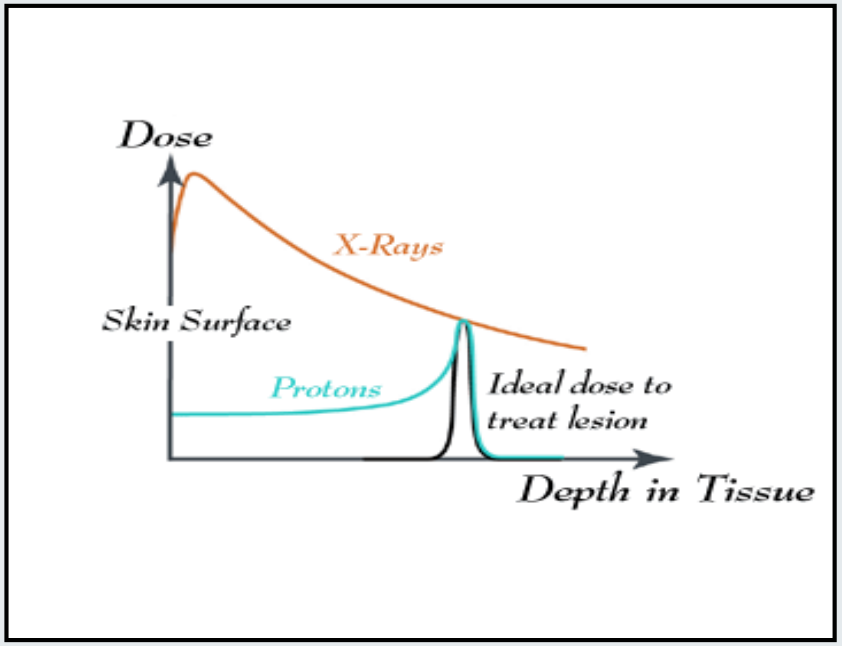
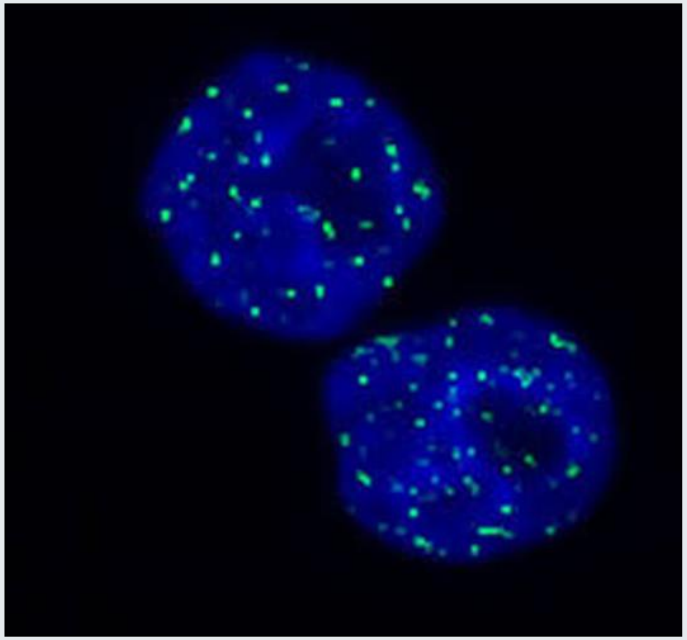
Role of Radiobiology in Particle Therapy

Martin Pruschy
University Hospital Zurich, Switzerland





ENLIGHT virtual meeting for SEIIST
July 23, 2020

USZ Universitäts Spital Zürich
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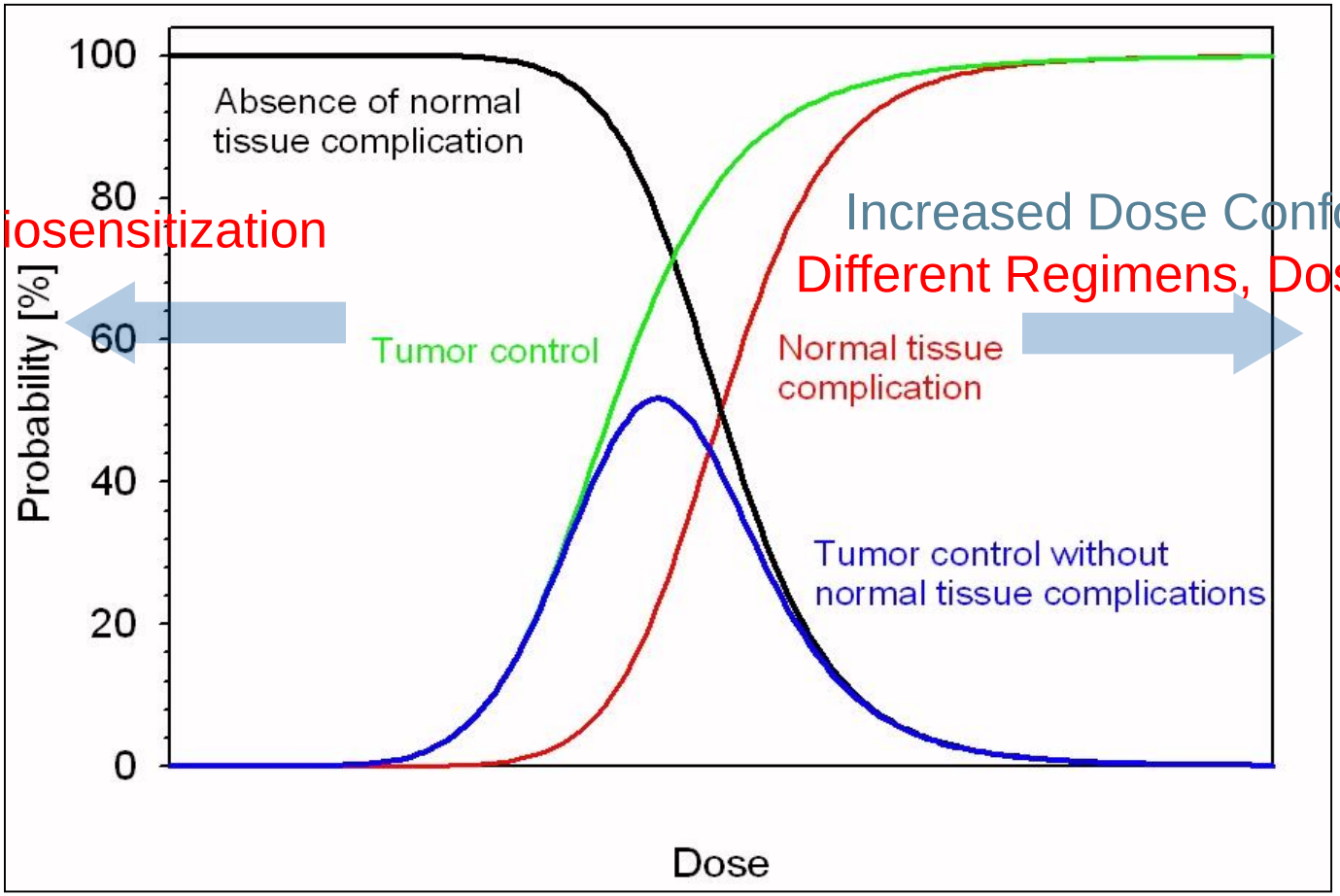
The Therapeutic Window



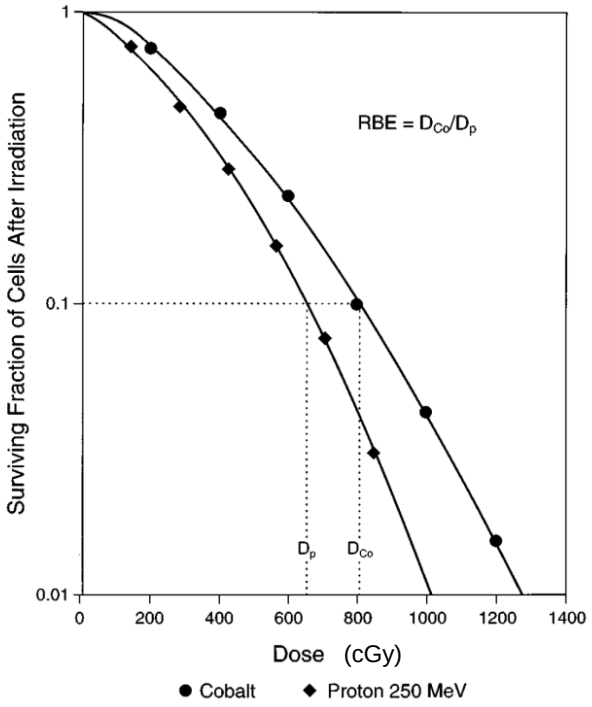
Radiosensitization

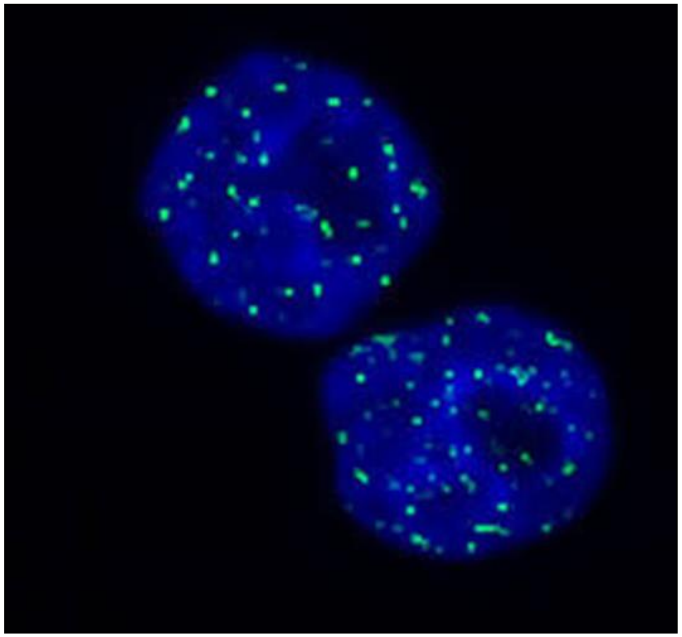
Increased Dose Conformity;
Different Regimens, Dose Rates

