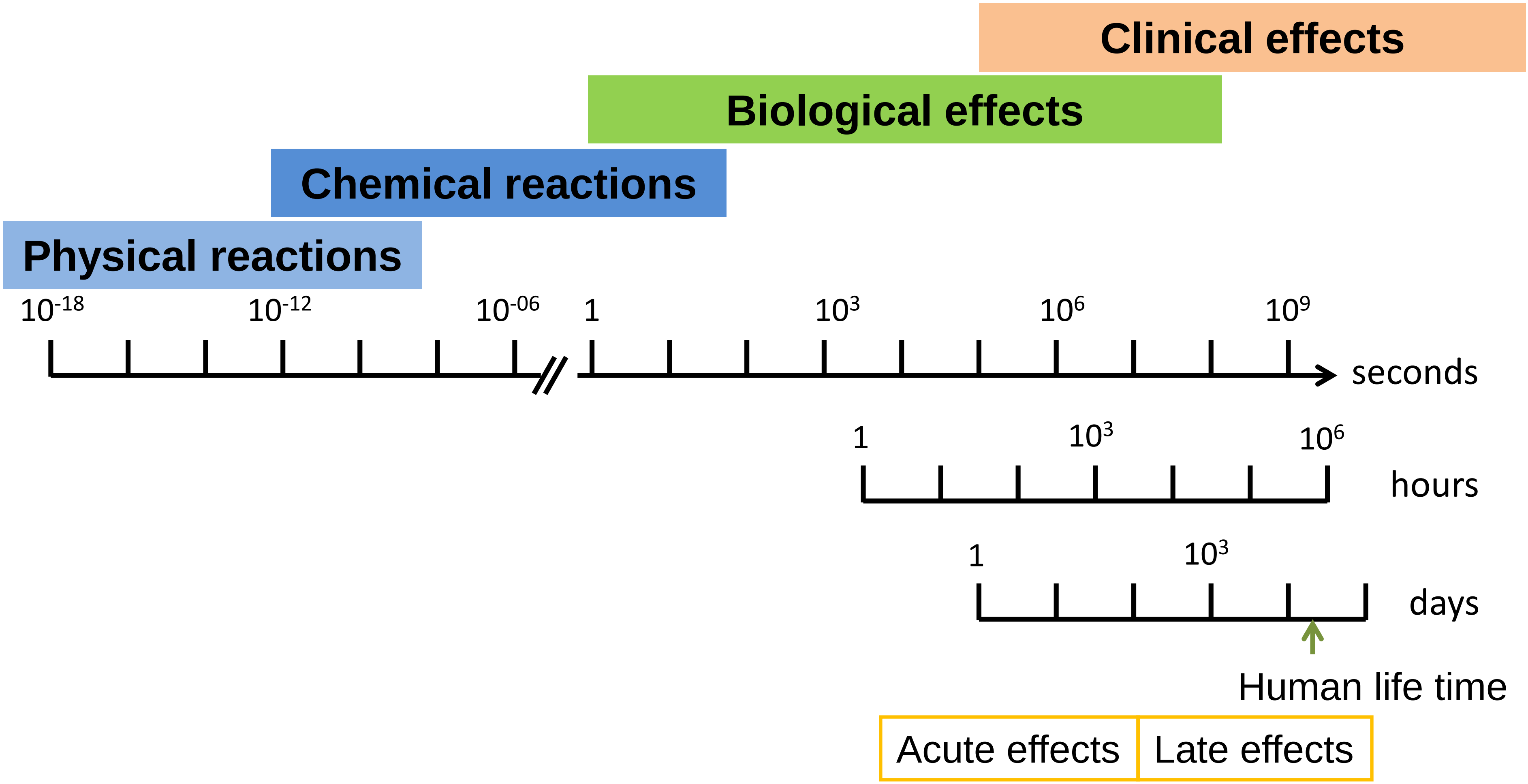
	Early 1980s	2006
Collective effective dose (person-Sv)	835,000	1,870,000
Effective dose per individual in the U.S. population (mSv)	3.6	6.2

Ionizing radiation is omnipresent for human beings

→ Estimation of biological effects and health risks

→ Handling, protection and application of radiation

1. Timescale of radiation action



Time scale of radiation action;
Steel: Basic clinical radiobiology, 1997; modified

1. Primary events of radiation action

Time (s)	Process occurring
Physical stage	
10^{-18}	Fast particle traverses small atom
10^{-16}–10^{-17}	Ionization: $H_2O \rightsquigarrow H_2O^+ + e^-$
10^{-15}	Electronic excitation $H_2O \rightsquigarrow H_2O^*$
10^{-14}	Ion-molecule reactions, e.g., $H_2O^+ + H_2O \rightarrow {}^{\bullet}OH + H_3O^+$
10^{-14}	Molecular vibrations — dissociation of excited states: $H_2O^* \rightarrow H^{\bullet} + {}^{\bullet}OH$
10^{-12}	Rotational relation, hydration of ions $e^- \rightarrow e^-_{aq}$

Transfer of energy on a molecular level ~30 eV per ionisation

→ Generation of charged particles by water radiolysis and ion and radical formation

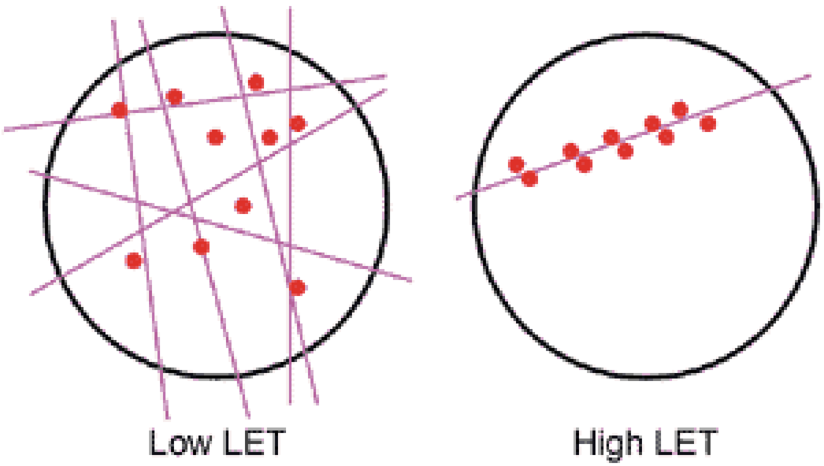
→…more details: reviews of Wardmann & O´Neill

→ Ionisation density depends on **incoming radiation quality and its LET**

Adams & Jameson, Radiat Environ Biophys 1980

1. Linear energy transfer (LET)

= amount of energy transferred to the local environment in the form of ionisations and excitations (ionisation density)



Type of Radiation	LET
25 MV x-rays	0.2
^{60}Co gamma rays	0.3
1MeV electrons	0.3
Diagnostic X-ray	3.0
10 MeV protons	4.0
Fast Neutrons	50.0

$$LET = \frac{dE}{dx}$$

Unit: keV/µm

High LET: Deposit a large amount of energy in a small distance

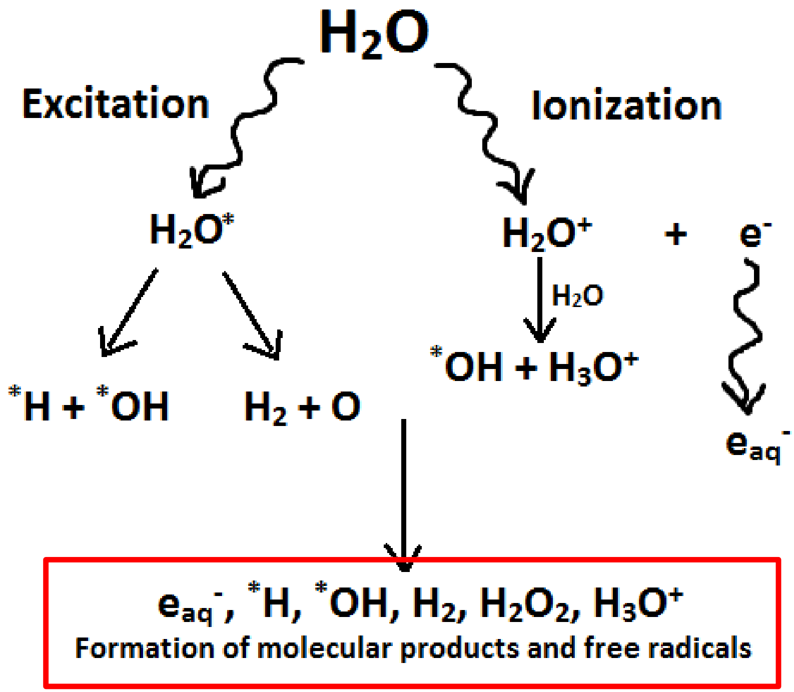
Low LET: Deposit less amount of energy along a track
Infrequent and widely spaced ionisation events

Japanese Radiation effects research foundation

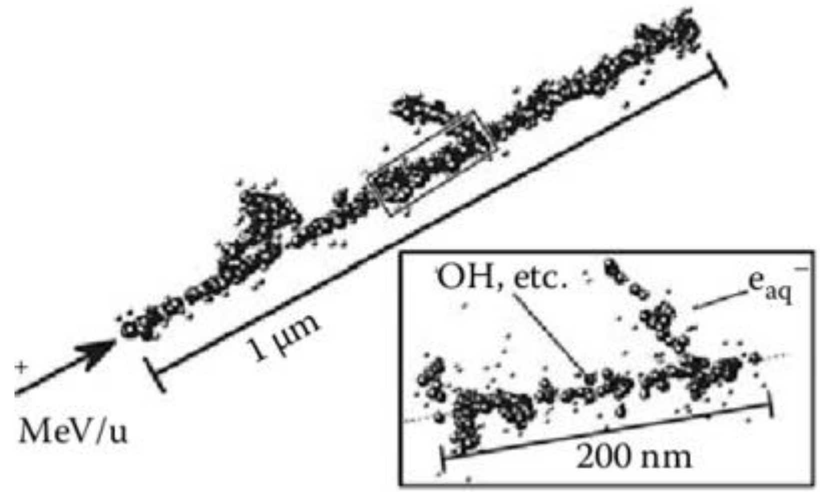
1. Water radiolysis & distribution of radicals

Physical reactions

Chemical reactions



http://large.stanford.edu/courses/2015/ph241/burkhard1/



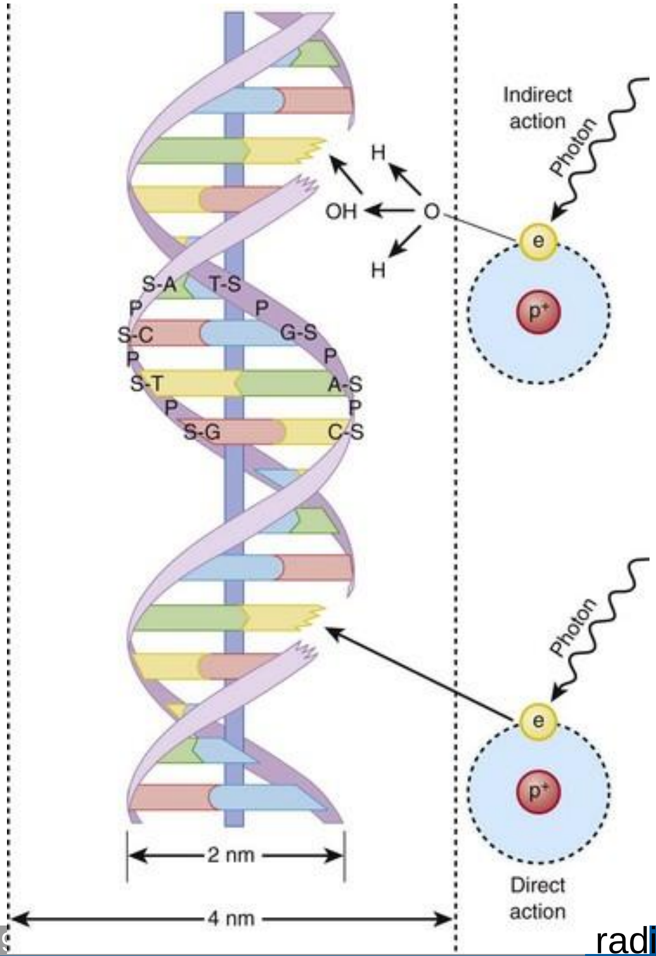
Yamashita et al. *Charged Particle and Photon Interactions with Matter—Recent Advances, Applications, and Interfaces. Taylor & Francis* (2010): 325-354.

Time (s)	Process occurring
Chemical stage	
$< 10^{-12}$	Reactions of e^- before hydration with reactive solutes at high concentration
10^{-10}	Reaction of e^-_{aq} and other radicals with reactive solute (concentration $\sim 1\ mol \cdot dm^{-3}$)
$< 10^{-7}$	Reactions in spur
10^{-7}	Homogeneous distribution of radicals

Adams & Jameson
Radiat Environ Biophys 1980

1. Direct and indirect radiation action

Time (s)	Process occurring
10^{-3}	Reaction of e^-_{aq} and other radicals with reactive solute (concentration $\sim 10^{-7}$ mol · dm^{-3}, i.e., ~ 0.01 ppm)
1	Free-radical reactions largely complete
$1-10^3$	Biochemical processes



Structural and functional changes of **nucleic acid**, proteins, lipid layers, carbohydrates, …

Indirect action:

- Low LET radiation (X-, γ-, β-rays, e^-)

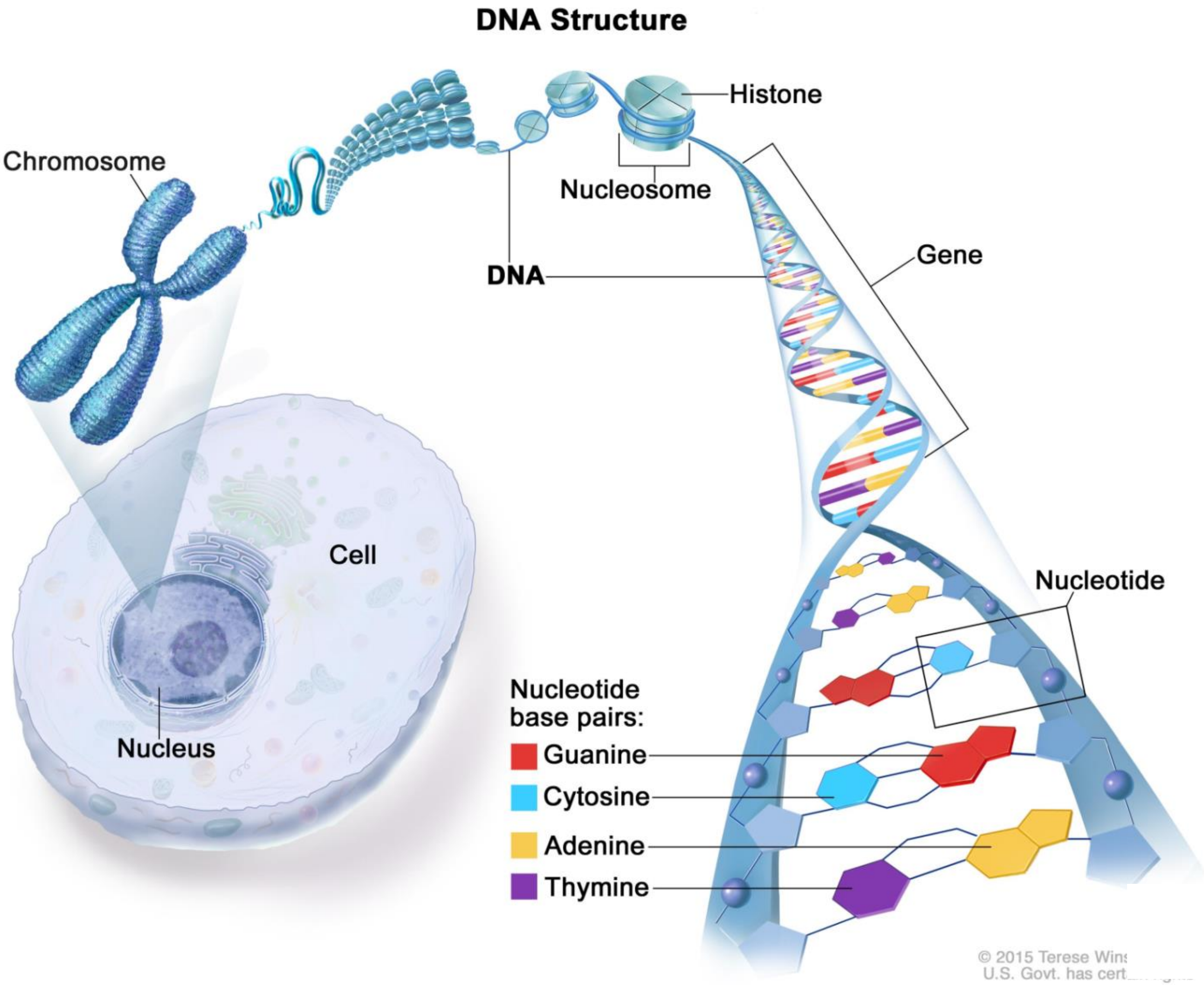
Direct action (w/o water radiolysis):

- High LET radiation (α-particle, neutrons)
- Direct interaction with **DNA** very seldom
- Human body: 80 % water / 1% DNA

radioactivityci2010.pbworks.com

1. Deoxyribonucleic acid (DNA)

Carries most of the genetic information necessary for growth, development, functioning and reproduction of all known living organisms and many viruses

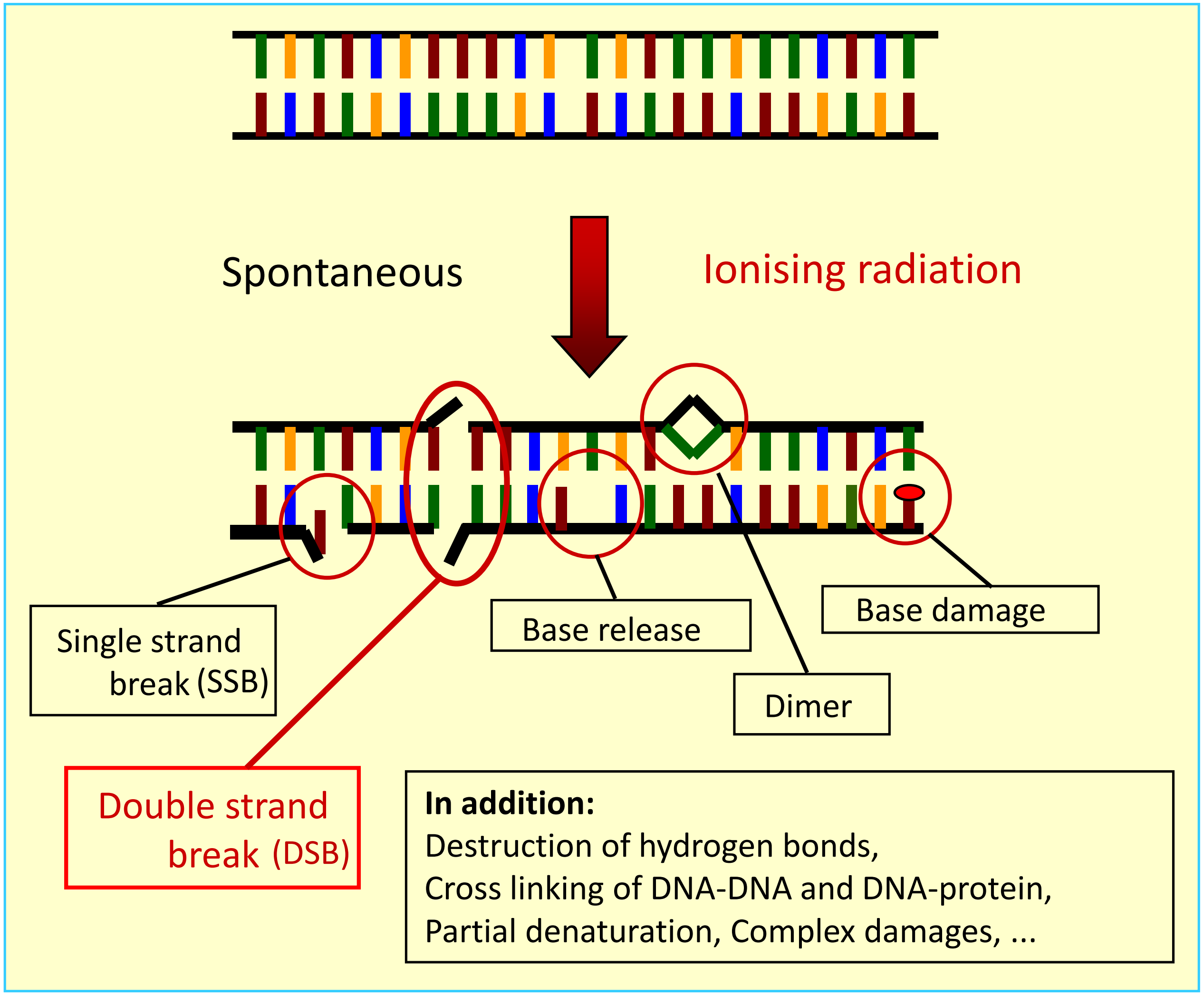


www.cancer.gov

1. Radiation damage to DNA

Biochemical reactions

Biological effects



1 Gy

~3000 base damages

~1000 SSB & 40 DSB

<u>…per cell!</u>

Vast majority is repaired by cellular repair mechanisms

>10 different pathways of different complexity and duration (s … min ... h)

1. Cell fate after DNA damage/DSB

Time (s)	Process occurring
Biological stage	
Hours	Cell division affected in prokaryotic and eukaryotic cells

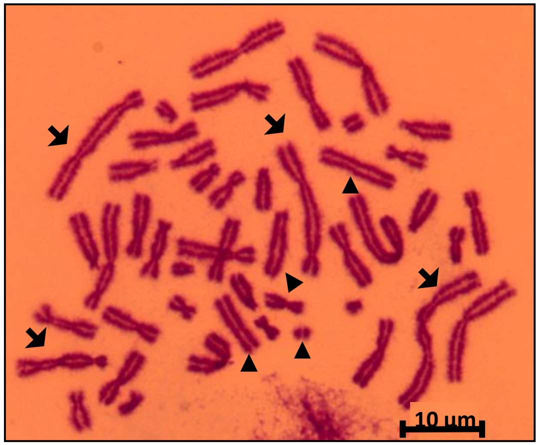
Adams & Jameson
Radiat Environ Biophys 1980

