Radiobiological modeling for carbon ion radiotherapy

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Preface

1. Thanks to Christin Glowa for providing some slides.

2. Further reading: Comprehensive review on radiobiological models in carbon ion radiotherapy by Christian Karger and Peter Peschke: *Karger CP, Peschke P. RBE and related modeling in carbon-ion therapy. Phys Med Biol. 2017 Dec 19;63(1):01TR02. doi: 10.1088/1361-6560/aa9102. PMID: 28976361.*

Outline

1. Effects of ionizing radiation on the DNA

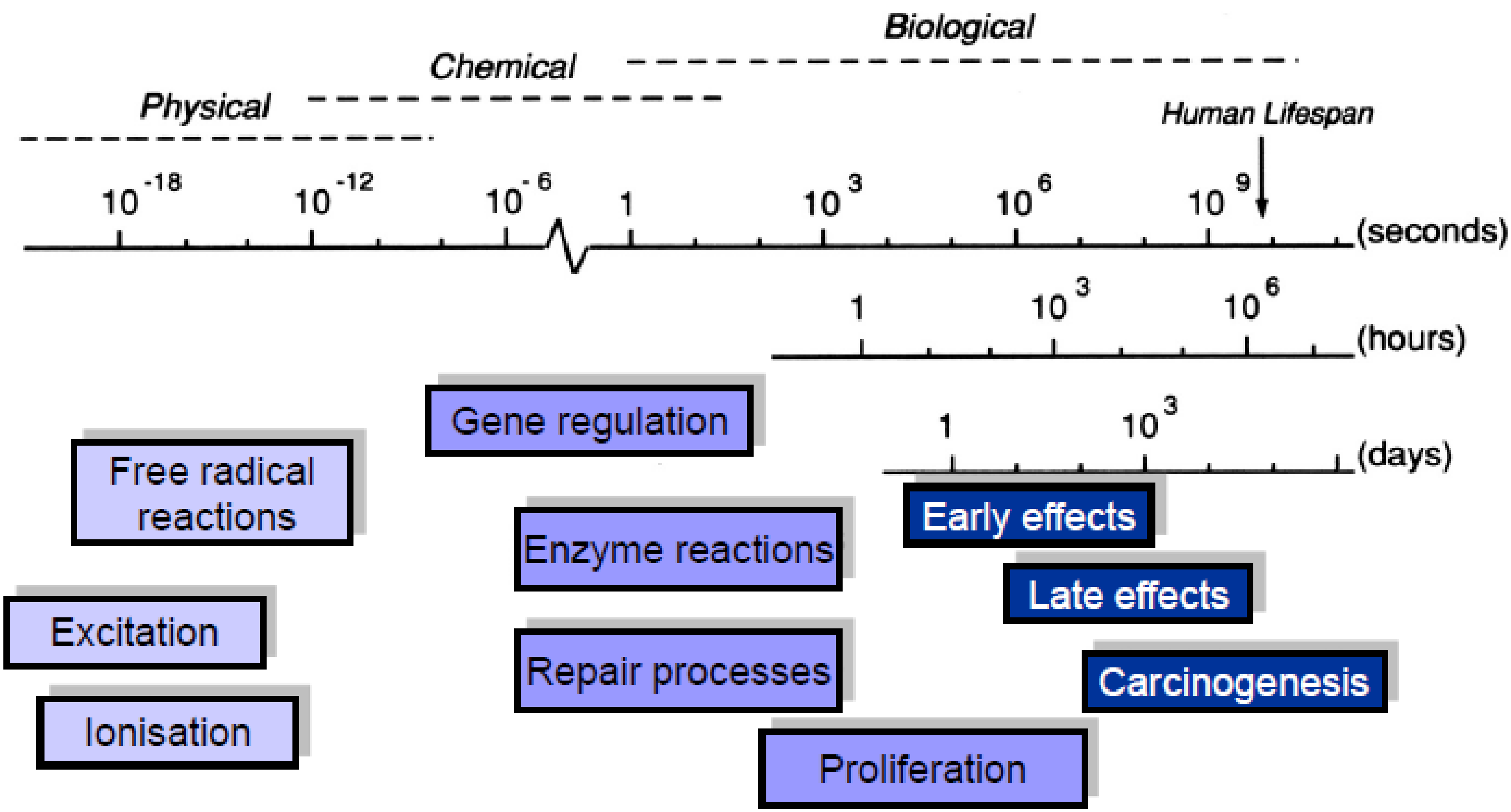
2. The 5 Rs of radiobiology

3. The relative biological effectiveness (RBE)

4. Modeling the relative biological effectiveness (RBE)

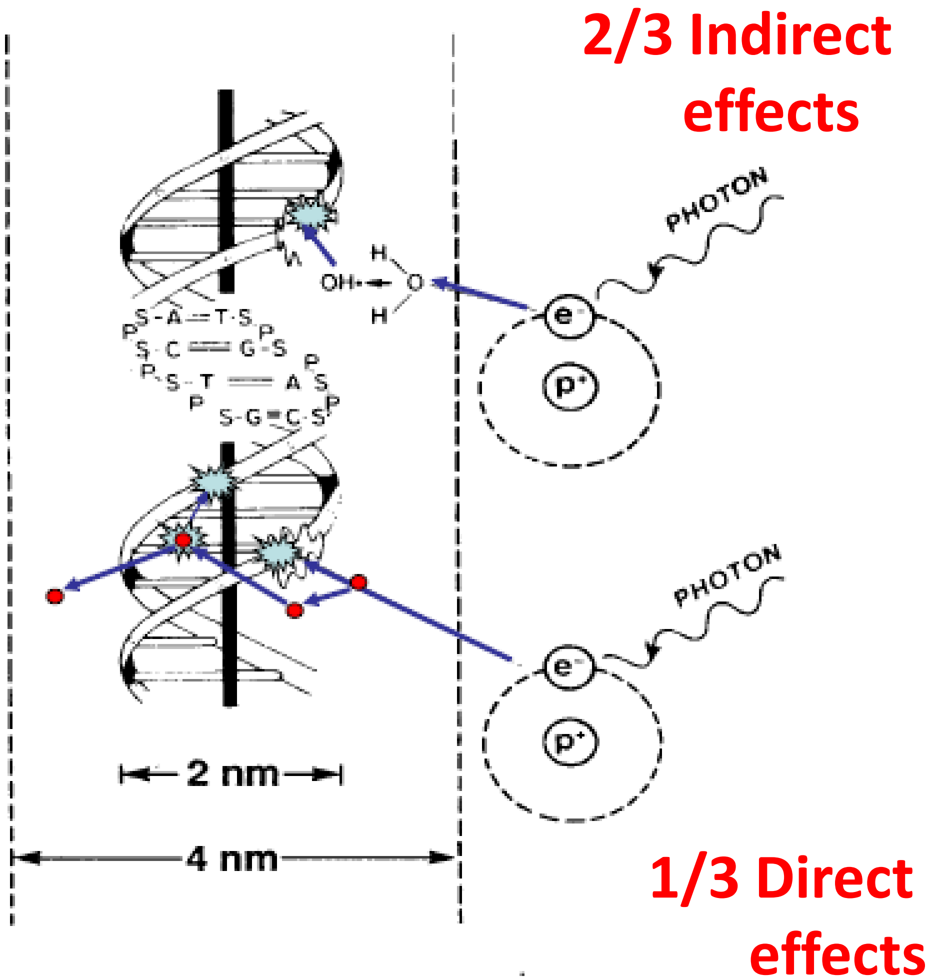
   LEM I vs. LEM IV

Time scale of radiation effects



Irradiation generates multiple processes that differ in time scale

Effect of ionizing radiation on DNA



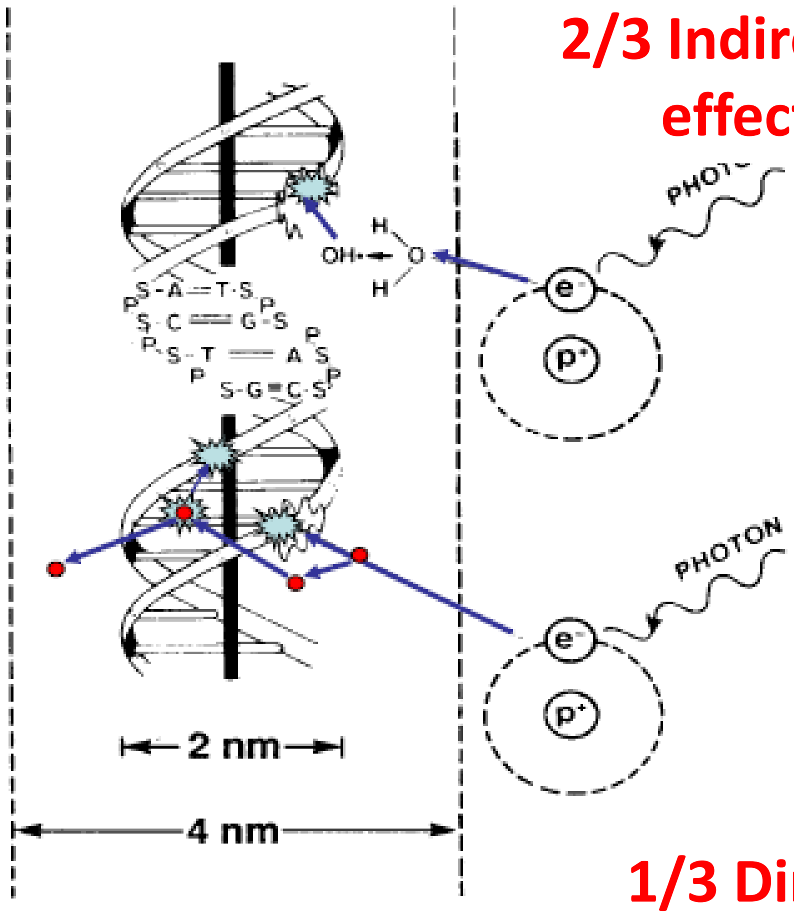
- Ionisation
- Ejection of electrons from molecules
- Breaking up of chemical bonds
- Destruction of the chemical structure

DNA damage per 1 Gy per cell:

SSB: 1000

DSB: 30-40

Effect of ionizing radiation on DNA



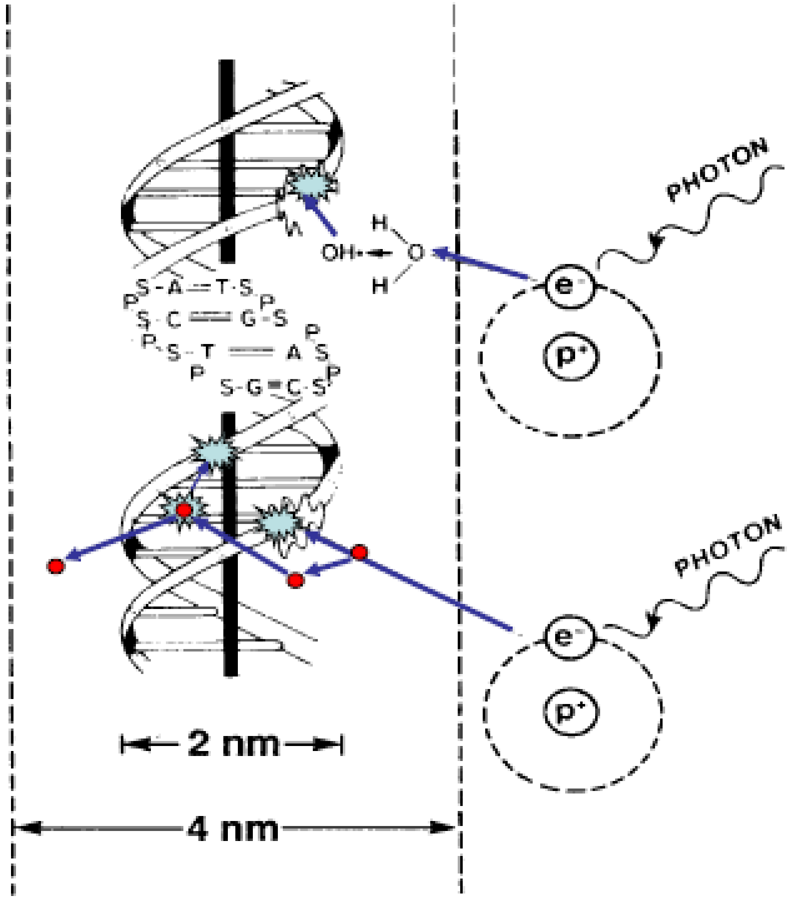
2/3 Indirect effects

1/3 Direct effects

Indirect effects:

- secondary electron interacts with another molecule, e.g H_2O
- radicals
- reactive oxygen species, e.g. hydrogen peroxide

Effect of ionizing radiation on DNA

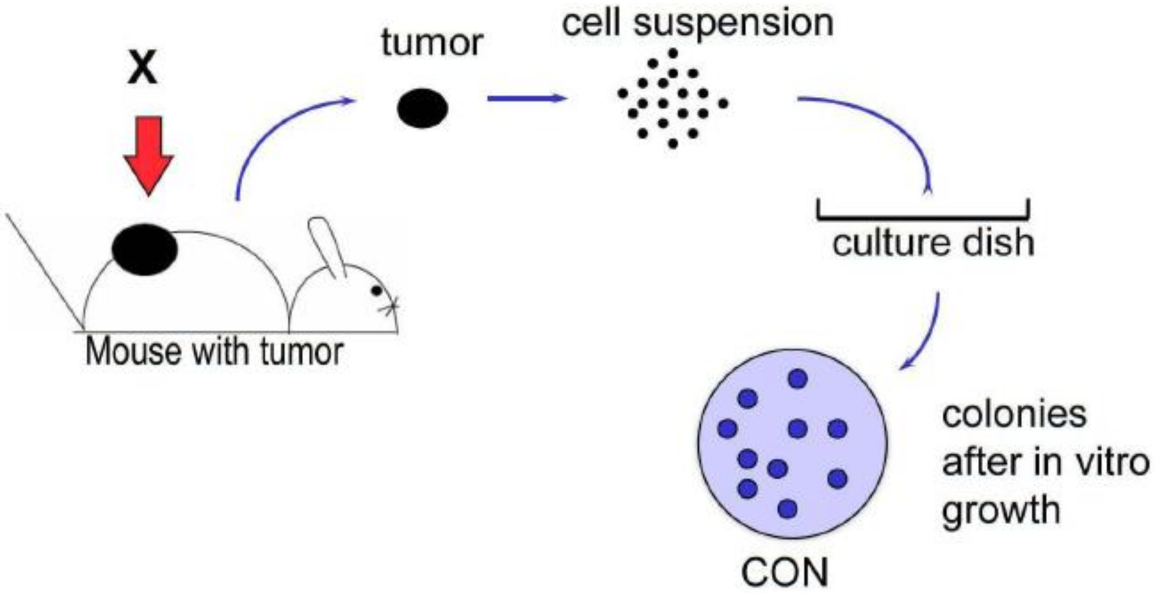


(clustered) DNA double-strand breaks (DSB) are most important

- complex
- difficult to repair
- loss of genetic information possible
- repair systems: HR, NHEJ

Clonogenic assays (*in vitro*)

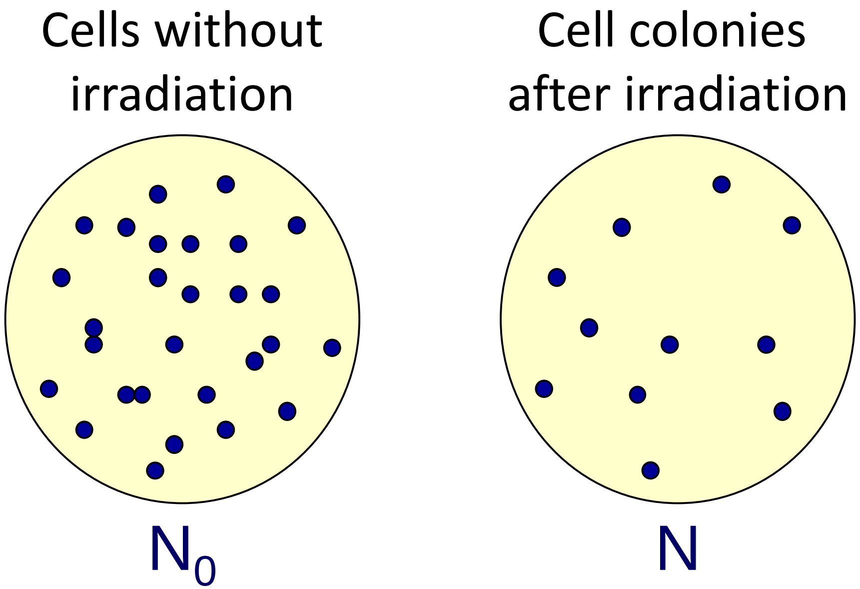
- tumor excision
- single cells plated on cell culture dish
- Cell culture

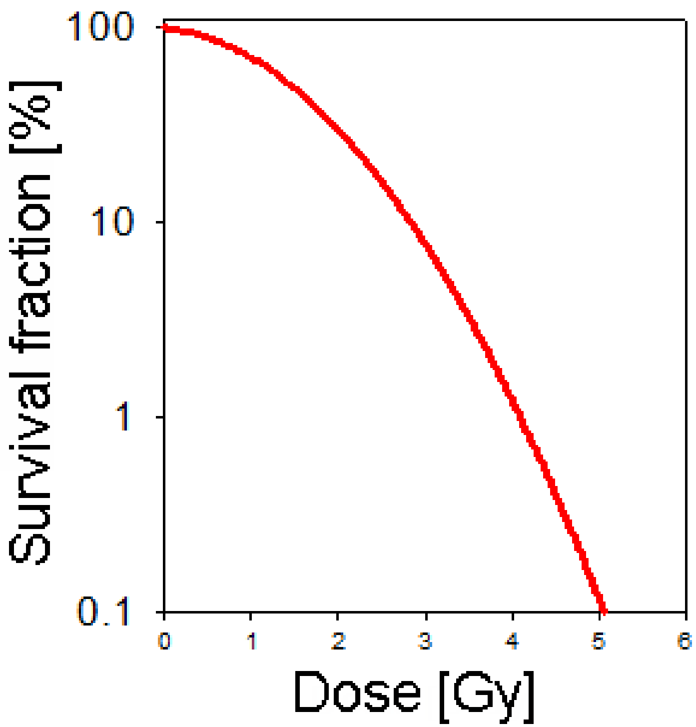


Cell survival curve - Clonogenic Assay

- Irradiation of cells with dose d
- Cell survival is dose dependent

$$SF(d) = \frac{N(d)}{N_0}$$





Factors influencing the radiation response

5R's of radiotherapy – radiobiological mechanisms which decrease the radiotherapy response (Withers, 1976)

Radiosensitivity → **Intrinsic biological factors**

Repair/ **R**ecovery

Reoxygenation

Repopulation

Redistribution

Factors influencing the radiation response

Intrinsic biological factors

- Mutated tumor suppressors
- DNA repair gene amplification
- Evading cell death (e.g. Bcl-2, Survivin)
- Up-regulation of stress response (e.g. Heat shock proteins)
- Activation of pro-survival oncogenes (e.g. EGFR)
- …

Factors influencing the radiation response

5R's of radiotherapy – radiobiological mechanisms which decrease the radiotherapy response (Withers, 1976)

Radiosensitivity → Intrinsic biological factors

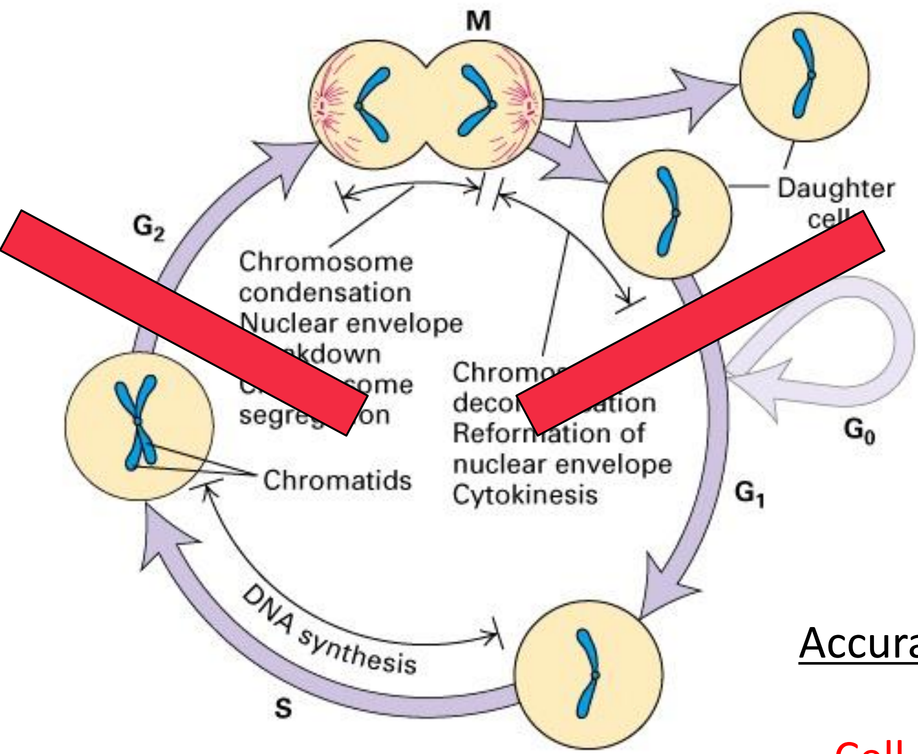
Repair/ **R**ecovery → **Damage, cell cycle, Fractionation scheme**