Therapeutic Index

Different Modalities of Ionizing Radiation

Photon-, Proton-, Particle based Radiobiology:
Understand the biological factors that influence the sensitivity to different types of ionizing radiation

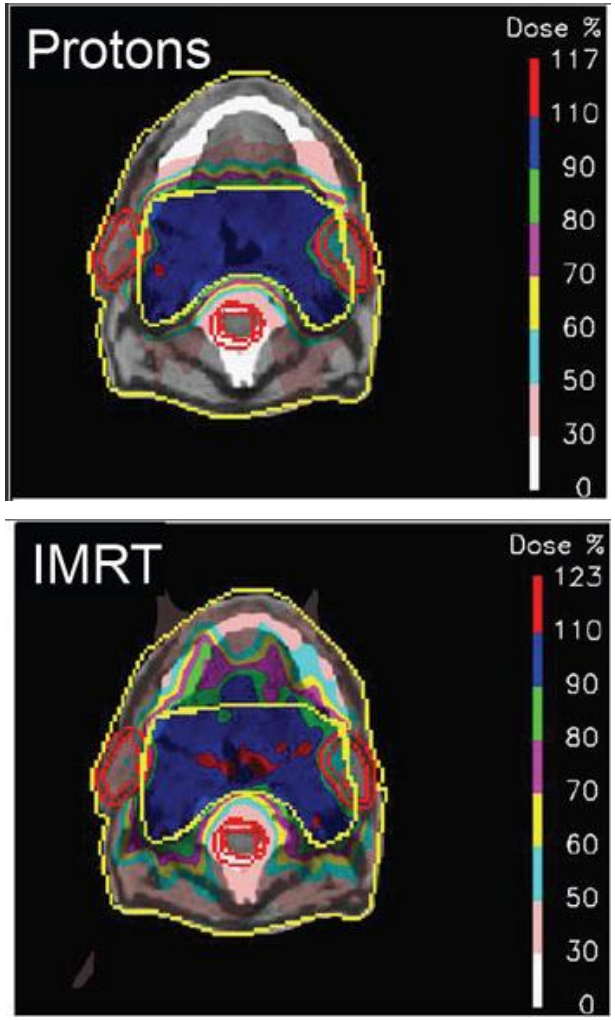




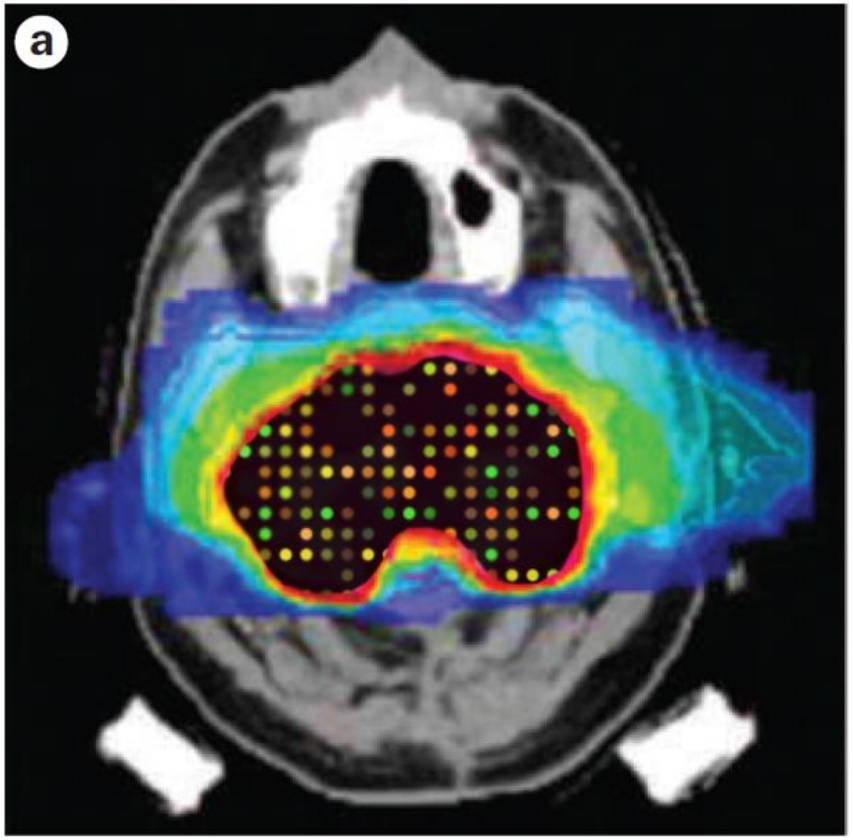
γH2AX-foci in response to IR

- What is the relevance of these differences?
- Have they to be taken into consideration?
- Can we exploit them?

Major Challenge: Personalized Treatment

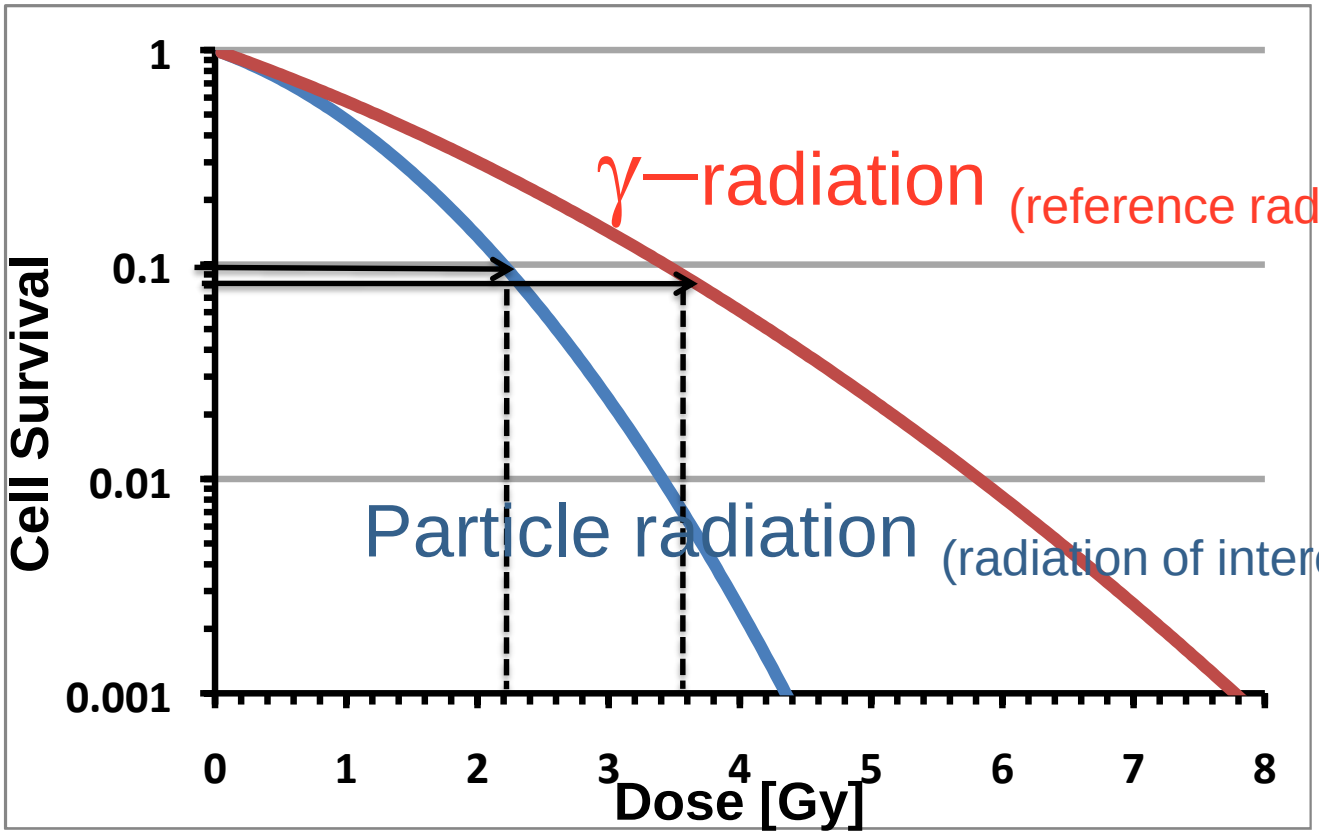


The integral dose difference between protons and IMRT



- Integration of Biological Parameters
- Stratification not only based on Clinical Parameters