Accurate DNA repair → Survival without DNA damage

Damage level too high/severe → Lethal chromosomal aberrations
Mutagenesis / Carcinogengesis
Cell death

Measurement of DNA damage:

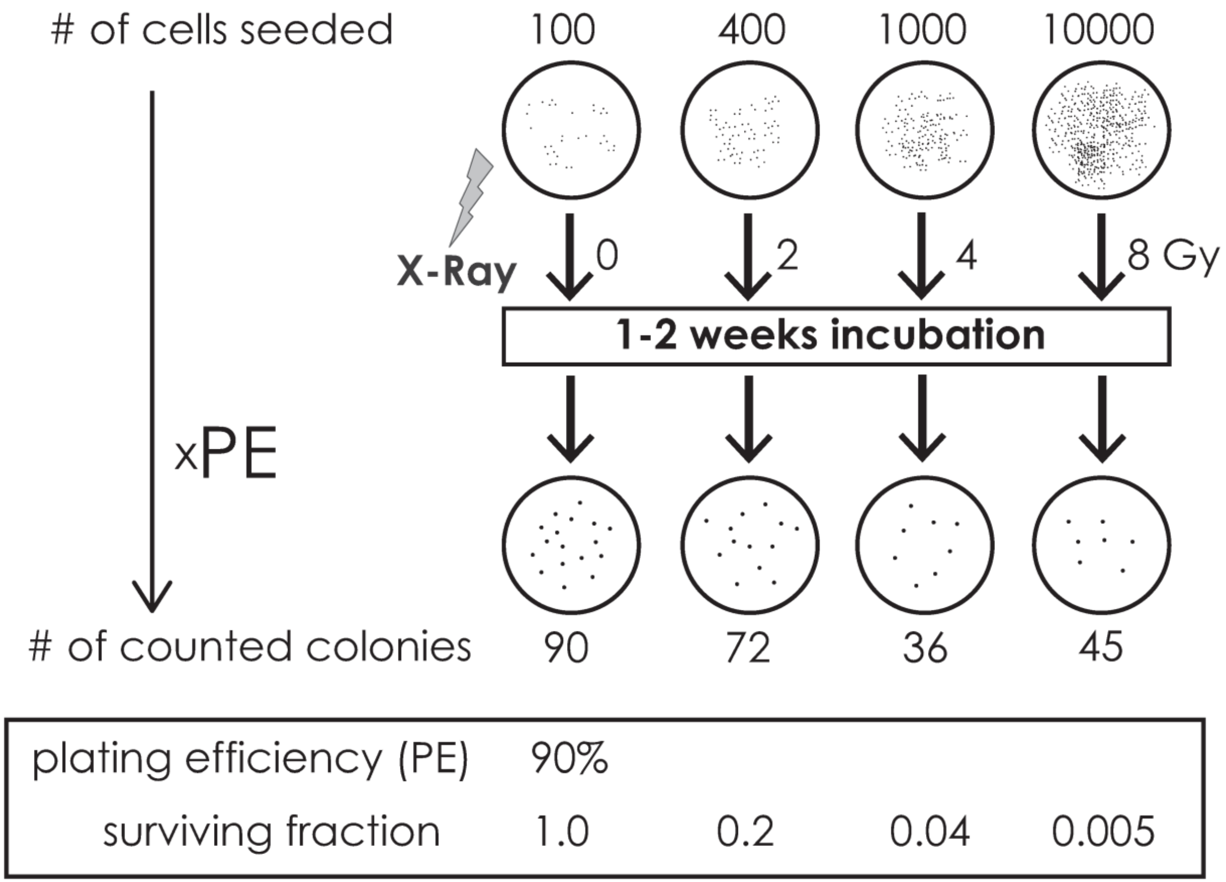
- Clonogenic survival assay
- Quantification of DSB repair proteins
- Determination of chromosomal aberrations
- …



Dicentric chromosome after DSB
Induction by 10 kV X-rays

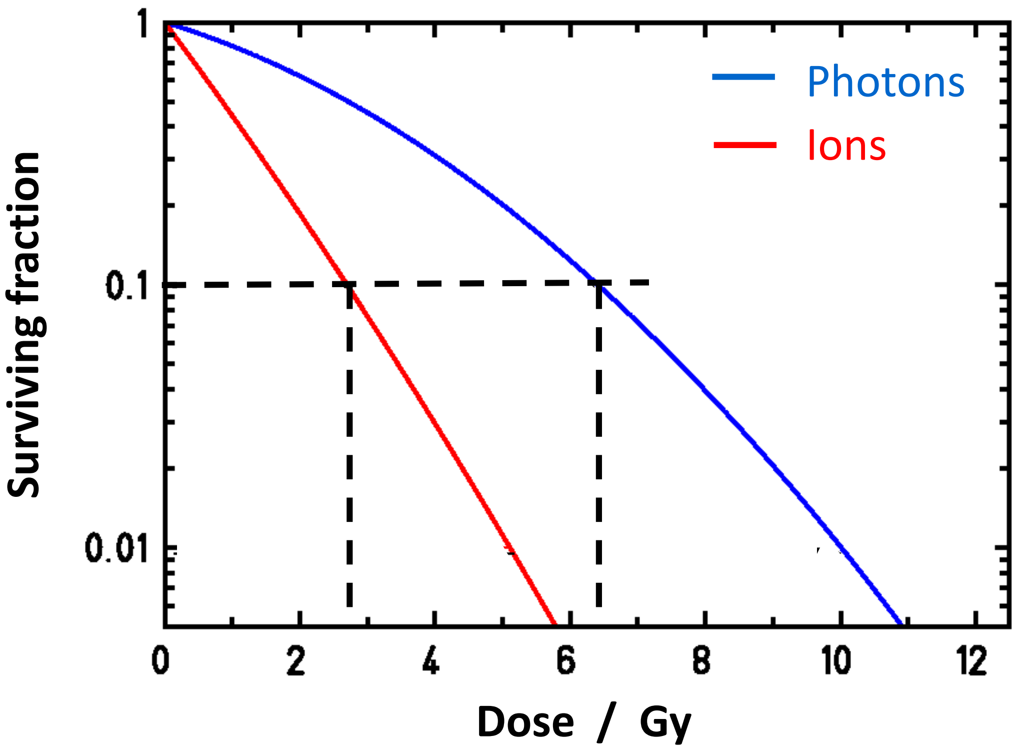
1. Clonogenic survival assay

- First developed by Puck and Marcus in 1955
- “Golden standard” in radiotherapy/biology
- Clonogenic survival = ability of unlimited cell division



Intechopen.com: Evolution of Ionizing Radiation Research 2015

1. Cell survival curves

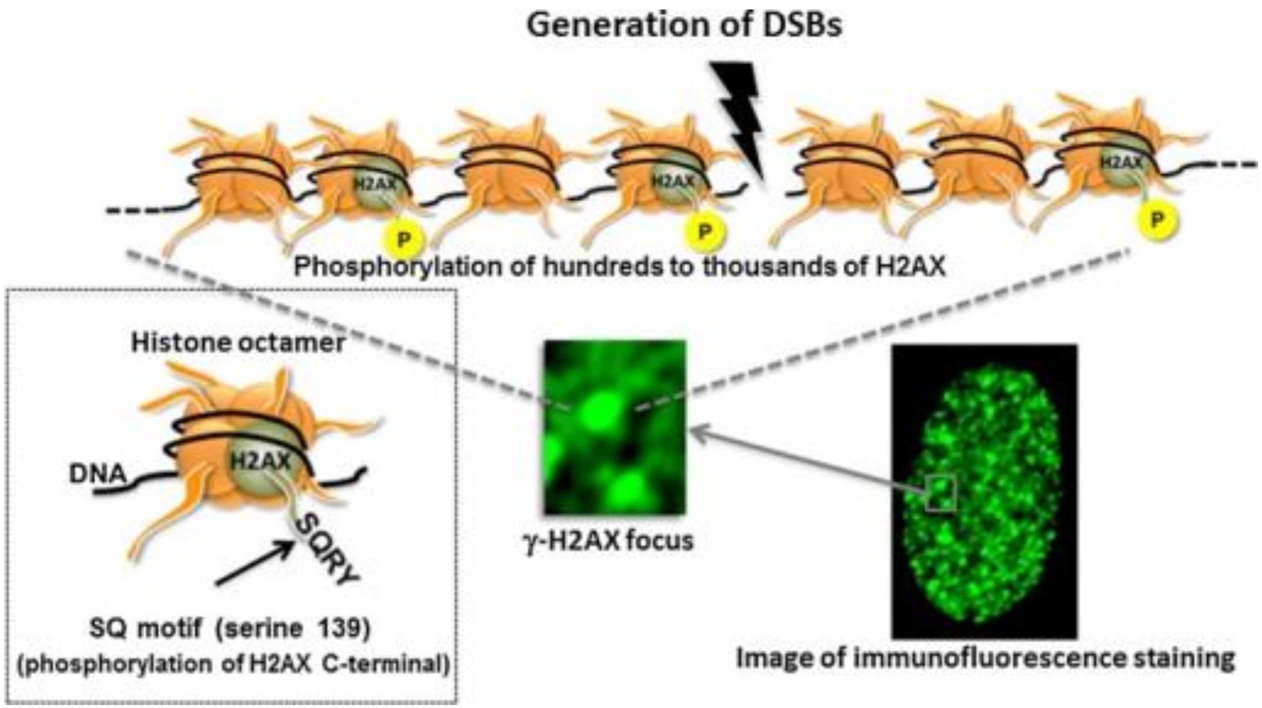


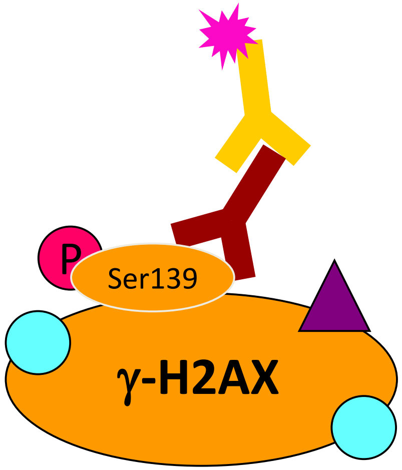
Relative biological effectiveness:

$$RBE = \frac{D_{Ref}}{D_{Test}}\Big|_{E_{Ref}=E_{test}}$$

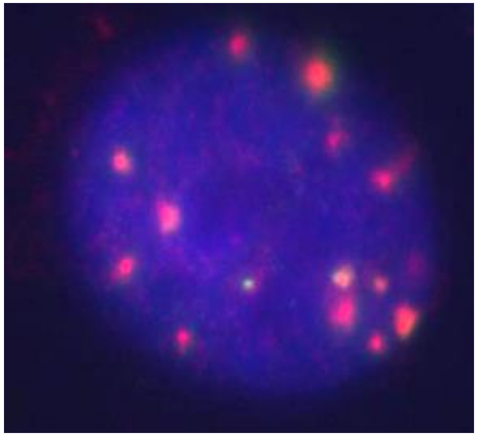
- Radiation: type, energy, LET, dose, dose rate, dose fractionation, …
- Cell/tissue: species, intrinsic (genetic) radiosensitivity, cell cycle, chromatin structure, cell age, …
- Micro milieu: temperature, perfusion, oxygen, hypoxia, cell-cell interaction, growth factors, …

1. Detection of DNA DSB repair proteins





- Detection of DNA DSB signaling and repair molecules as surrogate for DSB
- Methods: antibody labeling and microscopic or fluorescence intensity (FACS) analysis



Blue: DNA in cell nucleus
Pink: γH2AX foci ~ DSB
after 4 Gy X-ray irradiation

Ibuki & Tooyoka, J Radiat Res, 2015

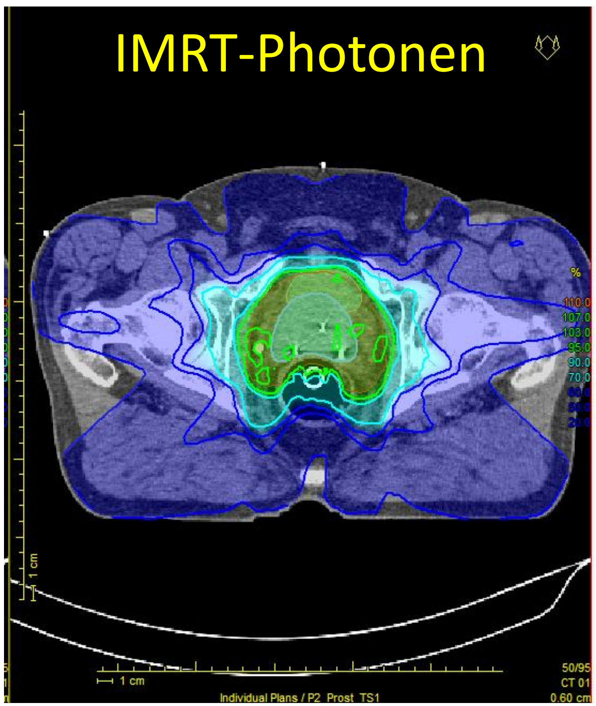
1. Long term effects

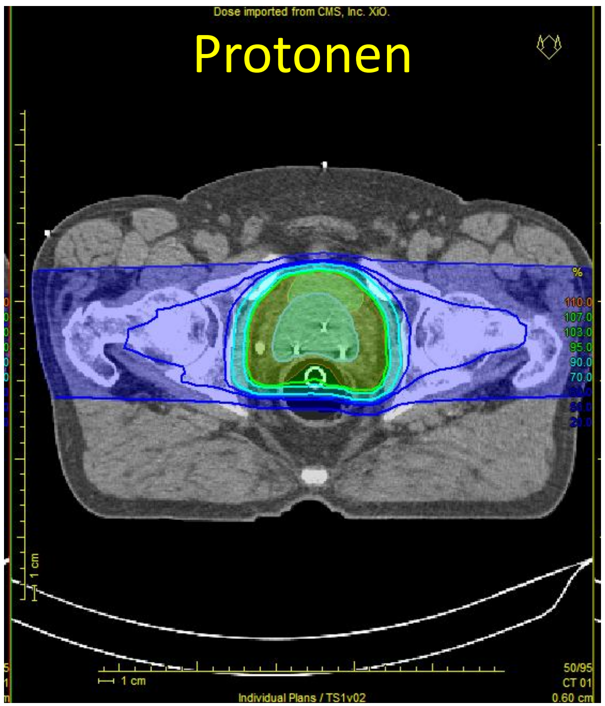
Biological effects

Clinical effects

Time (s)	Process occurring
Biological stage	
Hours	Cell division affected in prokaryotic and eukaryotic cells
Days	Damage to CNS and GI tract evident
~ 1 month	Haemopoietic death
Several months	Late kidney damage, lung fibrosis
Years	Carcinogenesis and genetic death

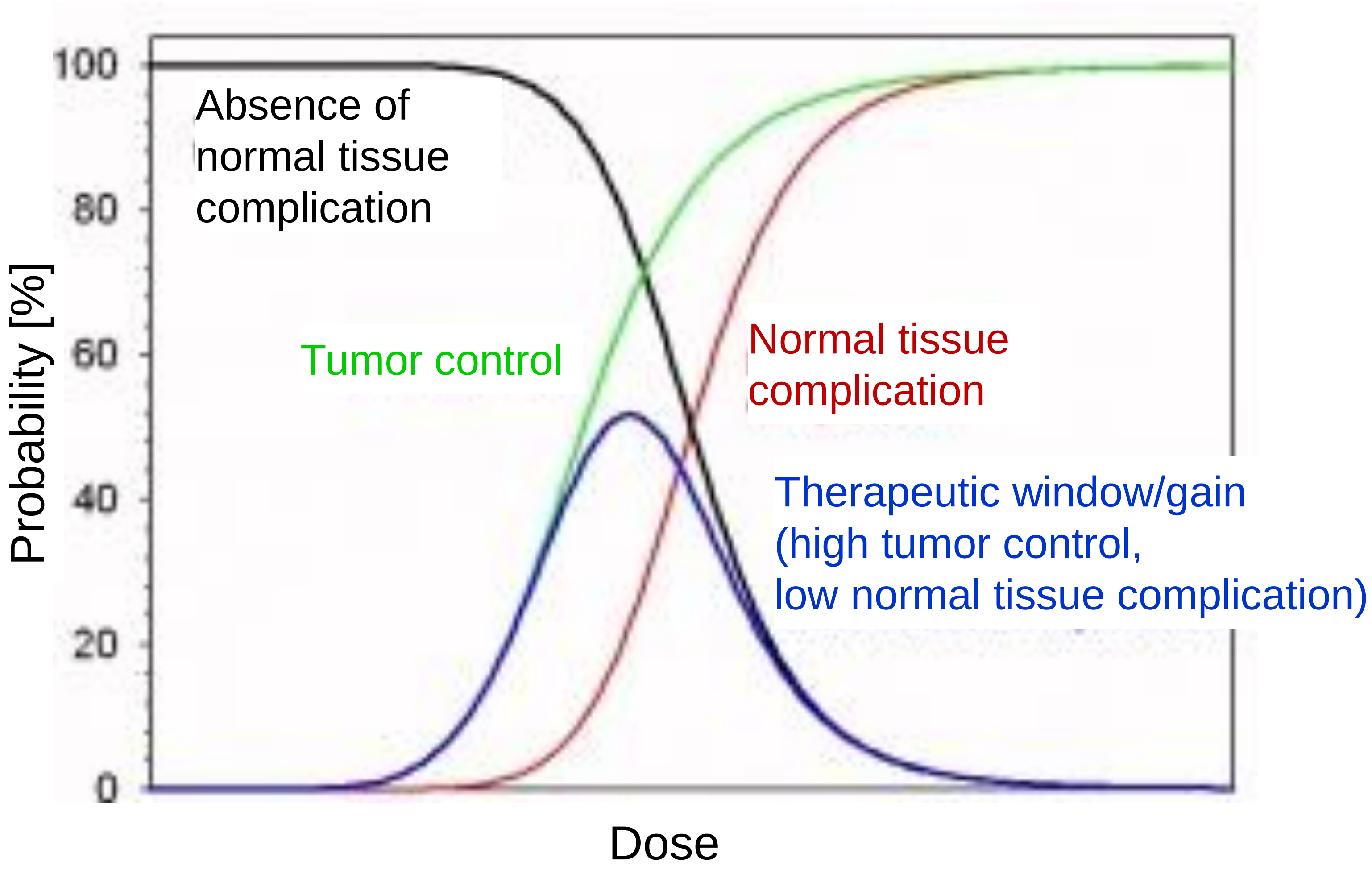
(Days – Years:) Radiotherapy acute/late effects





Adams & Jameson, Radiat Environ Biophys 1980

1. Long term effects: Holthusen diagram

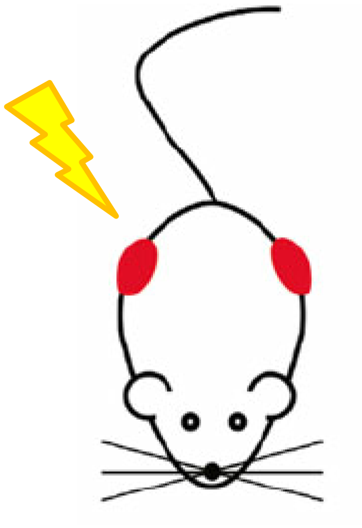


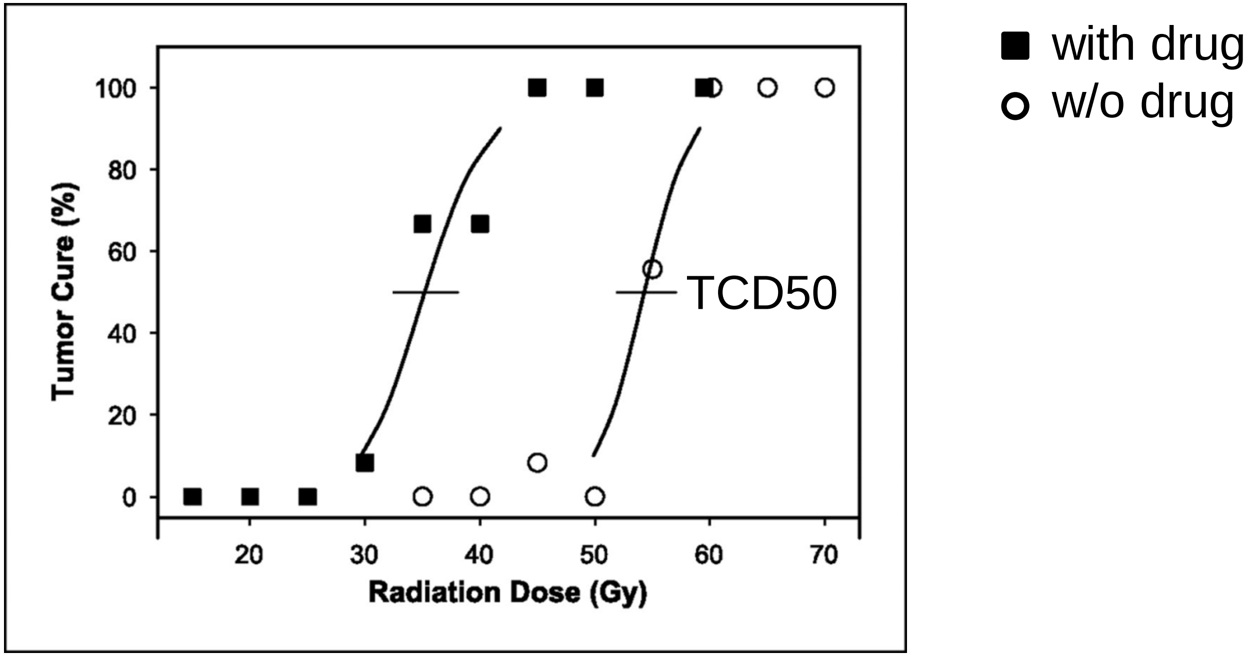
Holthusen 1928

1. Preclinical animal experiments – tumor control studies

- Animal studies are necessary to translate in vitro results into the clinics
- RT related research: **human tumor xenografts on mice**
  - Controlled investigation of factors influencing tumor response
  - Evaluation and pre-selection of treatment modalities