Reoxygenation

Repopulation

Redistribution

Radiation effects on cell cycle

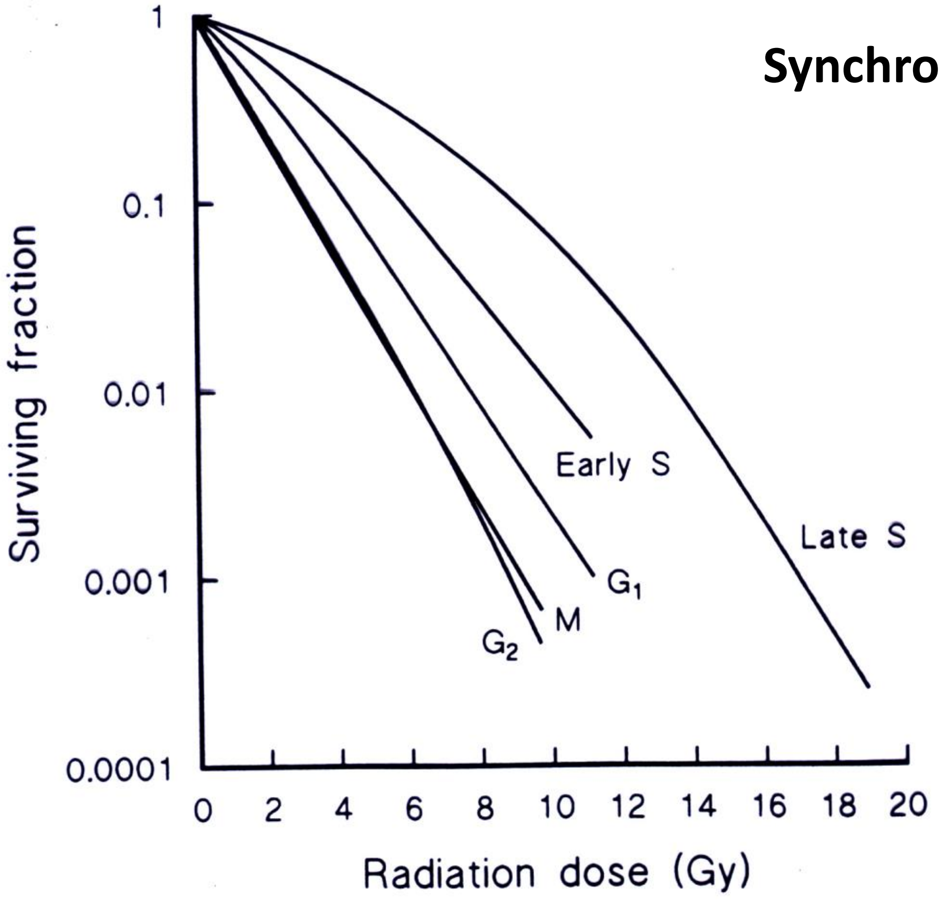


Lodish, 2000, Mol. Cell. Biol.

- Radiation usually first kills cells that are actively dividing.
- Doesn't work that well on cells in resting stage (G0).
- Cells exposed to radiation initiate complex response that includes arrest of cell cycle progression in G1 and G2.

Accurate repair:	Misrepair:	Inadequate repair:
Cell survives without damage	Cell survives but with genetic changes	Cell inactivation or cell death due to • mitotic death • apoptosis • permanent arrest

Radiation effects on cell cycle



Synchronized Chinese Hamster Cells (CHO)

Sensitive:

G2/M-phase

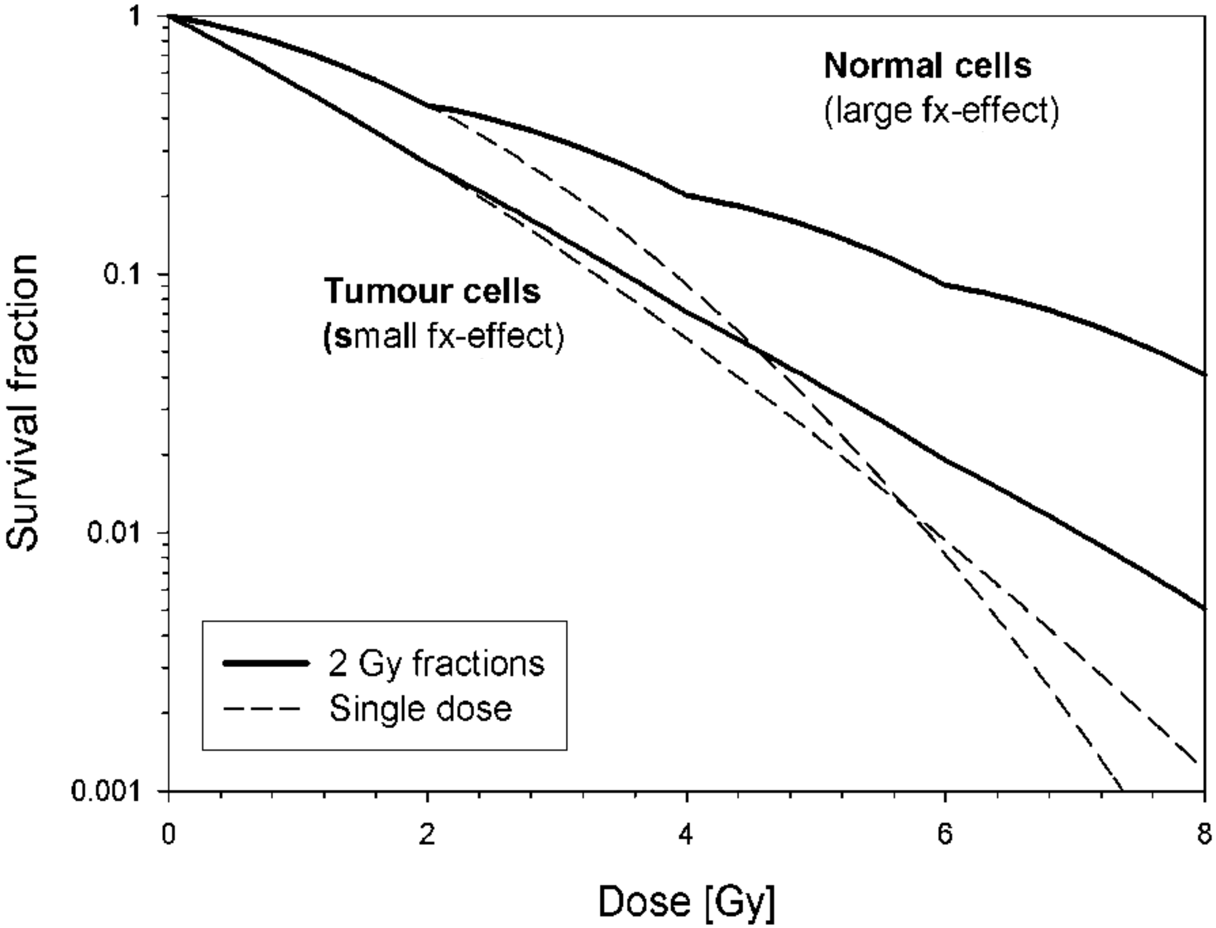
Resistant:

late S-phase

Sinclair & Morton, 1965, Biophy. J.

Fractionation effect

Healthy cells: greater ability to repair DNA damage than malignant cells → use **fractionation** to increase destructive effect on tumor cells while minimizing damage to healthy cells



Conventional fractions (fx)
30 fx: 2 Gy 5x per week

Hypofractionated fx
20 fx: 3 Gy 5x per week
-> shorter treatment time
-> more dose per fraction

Factors influencing the radiation response

5R's of radiotherapy – radiobiological mechanisms which decrease the radiotherapy response (Withers, 1976)

Radiosensitivity → Intrinsic biological factors

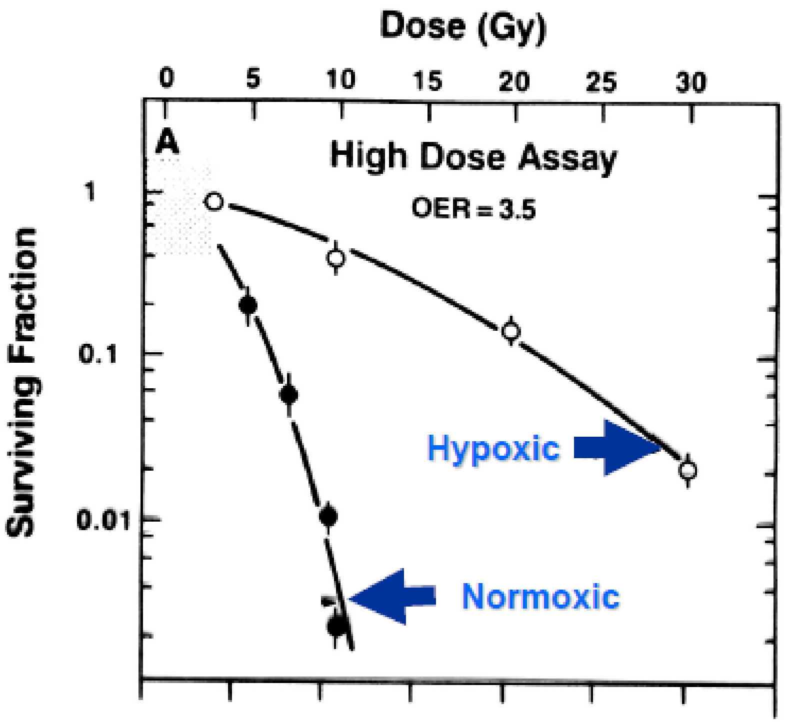
Repair/ **R**ecovery → Damage, cell cycle, Fractionation scheme

Reoxygenation → **Hypoxic (resistant) ↔ euoxic (sensitive)**

Repopulation

Redistribution

Reoxygenation influence on the radiation response



Gray, Br. J Radiol. 26: 1953

Oxygen enhancement ratio (OER)

$$OER = \frac{D_{hypoxia}}{D_{normoxia}}$$

- **Oxygen „fixates“ DNA-damage induced by radicals. Hypoxic tumors are radioresistant.**
- **Reoxygenation leads to less hypoxia in tumors before the next fraction of irradiation**

Factors influencing the radiation response

5R's of radiotherapy – radiobiological mechanisms which decrease the radiotherapy response (Withers, 1976)

- **R**adiosensitivity → Intrinsic biological factors
- **R**epair/ **R**ecovery → Damage, cell cycle, Fractionation scheme
- **R**eoxygenation → Hypoxic (resistant) ↔ euoxic (sensitive)
- **R**epopulation → **Fast tumor growth additionally enhanced**
- **R**edistribution