RBE: Relative Biological Effectiveness



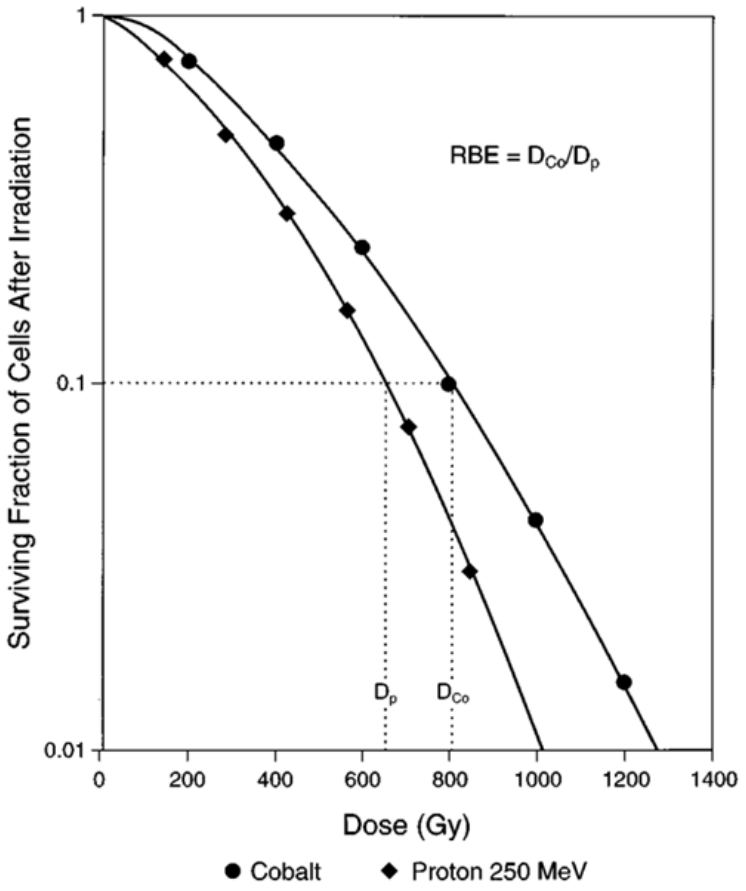
$$RBE = \frac{D_{\gamma}}{D_{particle}} \rangle effect \langle$$

The RBE is defined as the ratio of doses to reach the same level of effect when comparing two modalities, e.g. a reference radiation and proton radiation.

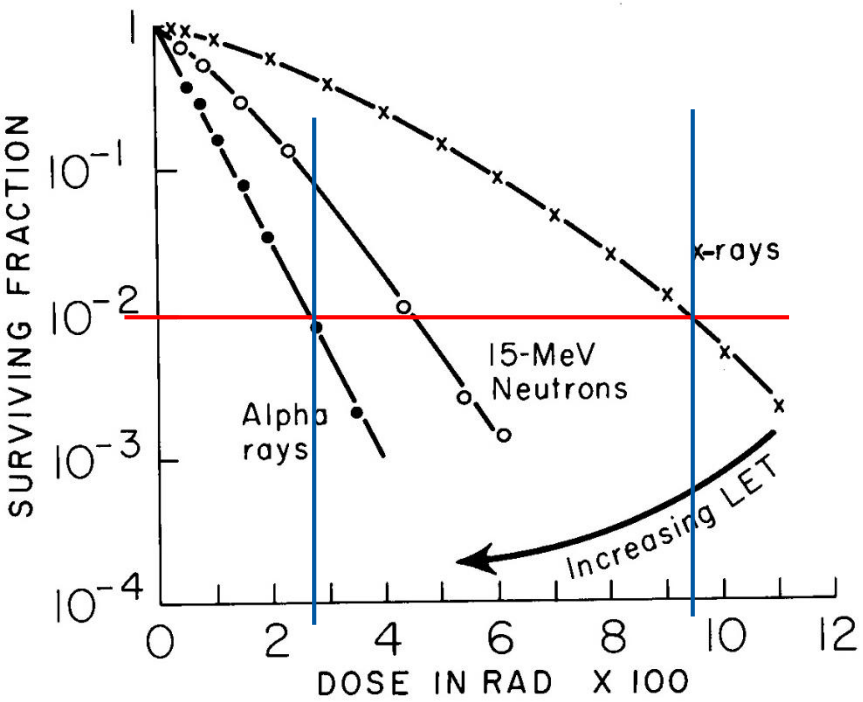
Definition of endpoint (effect) is relevant!

RBE is not an unique value; is dependent on:

- Cell line / Organ
- Endpoint
- α/β-ratio
- Recovery
- …
- Energy/LET
- Dose
- Dose rate
- Fractionation
- ….



LET dependence:



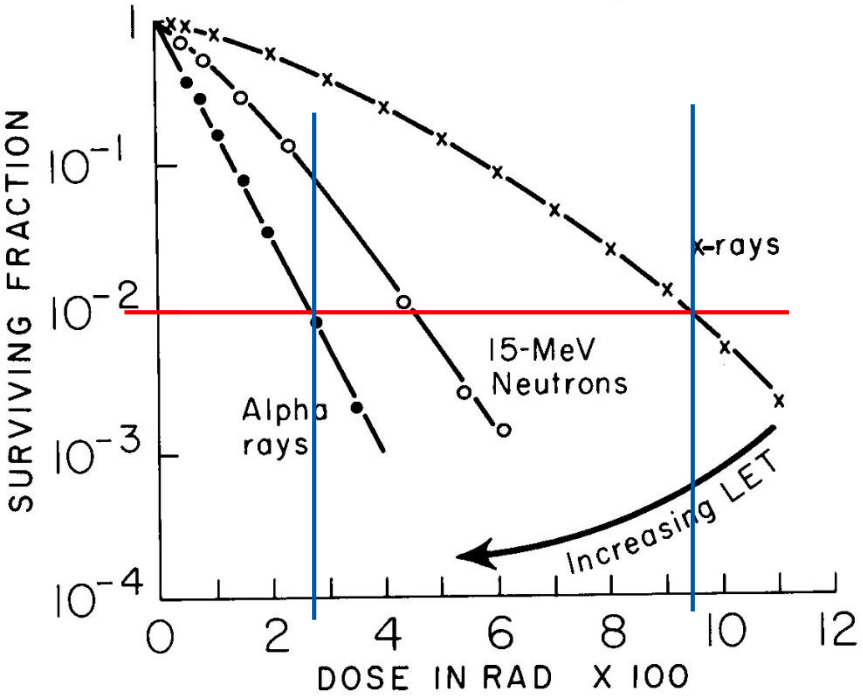
As the LET increases from about 2 keV/μm for x-rays up to 150 keV/μm for α-particles, the survival curve changes in two important respects:

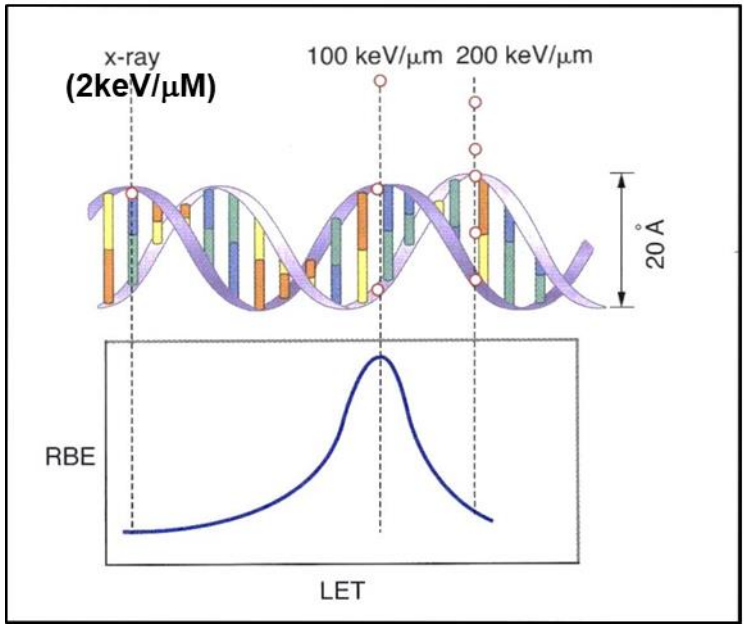
1. the survival curve becomes steeper.
2. the shoulder of the curve becomes progressively smaller as the LET increases.

9.5Gy:2.8Gy = 3.4

LET: descriptor of energy transferred from the beam to the irradiated material per units of particle path length (e.g. keV/μm)

The optimal LET: Biological Explanation



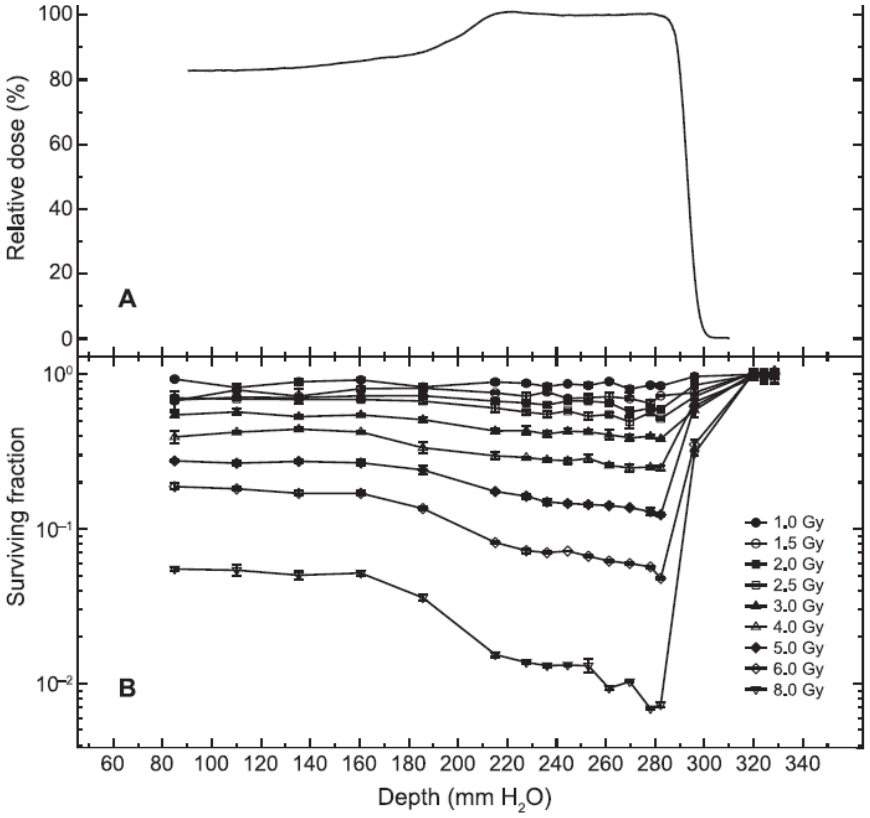


In the case of x-rays, which are more sparsely ionizing, the probability of a single track causing a double-strand break is low, and in general more than one track is required. As a consequence, x-rays have a low biologic effectiveness.

