HITRI plus
Heavy Ion Therapy Research Integration

RBE Models

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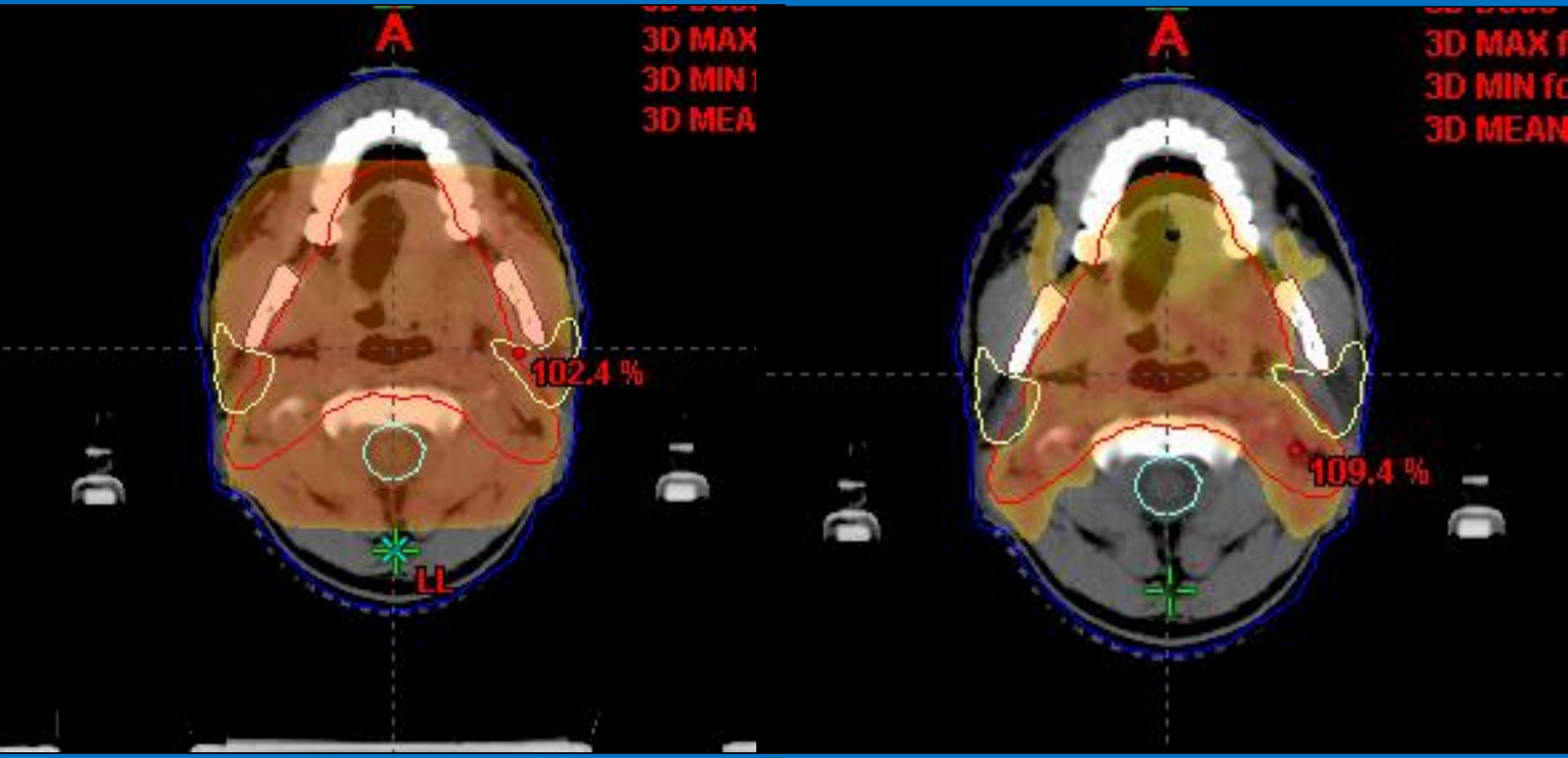
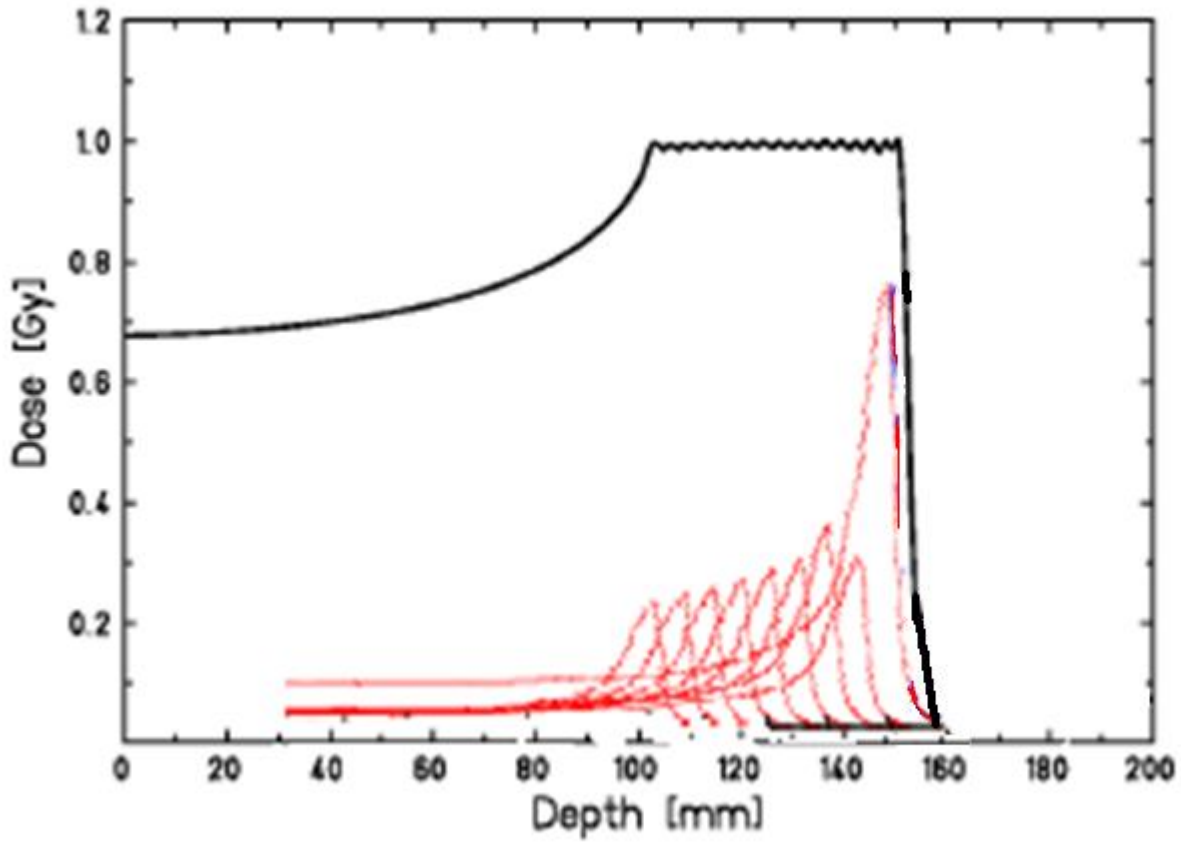
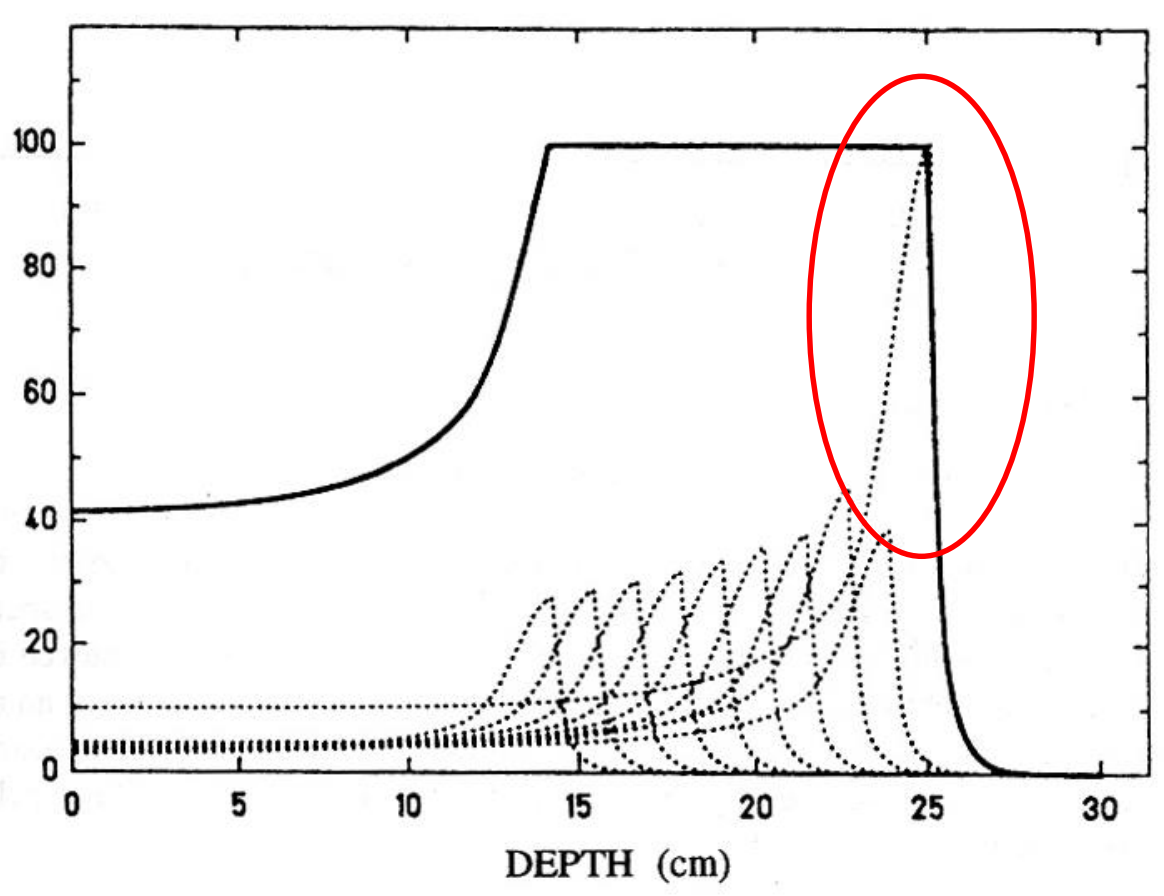
Photons : Dose → Resposne