Repopulation

Repopulation with tumor cells over time

→ trend for the curative radiation dose to increase with overall treatment time

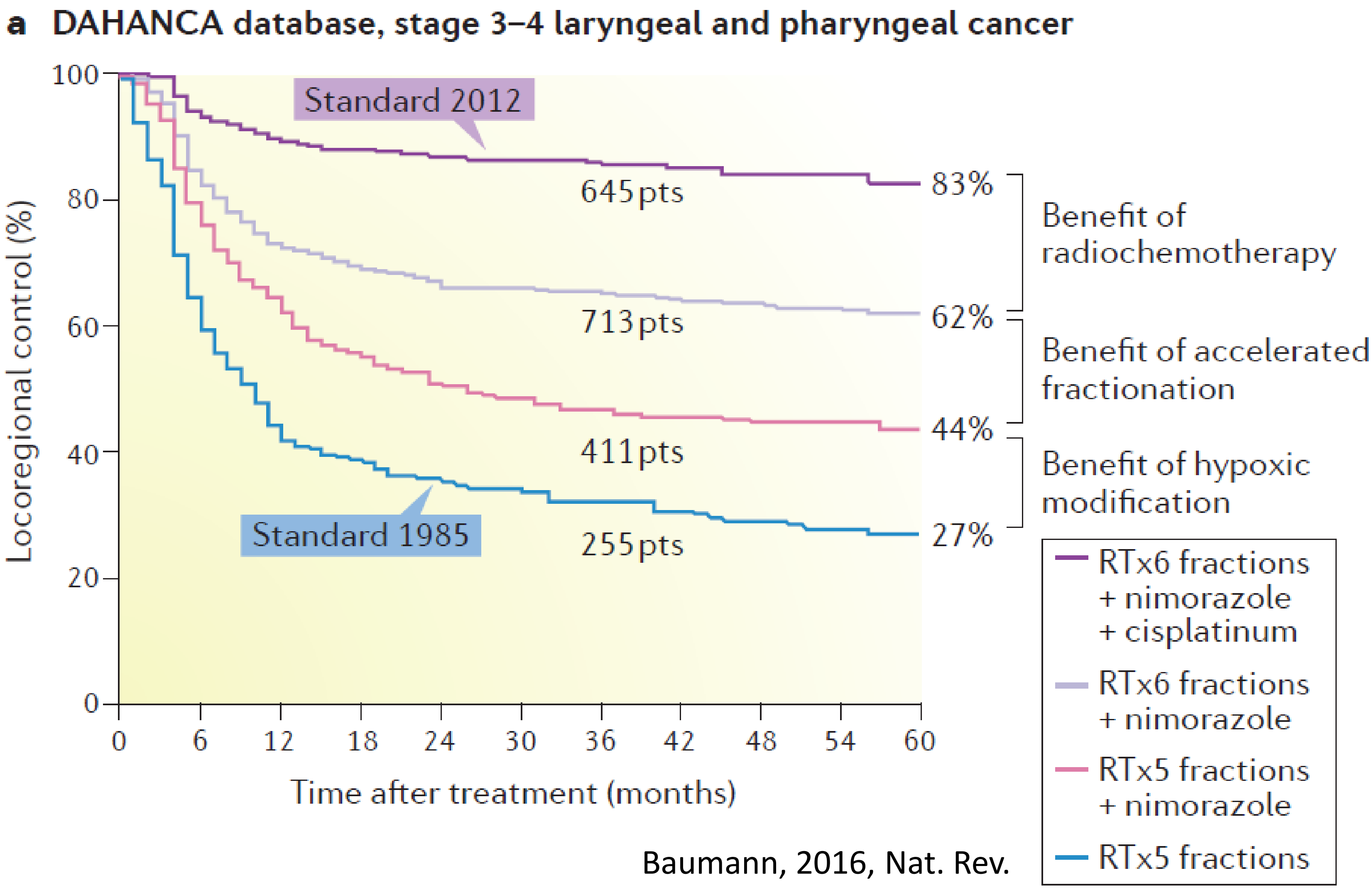
➡ **Accelerated treatment (shorter treatment time) favorable**

Factors influencing the radiation response

5R's of radiotherapy – radiobiological mechanisms which decrease the radiotherapy response (Withers, 1976)

Radiosensitivity →	Intrinsic biological factors
Repair/ **R**ecovery →	Damage, cell cycle, Fractionation scheme
Reoxygenation →	Hypoxic (resistant) ↔ euoxic (sensitive)
Repopulation →	Fast tumor growth additionally enhanced
Redistribution →	**Constant cell cycle distribution** (Cells in the radiation resistant cell cycle phases redistribute, clinically not relevant)

Transfer of radiobiology into the clinic



Baumann, 2016, Nat. Rev.

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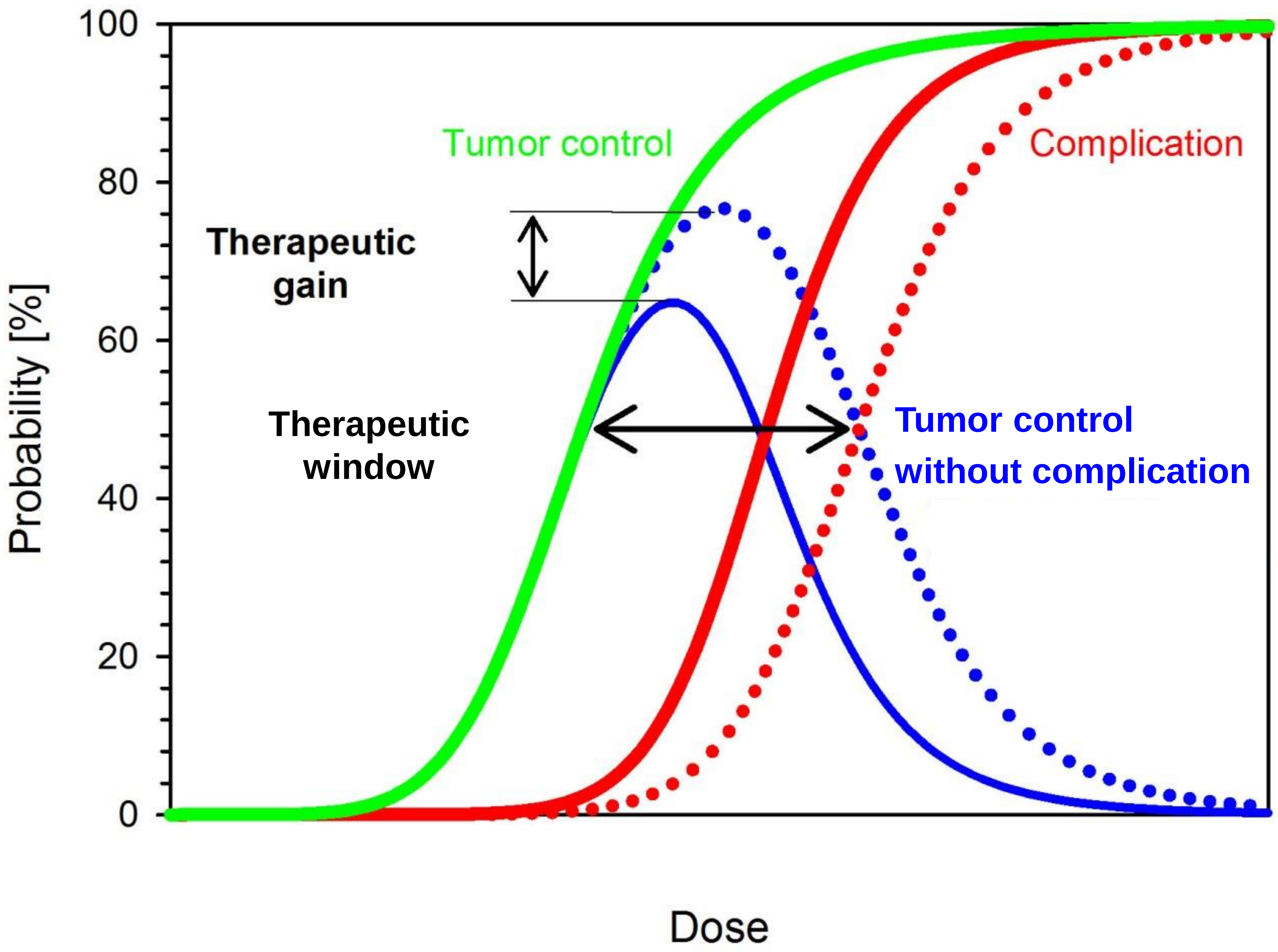
Therapeutic window



Widening the therapeutic window

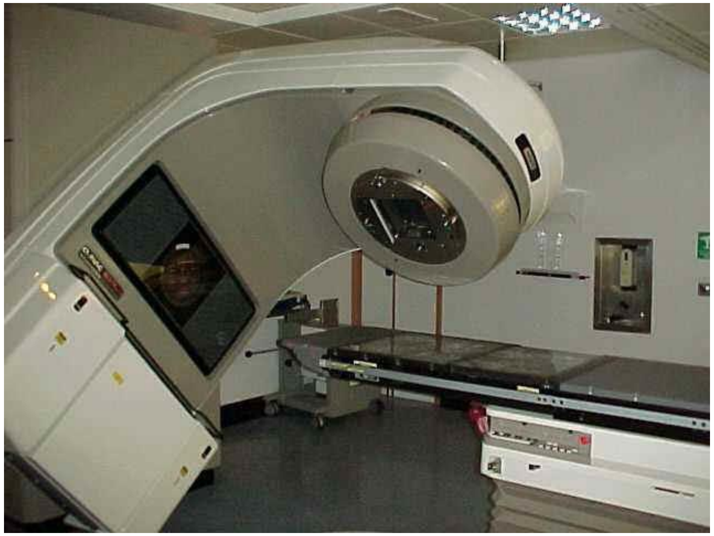
- drugs which decrease the radioresistance of tumors
- drugs which reoxygenate the tumor
- drugs which radioprotect the normal tissue but not the tumor

or varying the radiation type

- high-LET irradiation with high doses in the tumor and less normal tissue toxicity

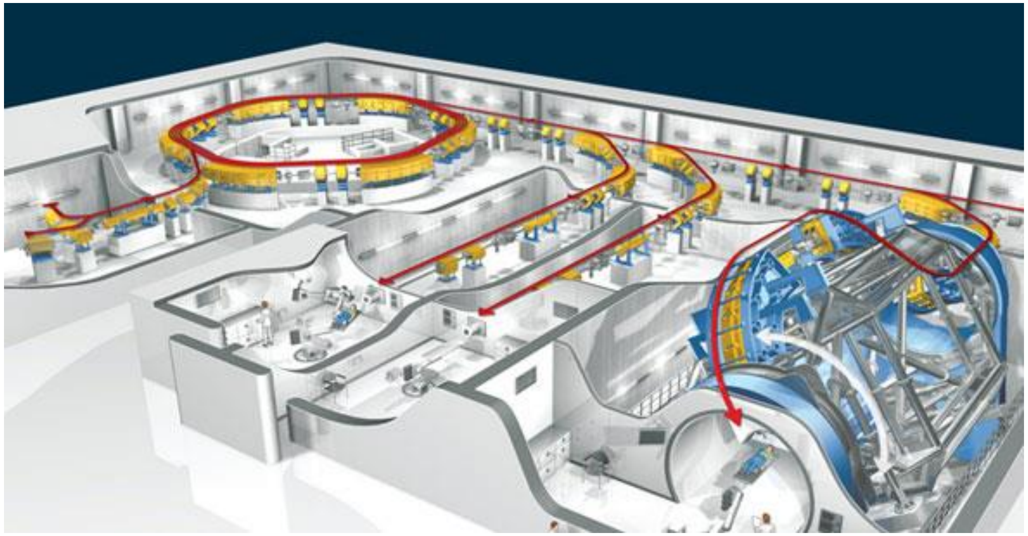
Radiation type

Photons linear accelerator
Low LET (< 20 keV/µm)