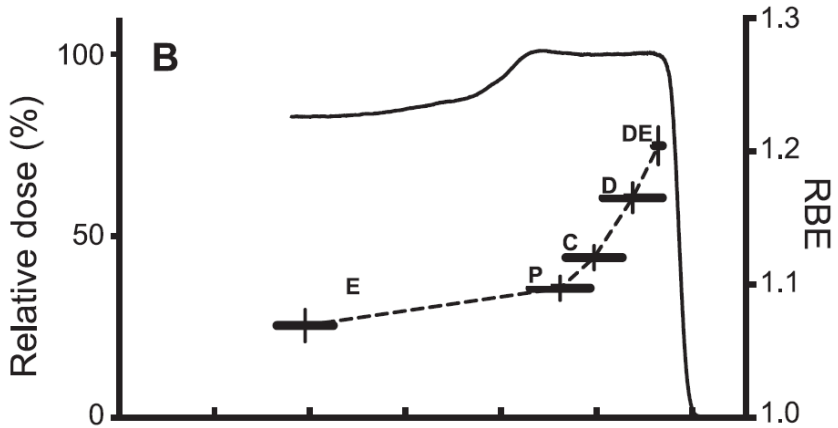
The localized DNA damage caused by dense ionizations from high-LET radiations is more difficult to repair than the diffuse DNA damage caused by the sparse ionizations from low-LET radiations.

Proton Radiobiology - RBE: LET dependence

Radiobiological Intercomparison of the 160 MeV and 230 MeV Proton Therapy Beams at the Harvard Cyclotron Laboratory and at Massachusetts General Hospital



Chinese hamster lung cells (low α/β value)



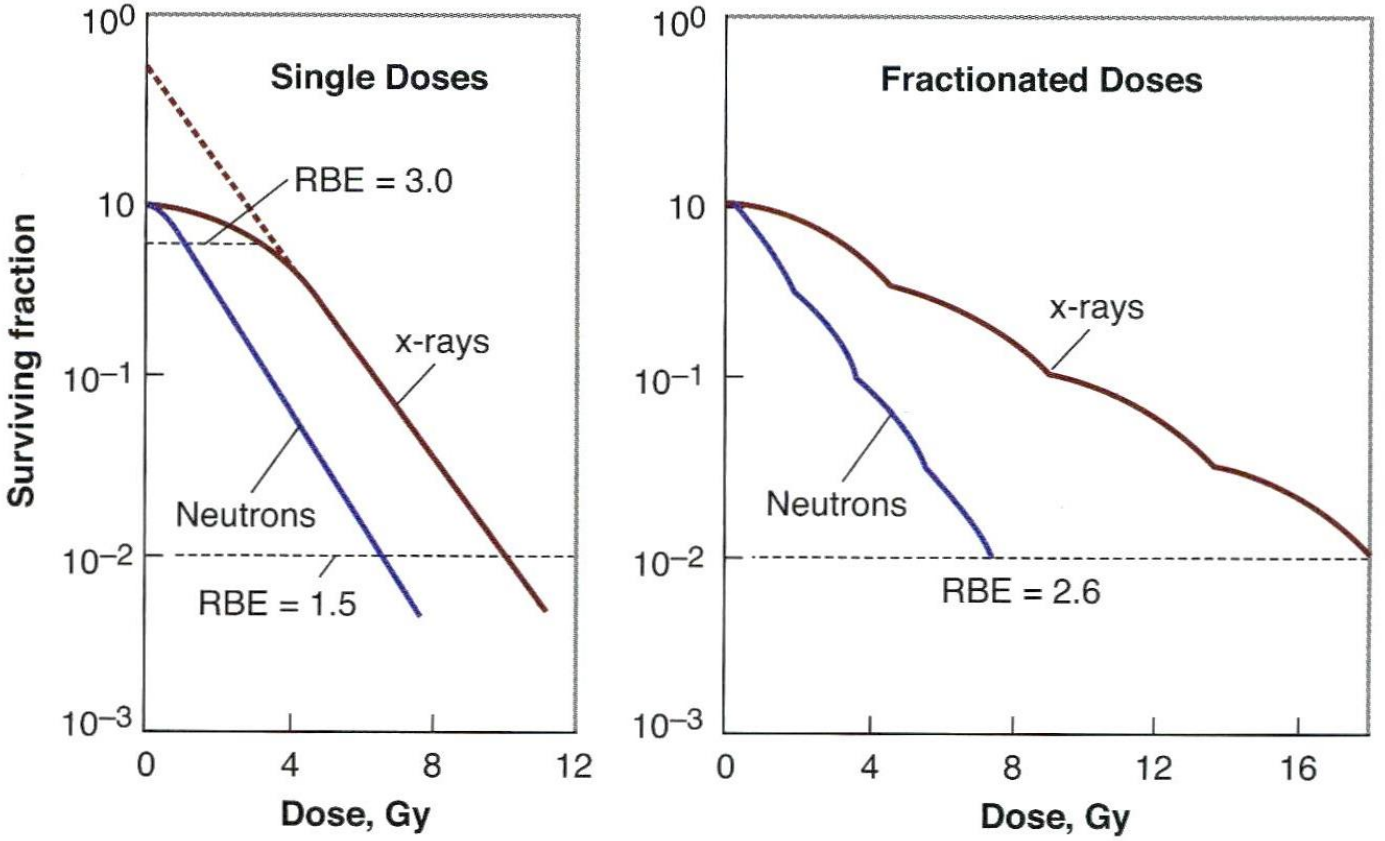
E: entrance
P: proximal
C: central
D: distal
DE: distal edge

Wouters et al., Radiat Res, 183, 174-187, 2015
see also: Wouters et al. Radiat Res 1996; 146, 159-170

Uniform dose over SOBP (range-modulated beam), but non-uniform LET over SOBP, with increased LET at distal edge

(also for animal studies)

The RBE has no unique value



Dose dependence

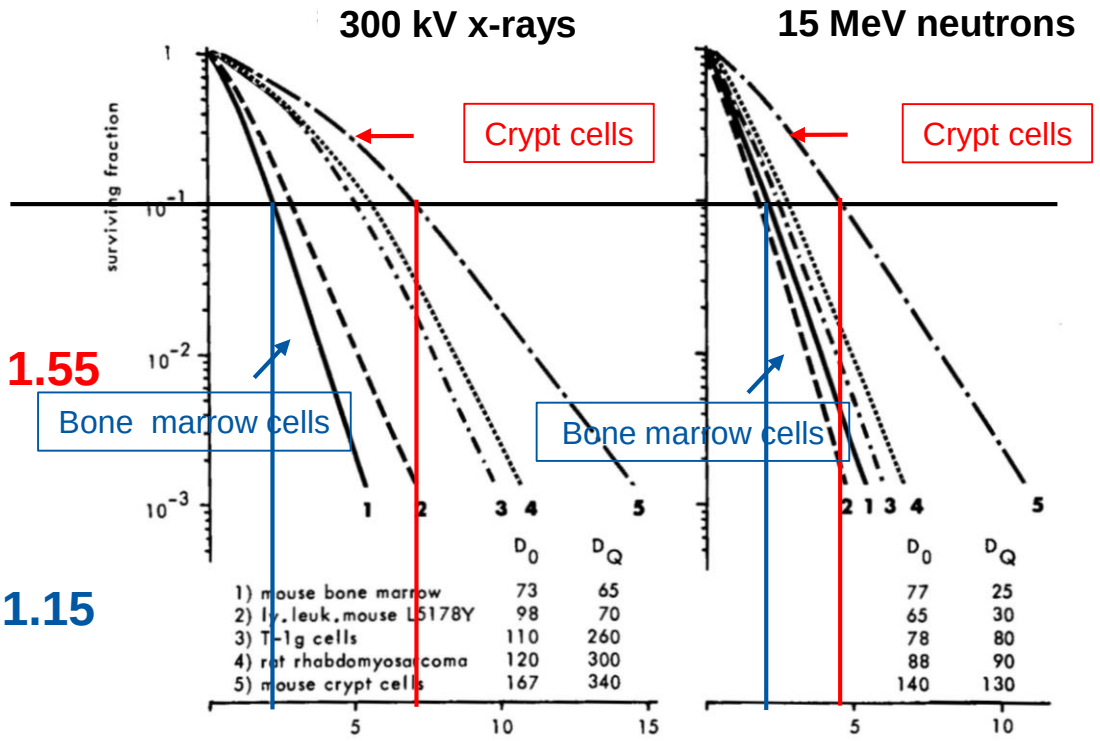
Regimen dependence

X-ray: large shoulder;

Neutrons: small initial shoulder

RBE generally increases as dose decreases

The RBE is different for each cell line / tissue



RBE 7 : 4.5 = 1.55

RBE 2.3 : 2 = 1.15

Cells characterized by an x-ray survival curve with a large shoulder, - indicating that they can accumulate and repair a large amount of sublethal radiation damage (sublethal damage repair) - show large RBEs for neutrons .