Protons uniform physical dose
Not different form photons

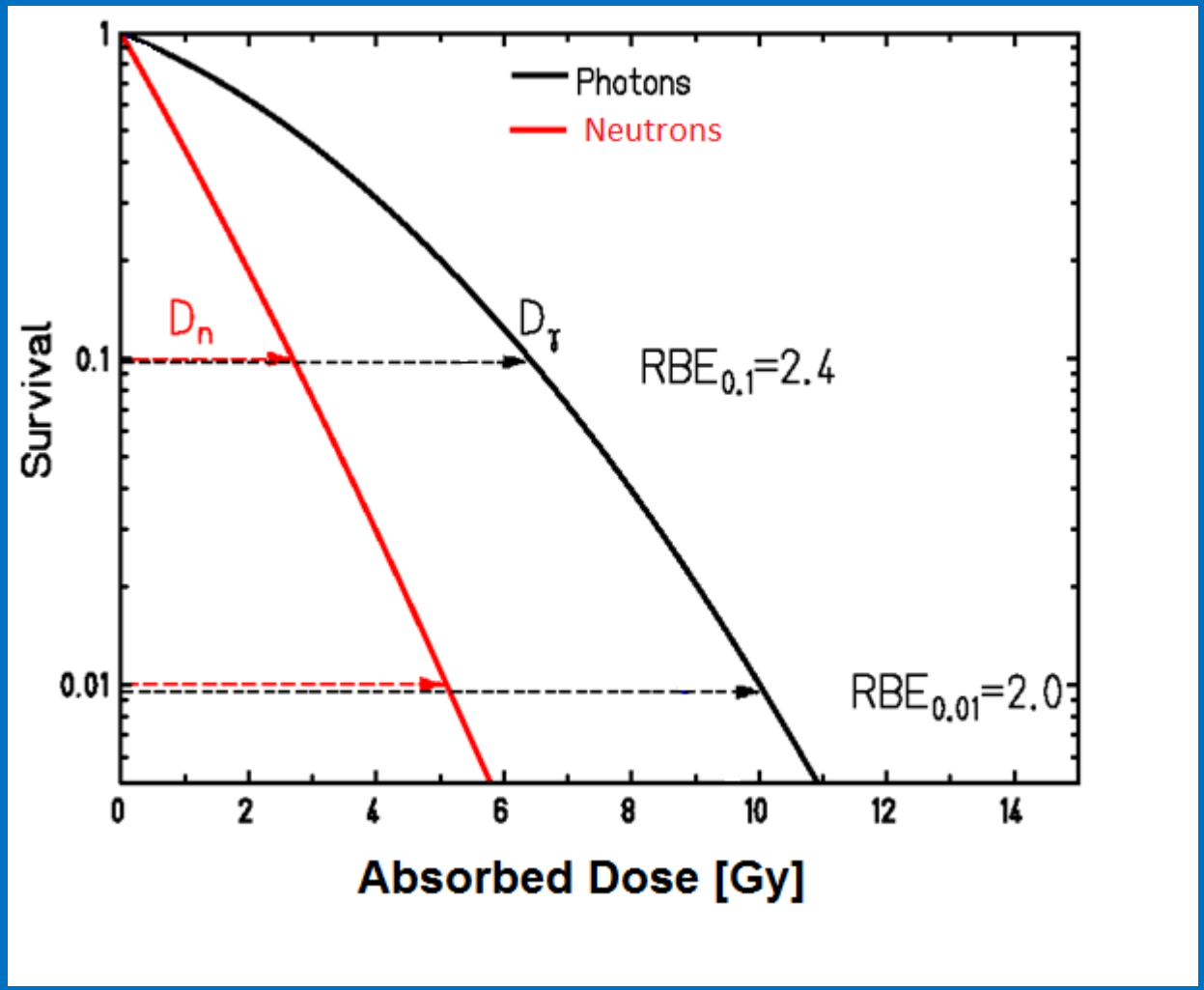


What if I give a uniform absorbed dose of carbon ions



More biological effect Whichever endpoint you choose

$$RBE = \left. \frac{D_{reference}}{D_{test}} \right|_{same\_effect}$$



Nuclear Instruments and Methods in Physics Research B 269 (2011) 664–670

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journal homepage: www.elsevier.com/locate/nimb

Therapeutic techniques applied in the heavy-ion therapy at IMP

Qiang Li [a,b,*], Lembit Sihver [c,d,e]

> 100 patients

Table 3
Skin acute and late side effects of the superficially-placed tumor patients treated with carbon ions at IMP.

No. of patients	Acute reaction (CTC)					Late reaction (CTC)				
	Grade					Grade				
	0	1	2	3	4	0	1	2	3	4
103	67	22	9	5	0	85	10	6	2	0

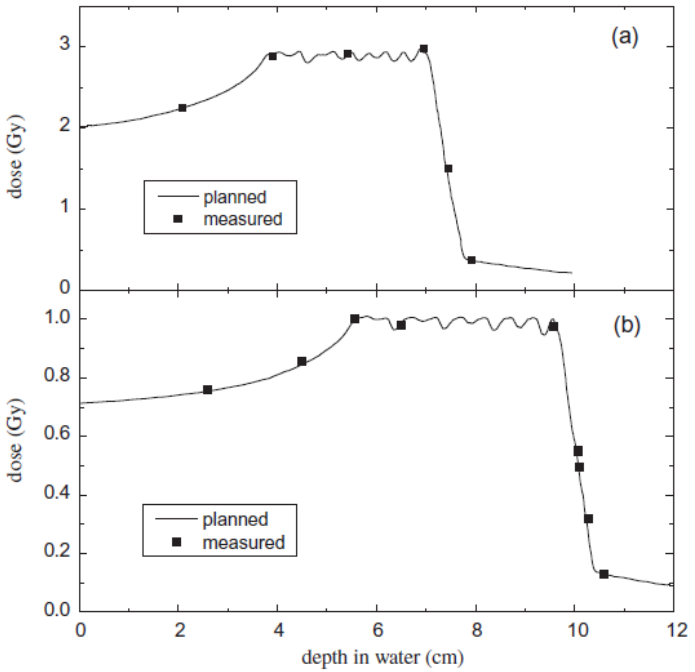


Fig. 3. Depth dose distributions for 195 (a) and 235 MeV/u (b) carbon-ion beams with 3 and 4 cm SOBPs generated by the mini-SOBP layer-stacking irradiation method respectively, where the planned depth-dose distributions were calculated using the current TPS at IMP.

→ All other systems used in the clinics are based on a very simple concept: **Less dose where there is higher LET**

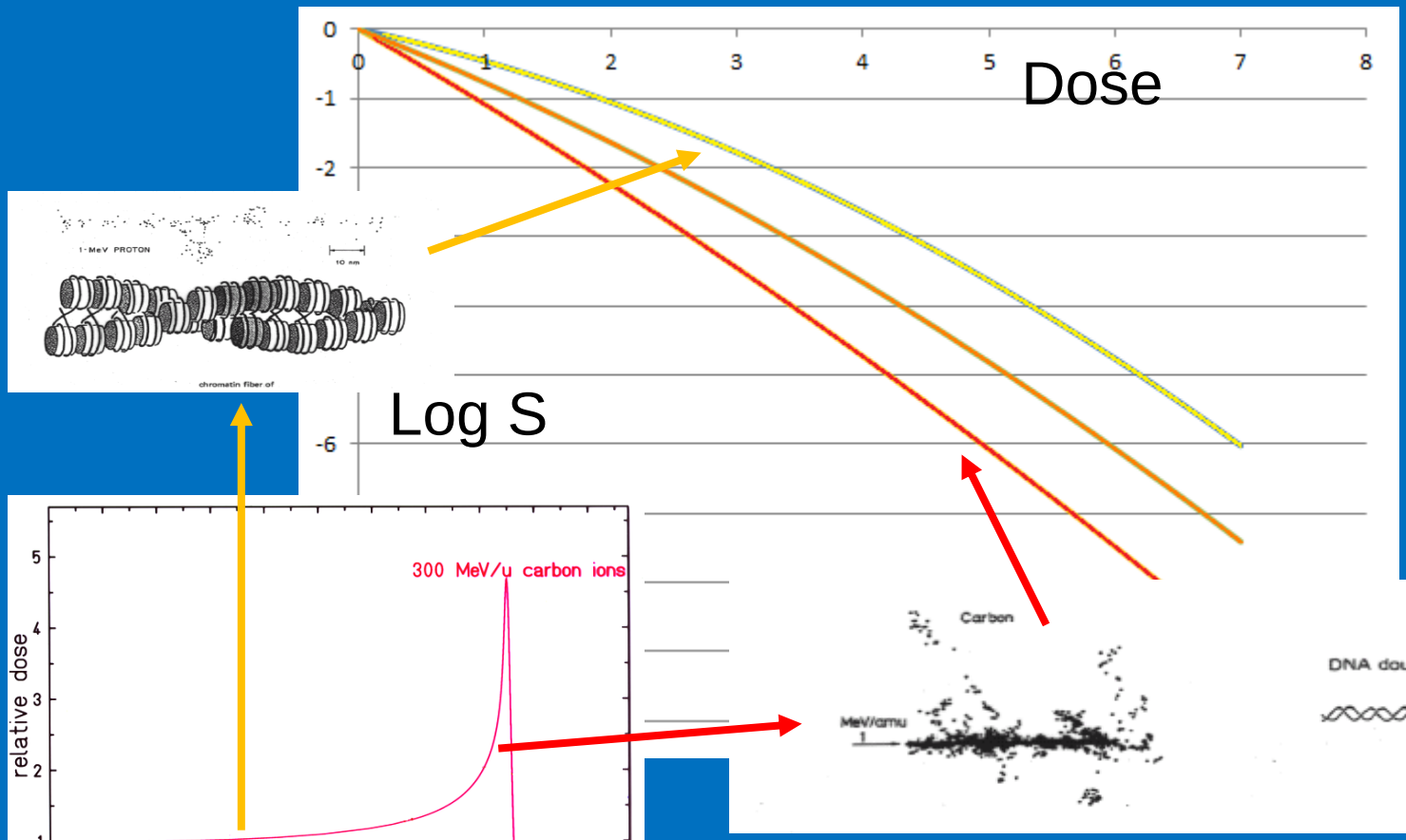
How much less? - How much more?

All clinical results from Japan (NIRS, Hyogo and Gunma) are based on **Kanai Model semi empirical model and then on mMKM**

All clinical results from Europe (GSI, HIT , CNAO and MedAustron) + SPHIC in China are based on **LEM I** (Local Effect Model) with an idealized chordoma cell line (α/β 2)

• Biophysiscal characteristics of Himac clinical irradiation system for heavy-ion radiation therapy
Kanai T et al. IJROBP 1999 – 44 (1)
• Examination of GyE system for Himac Carbon Therapy
Kanai T et al. IJROBP 2006 - 64 (2)

• Treatment planning for heavy-ion radiotherapy: calculation and optimization of biological effective dose
Kraemer M and Scholz M. PMB 2000 45 (11)



$$\alpha_{mix} = \frac{d_1}{D}\alpha_1 + \frac{d_2}{D}\alpha_2$$

$$\sqrt{\beta_{mix}} = \frac{d_1}{D}\sqrt{\beta_1} + \frac{d_2}{D}\sqrt{\beta_2}$$