Tumor control studies – "Standard" in RT related research



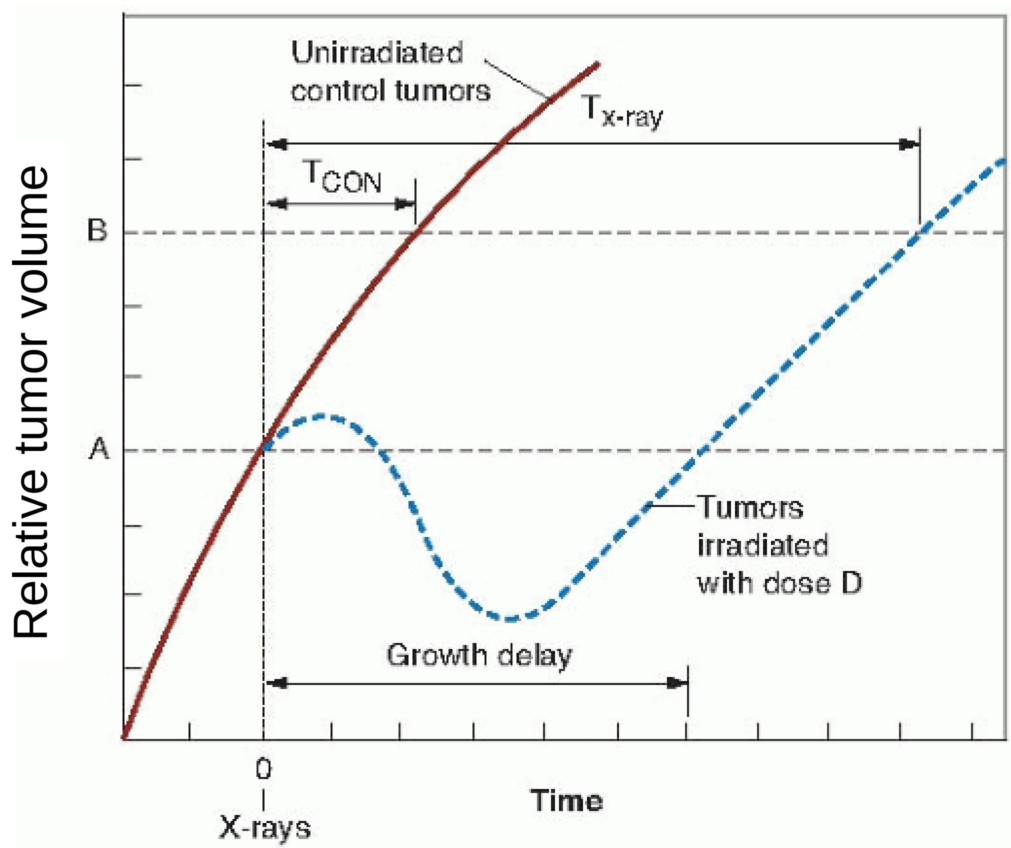


Biological effects **Preclinical effects**

1. Preclinical animal experiments – tumor growth delay

Tumor growth delay (GD)
Difference between the mean time spans non-irradiated and irradiated tumors need to achieve a certain size or relative volume increase

$$GD_{V_i} = t_{V_i,Dose} - t_{V_i,Control}$$
$$i \ldots 3,5,7,10$$



https://radiologykey.com/model-tumor-systems/

Biological effects **Preclinical effects**

Summary: Radiobiology reaction cascade

Phase	Processes	Time scale
Physical phase	Energy transfer: ionisations and excitations Ionisation density ~ radiation quality	10^{-18}-10^{-12} s
Chemical reactions	Radiolysis of water → formation and diffusion of radicals and molecular products	10^{-7} s 10^{-3} s
Biochemical reactions	Direct and indirect interaction of radiation and cellular macromolecules → Cleavage of bonds, induction of DNA damage	10^{3} s
Biological effects	Repair or manifestation of DNA damage → Aberrations of chromosomes and genes → Altered morphology and cell cycle	s - h h - d
Clinical effects	→ Cell death, mutagenesis, cancerogenesis → Acute and late effects of radiation → Death of the organism	weeks…a

Radiobiology – aims and responsibilities

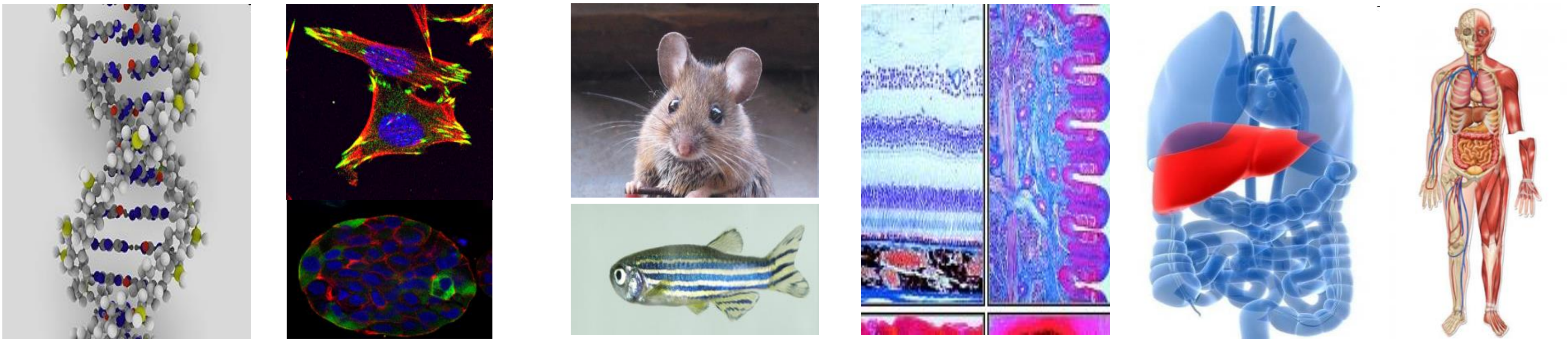
Biological effects

Clinical effects

- Detection, description and quantification of radiation effects
- Clinical purposes:
  - Optimal strategy for tumor control but normal tissue sparring in RT
  - Prevention of normal tissue complication in radiation diagnostics

Clinical application: Requires translational research

From molecule to organism



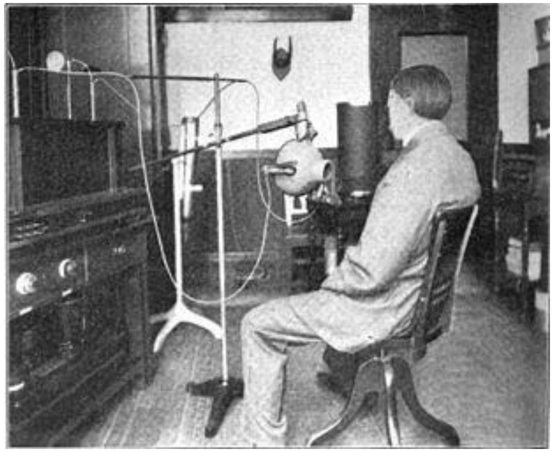
2. The time factor in conventional radiotherapy

- **Brief history of conventional RT accelerators**
- **Time factor in medical dose delivery**
- **Summary of previous studies (1950…1990)**
  - **Low dose rate and the 4R of radiobiology**
  - **High dose rate and the oxygen effect**

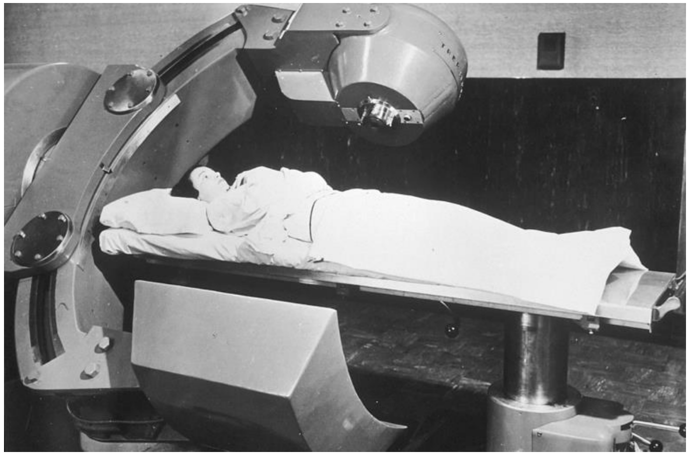
2. Radiotherapy treatment started continuous radiation sources

- Prior World War II: X-ray tubes and Radium/Radon sources
- After 1945 artificial isotopes available: ^{137}Cs and ^{60}Co

Treatment of lupus with radon salts, 1905



X-ray treatment of Tuberculosis; ~1910



^{60}Co Teletherapy early 1950s National Cancer Institute/USA

- Continuous irradiation with fixed (natural) dose rate
- “Trial and error” phase, treatment time and direction decisive
- 1919: first investigations of the time factor in radiotherapy by Regaud

Biological effects

2. Accelerated radiation brings along the time factor

- 1930 1st HF-linear electron accelerators developed by Wideröe
  → 1st patient treatment in 1953 in London/Hammersmith hospital
- Widespread distribution and replacement of ^{60}Co-units since the 1980s
- Particles: 1st cyclotron by Lawrence in 1932
  1st p-therapy 1958 (Sweden)

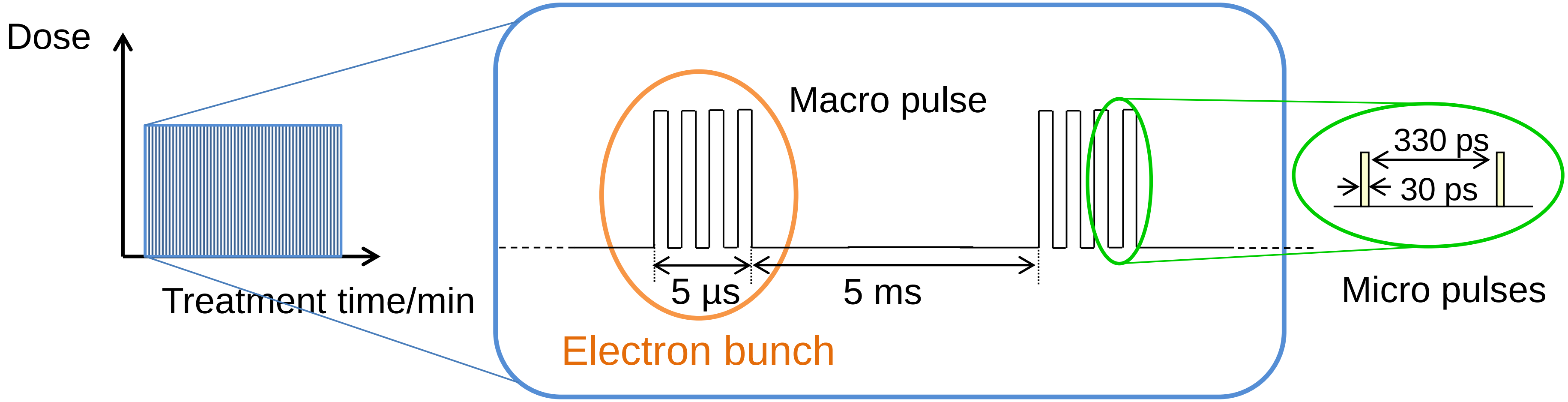
Linac (e^-) treatment of an eye tumor / 1957 National Cancer Inst.

Cyclotron C230/ **IBA**
University Proton Therapy Dresden

Synchrotron
Heidelberg Ion-Beam Therapy Center HIT

2. Medical beam delivery: conventional electron Linac

- Electrons 3 – 10 GHz by Linac
- Quasi-continuous, but different beam pulse structure



	Mean (s)	Macro pulse	Micro pulse
Frequency		50-200 Hz	3 GHz
Pulse duration	1 s	5 µs	30 ps
No. of electrons	$3 \cdot 10^{10}$	$1.5 \cdot 10^{8}$	10^{4}
Mean dose rate[1])	**6 Gy/min**		
Pulse dose rate		**6 kGy/min**	**60 kGy/min**

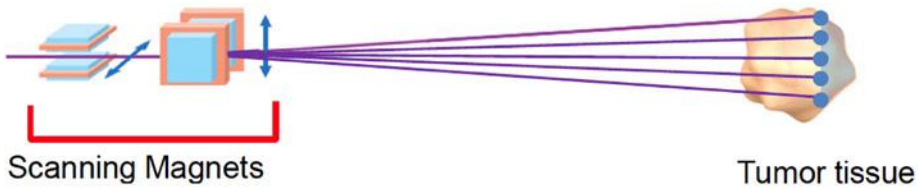
E_{kin} = 20 MeV

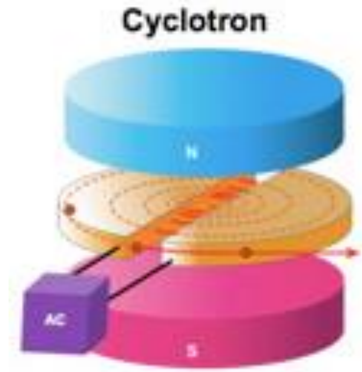
After: H. Krieger, Strahlenphysik, Dosimetrie und Strahlenschutz, Bd.2, 2001

[1]) Irradiation field of 10 × 10 cm^2

2. Medical beam delivery: cyclotrons

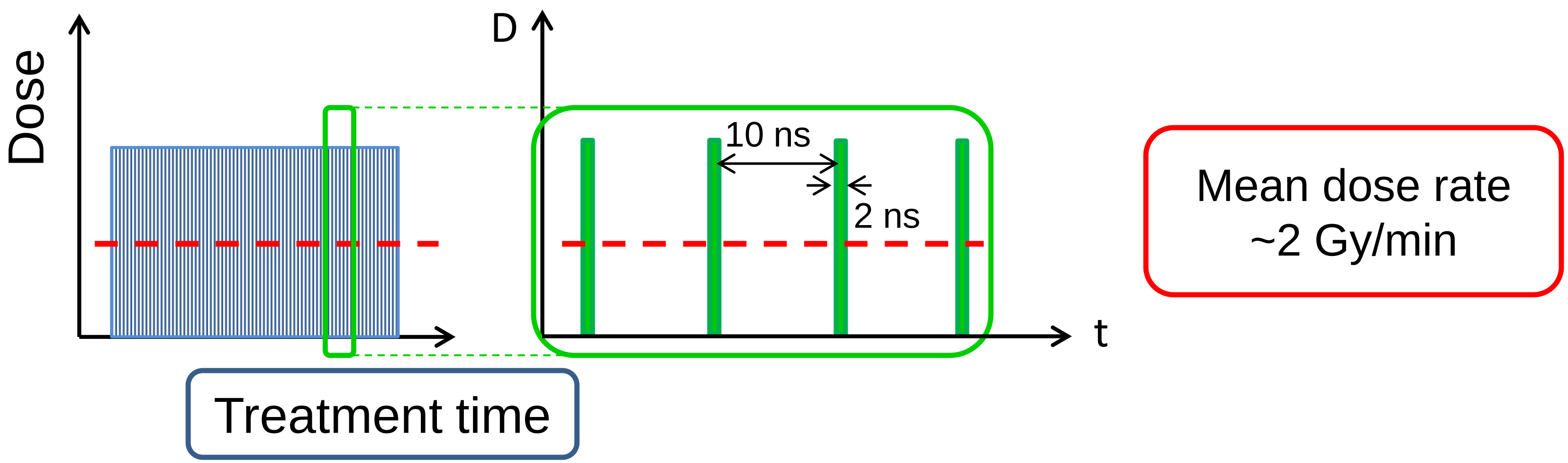
- Most frequent clinical/conventional proton accelerators
- Quasi-continuous beam delivery and pencil beam scanning





http://www2.kek.jp

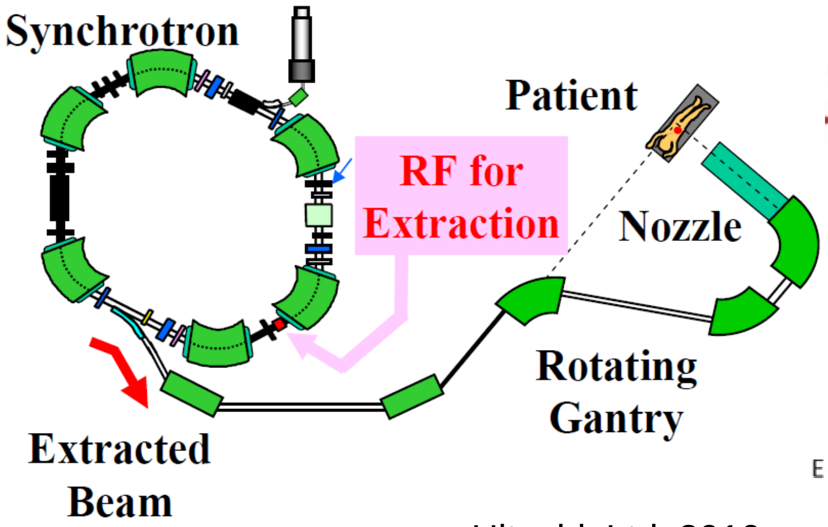
Example: IBA C230 isochronous cyclotron / University Proton Therapy Dresden



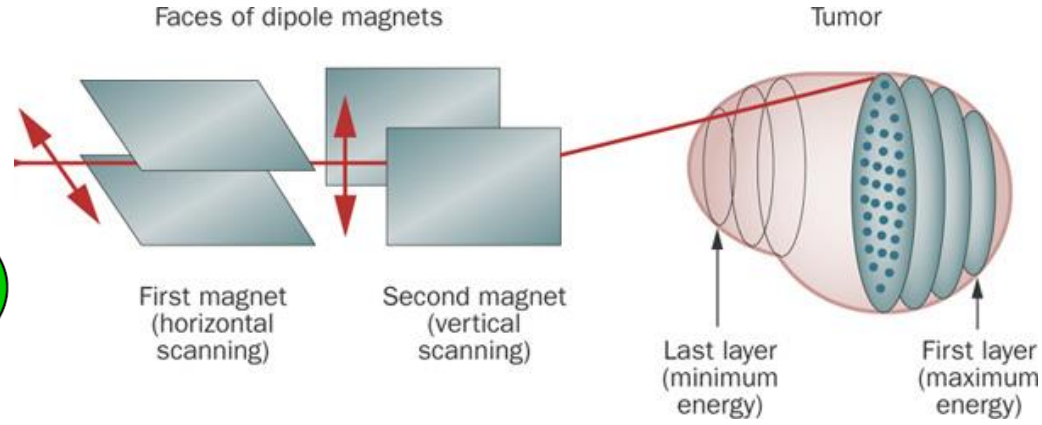
	Micro pulse	PBS-Spot
Frequency	100 MHz	~1 MHz
Pulse duration	2 ns	10 ms
Pulse dose rate	**~10 Gy/min**	**~ 6 kGy/min**

Rep. Prog. Phys. **79** (2016) 096702

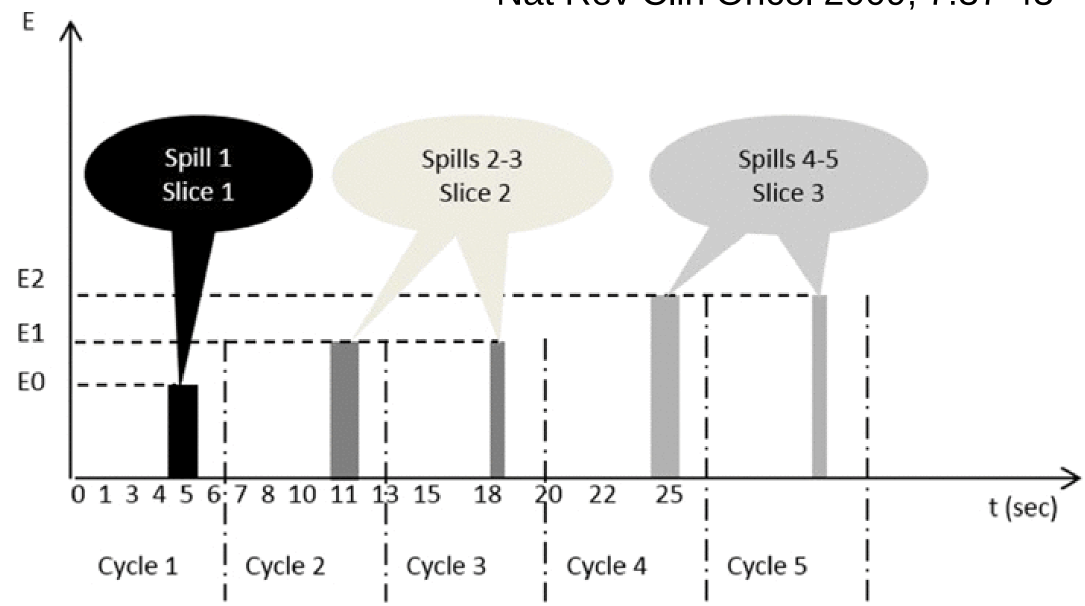
2. Medical beam delivery: pencil beam scanning @synchrotron



Hitachi, Ltd. 2010



Nat Rev Clin Oncol 2009; 7:37-43



"Macro pulse"

"Pulse" duration

	Spill	~ 1 s
	Spot	< 10ms

Pulse dose rate

	Spot	**~100 kGy/min**

Giordaneggo et al. Med Phys 2015

2. Time factors in clinical dose delivery

Physical phase	Chemical reactions	Biochemical reactions	Biological effects	Clinical effects