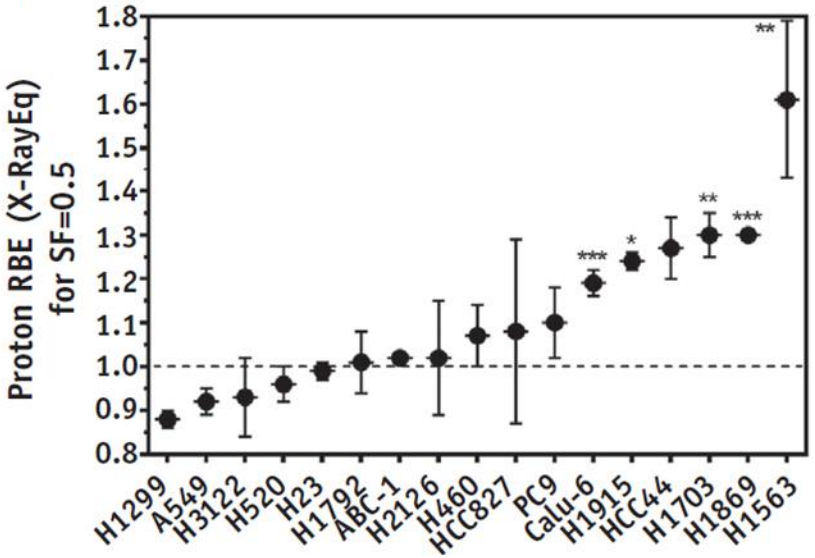
Conversely, cells for which the x-ray survival curve has little if any shoulder exhibit small neutron RBE values.

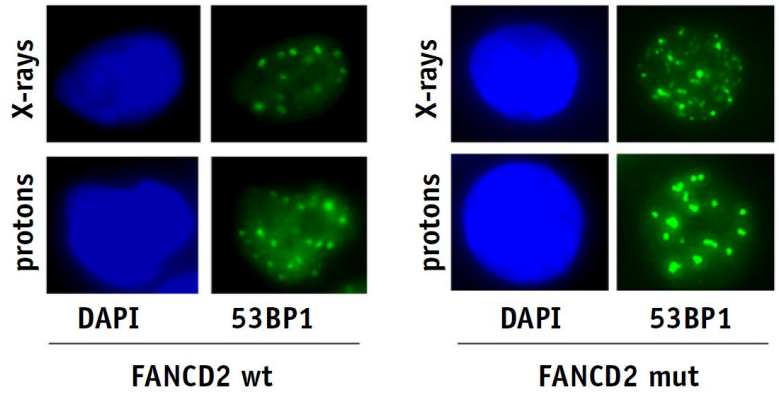
- **Differential Repair Capacity**

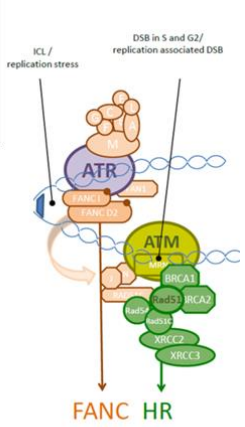
E.Hall:Radiobiology for the Radiologist

RBE depends on mutational status

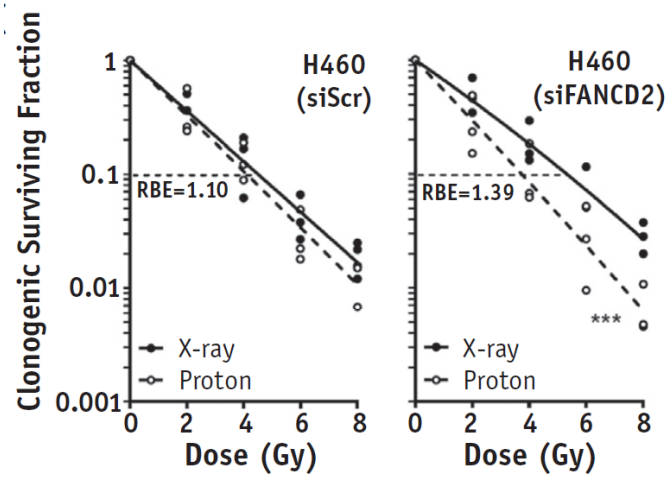
Lung Cancer Cell Line Screen Links Fanconi Anemia/BRCA Pathway Defects to Increased RBE







FANC-pathway: replication fork maintenance

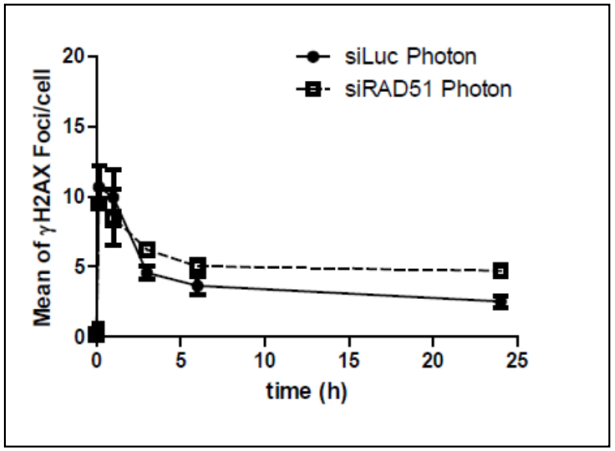


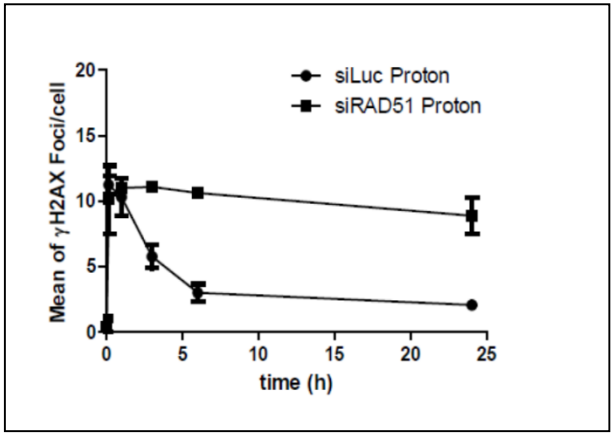
53BP1-Foci-size as putative Biomarkers

Fontana, Pruschy et al. IJROBP,2015
Liu, Willers et al, IJROBP, 2015/16

«To Proton» or «To Photon»

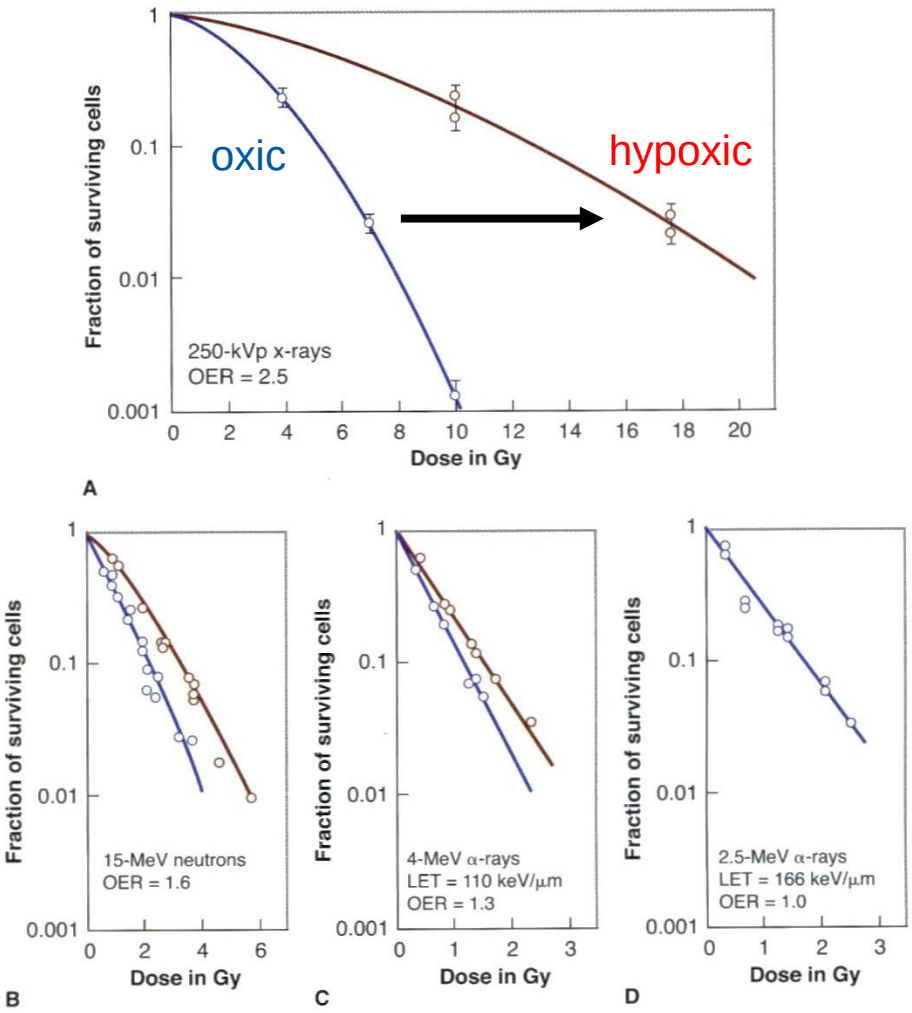
- taking the genetic background into consideration
- in combination with anticancer agents