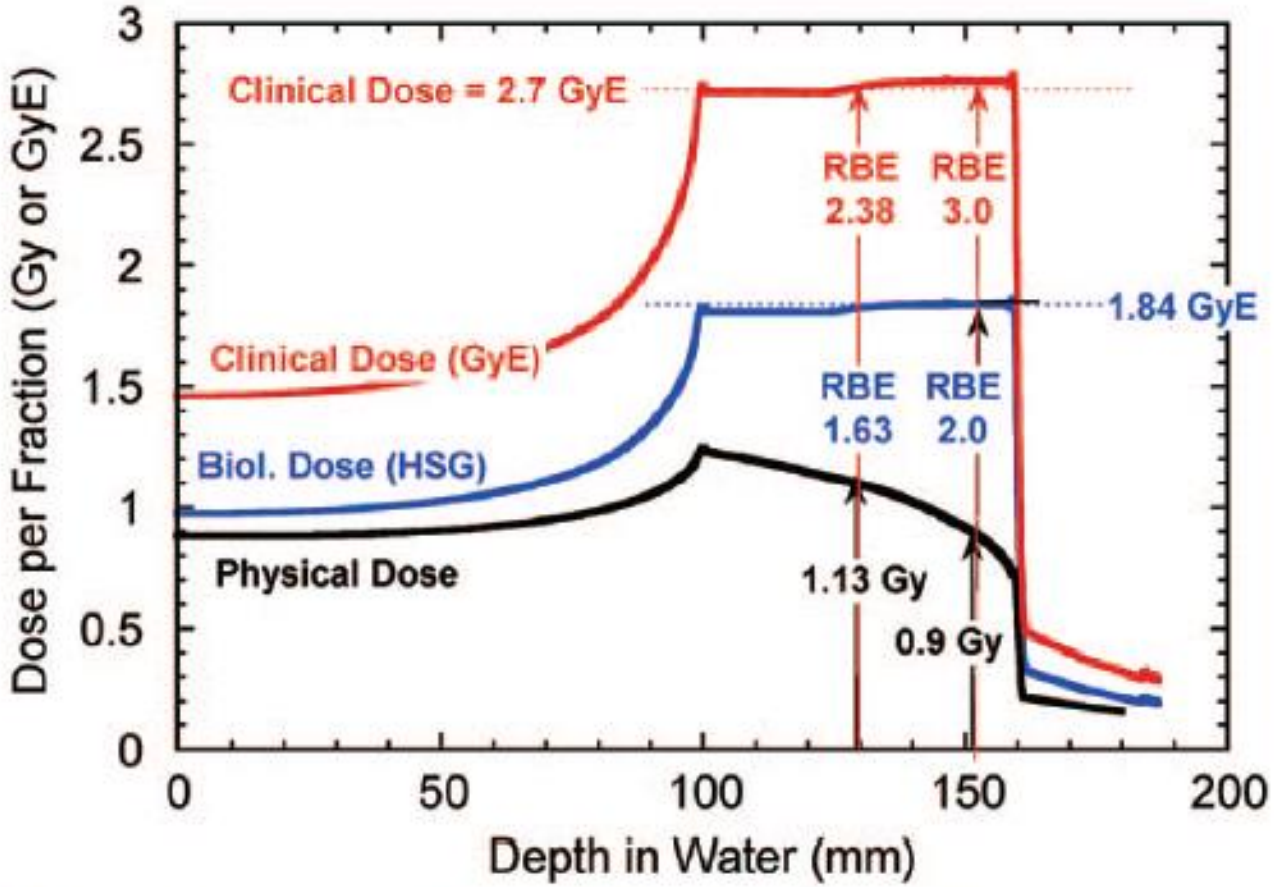


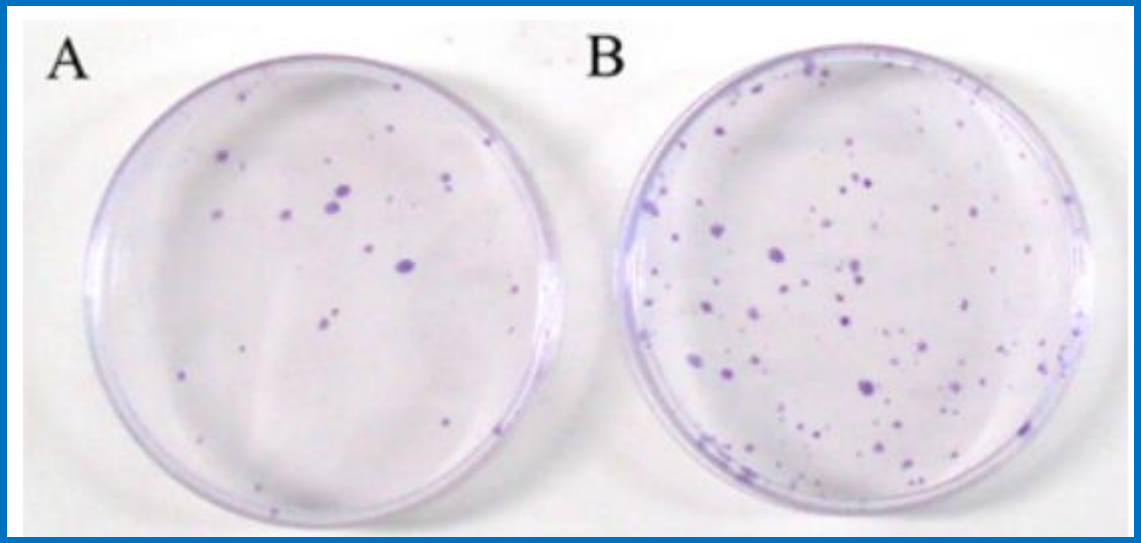
Fig. 5. Schematic method used to determine RBE at the center of SOBP for the clinical situation.

This talk

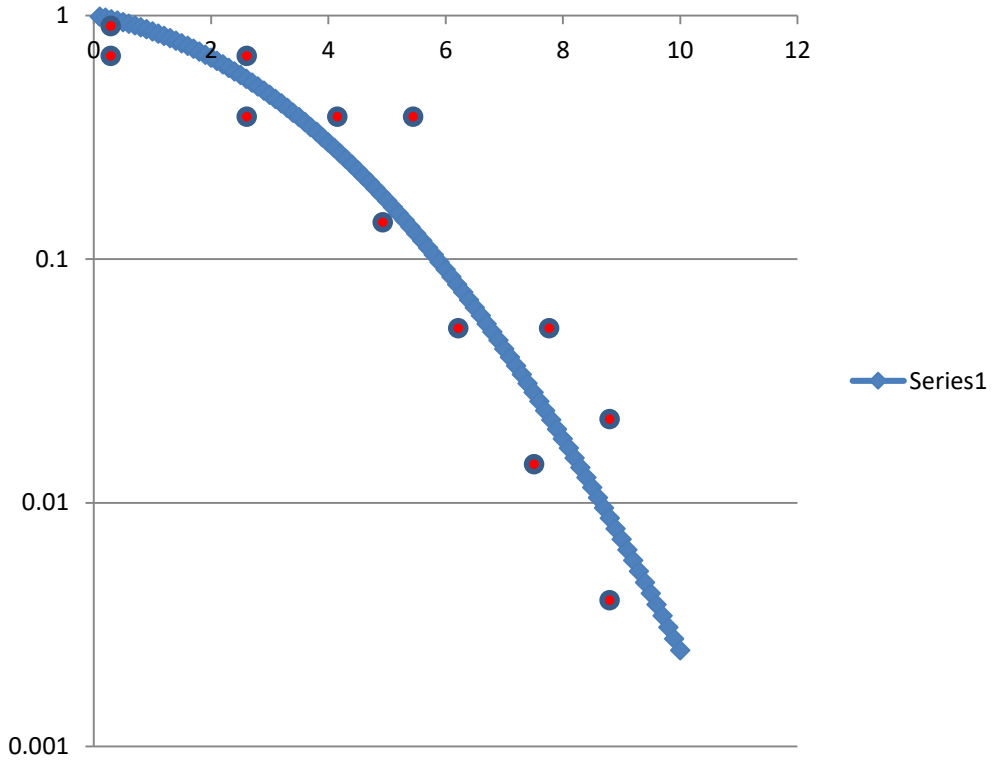
1. Fractionation
2. Micro vs Macroscopic endpoints
3. RBE models
4. RBE conversion and Clinical implications

Fractionation

LQ model for single exposure in vitro endpoints

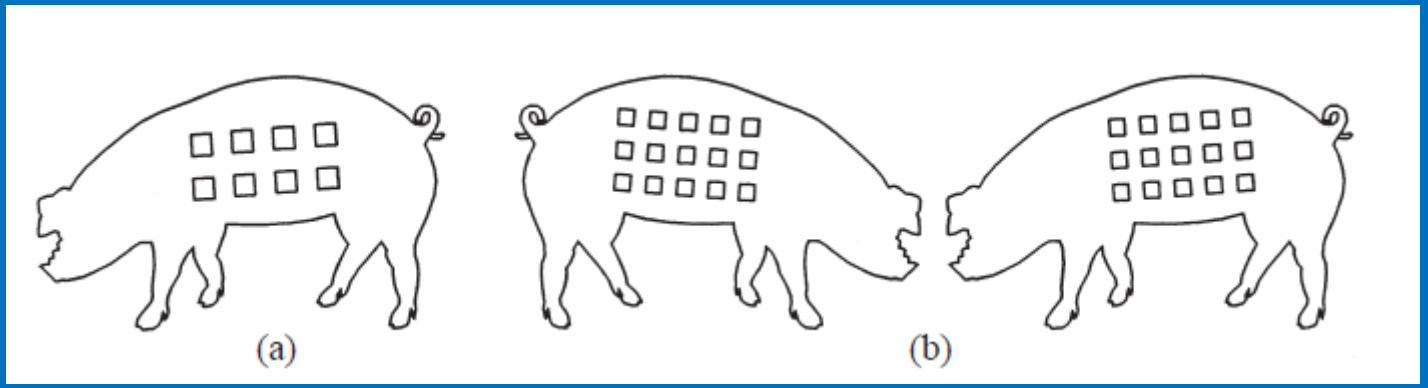


$$\log(S) = -\alpha D - \beta D^2$$



Log S

Gy



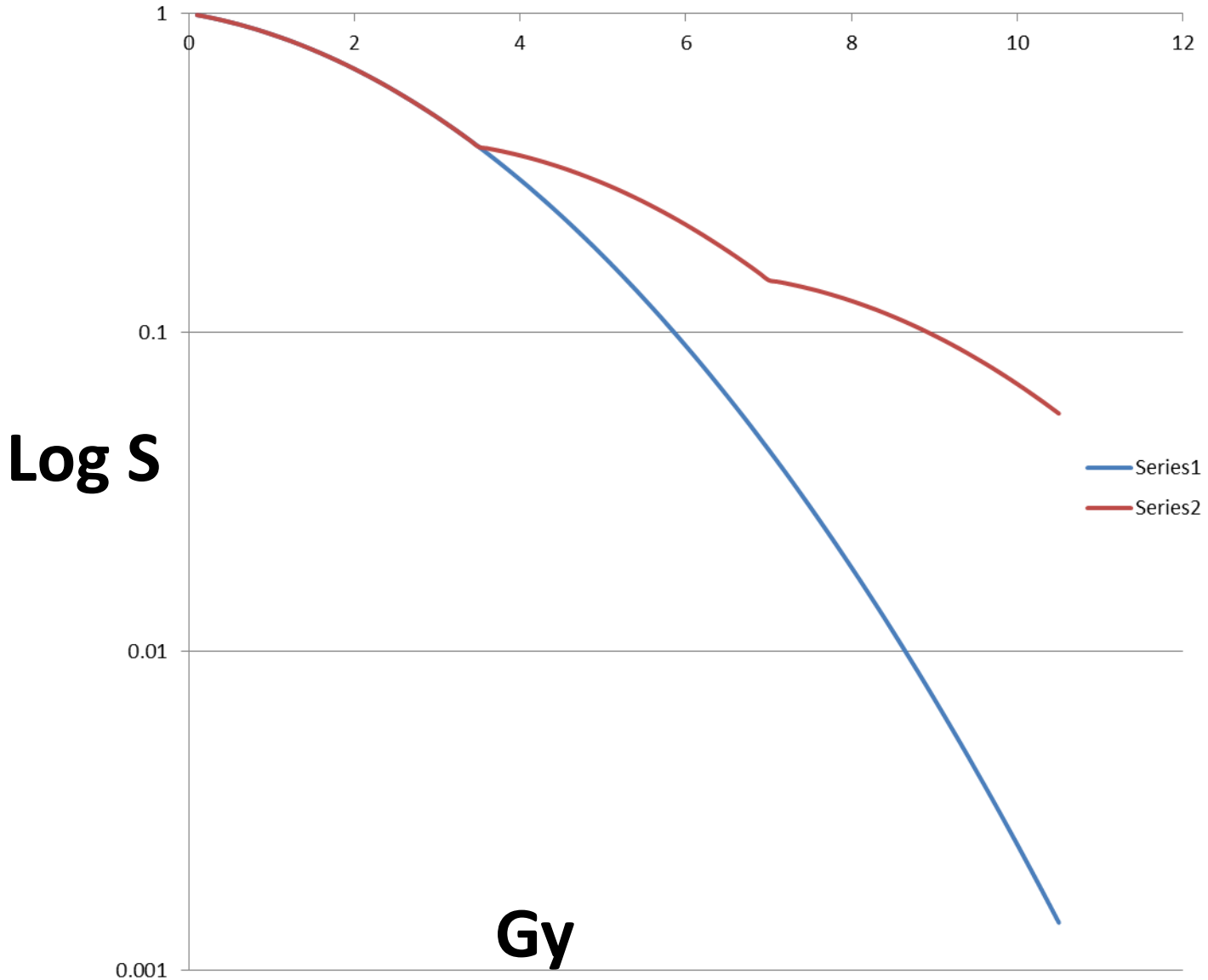
Twice a week, three observers assessed the irradiated skin fields using a scoring system that describes separately the acute epidermal reactions of erythema, and dry and moist desquamation, and the late dermal reactions of dusky mauve erythema and dermal necrosis. This scoring system was developed to study radiation reactions in the skin of Large White pigs [35]. Erythema was assessed at several levels: absent, mild, moderate and severe, with intermediate variants. Moist desquamation, dusky mauve erythema and dermal necrosis were assessed for their absence or presence in each field.