www.psi.ch

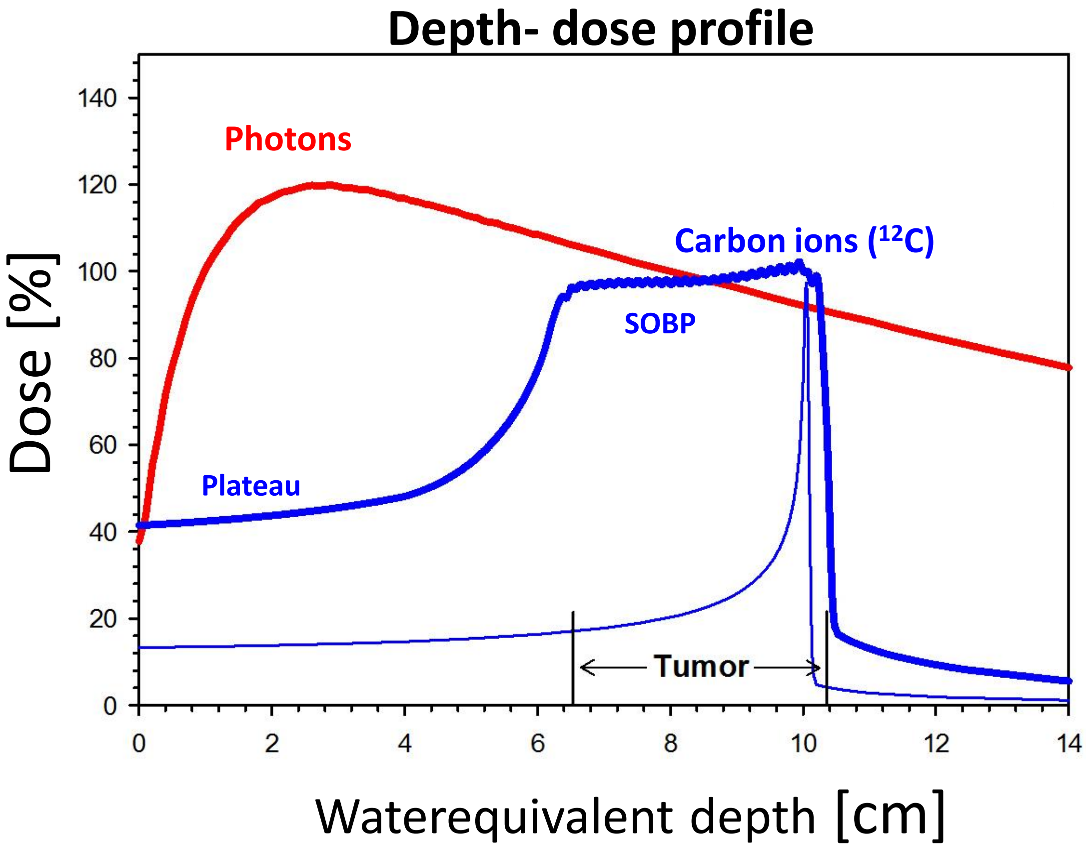
Particles e.g. protons, **carbon ions**
High LET (> 20-100 keV/µm)



HIT

Advantages of Carbon ions (^{12}C-ions)

Physical

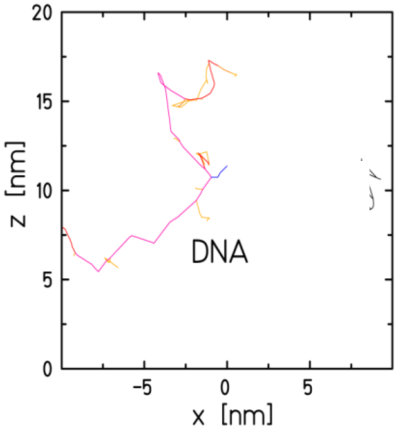


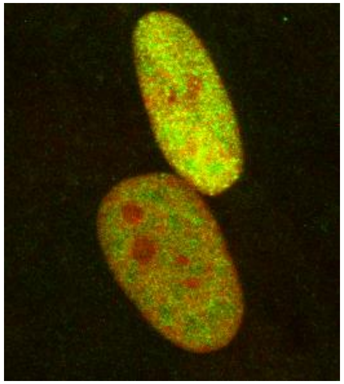
- inverted depth dose profile
- defined penetration depth
- less lateral scattering
- highest dose in SOBP

Advantages of Carbon ions (^{12}C-ions)

Biological

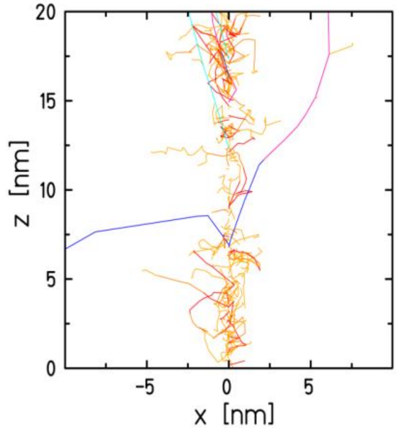
Ionization tracks | Damage in nucleus

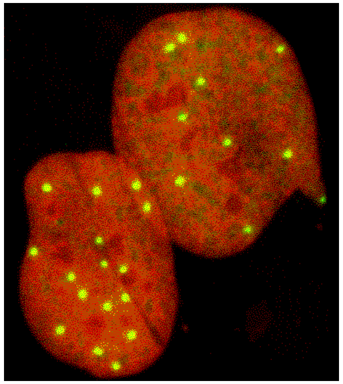




Photons: Low LET (< 20 keV/µm)

- Homogeneous dose deposition
- Sparsely ionizing photons



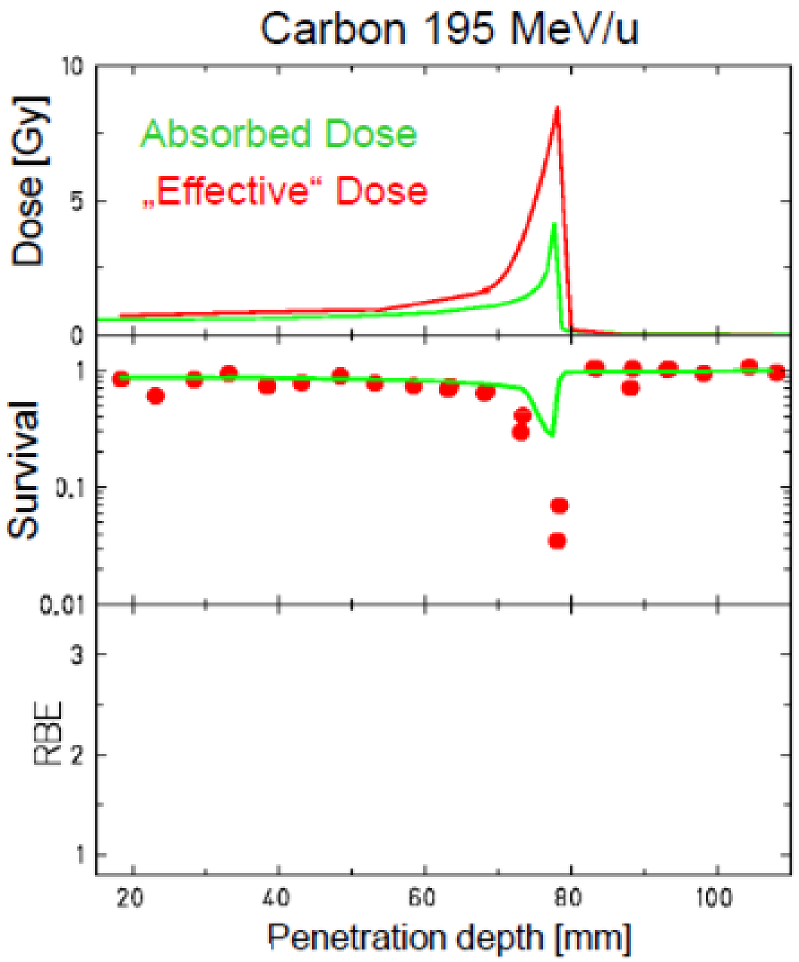


Carbon ions: High LET (> 20-100 keV/µm)

- Local deposition of high doses
- Densely ionizing particles

M. Scholz et al. Rad. Res. 2001 Immuno-flourescence image of the repair protein p21

Advantages of Carbon ions (^{12}C-ions)



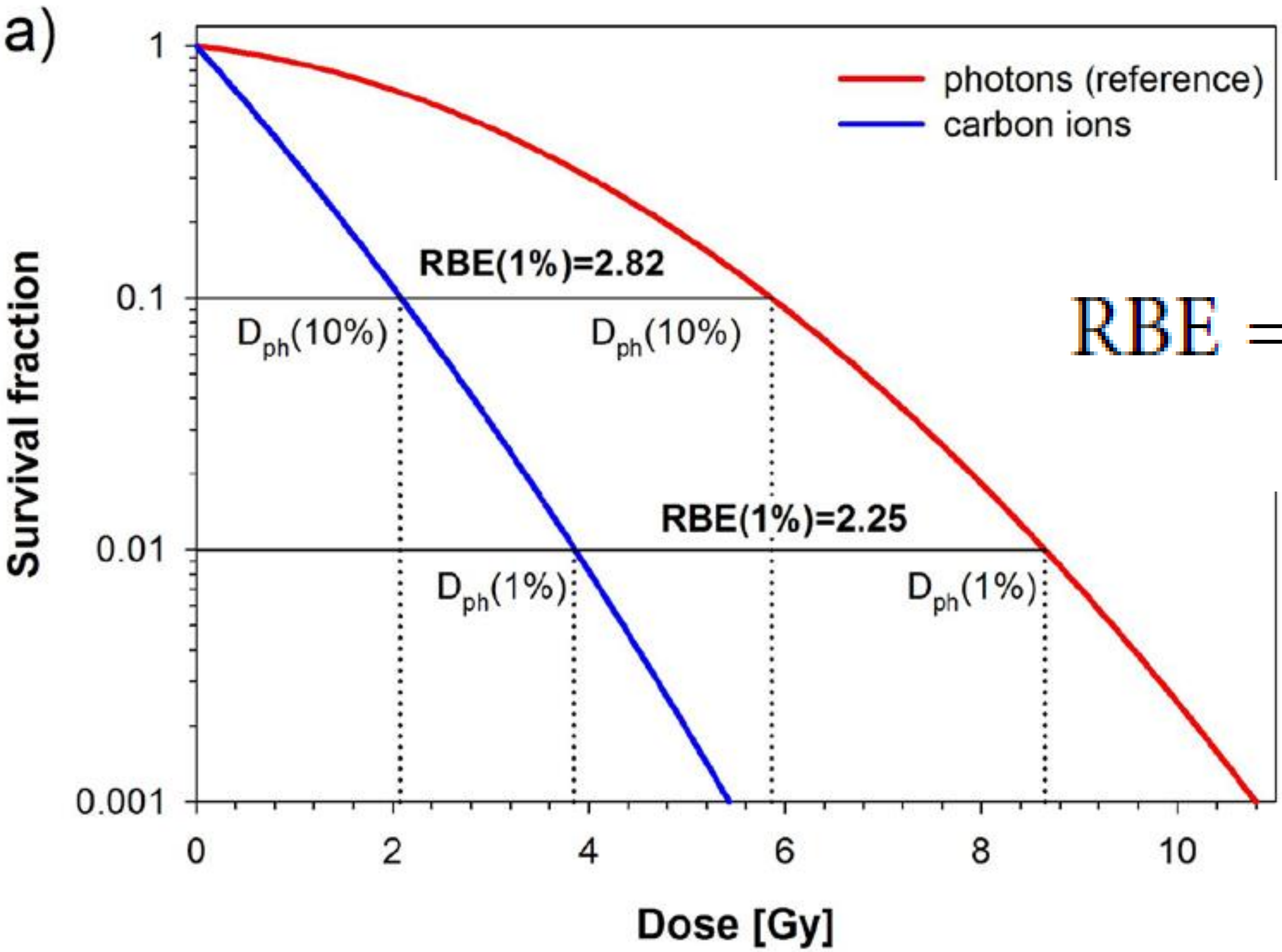
Data: GSI

Non-linear relationship between physical dose and cell killing

Relative **B**iological **E**ffectiveness depends on:

- Dose
- LET
- Repair capacity (α/β)
- Biological system (cell line, tissue)
- Biological endpoint (early, late, method of detection)

The relative biological effectiveness (RBE)



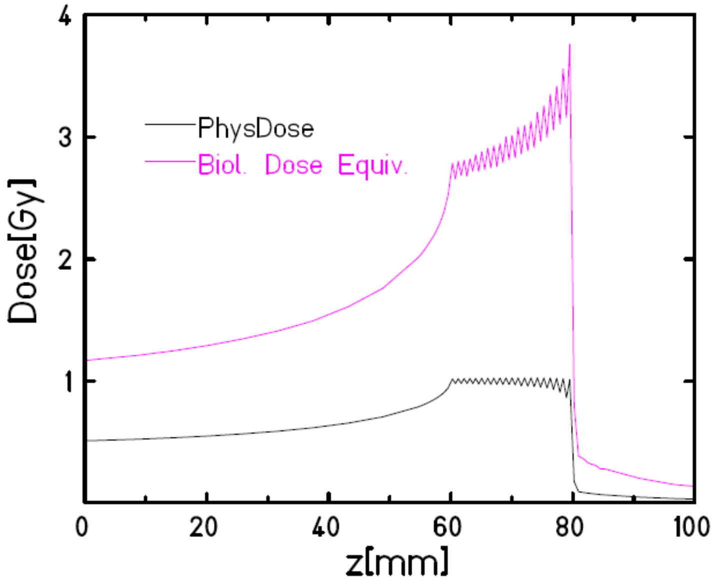
$$\mathrm{RBE} = \left.\frac{D_{\mathrm{ph}}}{D_{\mathrm{ion}}}\right|_{\mathrm{isoeffect}}$$

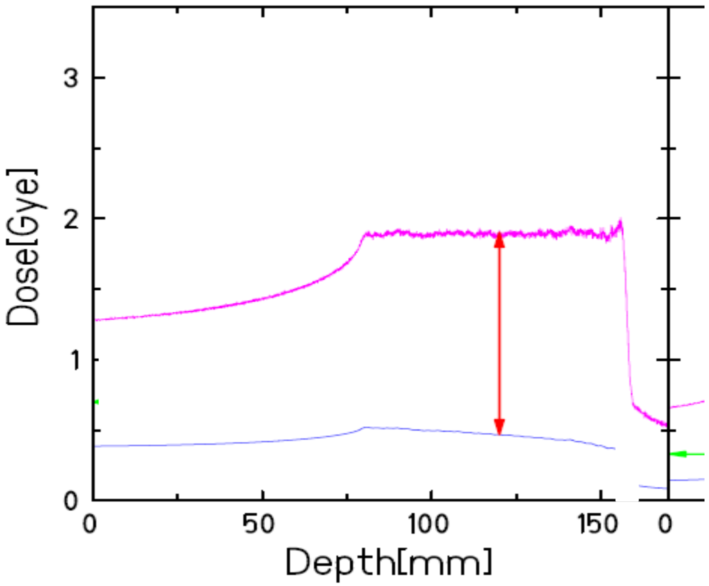
Karger CP, PMB 2018

Radiobiological models

RBE model

Computation of physical dose → Biological dose





Radiobiological models

1. **Mixed beam model**
   - Purely phenomenological approach
   - RBE calculated from cell survival curves of photons and ions using a specific effect value
   - Used for passive beam delivery (e.g. in Japan)

2. **Microdosimetric kinetic model (MKM)**
   - Follows microdosimetric principles
   - Number of lethal events in cell nucleus proportional to square of specific energy z
   - Used for active beam delivery (scanning) (e.g. in Japan)

3. **Local effect model (LEM)**
   - Uses microscopic features of the energy deposition of the ions around their tracks
   - Damage probability depends only on the amount of the locally deposited energy
   - Used for active beam delivery (HIT)

Karger CP, PMB 2018

Development of the local effect model

1997: **LEM I**

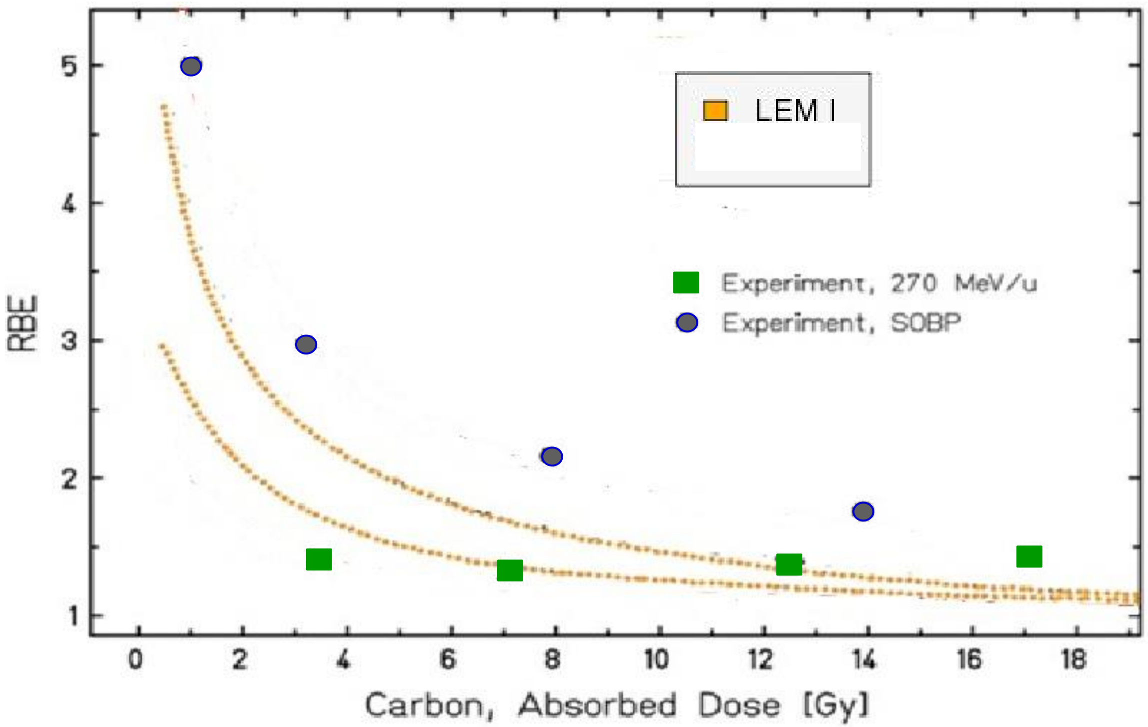
- Routine clinical use for more than 5000 patients

2010: **LEM IV**

- New track structure model
- Diffusion of radicals
- Clustered double strand breaks
- no clinical use so far

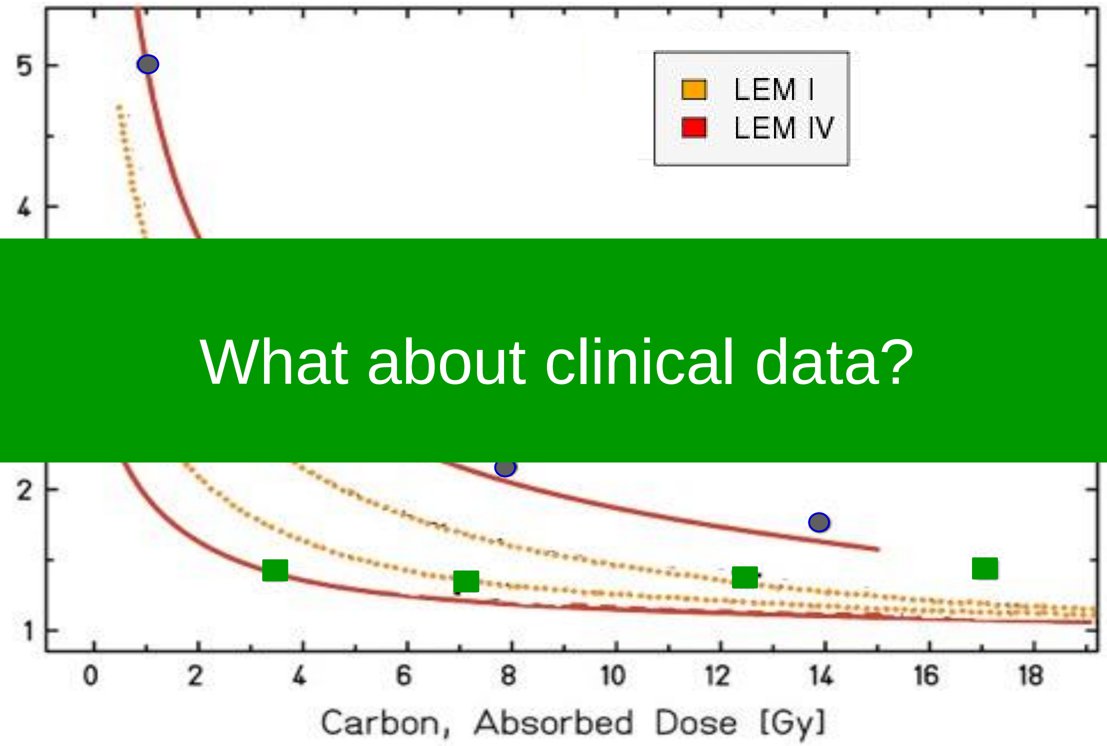
Scholz M (1997) Radiat Environ Biophys., Mozumder A (2003) J of Chemical Physics,
Elsässer T (2007) Rad Research, Elsässer T (2010) IJROBP

Experimental comparison LEM I and LEM IV



Karger CP (2006) IJROBP

Experimental comparison LEM I and LEM IV



What about clinical data?

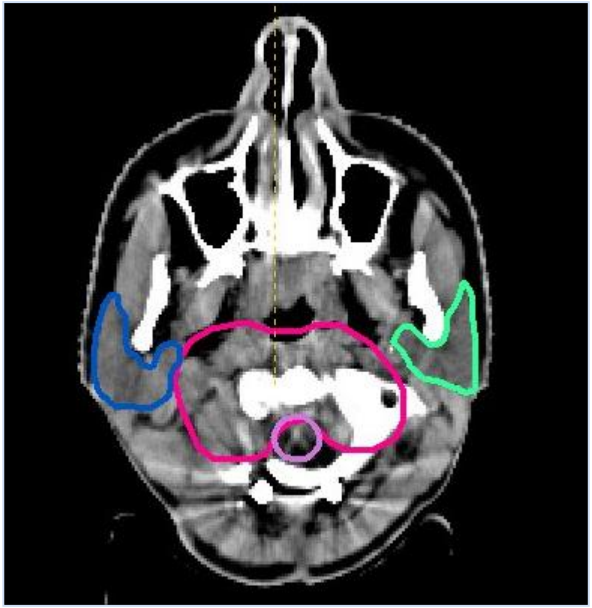
Aim of our study

Which model (LEM I or LEM IV)

describes the biological dose

in normal brain tissue more accurately?