10^{-18}-10^{-12} s — 10^{-7} s — 10^{-3} s — 10^{3} s — s - h — h - d — weeks…a

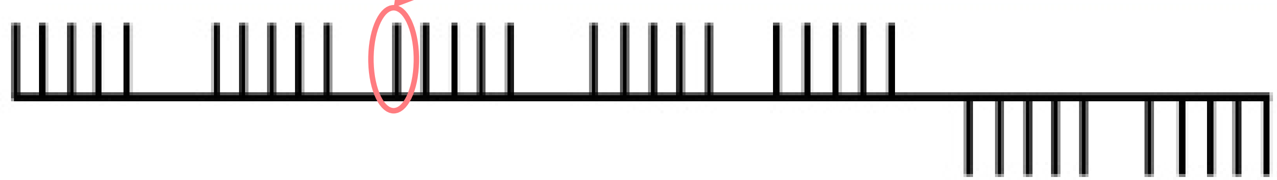
Micro pulses
t_{Puls} ~ ps… ns

Macro pulses
t_{Puls} ~ µs… s

Fraction time
t ~ min

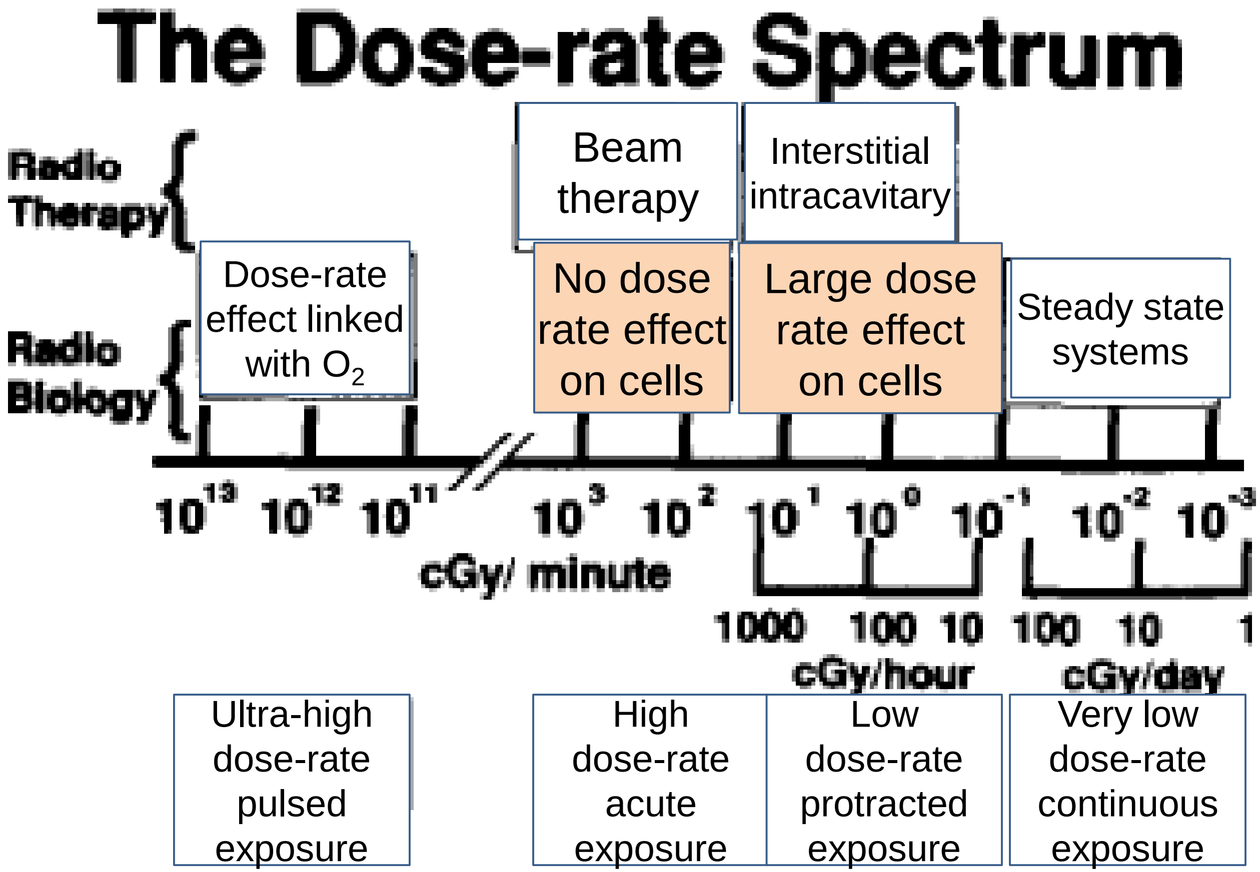
Overall treatment time
t ~ d…weeks

Conventional fractionation **external RT**: 70 Gy/35F/7 **weeks**



How did the radiation action on the different time scale influence the upstream phases?

2. Preceding studies define the parameters for clinical RT



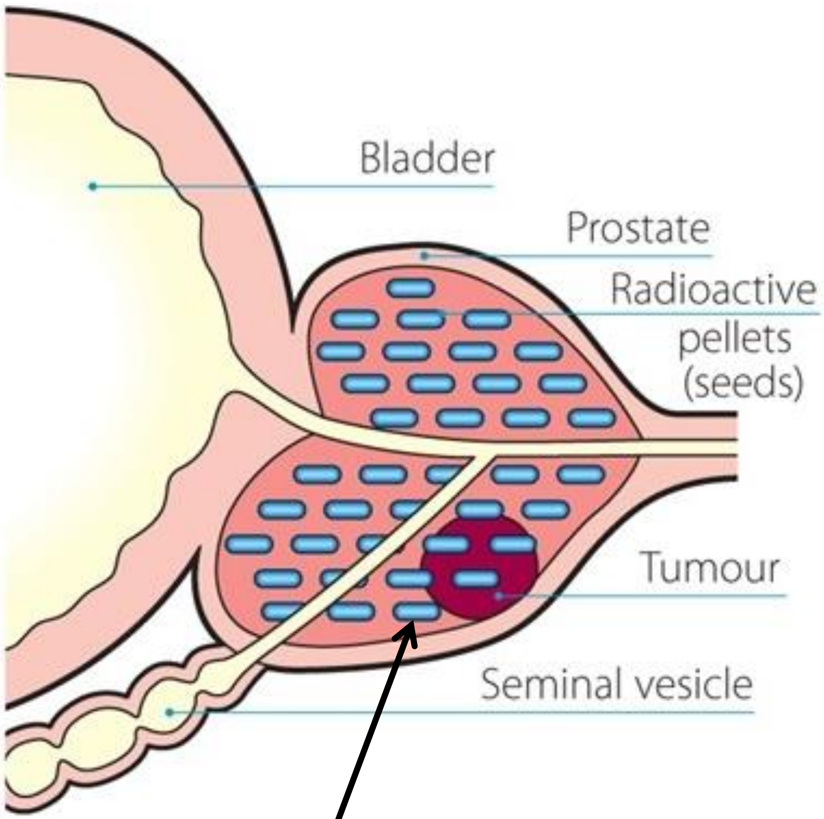
- Large dose-rate effects below 1 Gy/min
- Constant biological effect expected for higher dose rates

Hall & Brenner, IJROBP 1991

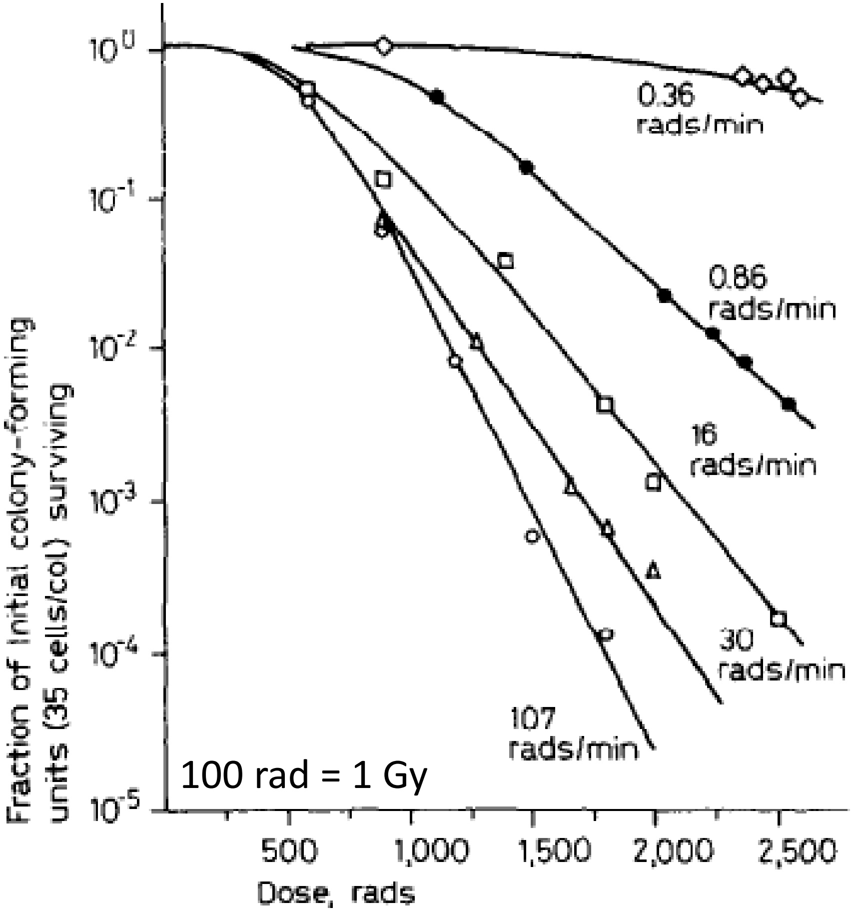
2. Low dose rate clearly influence the radiobiological outcome

Example: Brachytherapy

2 ~12 Gy/h, treatment of cervix, prostate and lung cancer



Radioactive seeds implanted in prostate



Dose response curves Chinese hamster cells; ^{60}Co γ-rays

http://oxfordurologyassociates.uk/brachytherapy

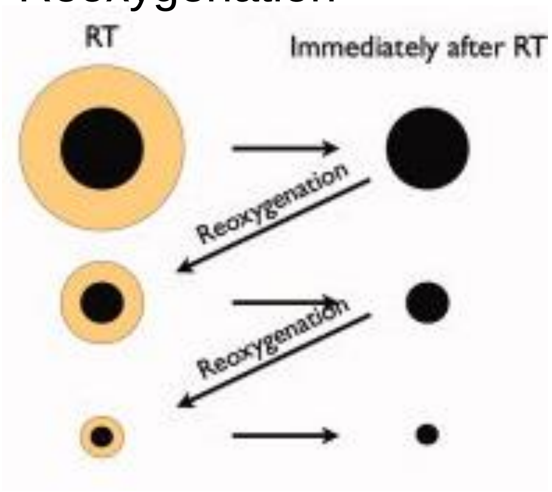
Bedford & Mitchell Rad Res 1973

2. Prolonged irradiation in conflict with the 4R of radiobiology

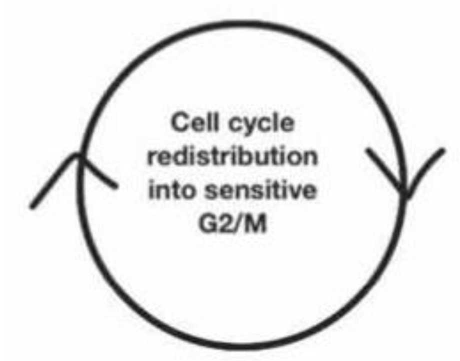
Improves cell death

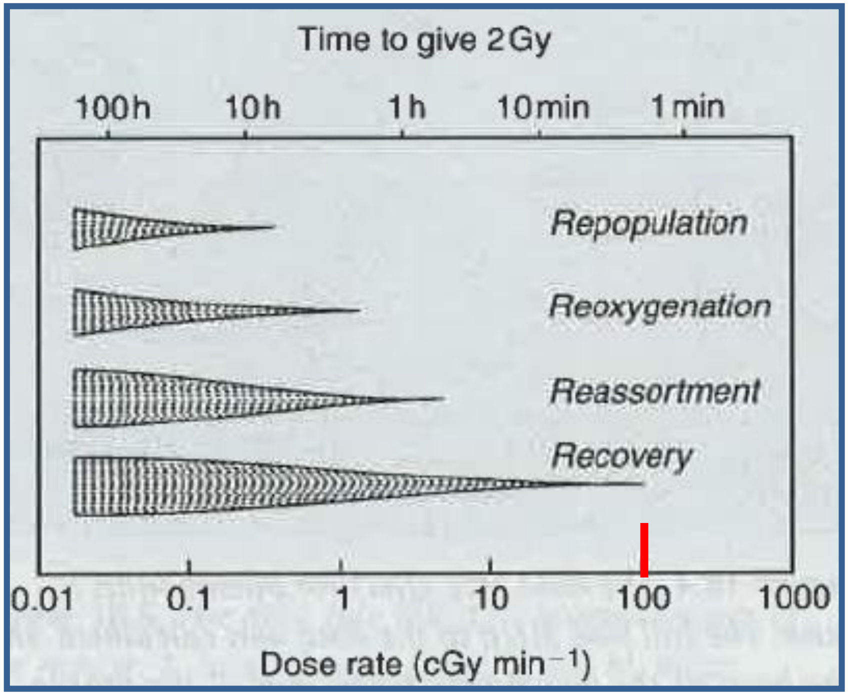
Improves cell survival

Reoxygenation



Reassortment/
Redistribution

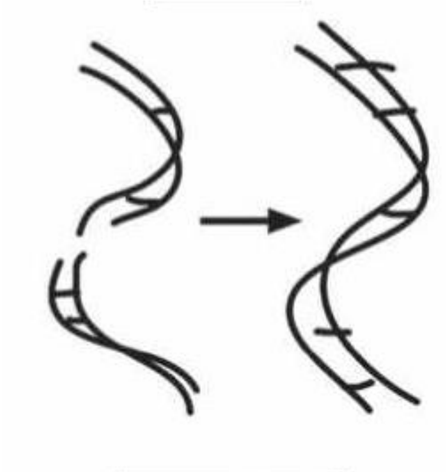




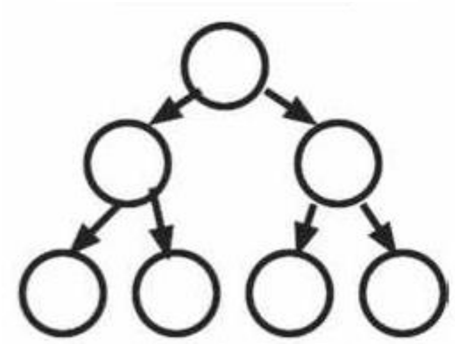
Steel: Basic Clinical Radiobiology, 2002

External RT: >1 Gy/min

Repair/Recovery



Repopulation



http://aibolita.com/cancer/49854-tumor-response.html

Pajonk et al. Stem Cells 2010; 28(4):639-48

Biological effects

2. 1960s…1990s experiments with ultra-high dose rates

Field emission sources:

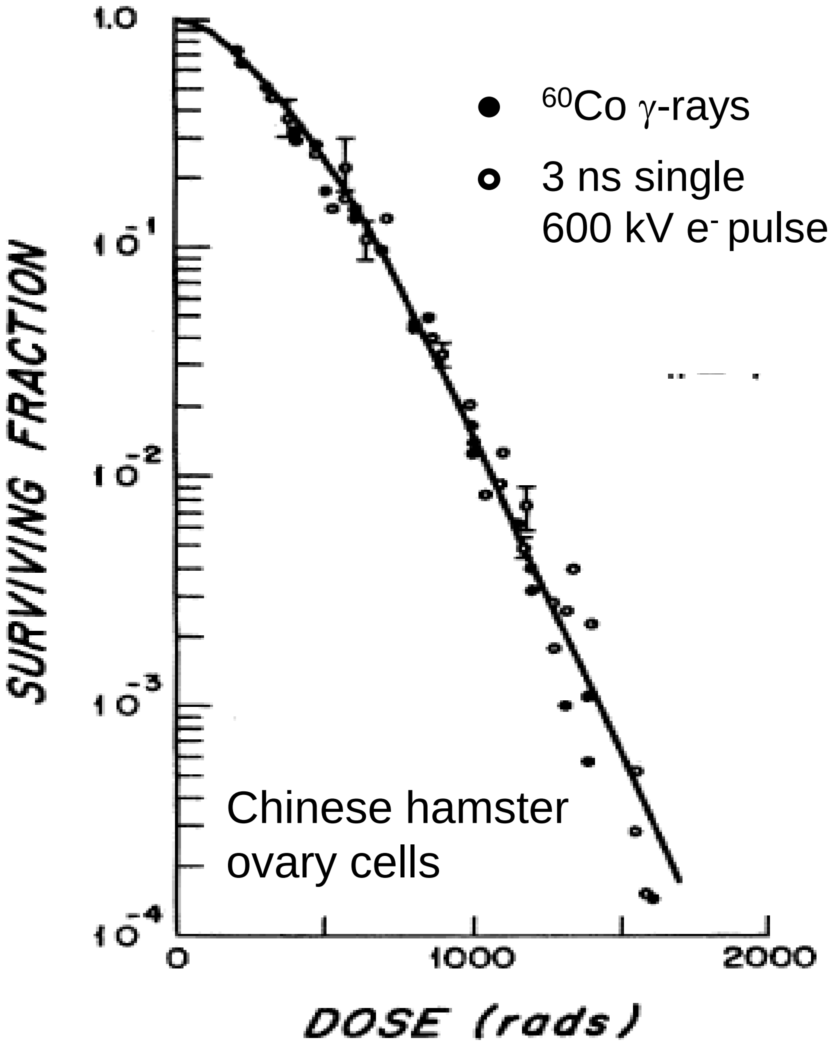
- 400 – 600 kV e⁻
- **ns** single shots of ~10^9 Gy/s

Electron linacs:

- 15 – 35 MeV
- **40 ns – few µs** shots of 10^8 Gy/s

Several studies with different animal and human tumor and normal tissue cell lines

Majority of studies reveal no influence of UHDR on radiobiological response, but some…

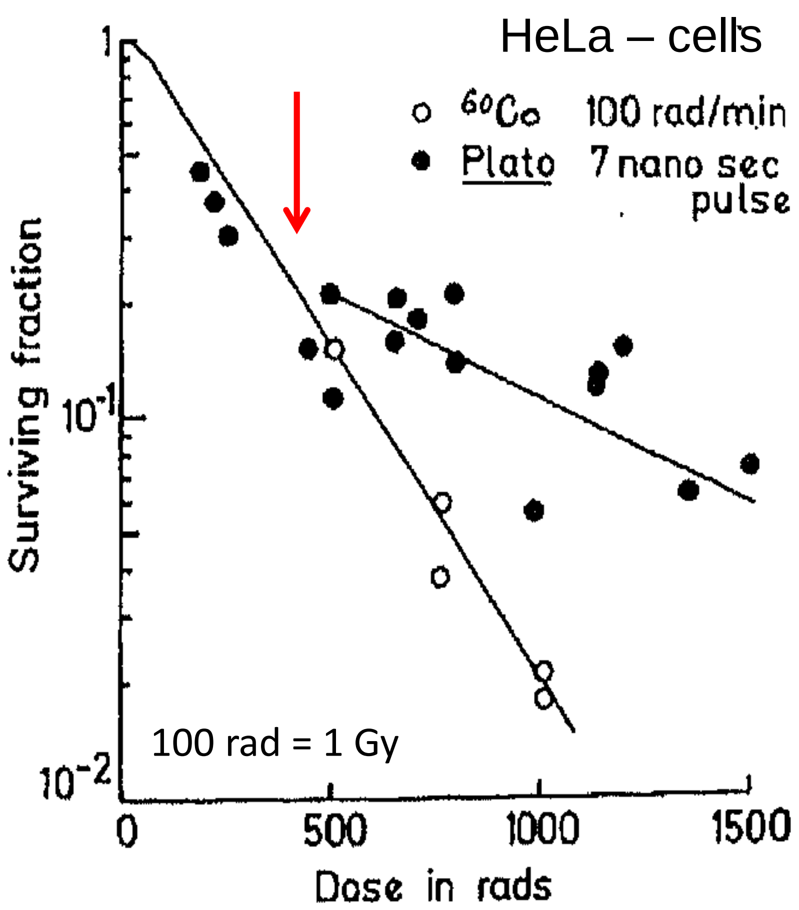


100 rad = 1 Gy

Michaels et al. Rad Res 1978

Physical phase | Chemical reactions

2. … hockeystick curves and the altered oxygen effect



Berry et al. Br J Radiol 1972

Reduced biological effectiveness for pulsed e$^-$ beams above a certain dose

Influence on radical reactions:

- Radical generation in short time
- Radical-radical interaction rather than interaction with DNA
- Reduced biological effectiveness

Missing confirmation and high dose limit prevent clinical implementation

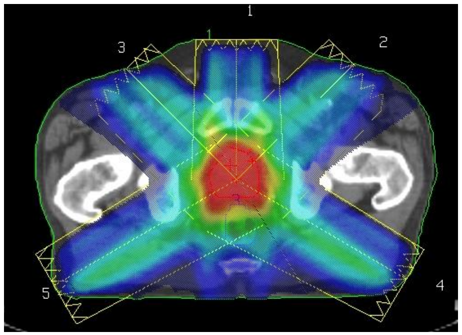
Physical phase | Chemical reactions

3. Current developments in clinical dose delivery

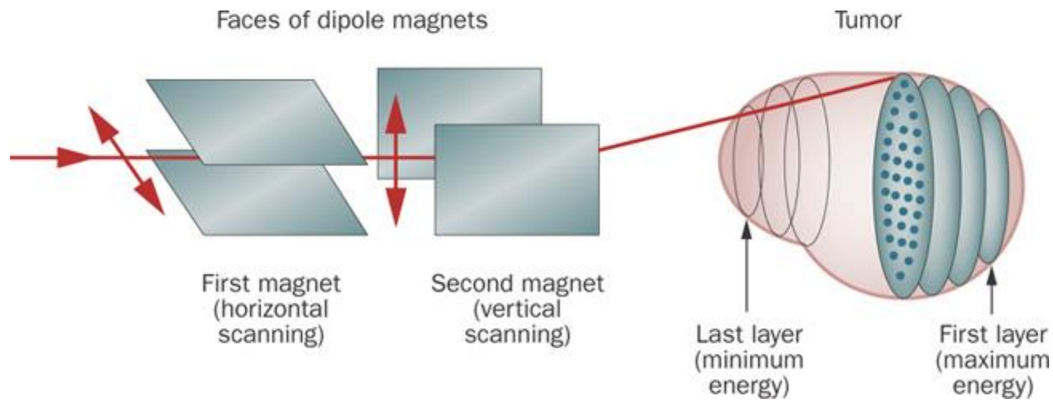
- **Advanced clinical beam delivery techniques**
  - **Protracted and varying pattern of dose delivery**
  - **Flattening filter free linacs**
  - **FLASH irradiation as alternative approach**
- **Laser driven acceleration**
  - **Laser driven soft X-rays: in vitro**
  - **Laser driven electron beams: in vitro & in vivo**
  - **Laser driven proton beams: in vitro & in vivo**

3. Protracted and varying patterns of dose delivery

- Protracted treatment in external beam radiotherapy (e.g. **gating**, IMRT)
- Varying dose delivery patterns over individual tissue voxels