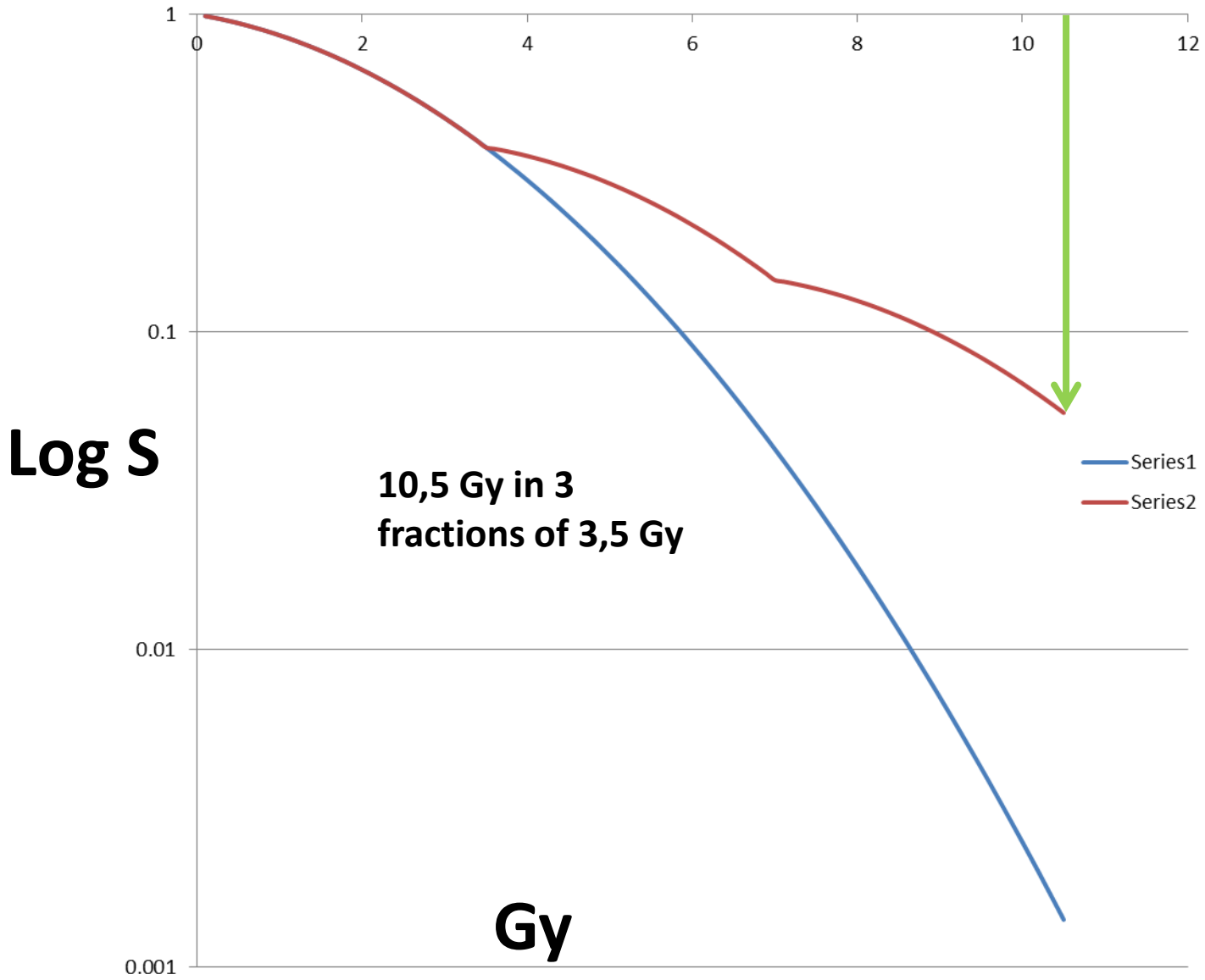
Hamm et al. British J. of Radiology 2000

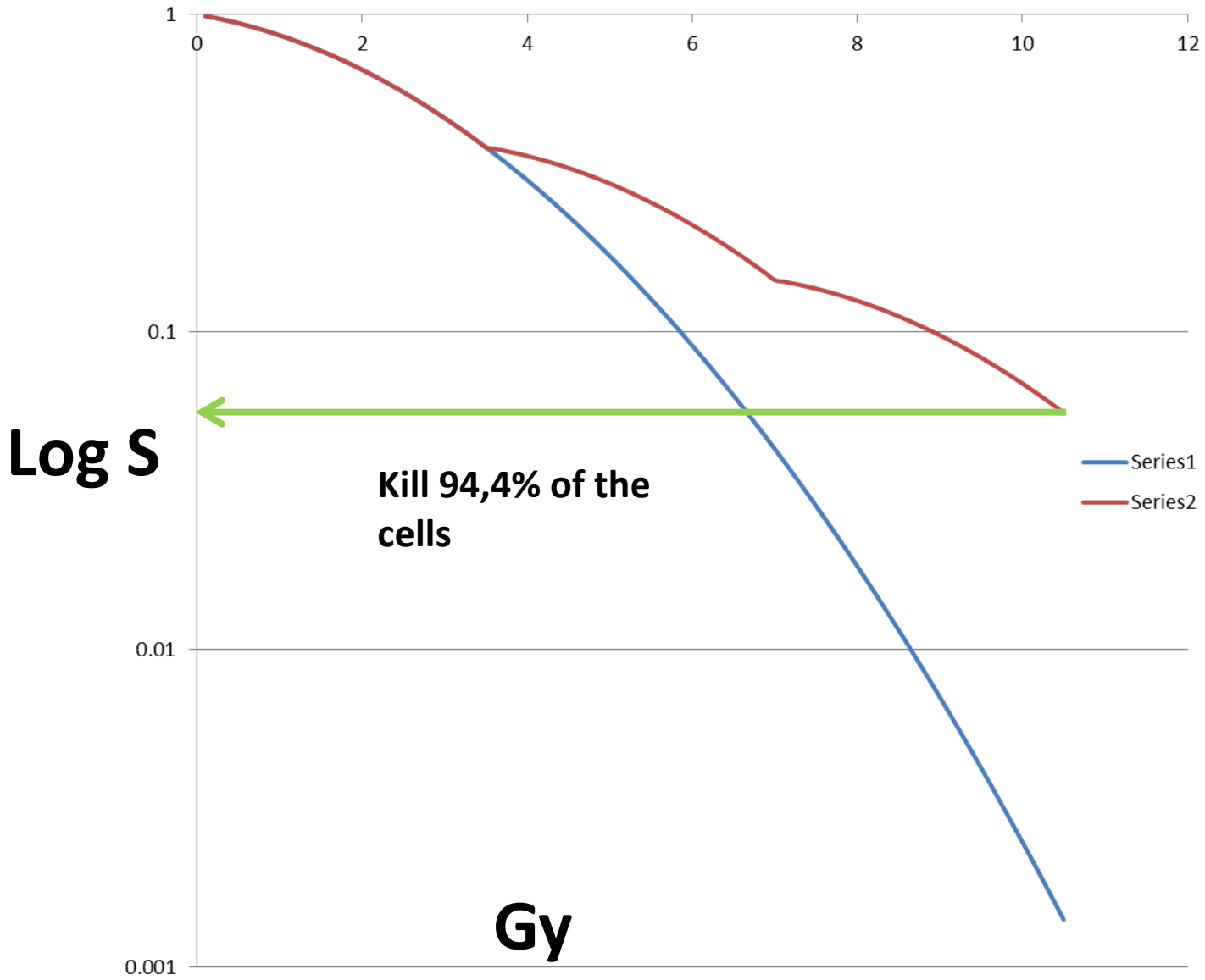
Fractionation schedules for breast cancer