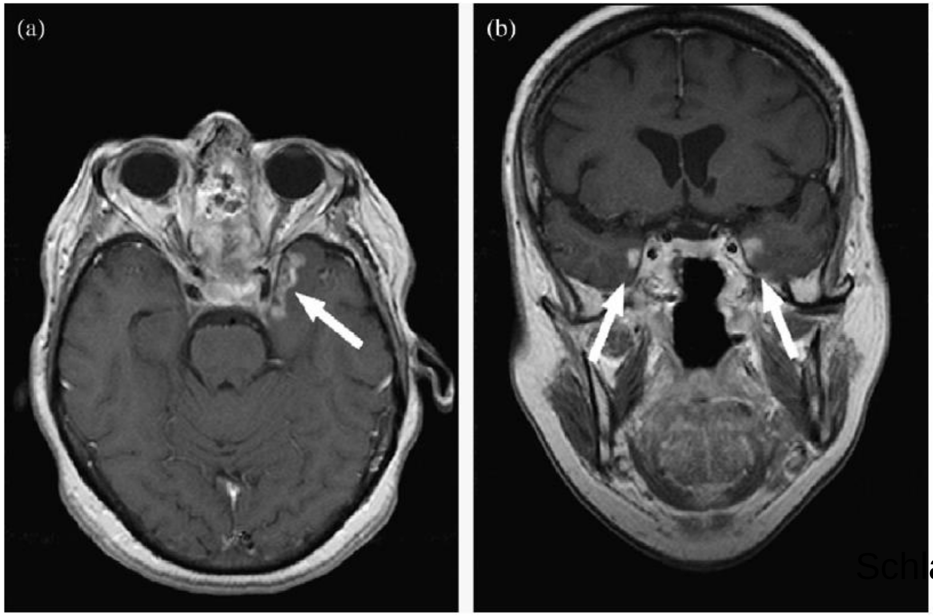
Patient collective



- 59 patients
- Low grade chordoma and chondrosarcoma
- Carbon ion radiotherapy at GSI in 2001 and 2002
- Median dose 75 Gy (RBE)

MRI follow-up

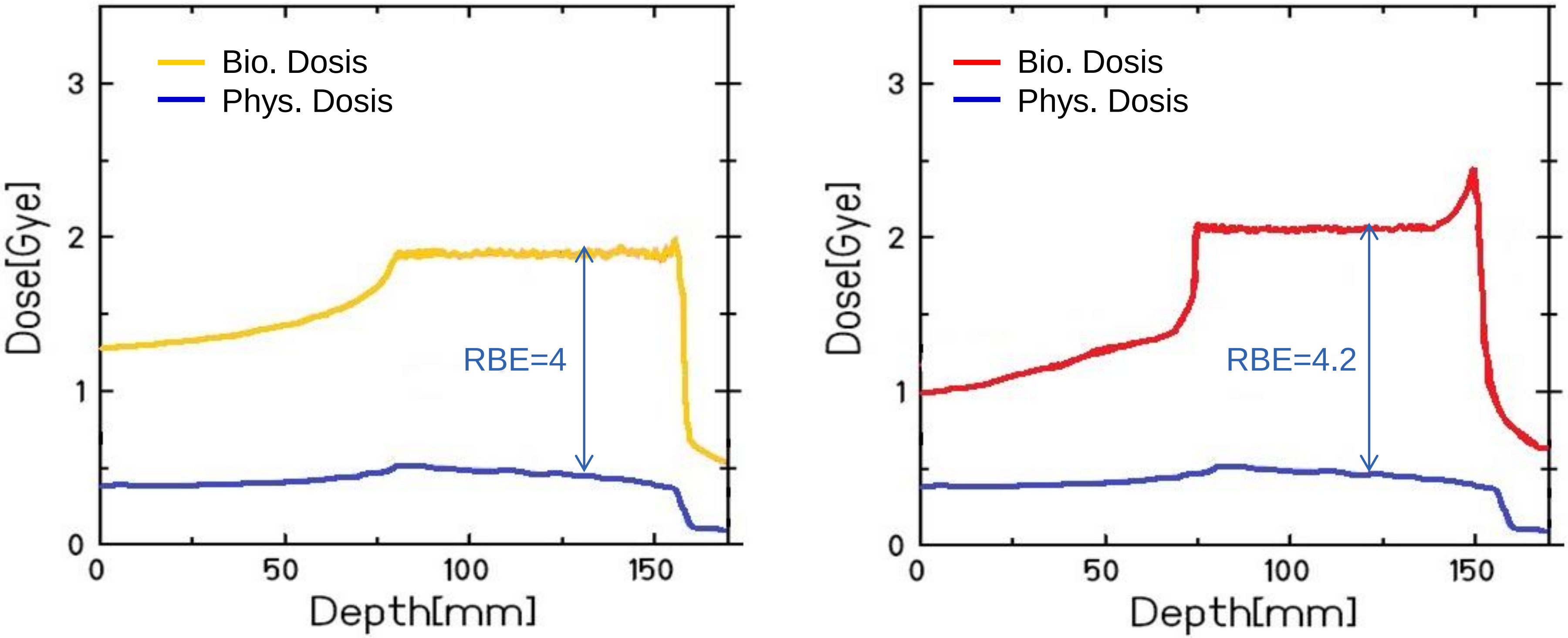
- 3 months, 6 months, 12 months and every year after treatment
- Median follow-up time: 2.5 years
- Detection of contrast enhancement (CE) in10 patients
- 5 patients unilateral, 5 patients bilateral
- 118 TL: 15 responders, 103 non-responders



Schlampp I et al (2010) IJROBP

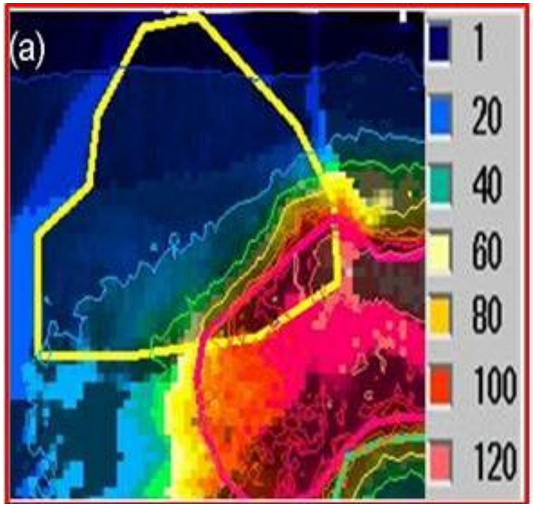
Recalculation of original clinical dose distributions

Original (LEM I) → Recalculated (LEM IV)

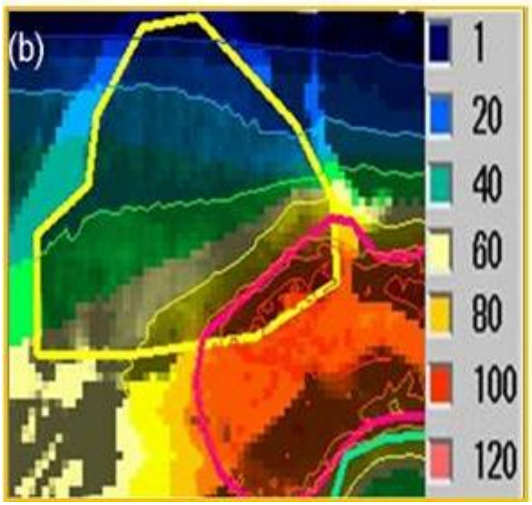


Comparison of dose distributions in the temporal lobe

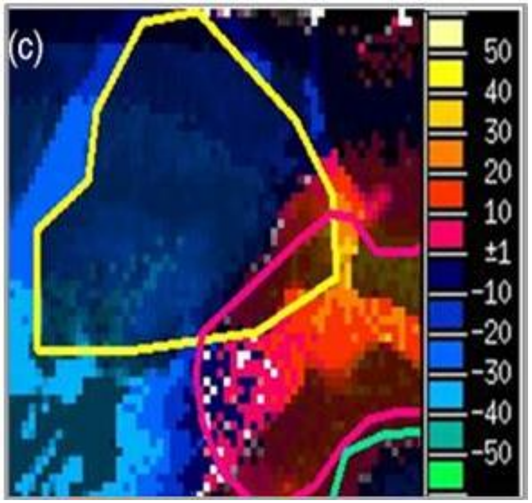
LEM IV



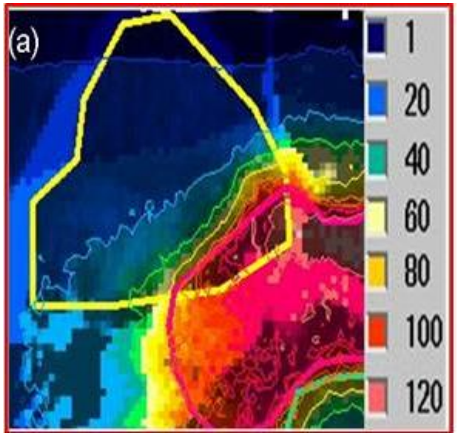
LEM I

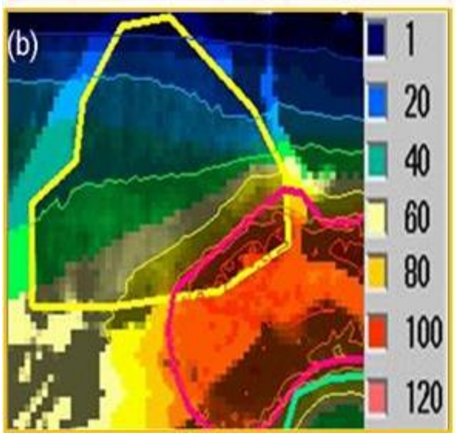


LEM IV - LEM I



Statistical analysis of dose-volume parameters





- D_{max}?
- D_{mean}?
- D_{median}?
- $V_{,D > 50, 60, 70, 80, 85\ Gy\ (RBE)}$?
- ...?