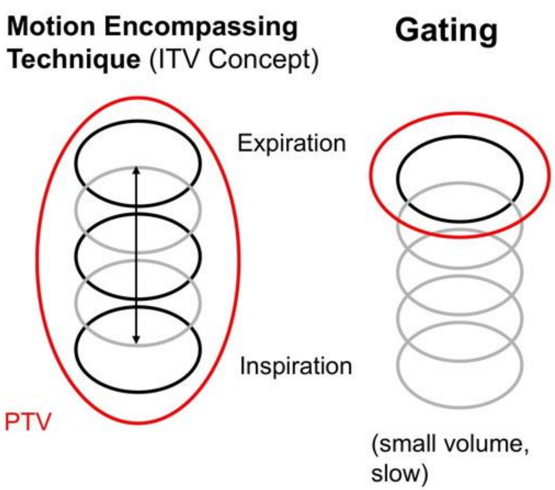


IMRT, varian.com

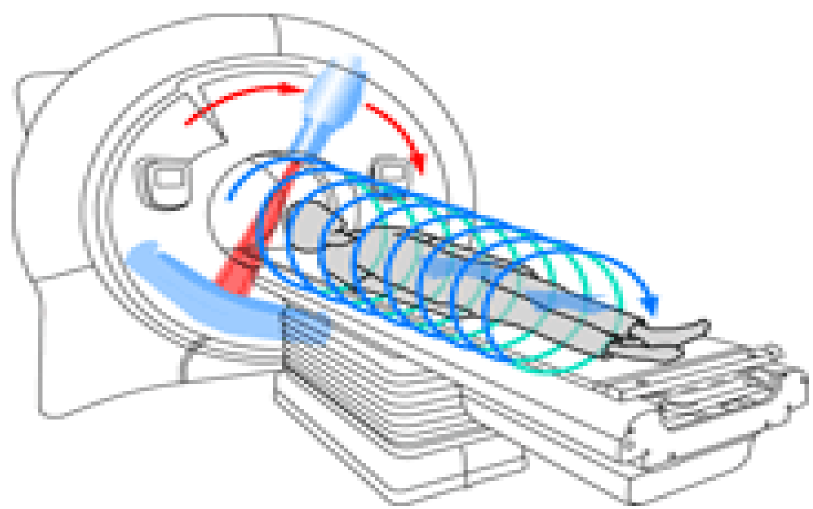


Pencil beam scanning

Nat Rev Clin Oncol 2009; 7:37-43



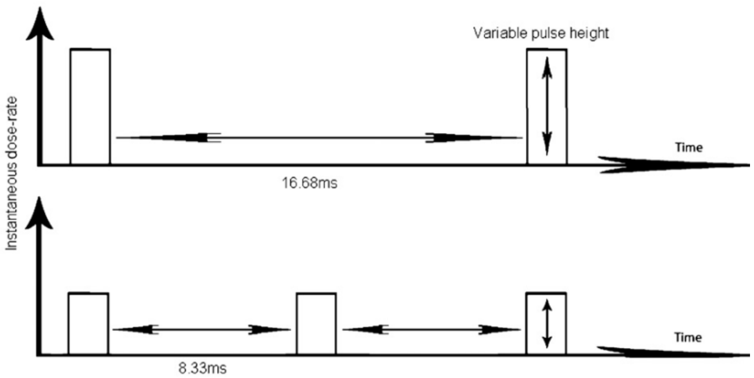
sps.ch



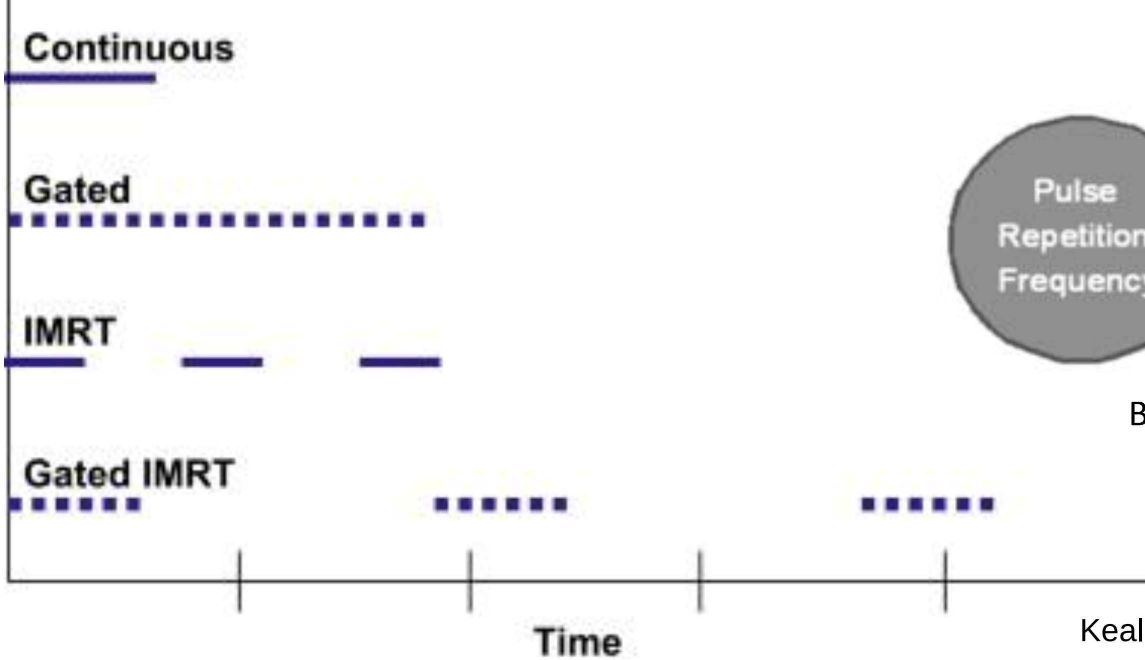
TomoTherapy®

3. Protracted dose delivery: example IMRT

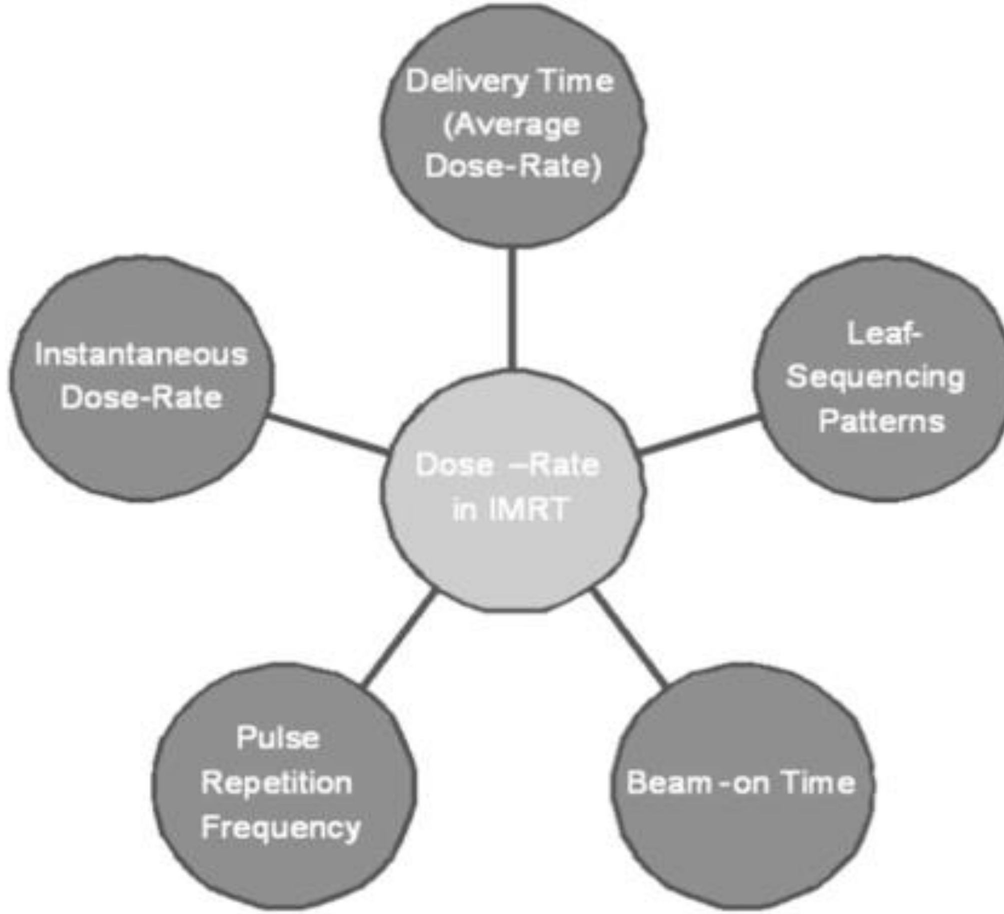
Instantaneous dose-rate



Delivery time



Keall et al. IJROBP, 2008



Bewes et al Phys. Med. Biol. 53 (2008)

3. Example: intermitted dose delivery of IMRT

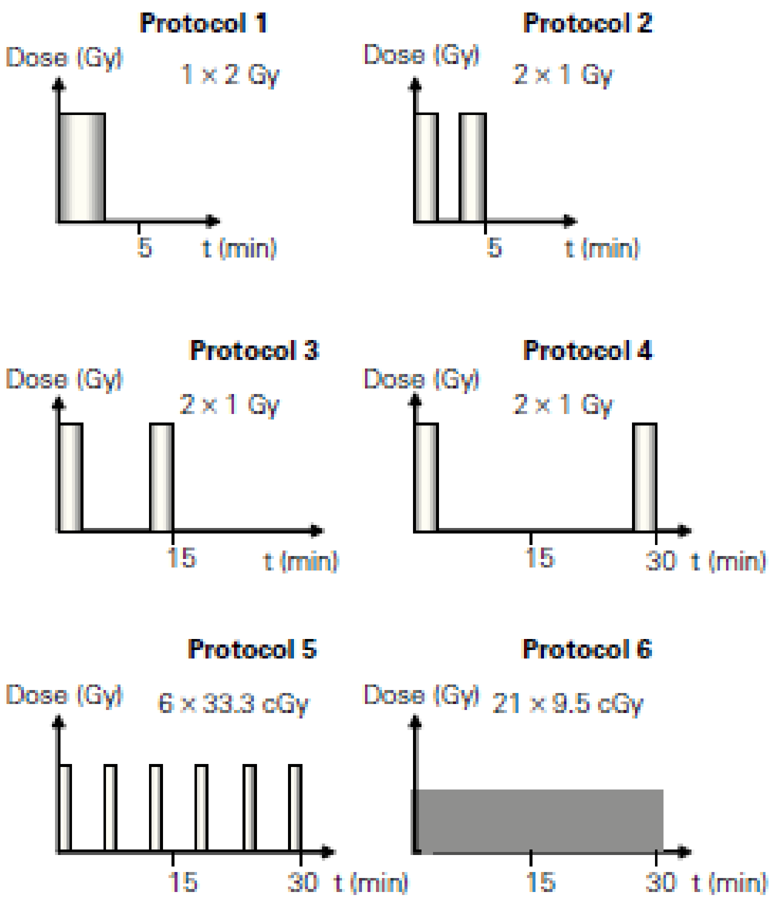
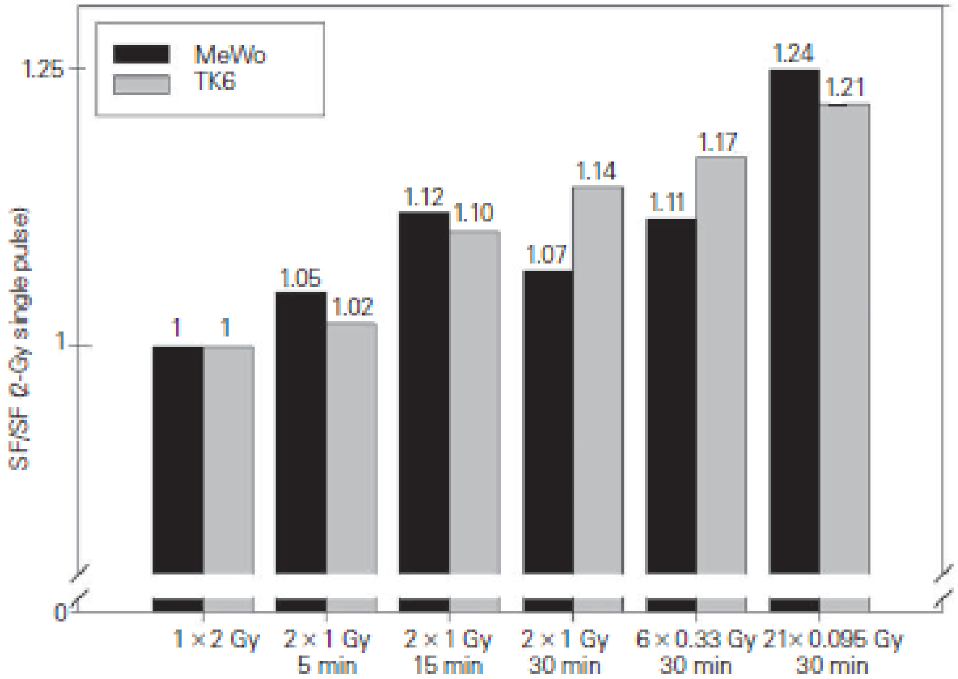


Figure 2. Six irradiation protocols with decreasing dose rate and increasing number of dose pulses, overall dose always 2 Gy.



Relative survival of the different irradiation protocols, normalized to SF after 2 Gy delivery with Protocol 1

Sterzing et al. Strahlenth & Onkol 2004 modified

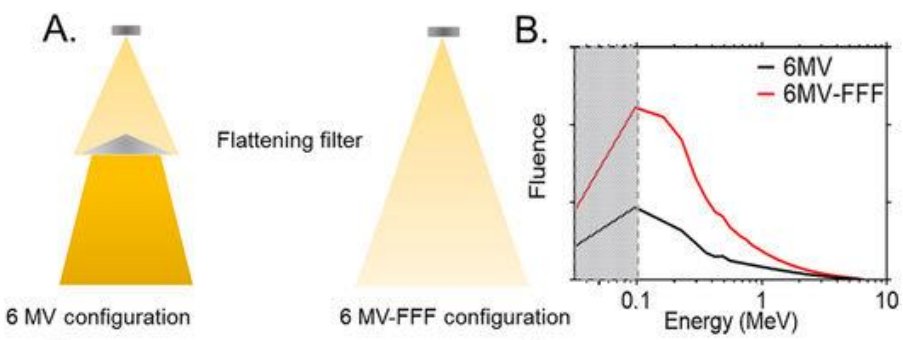
Treatment times >20 min or beam interruptions >8 min reduce radiation effect (Shibamoto et al. IJROBP 2004)

3. Increase of dose rate to compensate for prolonged time

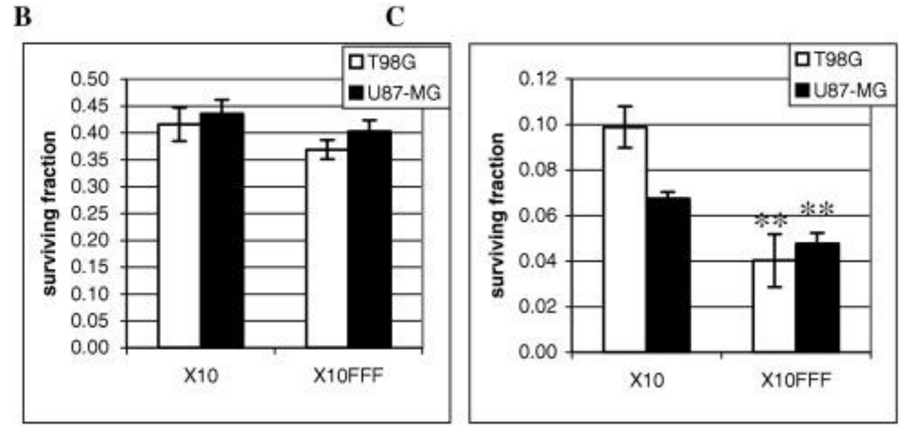
Flattening filter free e⁻ linacs deliver higher pulse dose rates

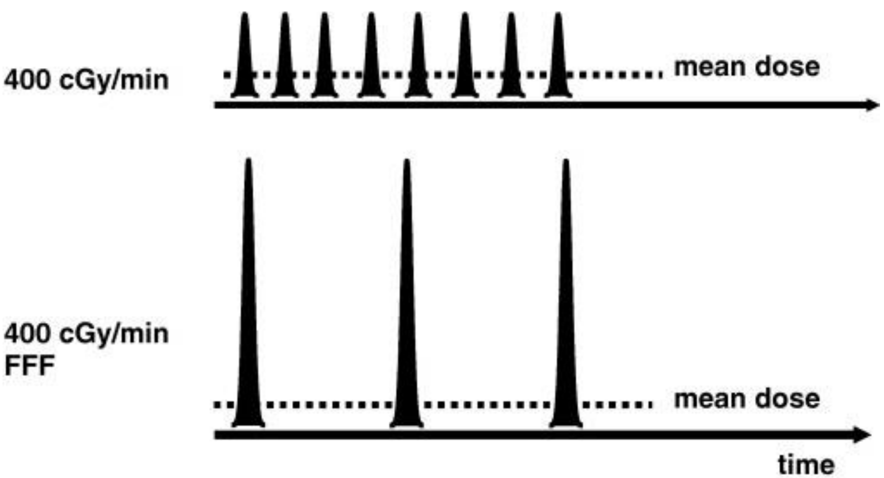
→ Dose rates ≤ 20 Gy/min

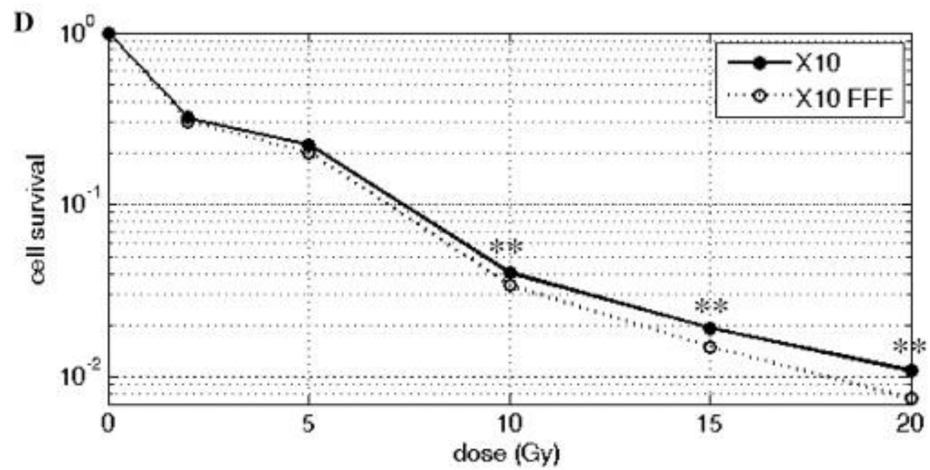
→ In clinical use since ~2010



Detappe et al. Sci Reports 2016



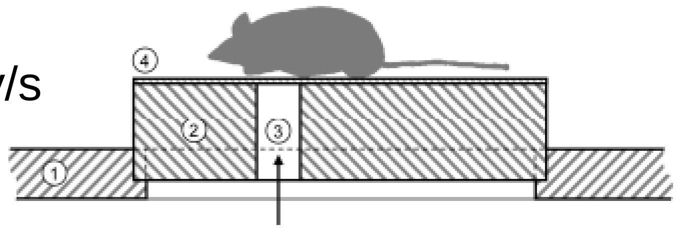




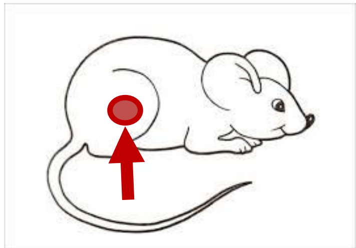
Lohse et al. Radiother Oncol 2011

Normal tissue protecting effect of FLASH irradiation – 1st exp.