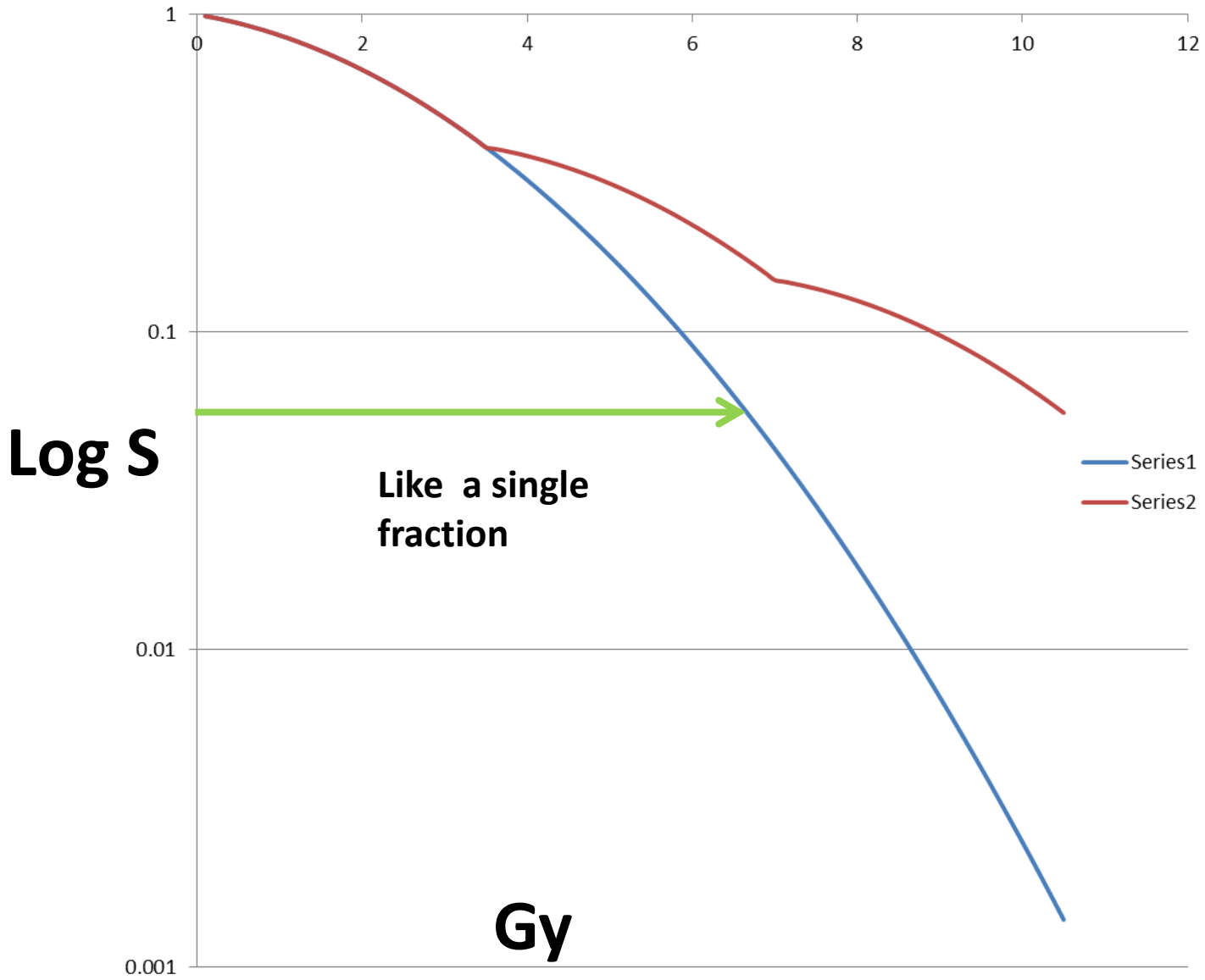
- 2 Gy x 25 fr → 50 Gy
- 2.25 x 20 fr → 45 Gy
- 2.67 x 15 fr → 40.05 Gy
- 6.0 x 5 fr → 30 Gy

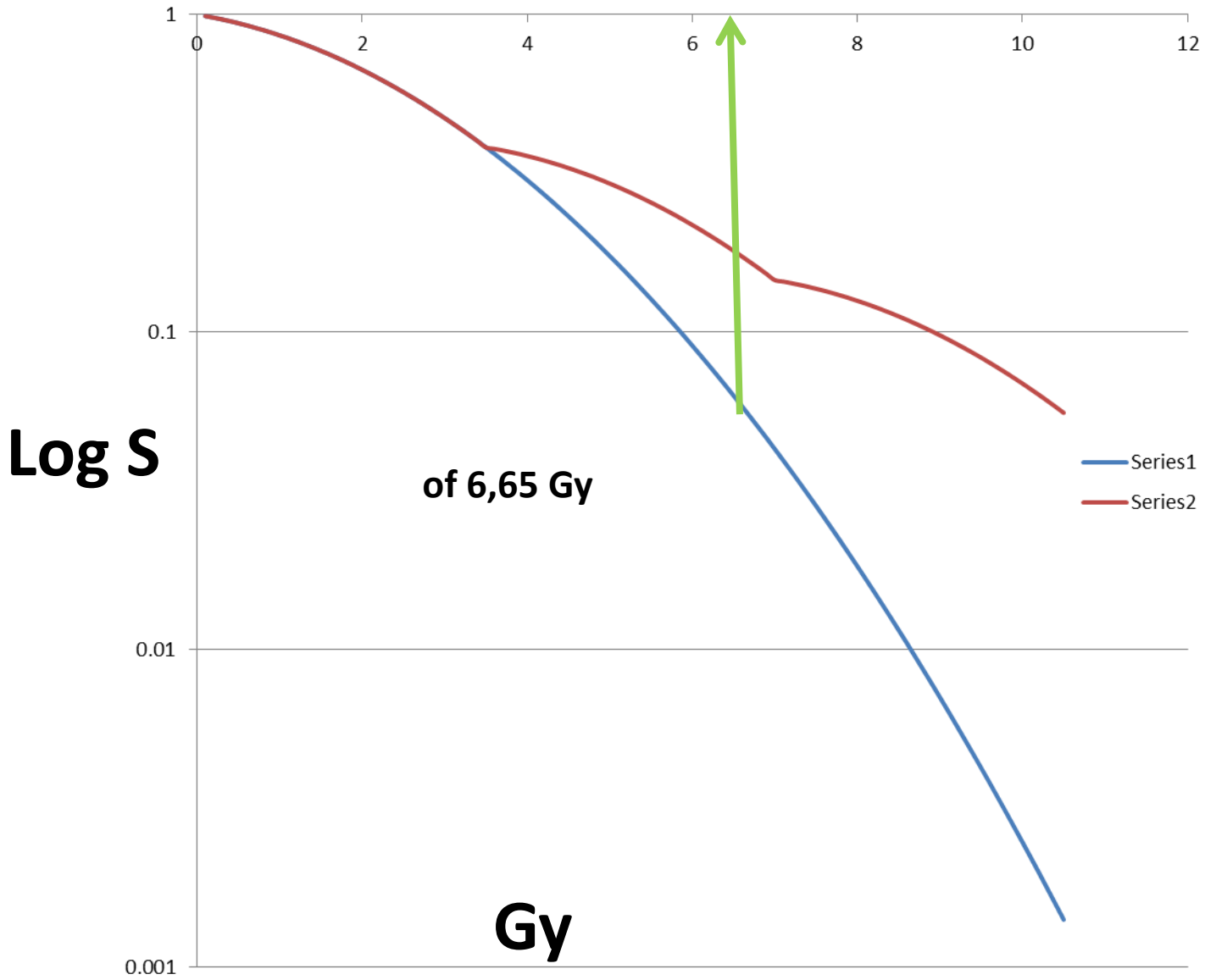
Endpoint	Alfa/beta
Erithema	7.5 -11.2 Gy
Tox (any tipe)	3.4 Gy (95% CI 2.3-4.5) (Start)
Fat necrosis	?
Local control (brest cancer)	4.1 Gy (95% CI 0.9-7.4) (Start)
teleangectasia	2.8 - 4.3 Gy


1
0
2
4
6
8
10
12
0.1
0.01
0.001
Log S
Gy
Series1
Series2


1
0.1
0.01
0.001
0
2
4
6
8
10
12
Log S
10,5 Gy in 3
fractions of 3,5 Gy
Gy
Series1
Series2


1
0
2
4
6
8
10
12
0.1
0.01
0.001
Log S
Kill 94,4% of the cells
Gy
Series1
Series2


1
0
2
4
6
8
10
12
0.1
0.01
0.001
Log S
Like a single fraction
Gy
Series1
Series2

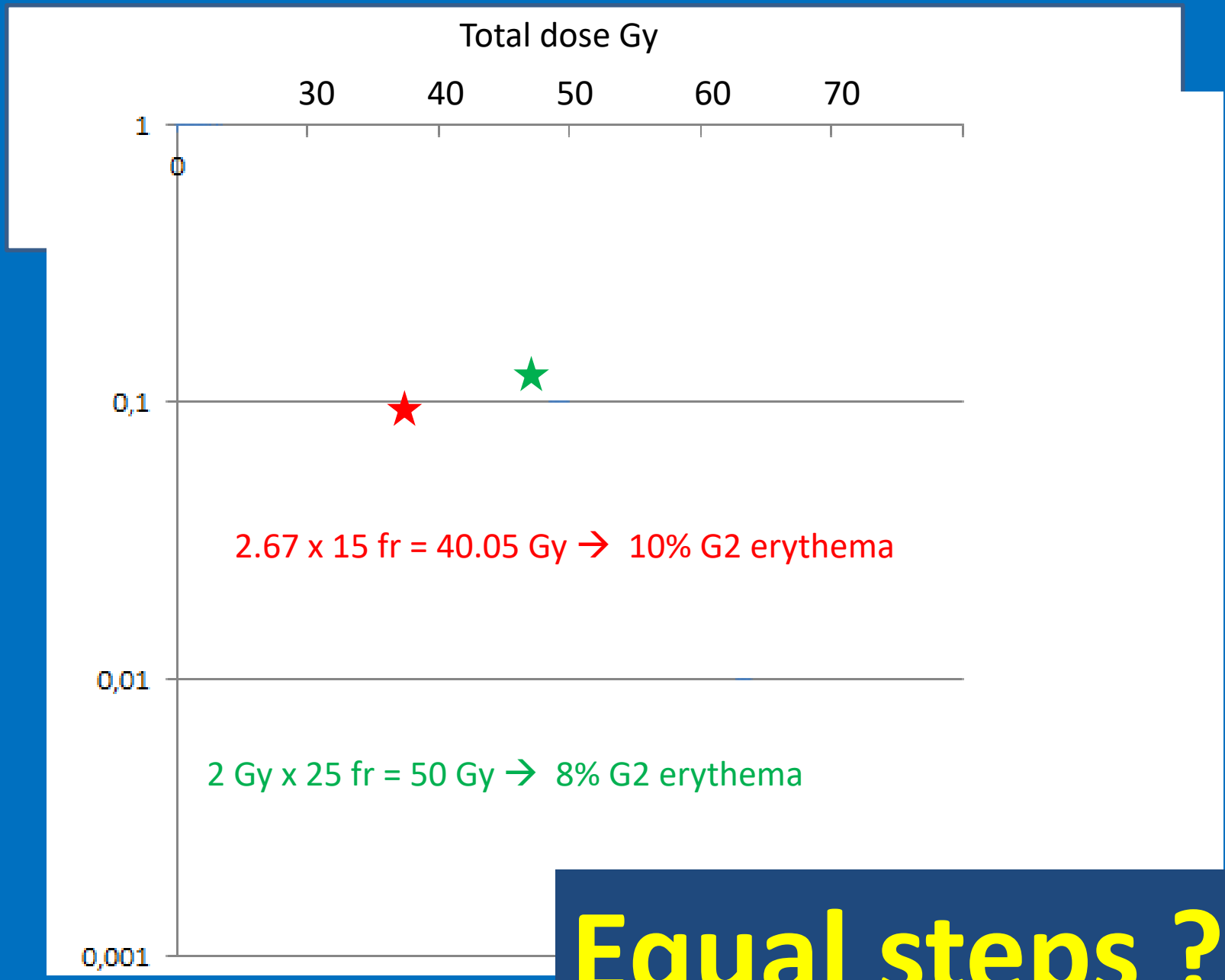

1
0.1
0.01
0.001
0
2
4
6
8
10
12
Log S
of 6,65 Gy
Gy
Series1
Series2

Therefore 10,5 Gy in 3 fractions of 3,5 Gy are equivalent to a single fraction of 6,65 Gy ?