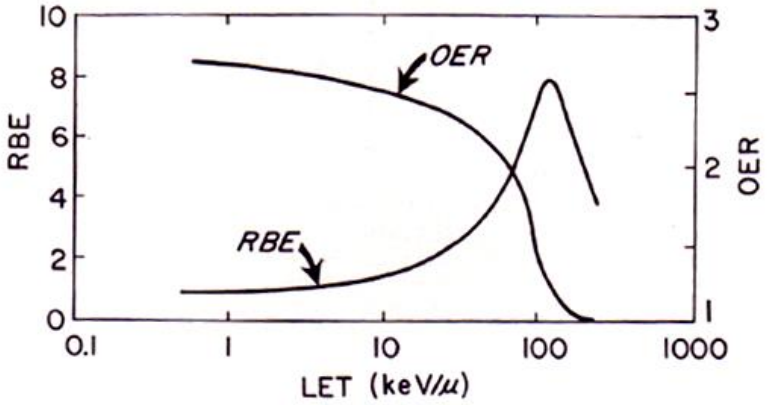
Differential Biological Responses Leading To Differential Outcome

Tumor Hypoxia, The Oxygen Effect and LET



blue circles: normoxic conditions
red circles: hypoxic conditions

Oxygen Enhancement Ratio
as a function of LET



At low LET, corresponding to x or γ-rays and protons, the OER is between 2.5 and 3; as the LET increases, the OER falls slowly at first, until the LET exceeds about 60 keV/μm, after which the OER falls rapidly and reaches unity by the time the LET has reached about 200 keV/μm(160 keV/μm).

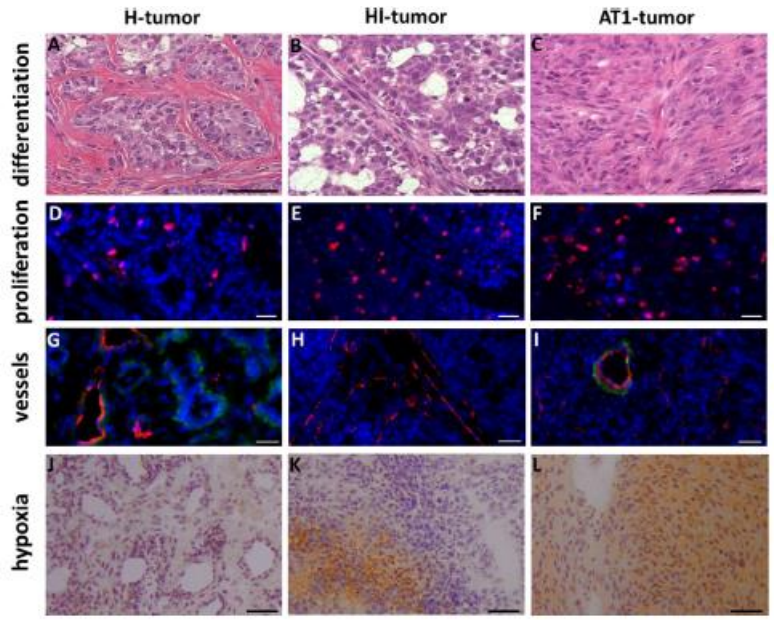
Original Articles

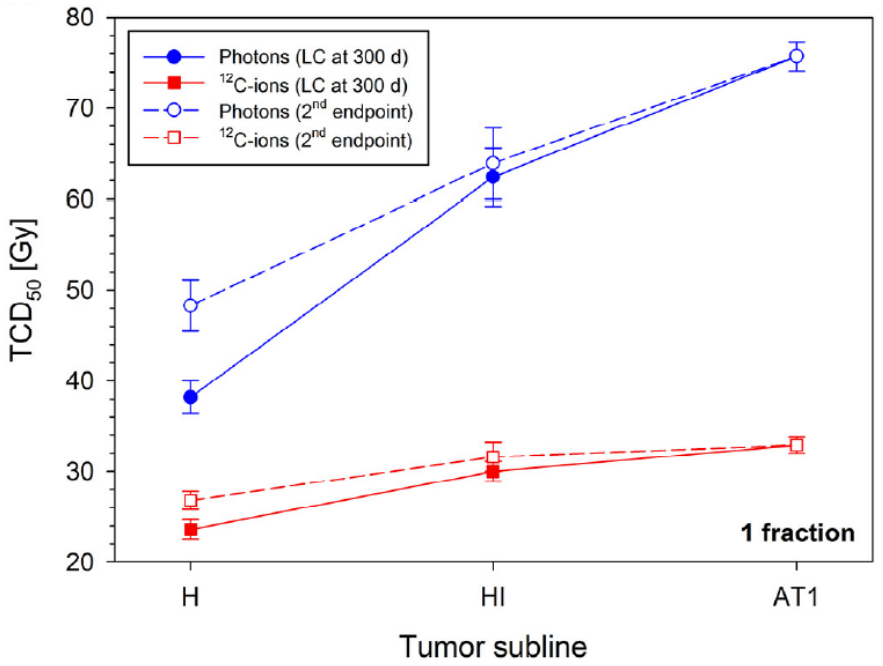
Carbon ion radiotherapy decreases the impact of tumor heterogeneity on radiation response in experimental prostate tumors

Christin Glowa [a,b,c,*], Christian P. Karger [b,c], Stephan Brons [c,d], Dawen Zhao [e], Ralph P. Mason [e], Peter E. Huber [a,c,f], Jürgen Debus [a,c], Peter Peschke [c,f]

[a] *Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany*

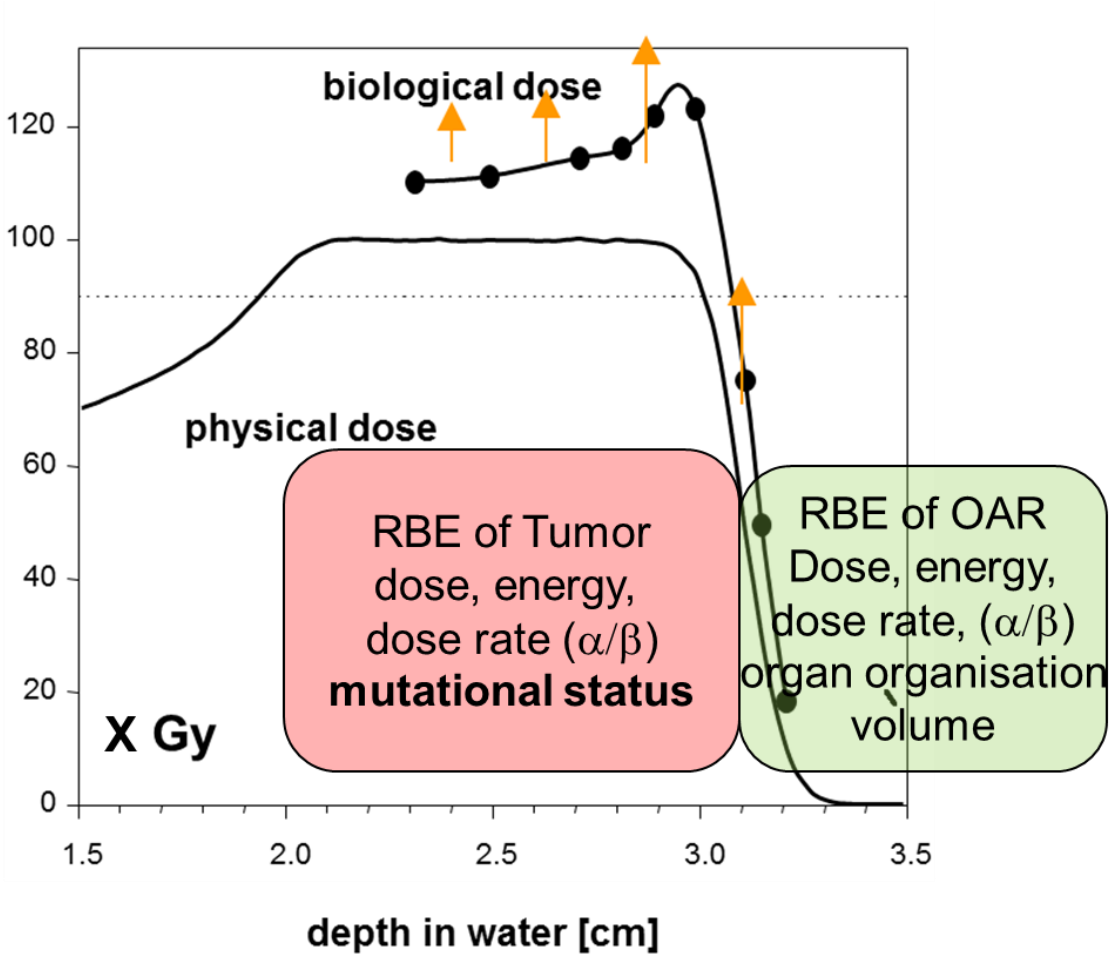
Cancer Letters 378 (2016) 97–103





Rat prostate tumors derived from 3 different sublines treated with photon and carbon ion radiotherapy