- 4.5 MeV electrons 17 Gy / < 0.5 s
- Dose rate: ~ 100 Gy/s
- Pulse dose rate: 10^5 Gy/s

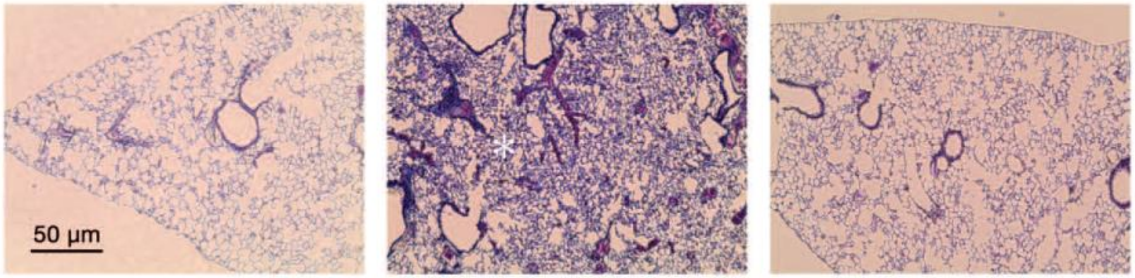


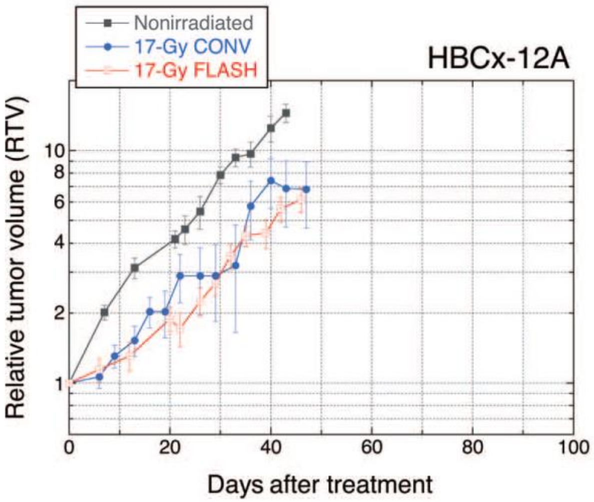
Similar tumor treating efficiency



Control | 17 Gy Conv γ-rays | 17 Gy Flash e⁻

24 weeks





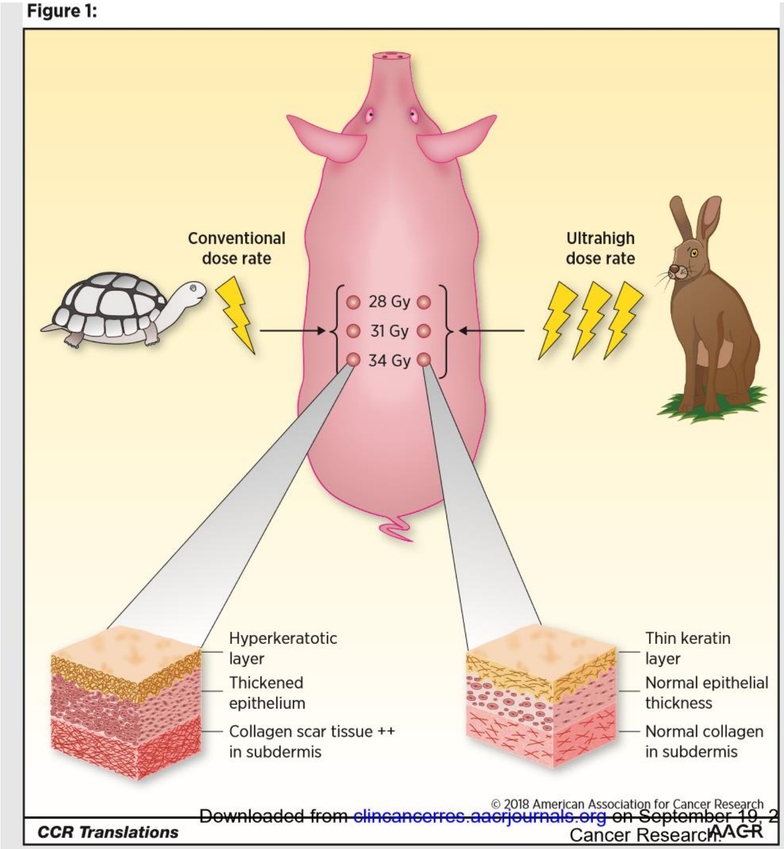
17 Gy CONV: cured, large alveolitis, inflammatory infiltration, prefibrotic remodeling, fibrosis (asterix)

17 Gy FLASH: lungs had a microscopic normal appearance, thin alveoli, normal vessels and bronchi, w/o inflammation

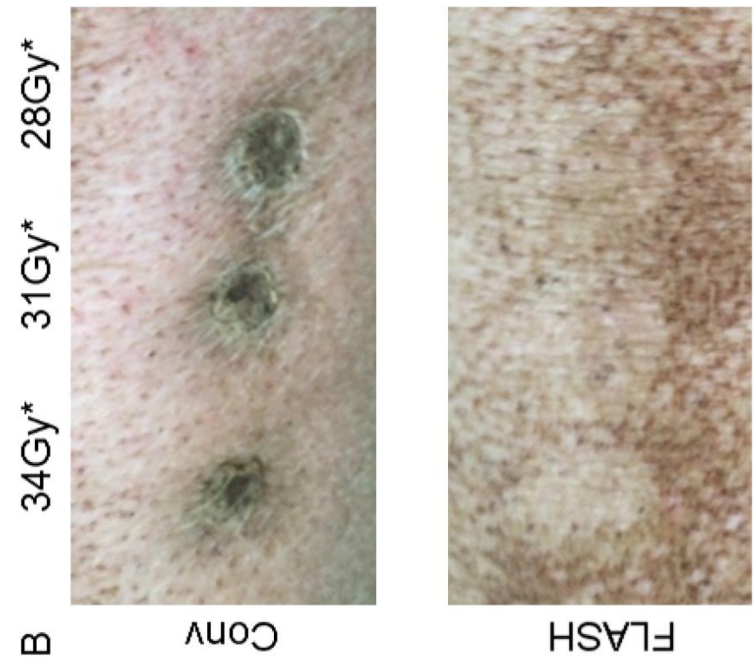
FLASH was as efficient as CONV in the repression of tumor growth, but more efficient in sparing of the normal tissue

Favaudon et al. Sci Transl Med 2014

Normal tissue protecting effect of FLASH – more evidence



(Harrington 2018)



(Vozenin 2018)

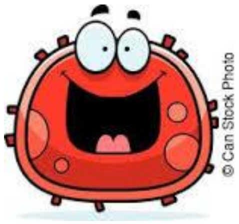
Less skin toxicity after treatment of minipigs

Research needed:
Other particles, e.g. protons? Which beam parameters required? Conventional accelerators or new ones? Patient safety?

3. Current developments in clinical dose delivery

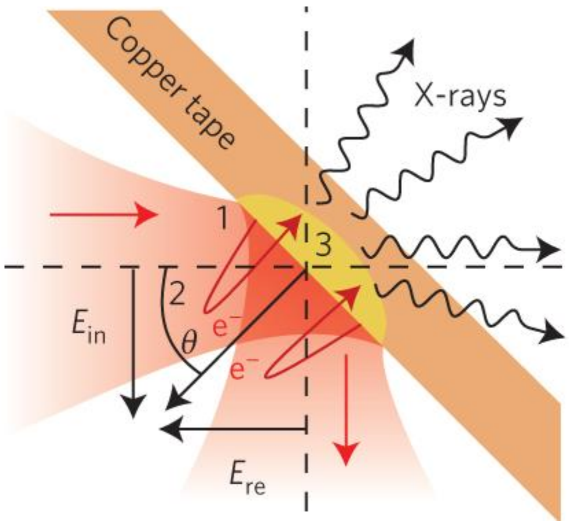
- Advanced clinical beam delivery techniques
  - Protracted and varying pattern of dose delivery
  - Flattening filter free Linacs
  - W-Effect and FLASH irradiation as alternative approaches

- **Status of laser driven acceleration**
  - **Laser driven X-rays: in vitro**
  - **Laser driven electron beams: in vitro & in vivo**
  - **Laser driven proton beams: in vitro** & in vivo

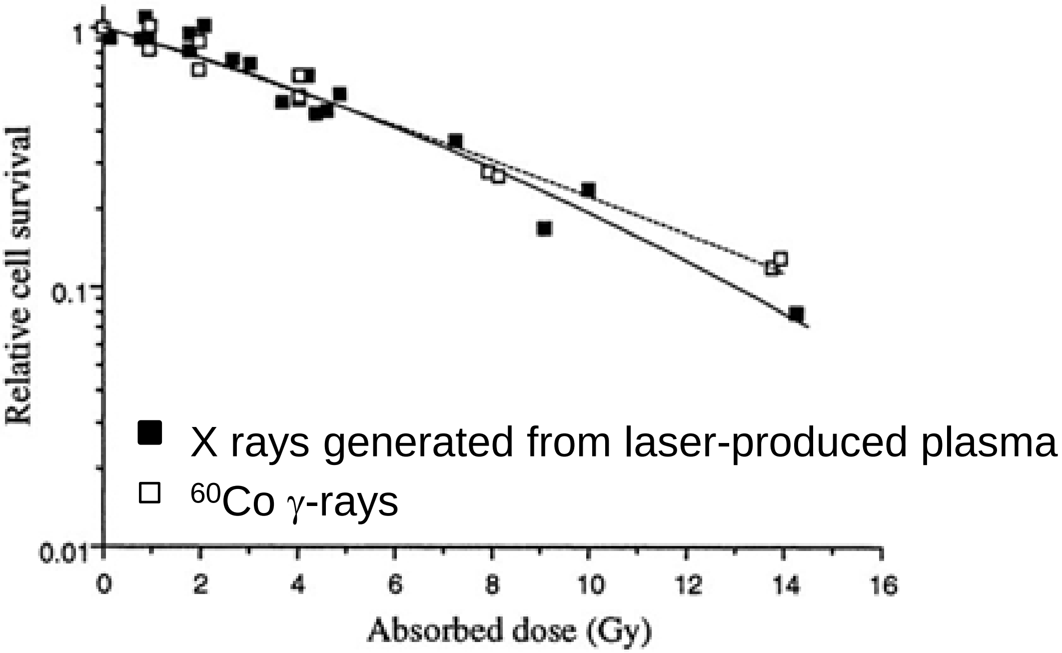


3. Laser driven ps x-ray pulses: soft – hard x-rays

- X-rays emitted from plasmas generated with **ps- to ns** laser
- Potential applications for X-ray microscopy and radiography
- Time gated radiology of humans → harmlessness must be proven
- 10^9 – 10^{13} Gy/s, mostly broad energy spectra few keV – 1MeV



Nature Photonics 8, 2014



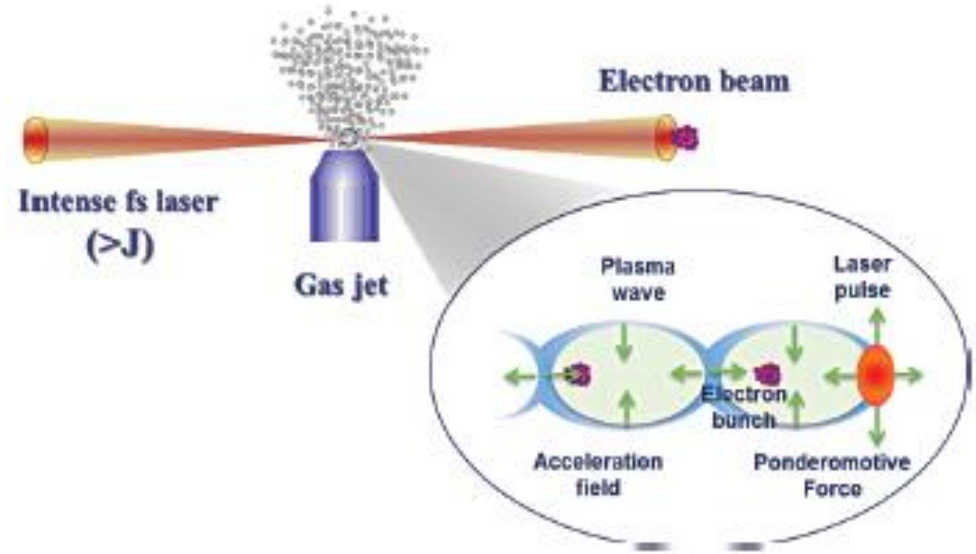
No significant difference in the radiobiological effectiveness due to ultra-high pulse dose rate

Tillman et al. *Radiology* **1999,** 213, 860-865.

3. Laser driven particle acceleration

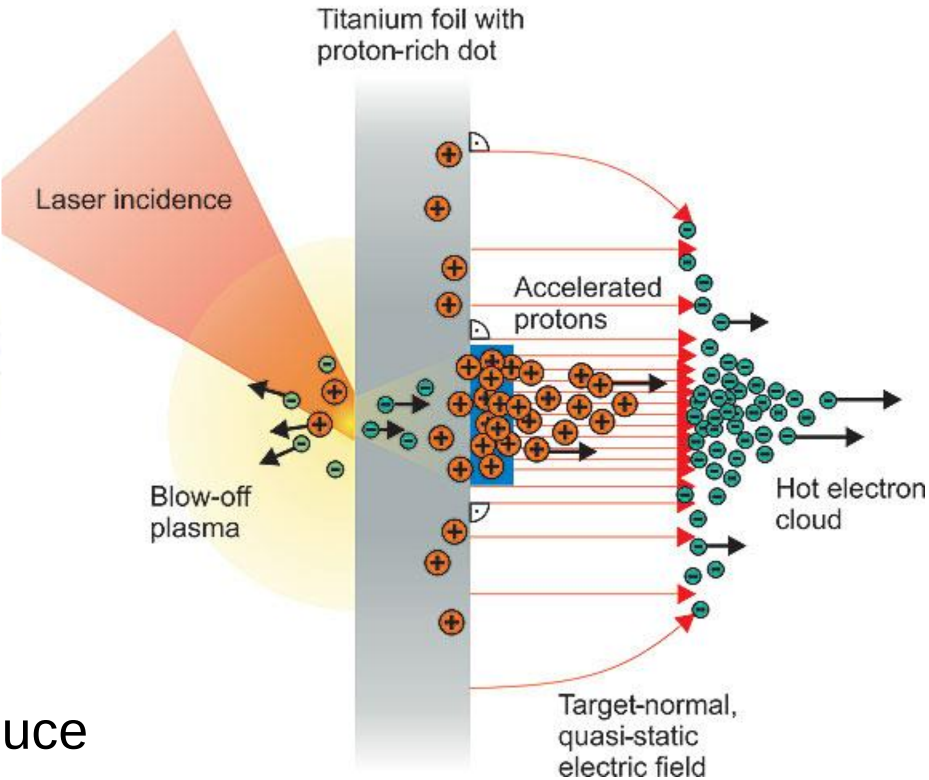
→ Ultra-high dose-rates >10^{10} Gy/min in fs…ps…ns pulses

Laser driven electron acceleration



www.aappsbulletin.org

Laser driven proton acceleration



Schwoerer et al. Nature 2006

Aim: reduction of accelerator size to reduce the cost of particle therapy and allow a more widespread distribution

3. Specific properties of laser accelerated particle beams

- Ultra-short beam pulses (~ 1 ps)
- Low pulse repetition rate (~ 1 - 10 Hz)
- High pulse dose (~ 1 Gy) and pulse dose rate (~ 10^{12} Gy/s)
- Pulse-to-pulse fluctuations
- Broad energy spectrum
- “Contaminated” beams (p, other ions, n, e^-, γ, X)

Investigation of consequences on beam transport, radiation field formation, dosimetry and **radiobiological effects** before clinical implementation

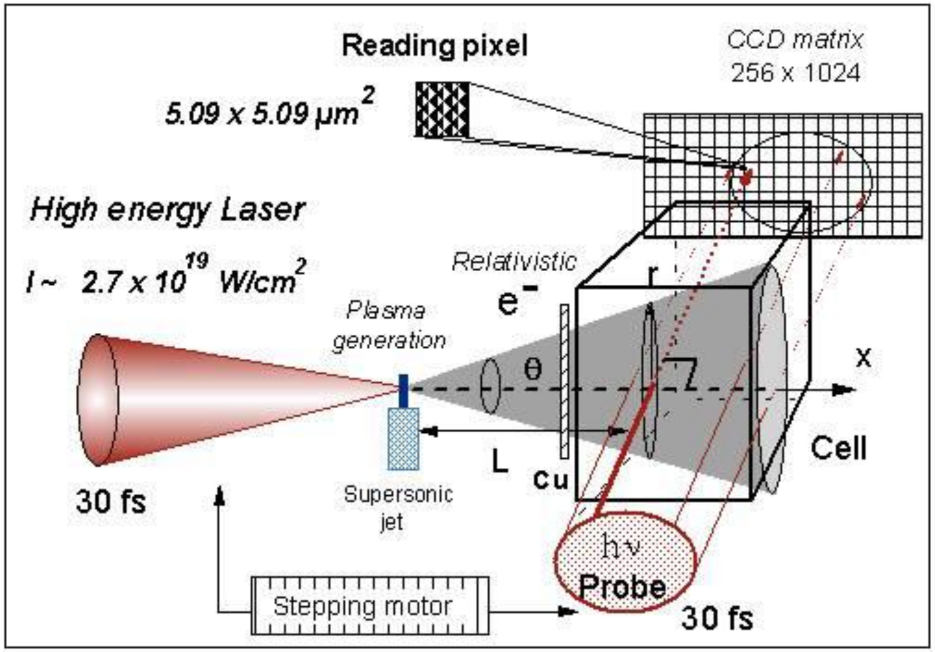
- ➢ Whole translational chain from bench to bedside
- ➢ Comparison to particle beams from conventional accelerators = medical devices

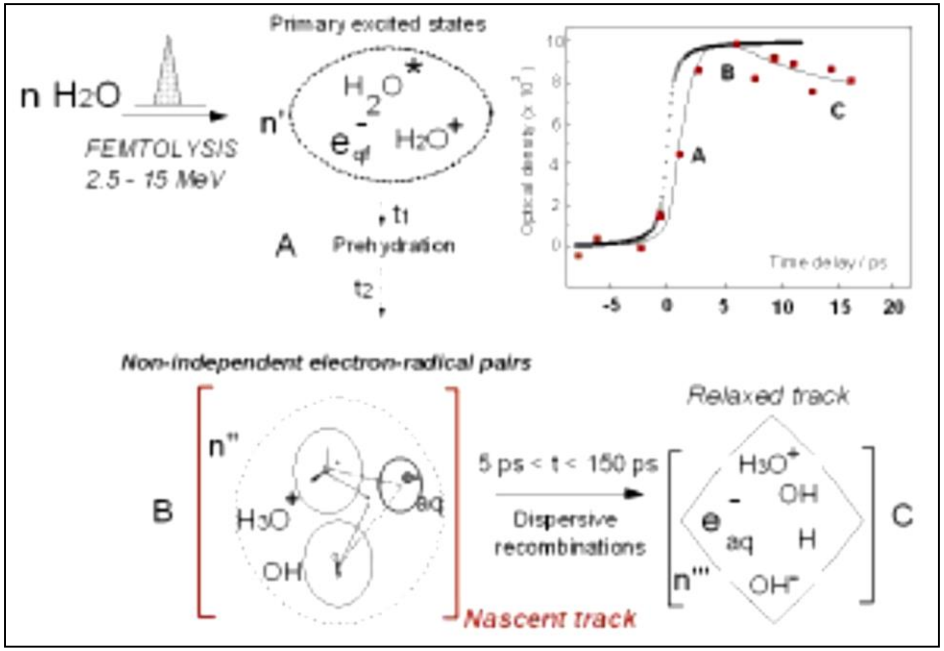
3. FEMTOsecond radioLYSIS by laser-driven e⁻ - bunches

Using fs-laser pulses to trigger radiochemistry reactions

→ Measurement of relaxation times, radical life times etc.

→ Understanding of early physical events



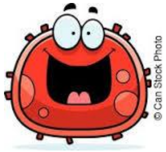


Physical phase

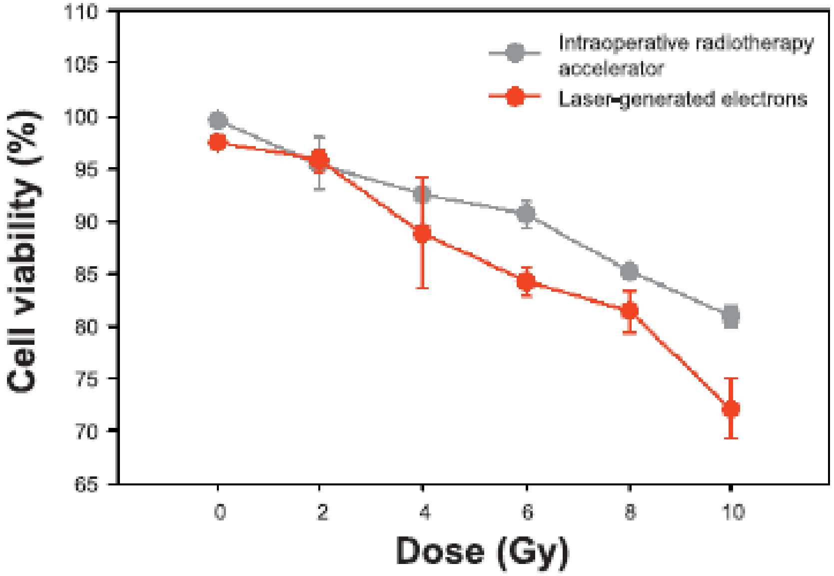
10^{-18}-10^{-12} s

Gauduel et al. 2012, 2017

3. Comparing laser driven e^- vs. conventional X-rays



- ILIL laser facility/Italy: multi-shot; 1.5 MeV e^- , 1 × 10^{10} Gy/s
- Blood lymphocytes and ovarian cancer cell line: DNA damage, cell survival (cancer cell line)
- Reference radiation: 7 MeV clinical Linac (survival)

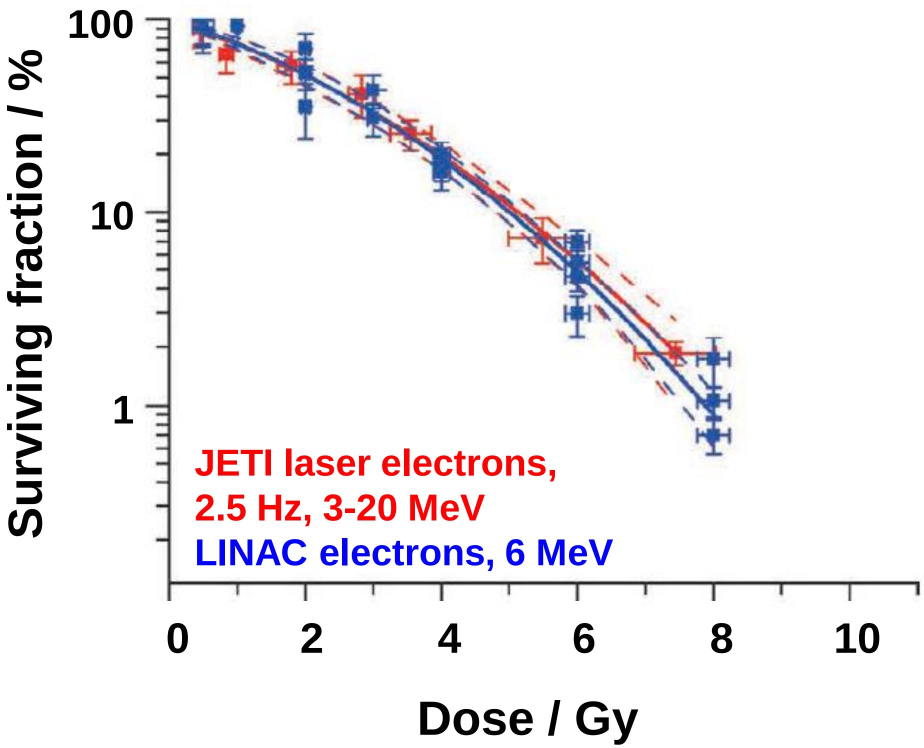


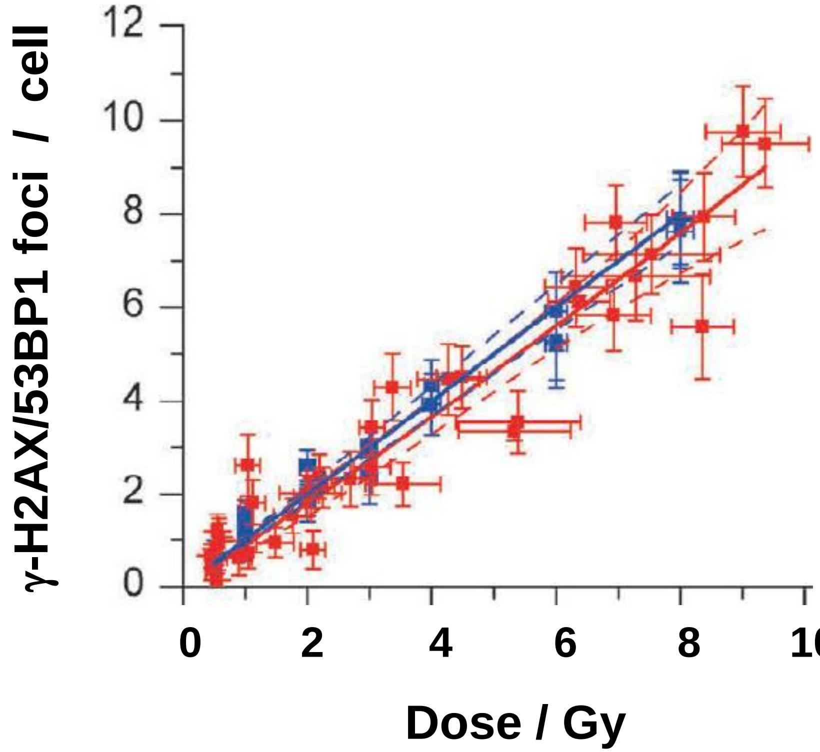
- Demanding interpretation: different endpoints, cell lines and reference sources