Fractionated exposure

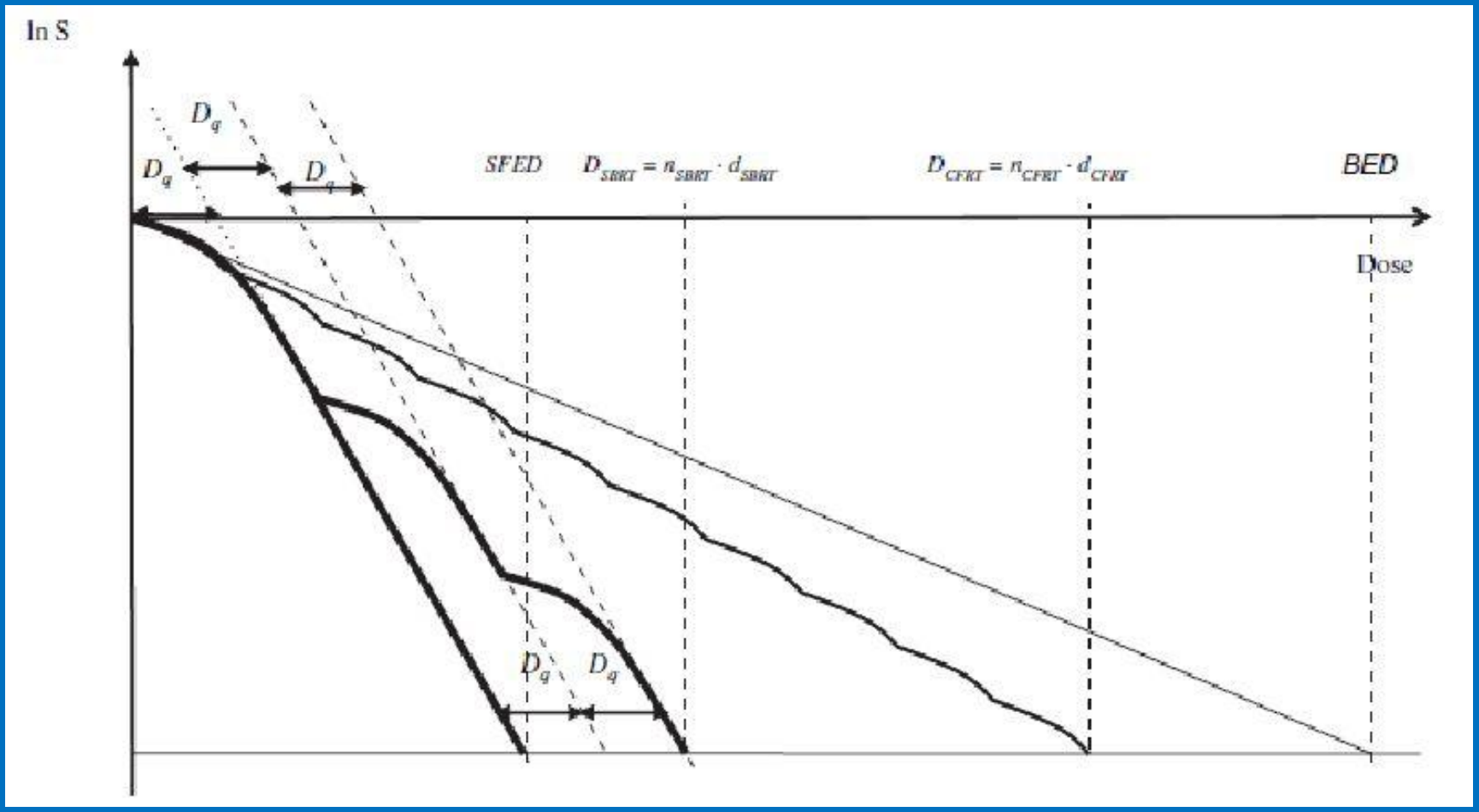
- Clinical endpoints
- e.g. breats cancer RT → erythema
- 2 Gy x 25 fr = 50 Gy → 8% G2 erythema
- 2.67 x 15 fr = 40.05 Gy → 10% G2 erythema

Janssen et al. Rad. onc. 2014
Haviland et al. Lancet Onc 2013


Total dose Gy
30
40
50
60
70
1
0
0,1
0,01
0,001
2.67 x 15 fr = 40.05 Gy → 10% G2 erythema
2 Gy x 25 fr = 50 Gy → 8% G2 erythema

Equal steps ?

Equal steps: classical radiobiology

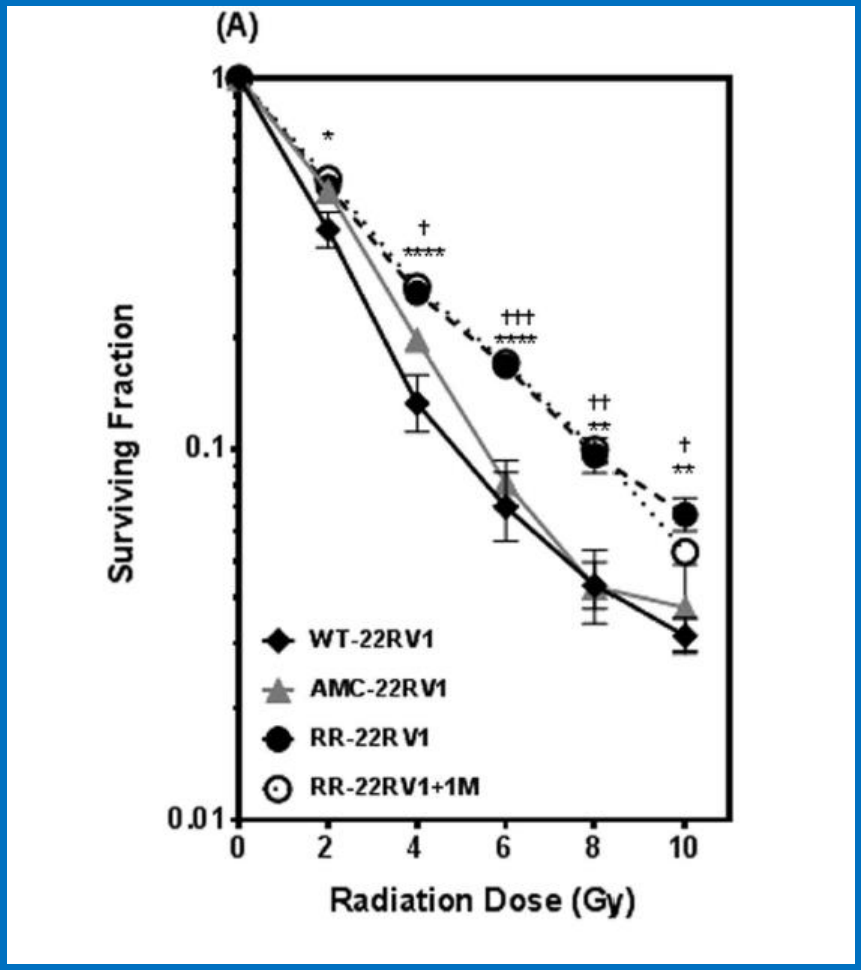


What are we assuming?

1. Complete repair of sublethal damage (> 8 hours) **OK**
2. No adaptive change **NO:**

- Reoxygenation

- **Recruitment of quiescent stem cells**
- **Signalling**
- **…….**



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SCIENTIFIC REPORTS

OPEN

Fractionated radiation exposure amplifies the radioresistant nature of prostate cancer cells

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Accepted: 19 September 2016
Published: 05 October 2016

N. McDermott[1], A. Meunier[1], B. Mooney[1], G. Nortey[2], C. Hernandez[2], S. Hurley[1,3], N. Lynam-Lennon[4], S. H. Barsoom[5], K. J. Bowman[5], B. Marples[6], G. D. D. Jones[5] & L. Marignol[1]

The risk of recurrence following radiation therapy remains high for a significant number of prostate

5 fractionation exp.

- Cells：LM8 (mice osteosarcomas)
- Radiations：
  - X-rays (200 kVp, 20 mA)
  - C-ions (290 MeV/u, center of 6cmSOBP)
- Fraction number: 5 fr.、24h interval
- Total dose: 5 Gy
- End points:
  - Cell death: colony formation assay
  - Invasion：Matrigel Invasion Assay

Dose division scheme of total 5 Gy

	Dose					
Group	1fr	2fr	3fr	4fr	5fr	Total
UFS-1/5D	4d	4d	2d	2d	2d	14d
UFS-2/5D	4d	2d	2d	2d	4d	14d
UFS-3/5D	2d	2d	2d	4d	4d	14d
5fr/5D	2.8d	2.8d	2.8d	2.8d	2.8d	14d