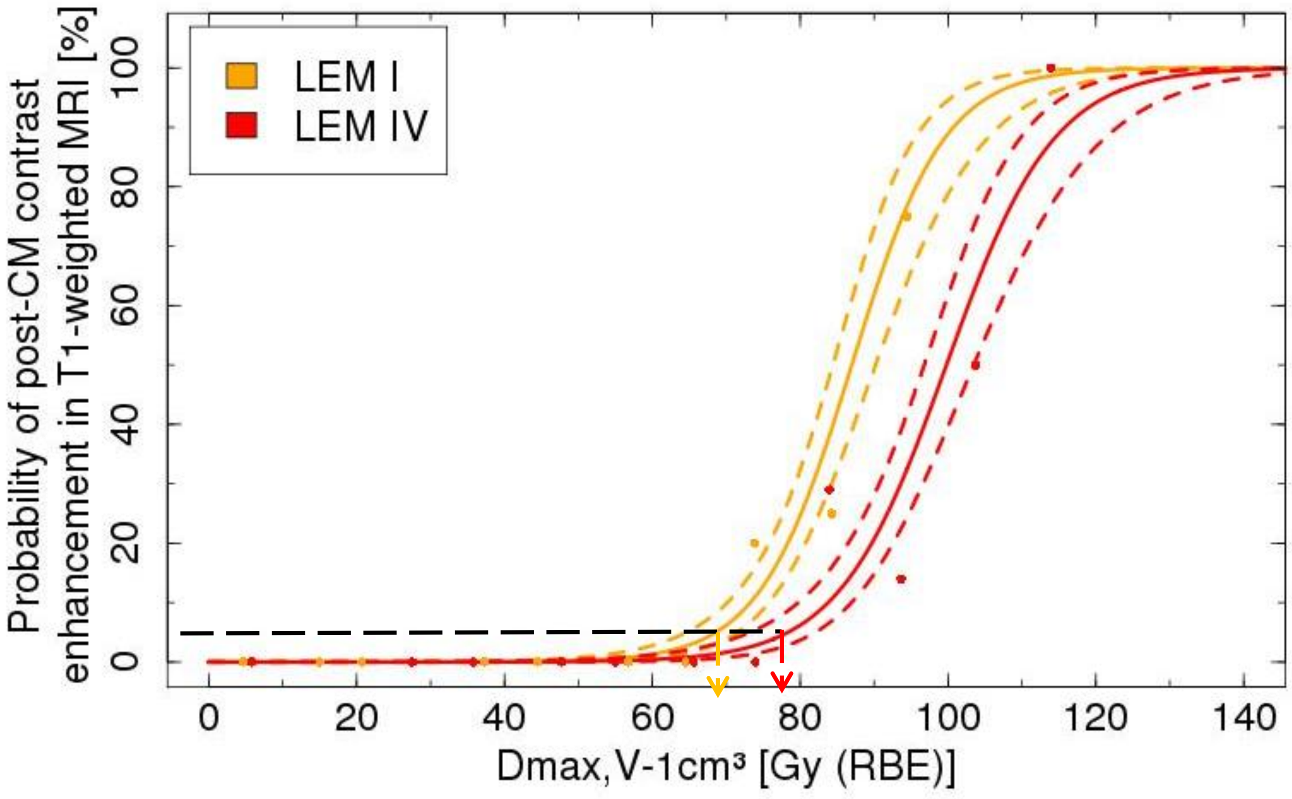
Statistical analysis

$D_{max,V\text{-}1cm^3}$ ist significant predictor for contrast enhancement

Correlation of contrast enhancement with dosimetric variables

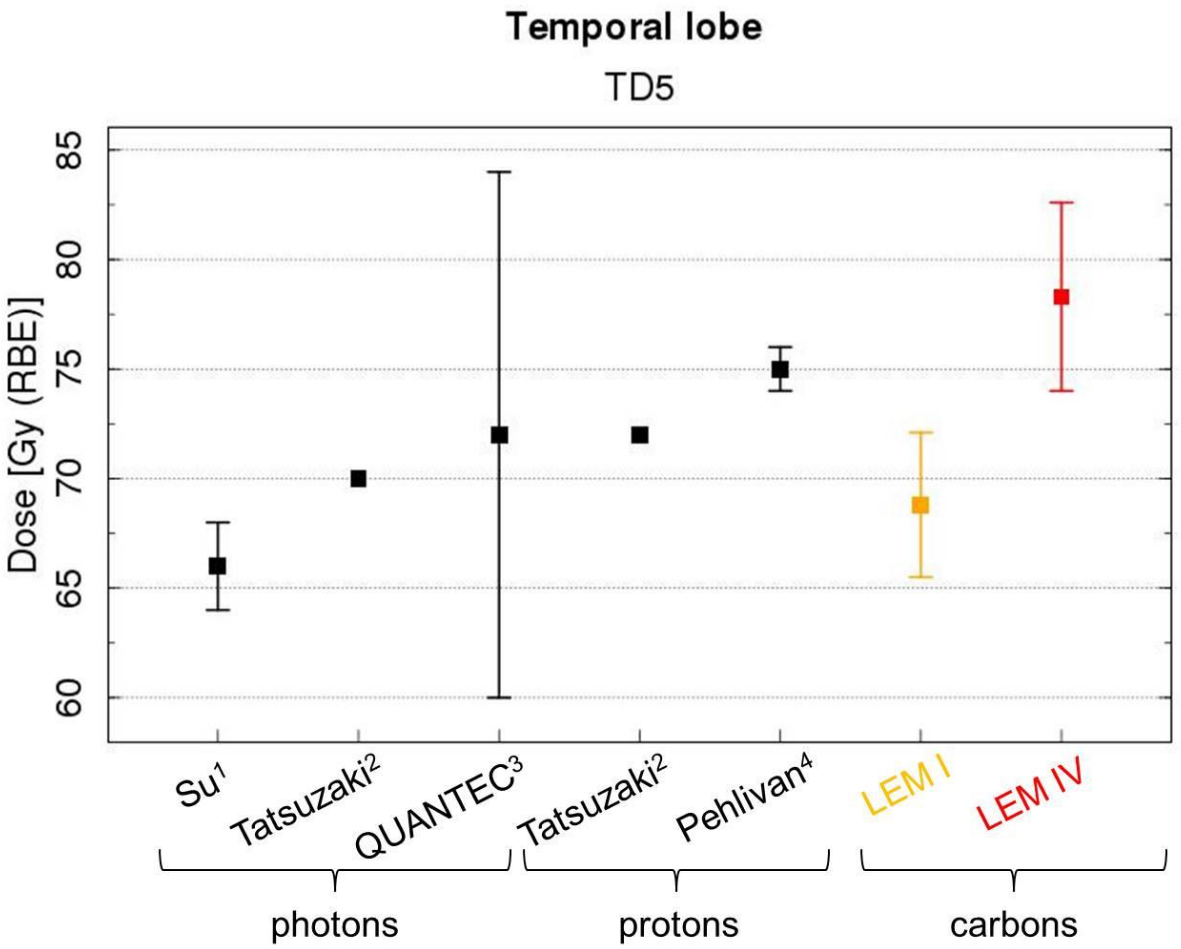
Patient	TL	KM	$D_{max,V-1cm^3}$ [Gy (RBE)]	
			LEM I	LEM IV
1	Right	1	100	105
	Left	1	102	107
2	Right	1	104	108
	Left	0	98	102
...	...	...	...	...

Dose-response curve



	LEM I	LEM IV
Tolerance dose 5 % [Gy(RBE)]	68.8 ± 3.3	78.2 ± 4.3

Comparison with literature data



[1]Su (2012), [2]Tatsuzsaki H (1991), [3]Lawrence (2010), [4]Pehlivan (2012), all: IJROBP

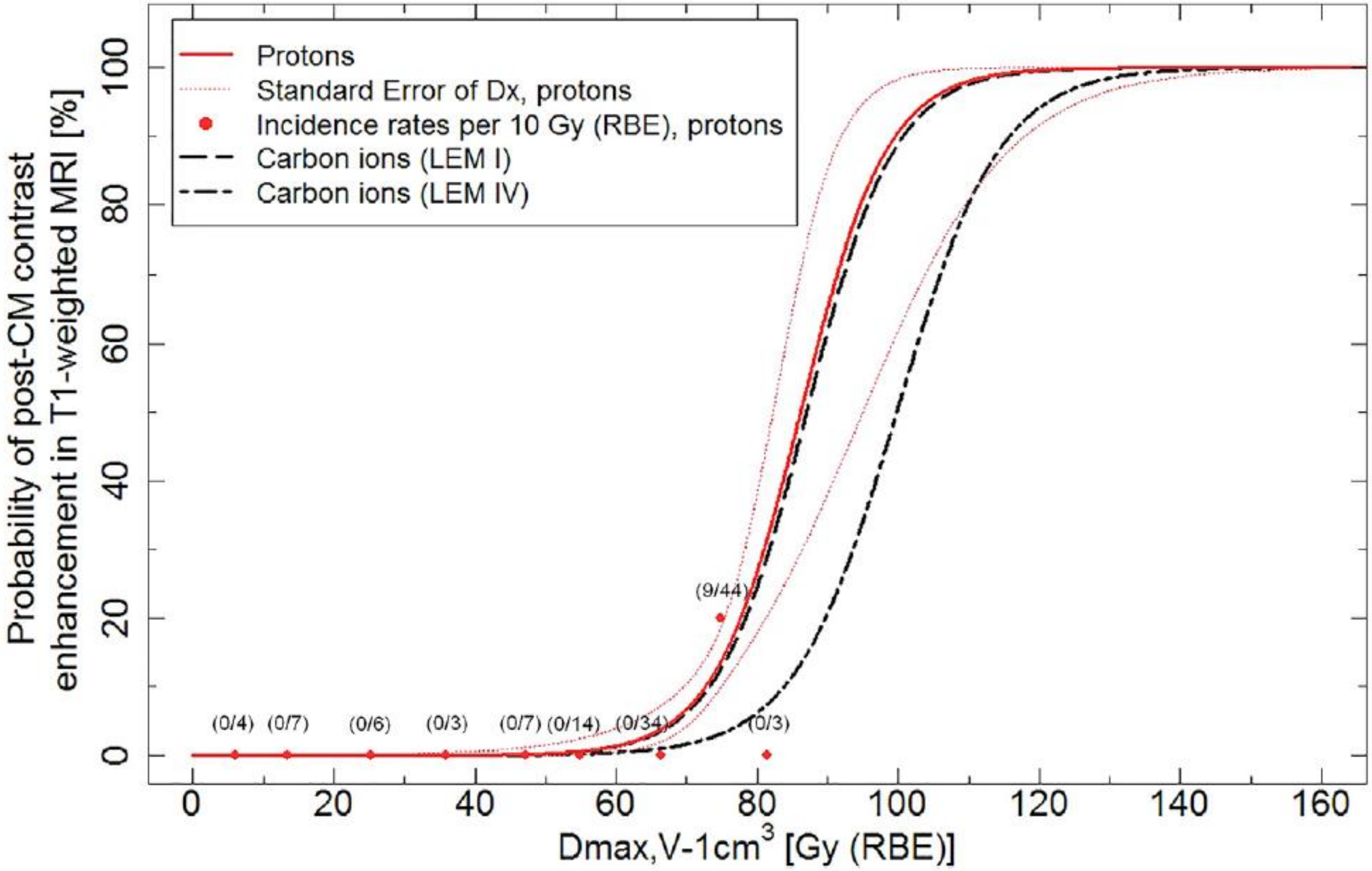
Comparison of LEM I and LEM IV with protons

Patient collective treated with protons at PSI, Villingen, Switzerland

Table 1
Characteristics of analyzed patients.

	Protons (PSI)	Carbon ions (GSI)
Number of patients (chordoma/chondrosarcoma)	61 (40/21)	59 (40/19)
Mean age [years]	45 (12–74)	50 (16–79)
Median prescribed dose [Gy (RBE)]	71.7 (63–74)	60 (60–75)
Median prescribed dose rescaled to 2 Gy per fraction [Gy (RBE)]	74 (53.9–75.5)	LEM I: 75 (75–82.5), LEM IV: 81.8 (81.8–89.3)
Mean follow-up time [months]	38 (14–92)	34 (4–79)
Number of patients with TLR [%] (unilateral/bilateral)	6 [9.7%] (3/3)	10 [16.9%] (5/5)
Overall TLR incidence	9 out of 122	15 out of 118

Comparison of LEM I and LEM IV with protons



Summary

1. Radiobiology is a very important factor for treatment outcome
2. The 5 R's of Radiobiology are:
   - Radiosensitivity
   - Repair/Recovery
   - Reoxygenation
   - Repopulation
   - Redistribution
3. The relative biological effectiveness of carbon ions depends on numerous factors (including LET, dose, type of irradiated cells…)
4. Several radiobiological models exist that show good clinical results. Finding the most accurate model remains a challenge.