Andreassi et al. Radiat Res 2016

3. Comparing laser driven vs. conventional Linac e⁻

- JETI laser: 80 fs, 10 Hz, multi-shot; 3…20 MeV e⁻ , 1 × 10^{10} Gy/s
- Reference radiation: 6 MeV clinical Linac
- Human head and neck tumor cell line FaDu



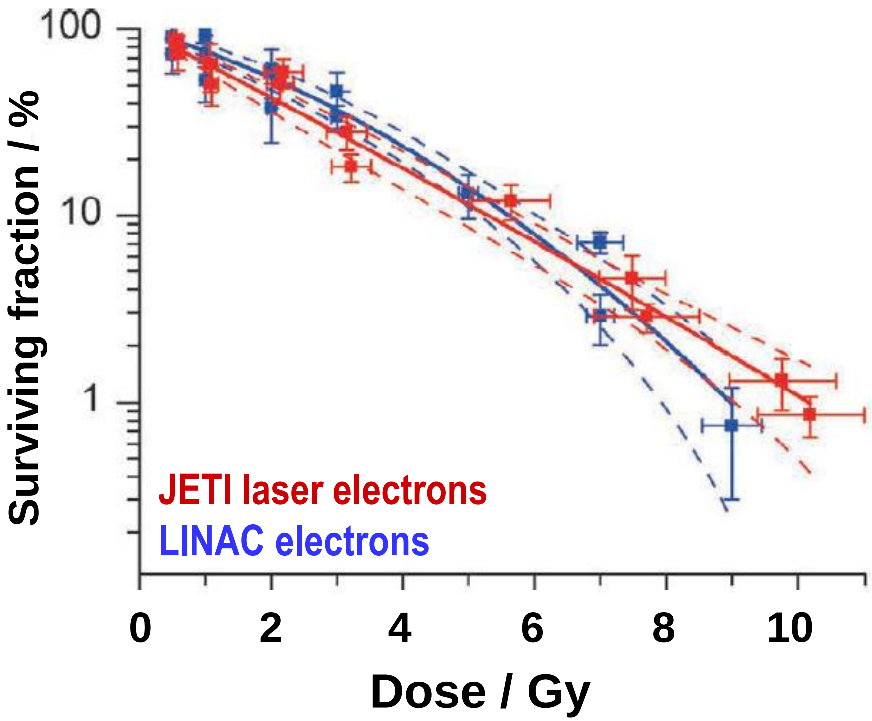


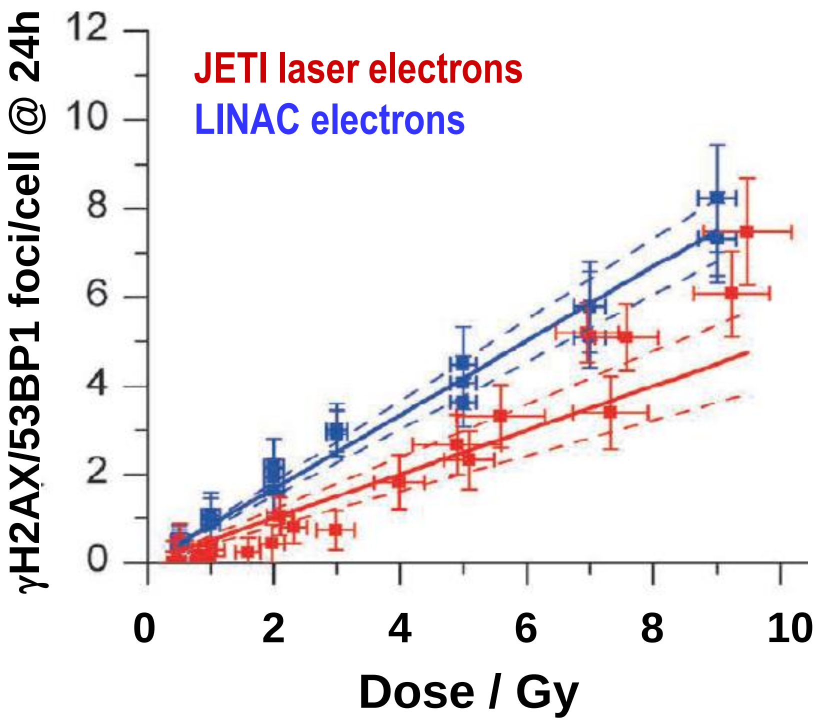
Laschinsky et al. J Radiat Res 2012

Physical phase | Chemical reactions

3. Comparing laser driven vs. conventional Linac electrons

Normal tissue cell line 184A1





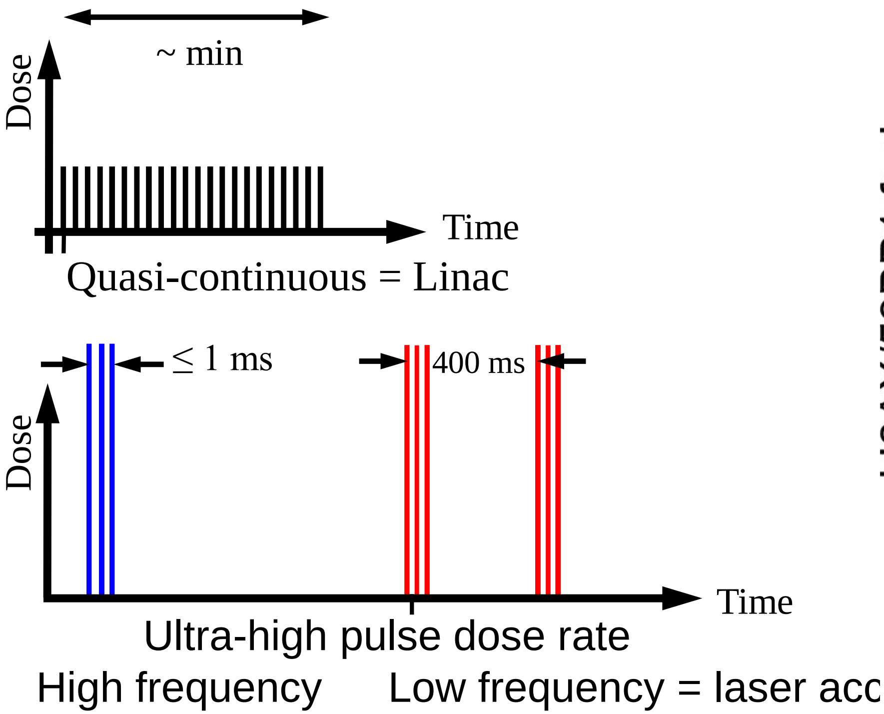
No significant difference for cell survival, but significant lower number of foci for laser driven electron pulse irradiation of normal tissue

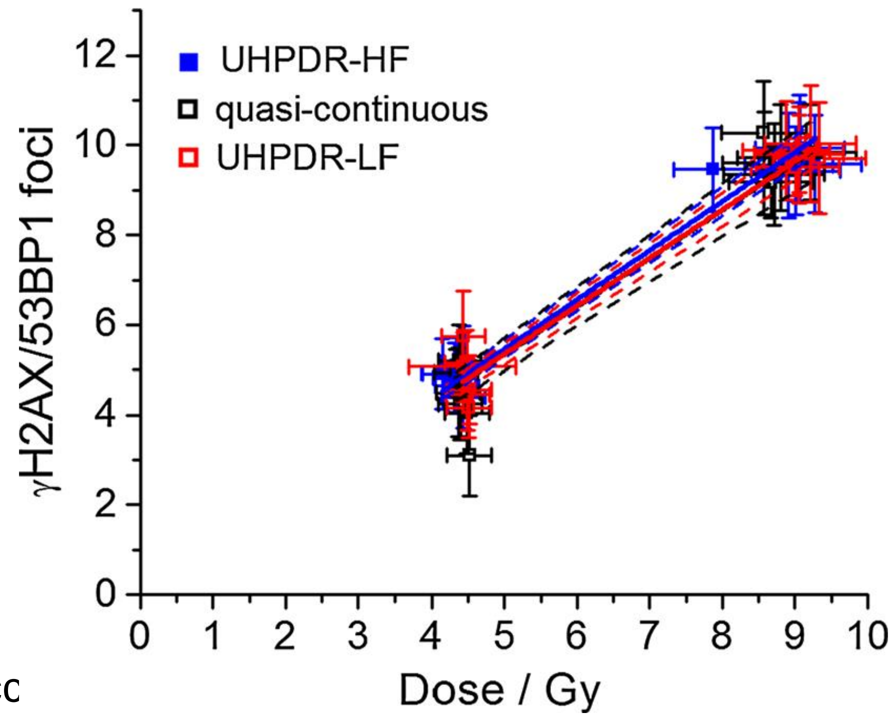
Beyreuther et al.: Med Phys 2010; Richter et al.: Radiat Meas 2011; Laschinsky et al. J Radiat Res 2012

3. Accompanied studies I: cell irradiation with UHPDR at ELBE

- **E**lectron **L**inac for beams with high **B**rilliance and low **E**mittance
- Highly variable electron pulse structure
- Comparison w/o shift in experiment time and location

→ minimizing external influences on cell results



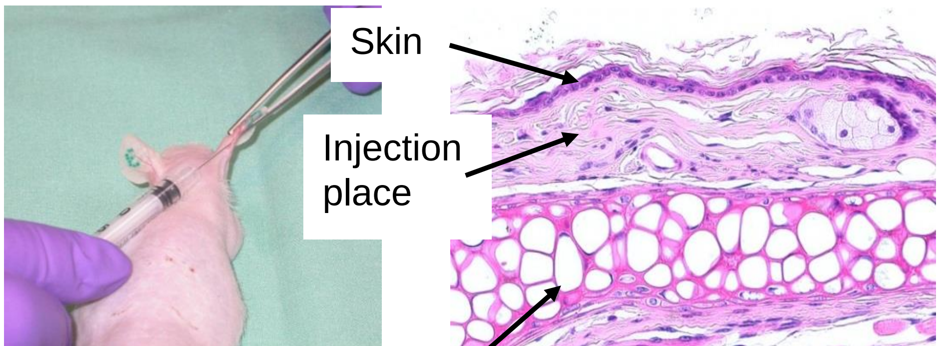


No influence of ultra-high pulse dose rate (~10^{10} Gy/min) on cell survival and number of residual DNA double-strand breaks

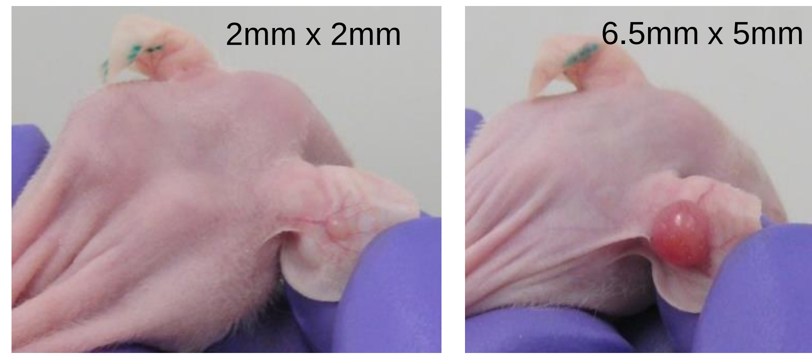
Beyreuther et al. Int J Radiat Biol 2015; Laschinsky et al. Radiat Environ Biophys 2016

3. Animal study with laser driven electrons

- Proton energies currently available at laser accelerators are to low (E ≤ 20 MeV) to penetrate standard tumors on mice legs
- **New small animal tumor** model established: human head & neck cancer FaDu and human glioblastoma LN229 on NMRI nude mouse ear



Cartilage: natural demarcation to deeper layers



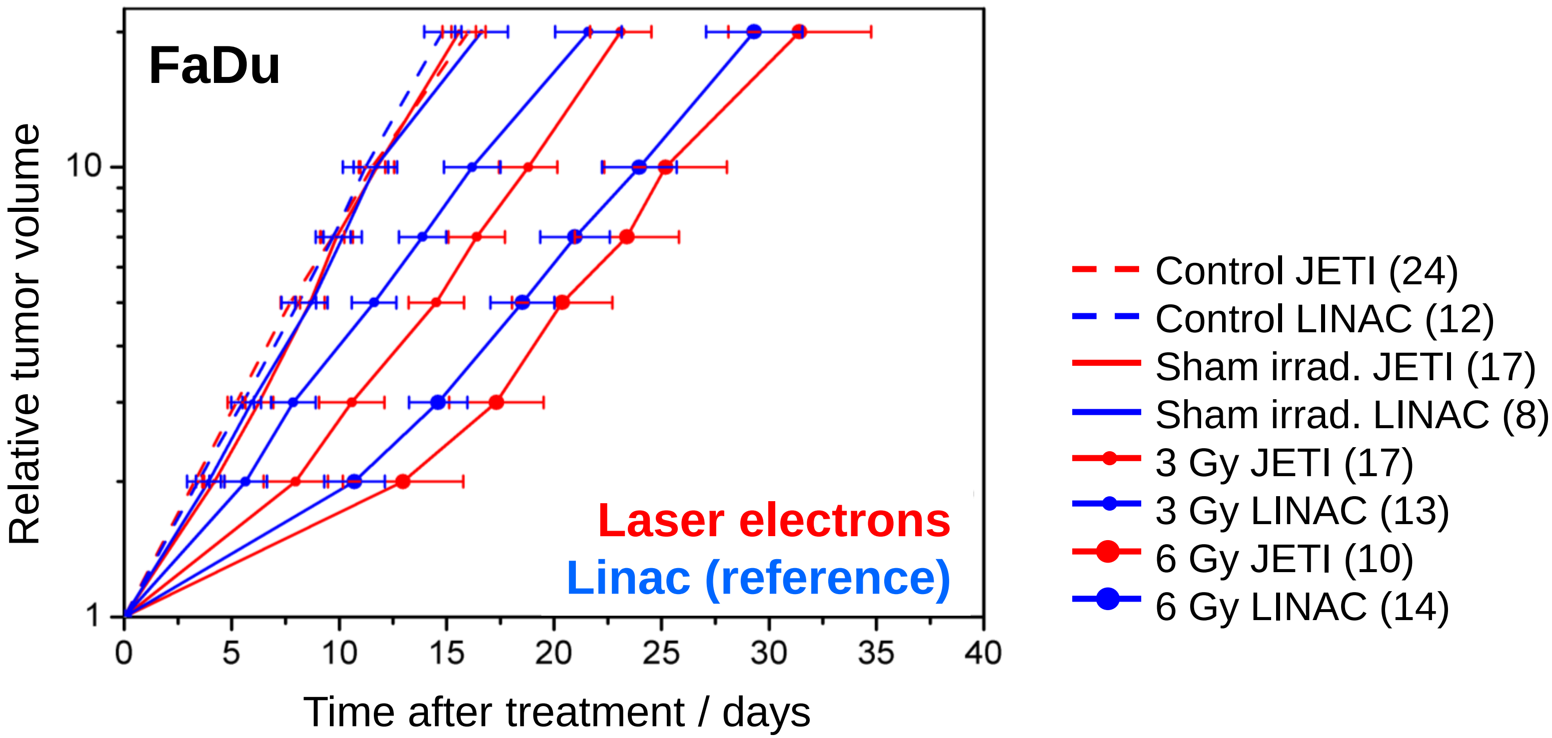
Growing LN229 tumors

- Host: NMRI nude mice, athymic → reduced number of T-lymphocytes
- Whole body irradiation with 4 Gy, 200 kVp X-rays 3 d before cell injection

Suit et al. Cellular Radiation Biology 1965, Brüchner, Beyreuther et al. Radiat Oncol 2014

3. Small animal experiment with laser accelerated electrons

- Reference irradiation: 21 MeV electrons (clinical LINAC)
- Full scale experiment: Σ 534 mice

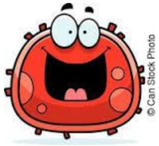


No significant difference in tumor growth delay due to ultra-short high-dose pulses of laser accelerated electrons

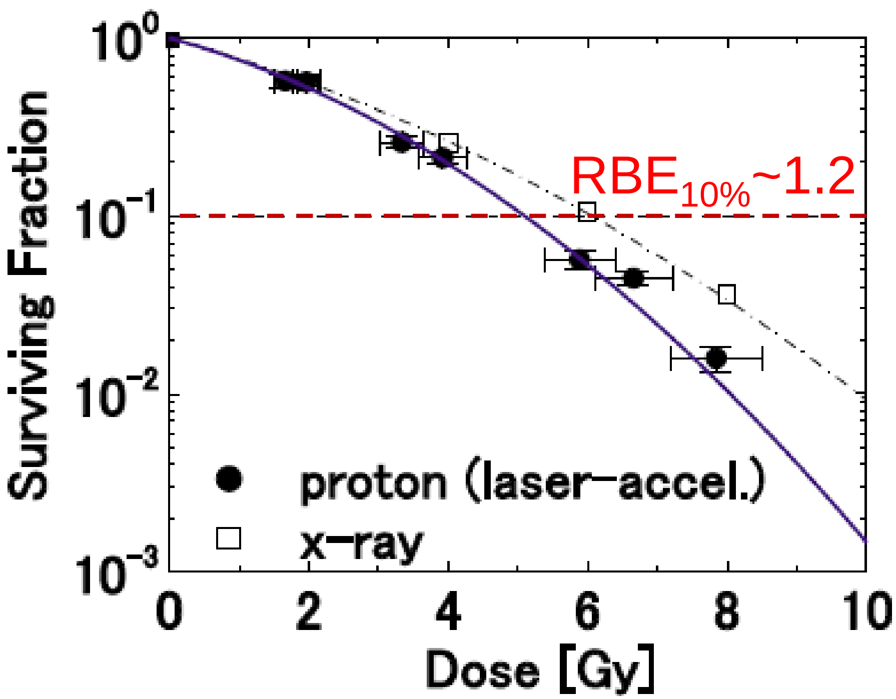
Oppelt et al.: Radiat Environ Biophys 2015

3. Laser driven protons vs. x-rays @ J-Karen

Physical phase



- 45 fs laser pulse, 1 Hz, multi-shot; 2.25 MeV p, ~10^7 Gy/s in pulse
- Cell survival for a human salivary gland tumour cell line
- Reference radiation: 4 MV X-rays; clinical Linac



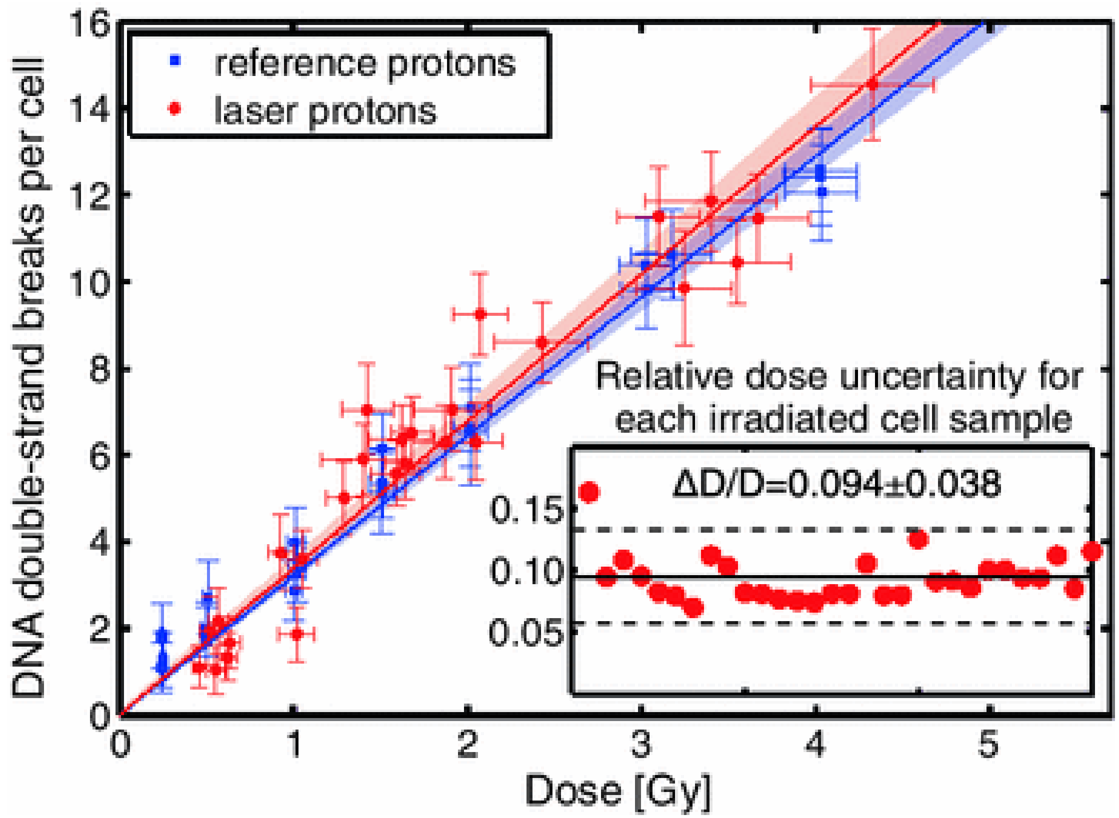
Biological effect comparable to conventional protons