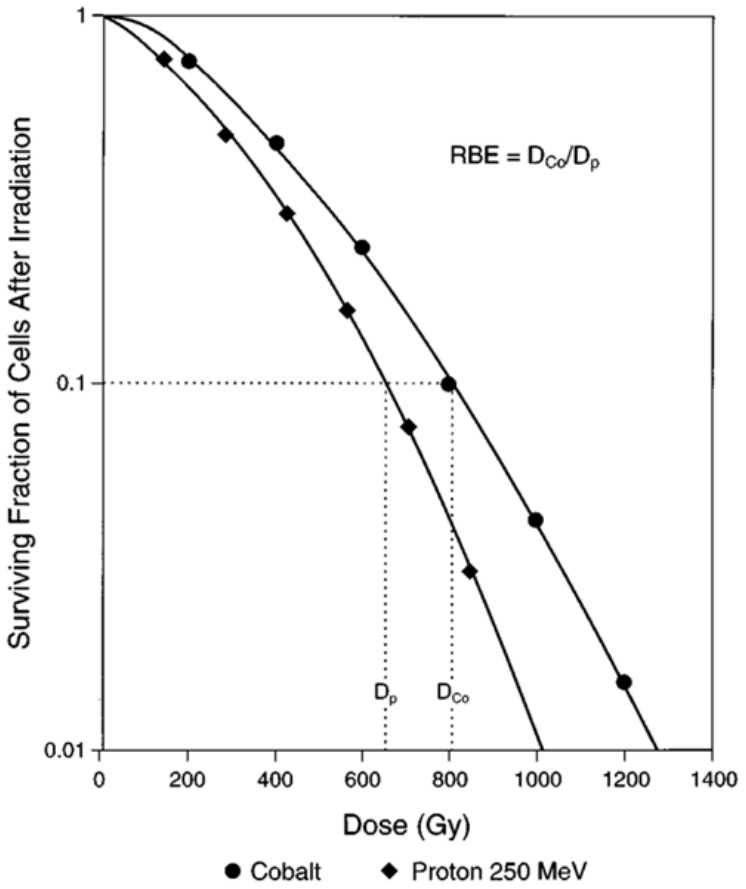
RBE is not a unique value – from the biological point of view



- Uniform physical dose over SOBP, but non-uniform biological dose over SOBP
- Mutational status of the tumor strongly influences response to biological dose:
  - personalized approaches

RBE is not an unique value; is dependent on:

- Cell line / Organ
- Endpoint
- α/β-ratio
- Recovery
- …
- Energie/LET
- Dose
- Dose rate
- Fractionation
- ….

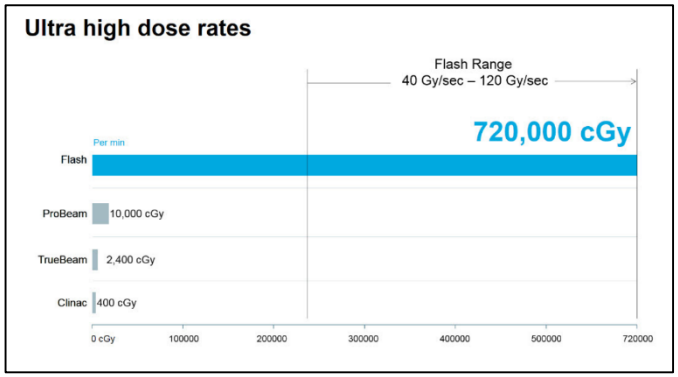


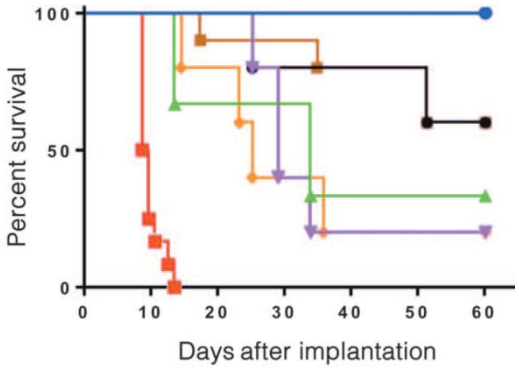
High Dose Rate Effect

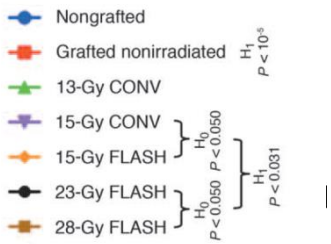
RADIATION TOXICITY

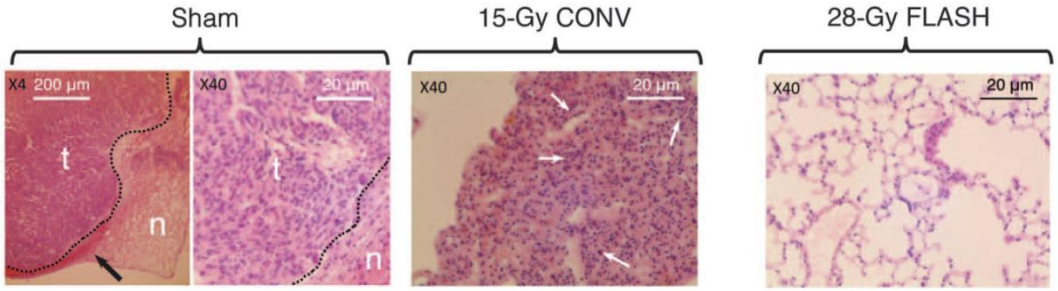
Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2]* Laura Caplier,[3]† Virginie Monceau,[4,5]‡ Frédéric Pouzoulet,[1,2]§ Mano Sayarath,[1,2]¶ Charles Fouillade,[1,2] Marie-France Poupon,[1,2]‖ Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]









- short pulses (≤ 500ms) of radiation
- ultrahigh dose rates ≥ 40Gy/s;

FLASH THERAPY

- This technology delivers the radiation dose almost **instantaneously** in milliseconds (ms), which is thought to induce a massive oxygen consumption and a transient protective hypoxia in normal tissue, as opposed to conventional RT delivering the same dose in minutes

- It is able to markedly improve the normal tissue tolerance, called the FLASH effect.

- In the tumors, which are generally hypoxic, the effect of FLASH-RT does not appear different from conventional RT.

- Instantaneous dose rate with Pencil Beam Scanning can be increased towards FLASH-Dose rate level (> 40-60Gy/s)

Physics Contribution

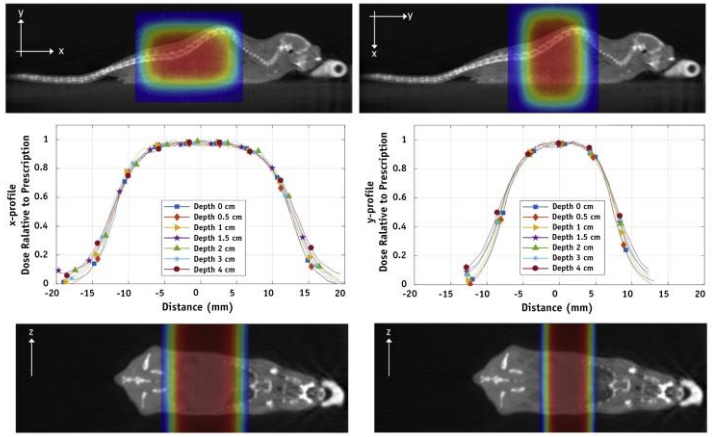
Design, Implementation, and in Vivo Validation of a Novel Proton FLASH Radiation Therapy System

International Journal of Radiation Oncology biology • physics

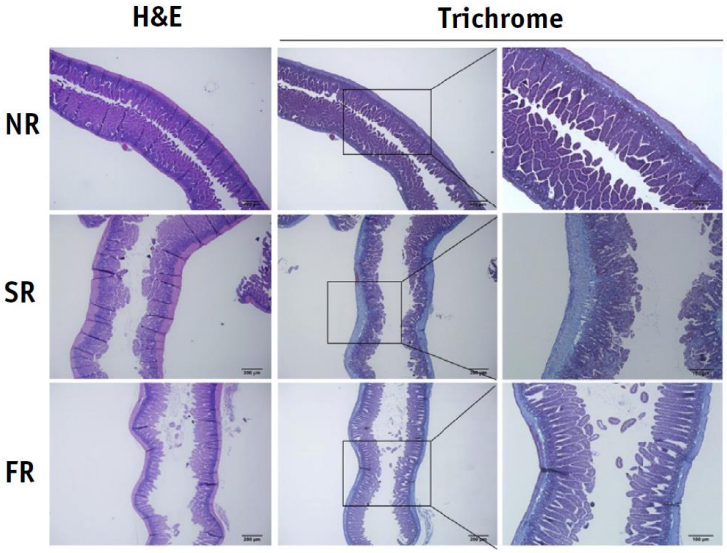
Vol. 106, 440ff 2020

Eric S. Diffenderfer, PhD, Ioannis I. Verginadis, PhD, Michele M. Kim, PhD, Khayrullo Shoniyozov, PhD, Anastasia Velalopoulou, PhD, Denisa Goia, MS, Mary Putt, PhD, Sarah Hagan, MS, Stephen Avery, PhD, Kevin Teo, PhD, Wei Zou, PhD, Alexander Lin, MD, Samuel Swisher-McClure, MD, Cameron Koch, PhD, Ann R. Kennedy, PhD, Andy Minn, MD, PhD, Amit Maity, MD, PhD, Theresa M. Busch, PhD, Lei Dong, PhD, Costas Koumenis, PhD, James Metz, MD, and Keith A. Cengel, MD, PhD