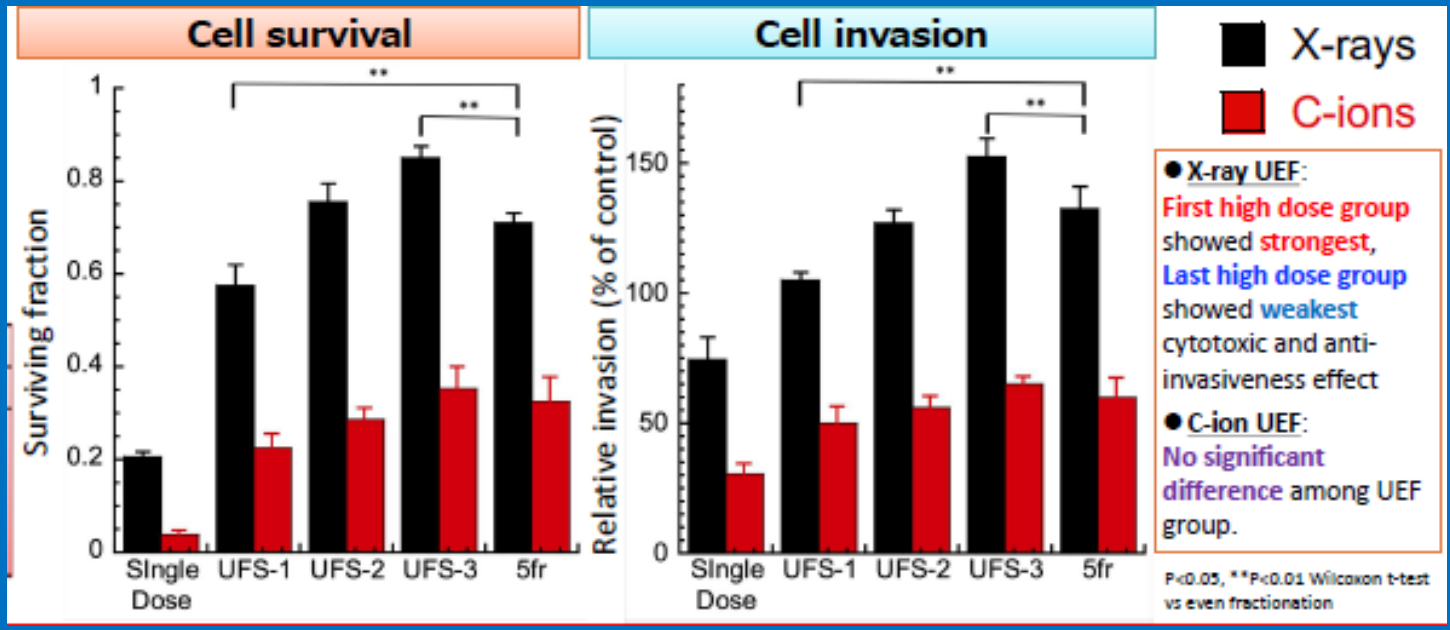
d = 0.36 Gy, 4d = 5.04 Gy

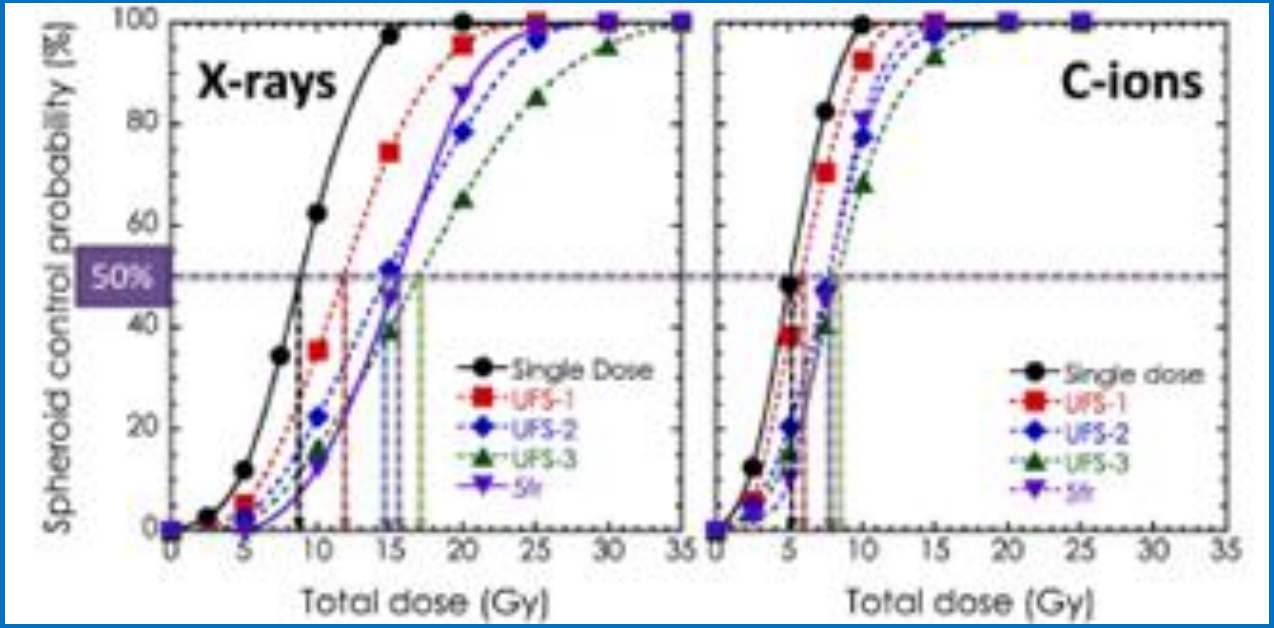
The effect of uneven fractionation using high LET carbon-ion beams for tumor metastatic abilities.

Yoshitaka MATSUMOTO[1]*, Yoshiya FURUSAWA[2], Huizi LI[2], Ryoichi HIRAYAMA[2], Akiko UZAWA[2], Koichi ANDO[3], Shin-ichiro MASUNAGA[4], Koji TSUBOI[1] and Hideyuki SAKURAI[1]

[1]University of Tsukuba, [2]National Institutes for Quantum and Radiological Science and Technology, [3]Gunma University, [4]Kyoto University

*Presenter: ymatsumoto@pmrc.tsukuba.ac.jp



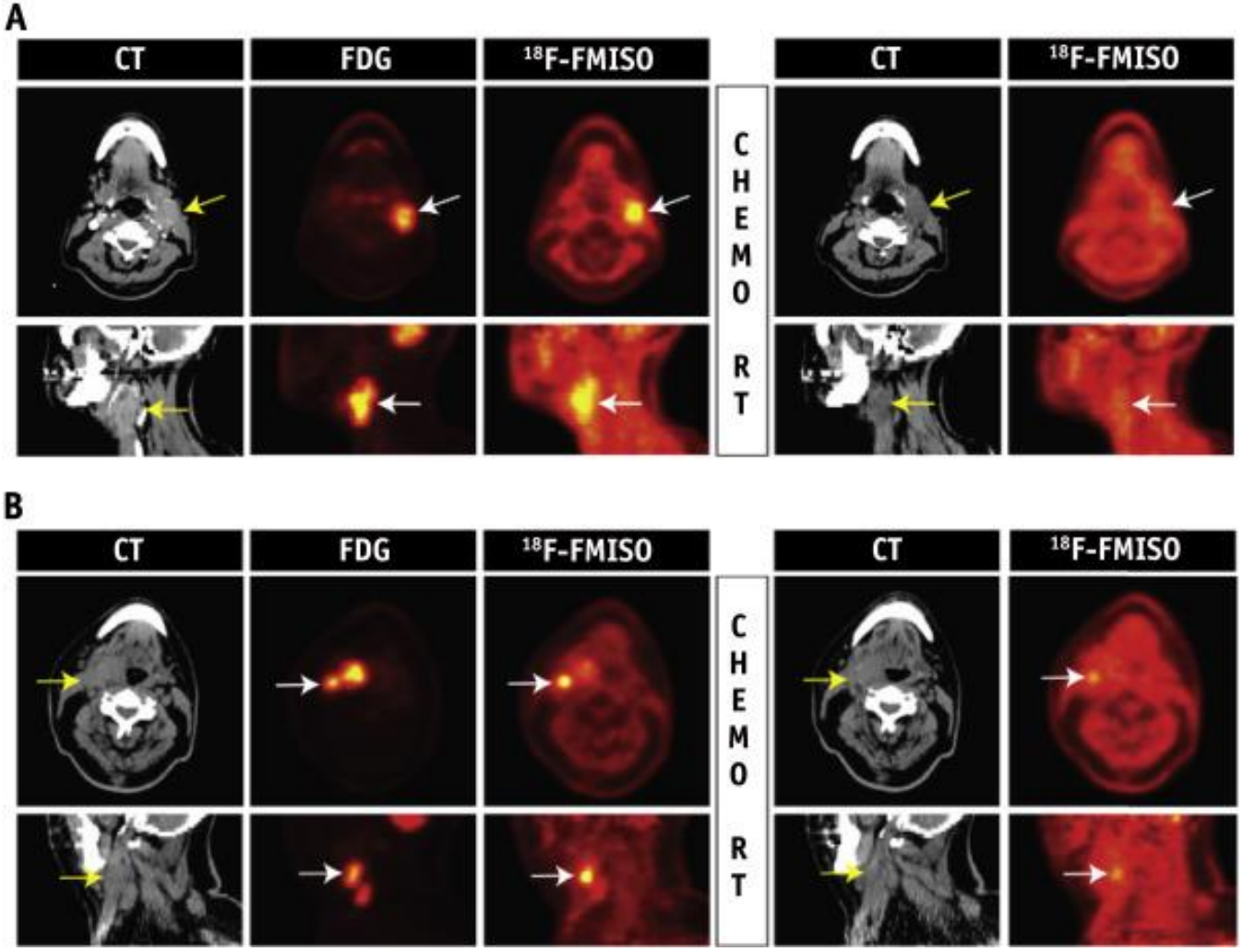


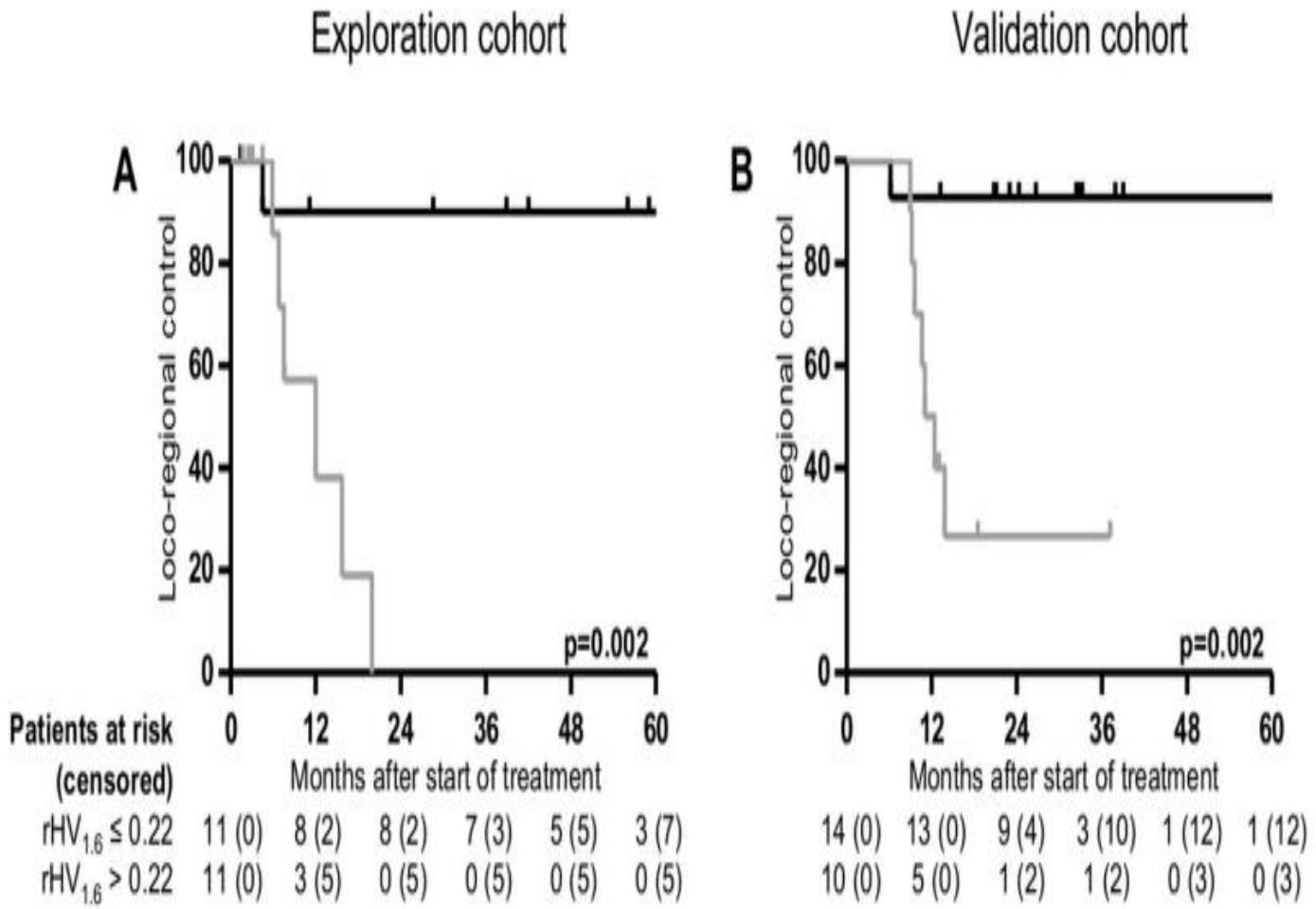
5 fractionation exp.