Yogo et al. Appl. Phys. Lett. 98, 2011

3. Laser driven : conventional protons @DRACO

Physical phase

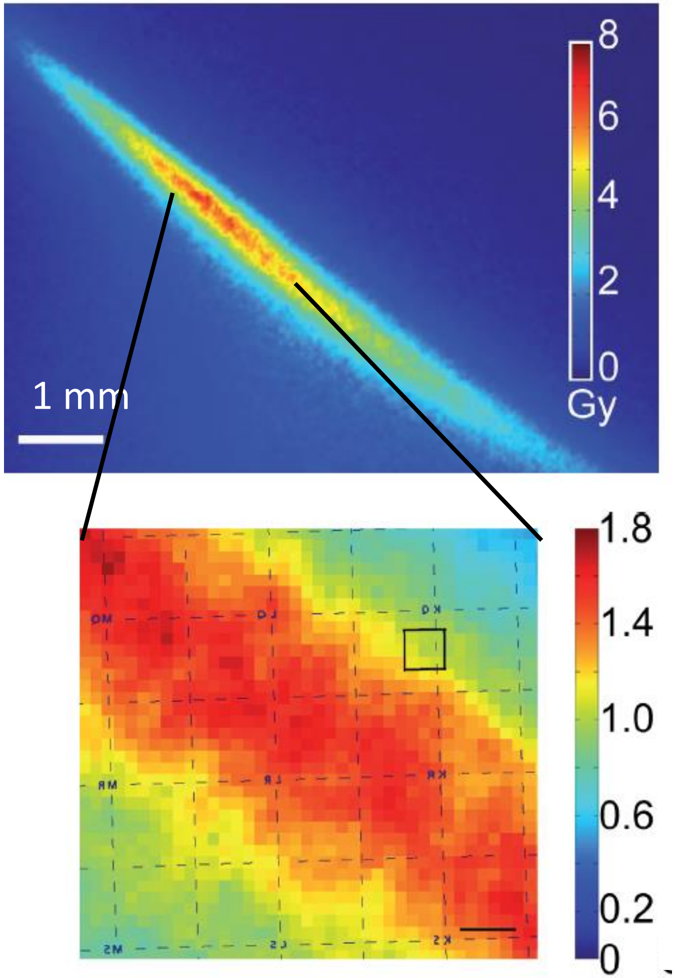
- **Multi-shot** irradiation, 6 – 18 MeV p, 0.1 Hz
- Reference: 7.2 MeV p from conventional van-de-Graaff accelerator
- Cell survival & DNA DSB (γ-H2AX foci, 24 h post irradiation)

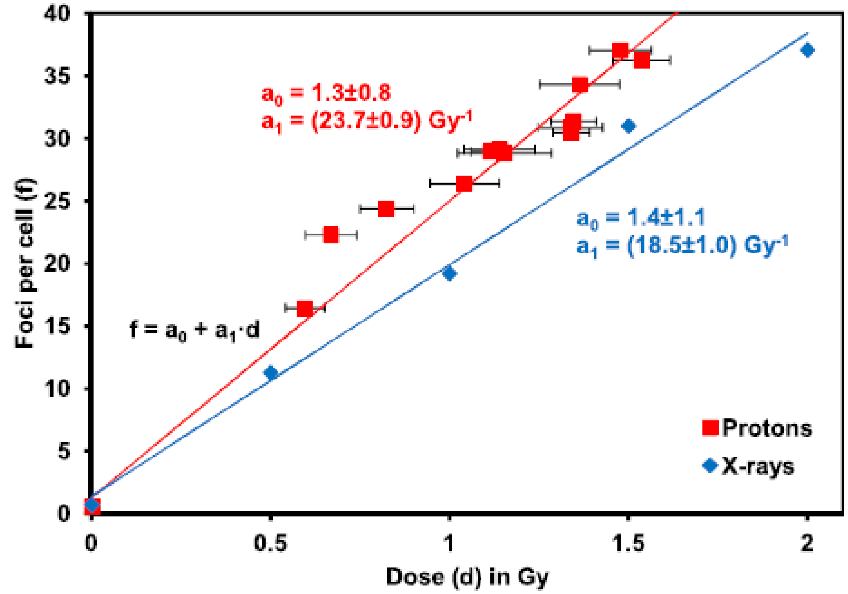


No significant difference between laser-driven, ultra-short pulsed proton beams and continuous proton beams (Zeil et al. Appl Phys B 2013)

3. Laser driven vs. conventional protons: dose picking @ ATLAS

- 30 fs, **single shot**; 5.2 MeV p (10^9 – 10^{10} Gy/s)
- DNA DSB for human tumour cells
- Reference radiation: 200 kV X-rays

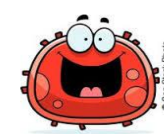




Mean number of γ-H2AX foci per cell (dose)

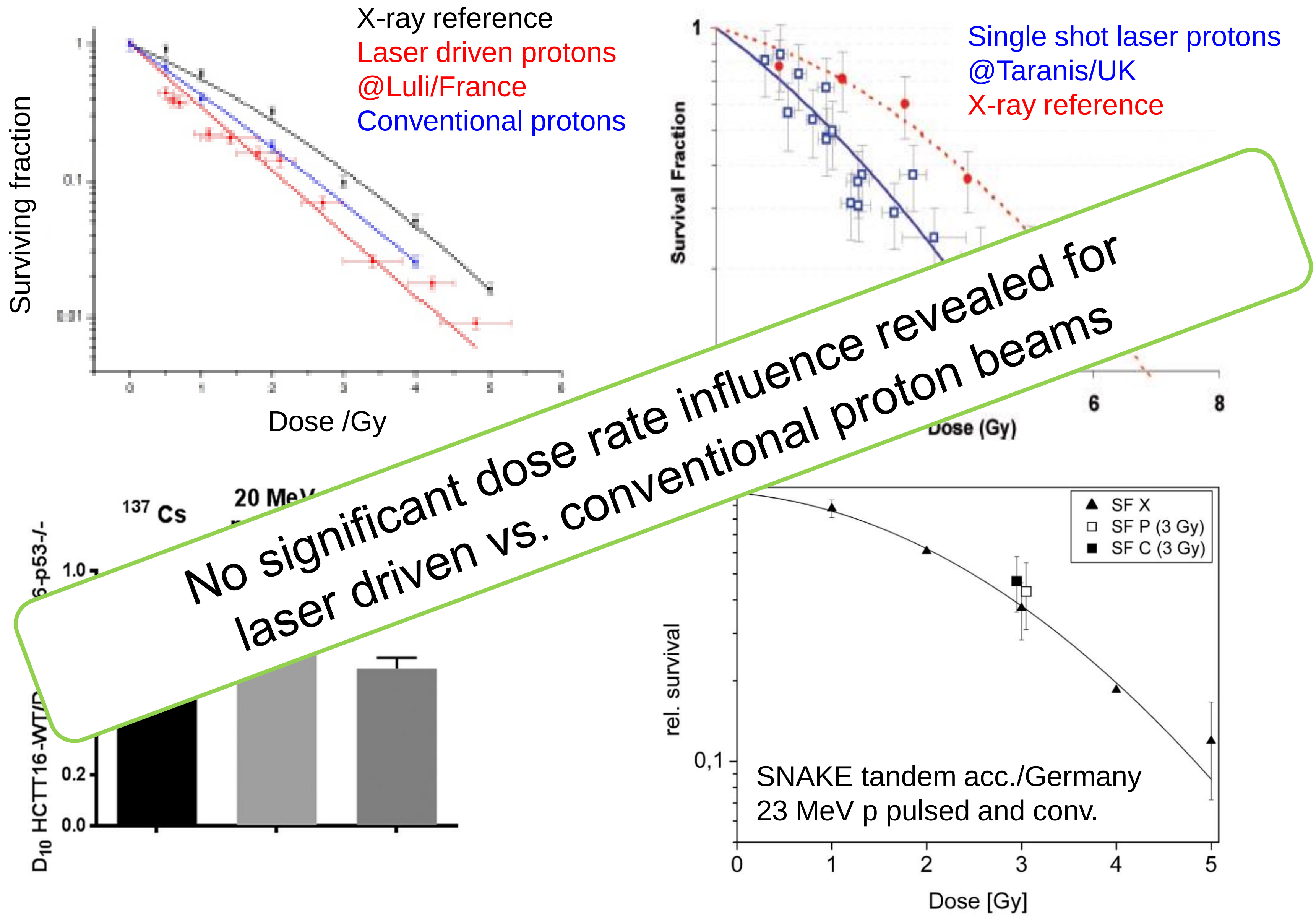
No significant difference between laser-driven, ultra-short pulsed proton beams and continuous proton beams

Lateral dose distribution at cell position measured with radiochromic film, max. 7.1 Gy in single laser shot



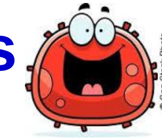
Bin et al. Appl Phys Letters 101, 2012

3. Radiobiological characterization of laser driven proton beams



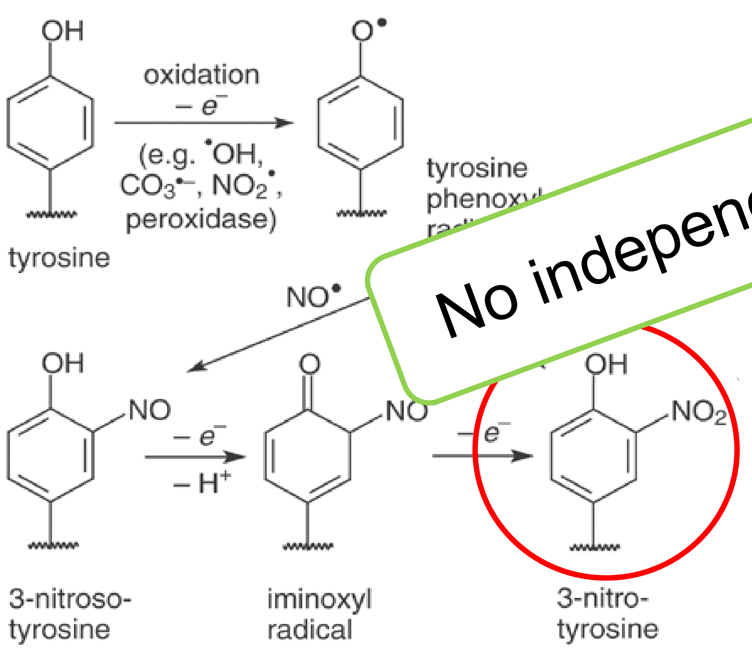
Manti et al. JINST 2017; Doria et al. AIP Advances 2012; Pommarel et al. Phys Rev Accel Beams 2017; Auer et al. Radiat Oncol 2011

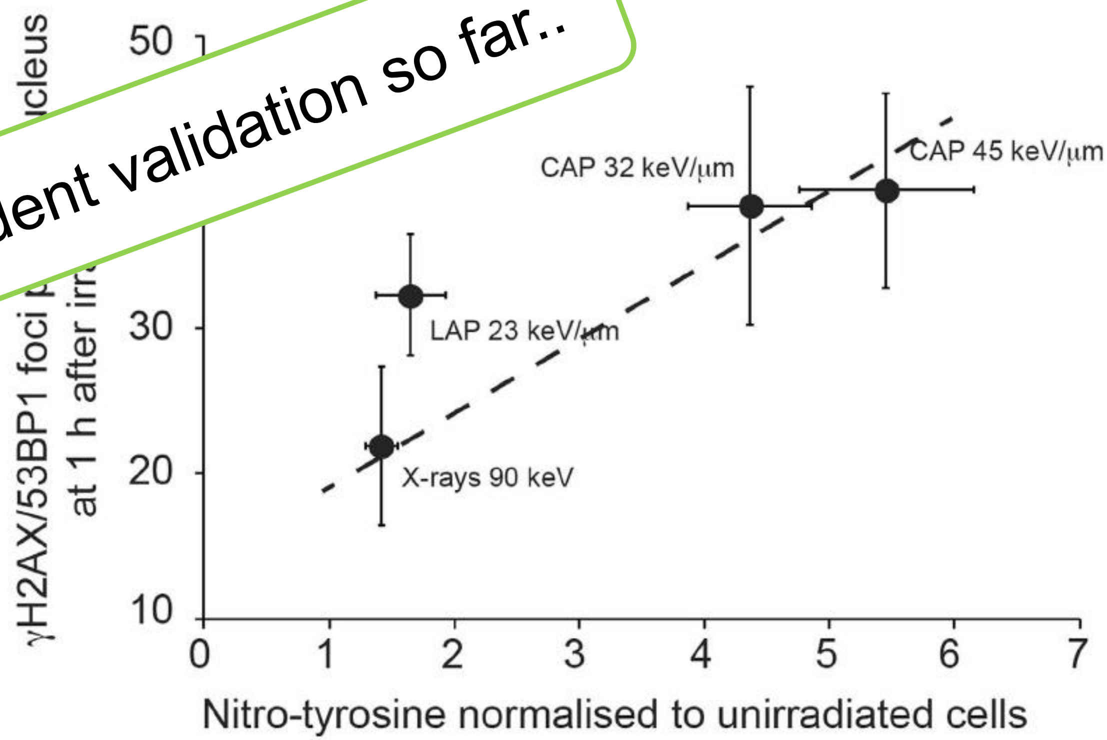
3. Incidence for an altered effect of laser driven protons



- Arcturus laser: ~2.1 MeV protons, multi-shot, 10^8 Gy/s, ~0.3 Hz;
- Less immediate nitroxidative stress but similar DSB for laser driven vs. conventional proton beams
- Reasons and consequences for RT has to be resolved

No independent validation so far..



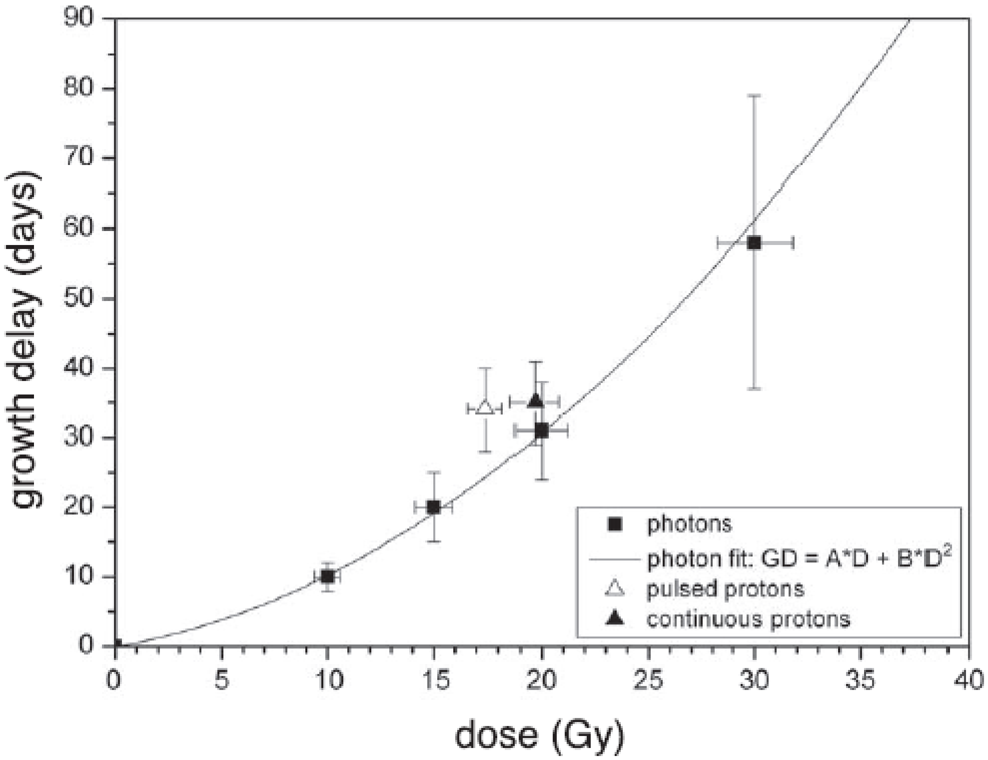


Mikkelsen & Wardman, Oncogene, 2003

Raschke et al. Sci Reports, 2016

3. Accompanied studies II: UHPDR protons at SNAKE

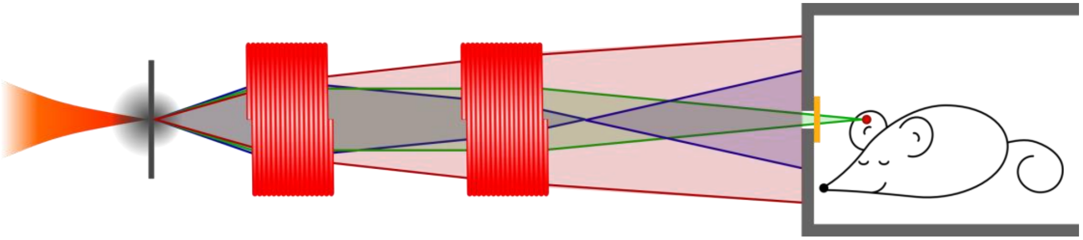
- 1 ns single shot irradiation; 23 MeV p (10^7 Gy/s)
- FaDu tumor growth delay, subcutaneous tumor on nude mice leg
- Reference radiation: continuous 23 MeV protons, 6 MV photons

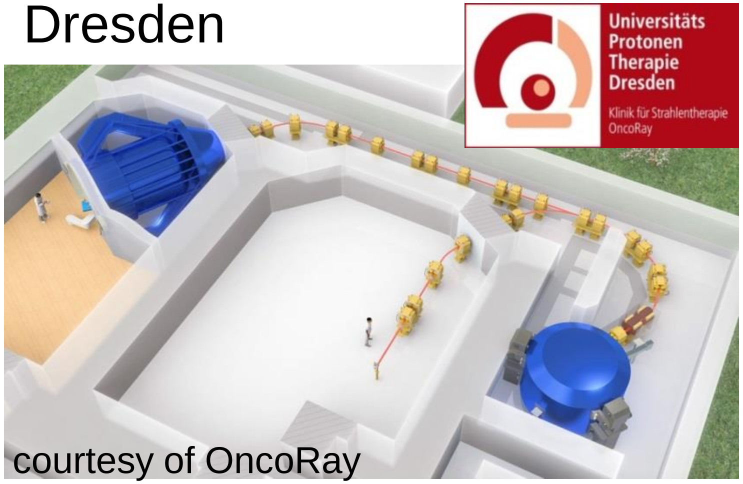


“No evidence for a substantially different radiobiology that is associated with the ultra-high dose rate of protons that might be generated from advanced laser technology in the future.” Zlobinskaya et al. Radiat Res. 181, 2014

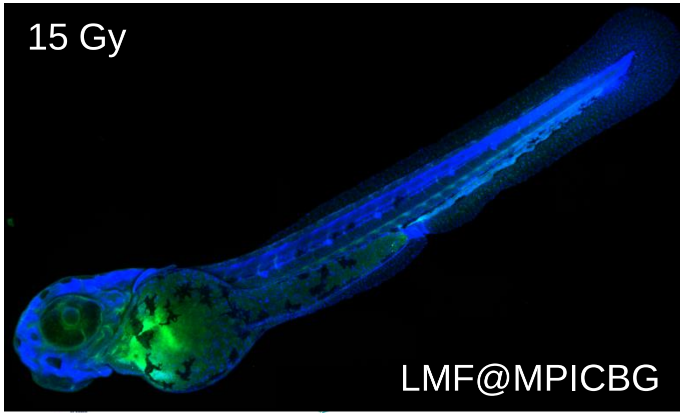
3. Perspective: preparation of animal experiments with laser driven protons at DRACO

DRACO Laser accelerator @HZDR vs. University proton therapy Dresden

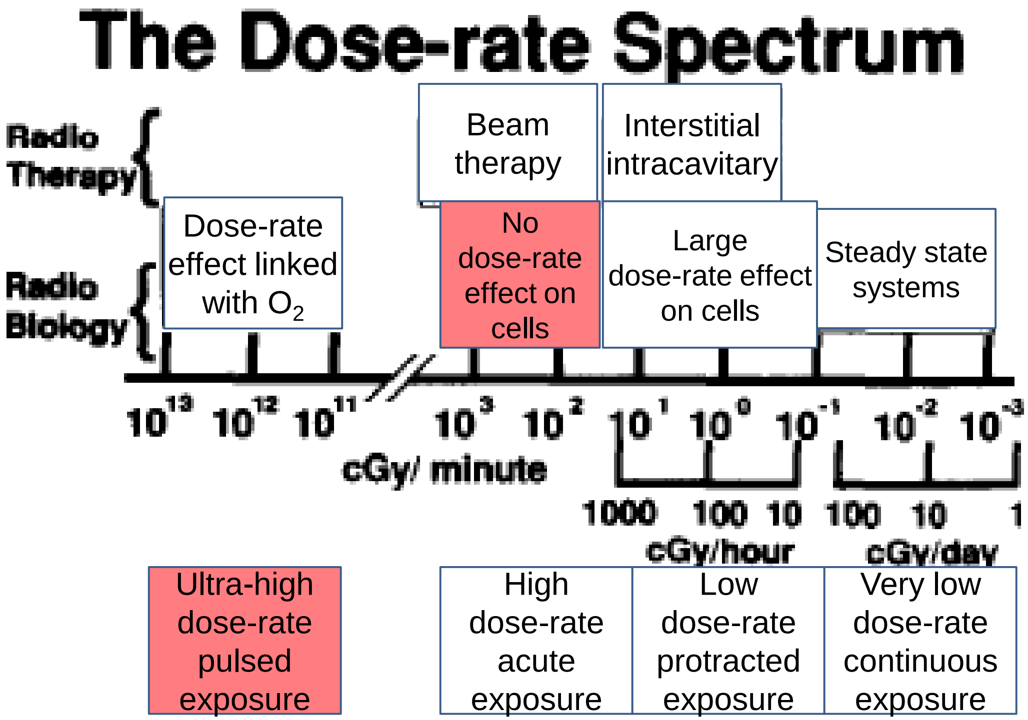




- ✓ Mouse ear tumour model
- ✓ Administrative requirements
- ✓ Setup, dosimetry and 3D dose delivery for animal irradiation @ UPTD
- → *Test of setup and 3D dose delivery @ DRACO by means of zebrafish embryo treatment*
- → *Performance …*



Summary



Hall & Brenner, IJROBP 1991

Recent research on pulsed beam delivery confirm:

- Influence of intra-fractional pulsing is linked to prolonged treatment time
- No influence on radiobiological response due to pulse dose rates $>10^7$ Gy/s
  - ➢ Translational research on laser driven particle acceleration can be continued w/o additional care because of ultra-high pulse dose rate

Acknowledgement

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Lydia Laschinsky
Elisabeth Lessmann
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