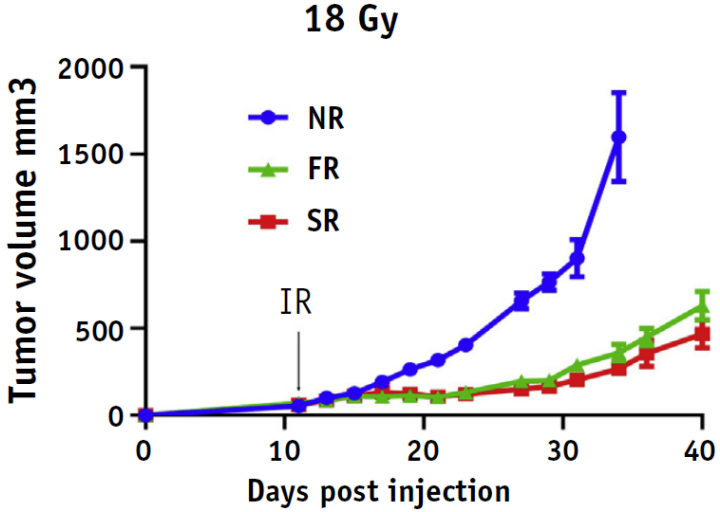
Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania



Abdominal irradiation for murine experiments



- Inhibition of IR-induced fibrosis in Flash (FR)-irradiated intestine (18Gy)
- Reduced loss of proliferating cells in intestinal crypts



No additional impact of standard (SR) vs Flash-dose rate on tumor growth control (18Gy)

Mechanism of Action

FLASH vs. conventional dose rate radiation chemistry: differential oxidative metabolism

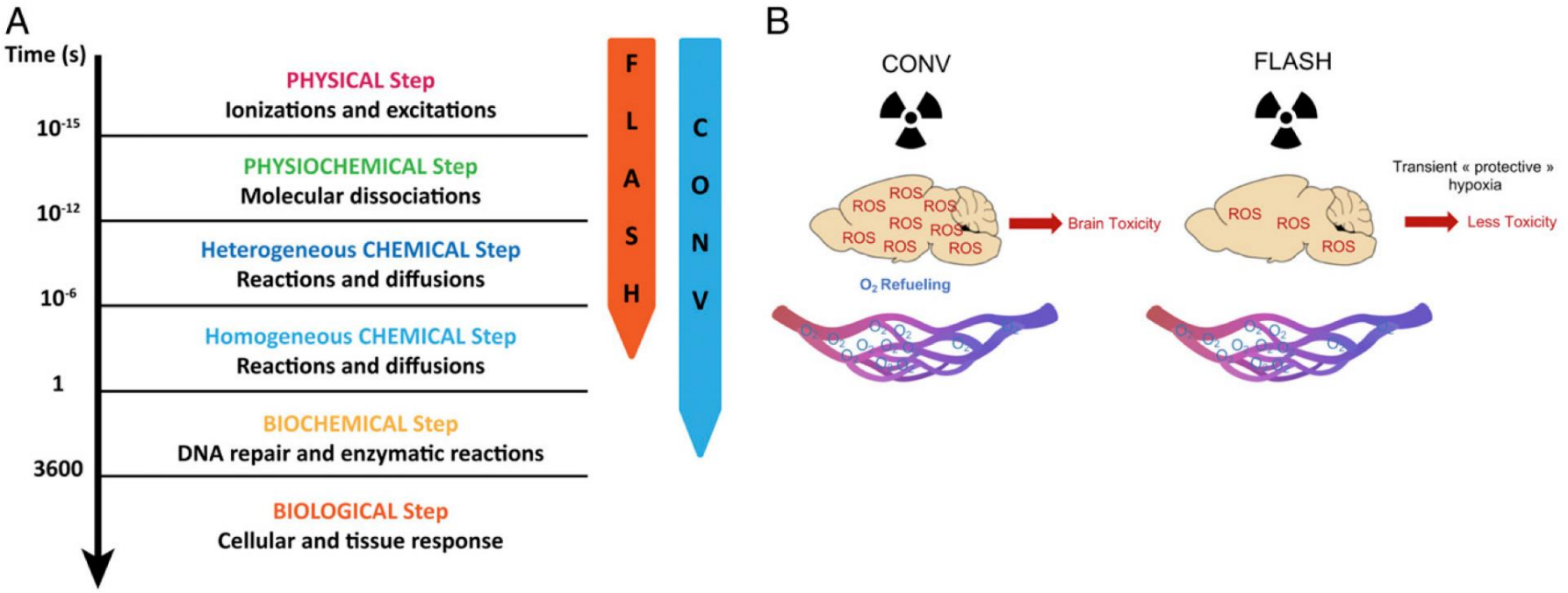


Fig. 5. Differential physicochemical events distinguish FLASH from CONV irradiation. For the delivery of a similar dose, FLASH irradiation is 1,000-fold more rapid than CONV irradiation. (*A*) While CONV irradiation transpires during ongoing chemical and biological responses, FLASH does not interact with these early radiation reactions. (*B*) FLASH induces the rapid depletion of oxygen and a transient local hypoxia, thereby reducing ROS levels and normal brain toxicity compared with CONV irradiation.

FLASH-RT could cause a rapid consumption of local oxygen that would occur much faster than any tissue reoxygenation kinetics. Rapid depletion of oxygen would therefore elicit a transient radiation induced hypoxia with reduced ROS levels.

Mechanism of Action

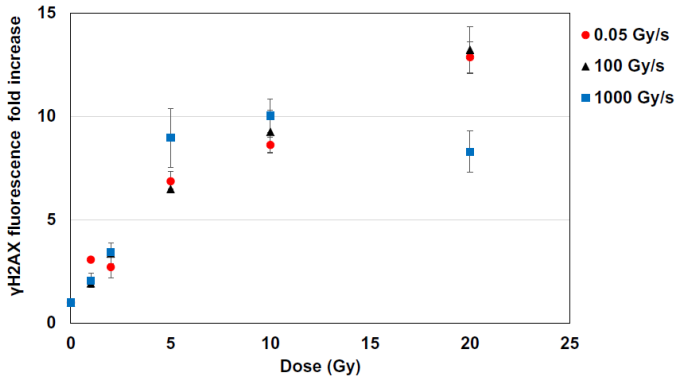


Fig. 2. The effect of proton dose rate on DNA damage. Fold change of γH2AX foci fluorescence intensity (normalized to controls) in normal human lung fibroblasts (IMR90) 30 min after exposure to different doses of 4.5 MeV protons delivered at 0.05, 100 or 1000 Gy/s.

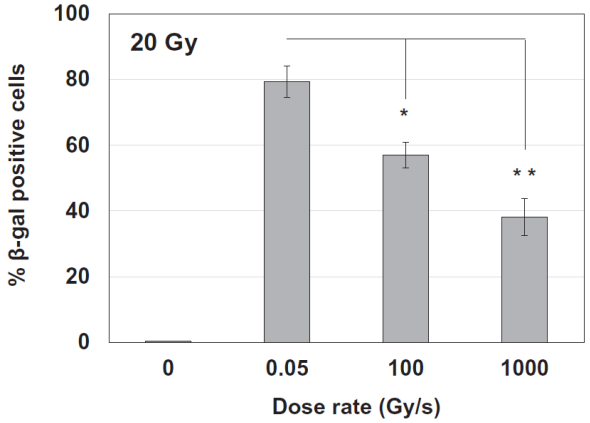


Fig. 3. The effect of proton dose rate on premature cell senescence. Percentage of β-gal positive normal human lung fibroblasts (IMR90) one month after exposure to 20 Gy of 4.5 MeV protons delivered at 0.05, 100 or 1000 Gy/s. $^{*}p < 0.05$, $^{**}p = 0.01$.

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Original Article

Biological effects in normal cells exposed to FLASH dose rate protons

Manuela Buonanno*, Veljko Grilj, David J. Brenner
Radiological Research Accelerator Facility (RARAF), New York, United States

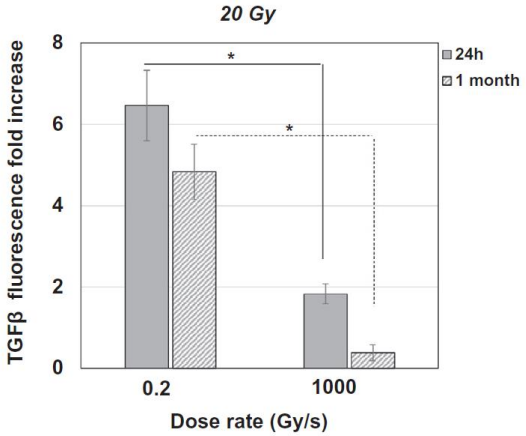

Fig. 4. The effect of proton dose rate on the expression of the inflammatory marker TGFβ. TGFβ1 fluorescence intensity fold increase in normal human lung fibroblasts (IMR90) 24 h and one month after exposure to 20 Gy of 4.5 MeV protons delivered at 0.2 or 1000 Gy/s. $^{*}p < 0.05$.

At very high dose rates and doses:

- Foci formation saturated
- Reduced number of senescence cells
- Reduced levels of inflammatory markers (TGFβ)

Hypothesis: FLASH affects long-term responses

FLASH THERAPY
(challenges – just a «few»)

- Mechanism of Action
- Cell level - (patho-)physiological level
- (Bio-)Dosimetry
- (Spatiotemporal) Fractionation
- Tumor Growth Delay versus Tumor Control
- Conformity, Tumor hypoxia
- Translation to Clinical Machines (electron, photon, proton)
- etc. etc.

➢ to be investigated as part of Radiobiological Research

Summary: Role of Radiobiology in Particle Therapy

Relative Biological Effectiveness: The RBE is defined as the ratio of doses to reach the same level of effect when comparing two modalities, e.g. a reference radiation and proton radiation.

The RBE is not an unique value and depends on multiple physics- and biology-related parameters

Differential “biologies” are induced by different modalities of ionizing radiation (photon versus particle radiation)

Understanding the biological factors that influence the differential responses to different types of ionizing radiation, is important to eventually integrate a biology-dependent RBE into treatment planning

➢ Towards Personalized Particle Radiotherapy Integrating Biological Factors