- LM8 Spheroids：96-well spheroid plate for 7days
  - Spheroid diameter = 628±28μm
- Radiations：
  - X-rays (200 kVp, 20 mA)
  - C-ions (290 MeV/u, center of 6 cm-SOBP)
- Fraction Number: 5fr., interval: 24h
- End points
  - Anti-tumor effect：Spheroid control probability (SCP)

Group	Spheroid control probability (SCP)		
	D_{50}@X-rays (Gy)	D_{50}@C-ions (Gy)	RBE
Single dose	8.9	5.1	1.75
UFS-1	11.9	5.8	2.05
UFS-2	14.8	7.7	1.92
UFS-3	17.0	8.3	2.05
5fr.	15.5	7.8	1.99

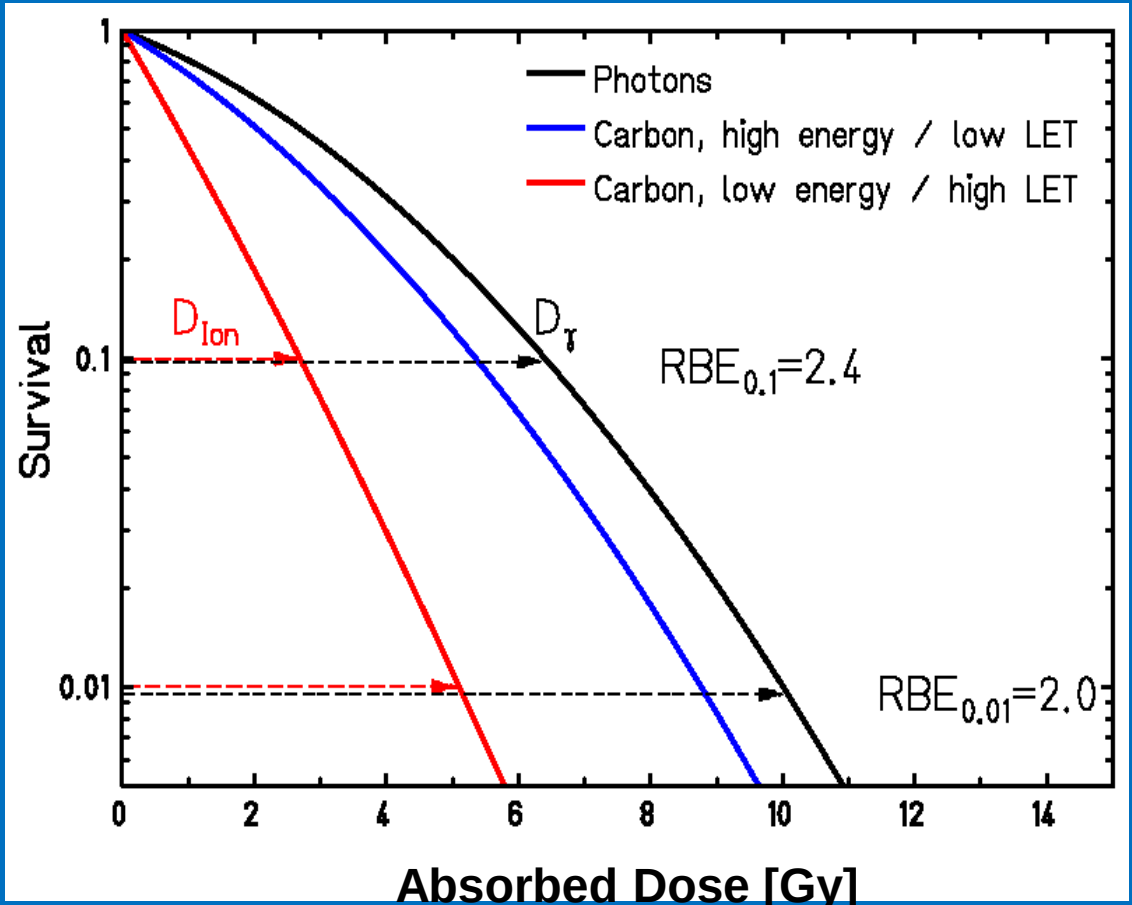
Lack of re-oxygenation at 2 weeks is the key




Exploration cohort
Validation cohort
A
B
Loco-regional control
100
80
60
40
20
0
p=0.002
0
12
24
36
48
60
Months after start of treatment
Patients at risk
(censored)
rHV1.6 ≤ 0.22 11 (0) 8 (2) 8 (2) 7 (3) 5 (5) 3 (7)
rHV1.6 > 0.22 11 (0) 3 (5) 0 (5) 0 (5) 0 (5) 0 (5)
14 (0) 13 (0) 9 (4) 3 (10) 1 (12) 1 (12)
10 (0) 5 (0) 1 (2) 1 (2) 0 (3) 0 (3)

Micro vs Macroscopic endpoints

$$RBE = \left. \frac{D_{reference}}{D_{test}} \right|_{same\_effect}$$


Photons
Carbon, high energy / low LET
Carbon, low energy / high LET
Survival
1
0.1
0.01
D_{Ion}
D_γ
$RBE_{0.1}=2.4$
$RBE_{0.01}=2.0$
0
2
4
6
8
10
12
14
Absorbed Dose [Gy]

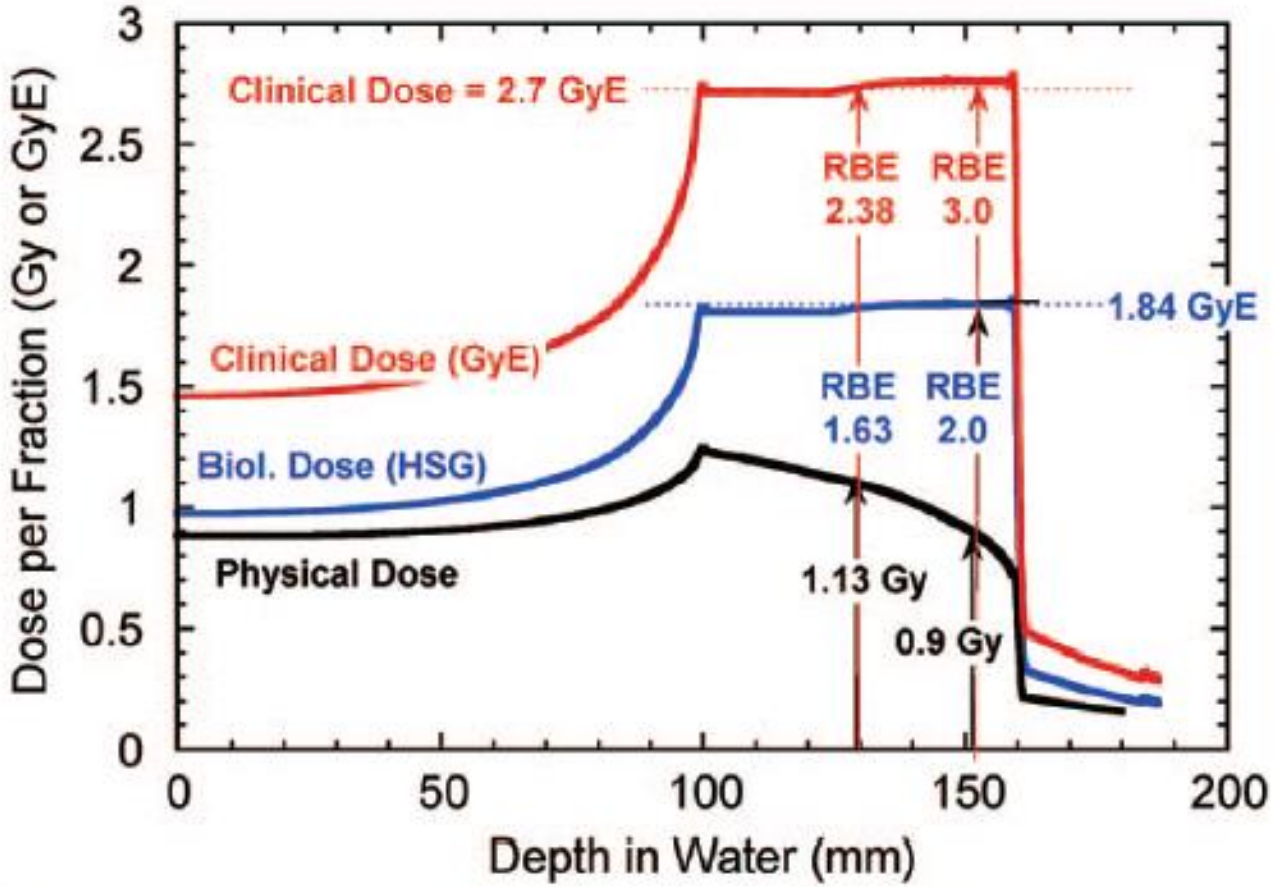
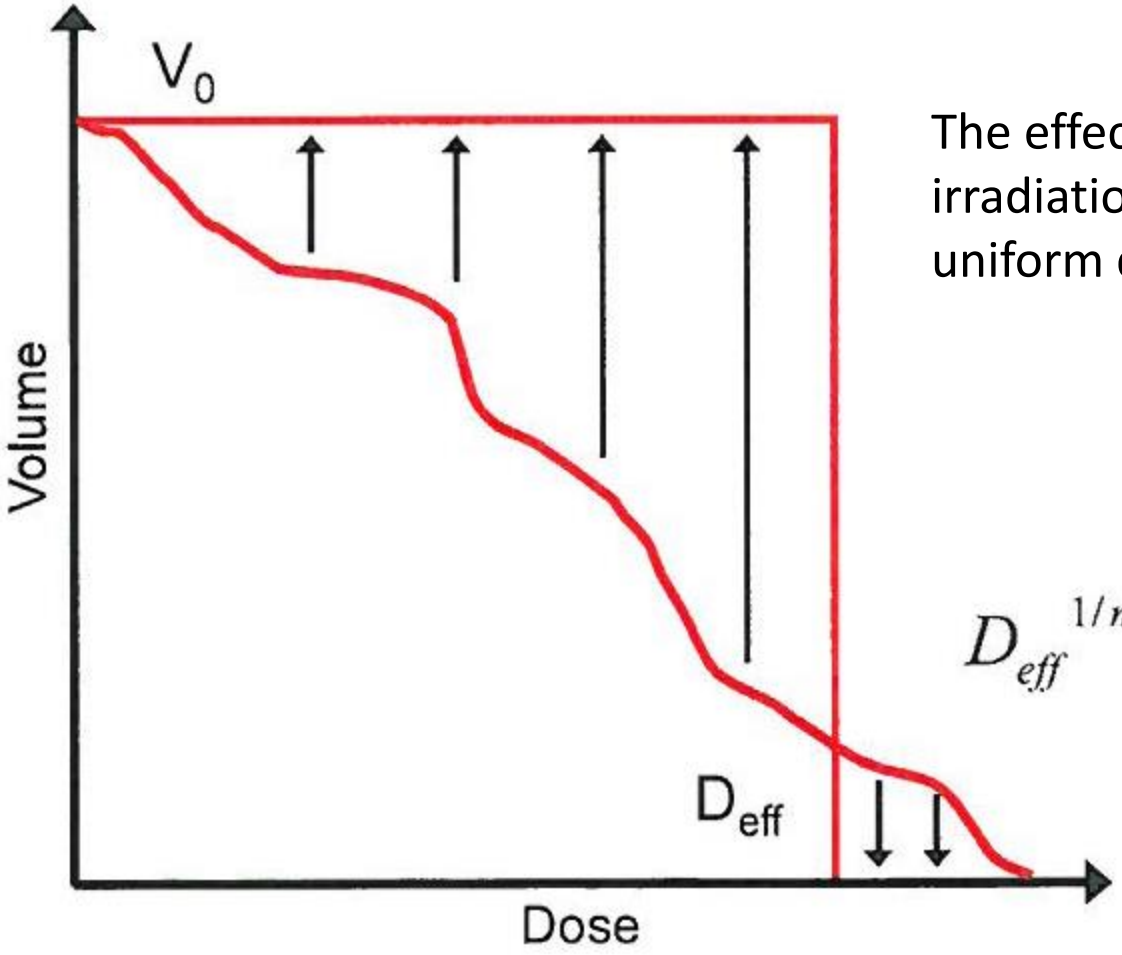


Fig. 5. Schematic method used to determine RBE at the center of SOBP for the clinical situation.

Effective Dose → EUD

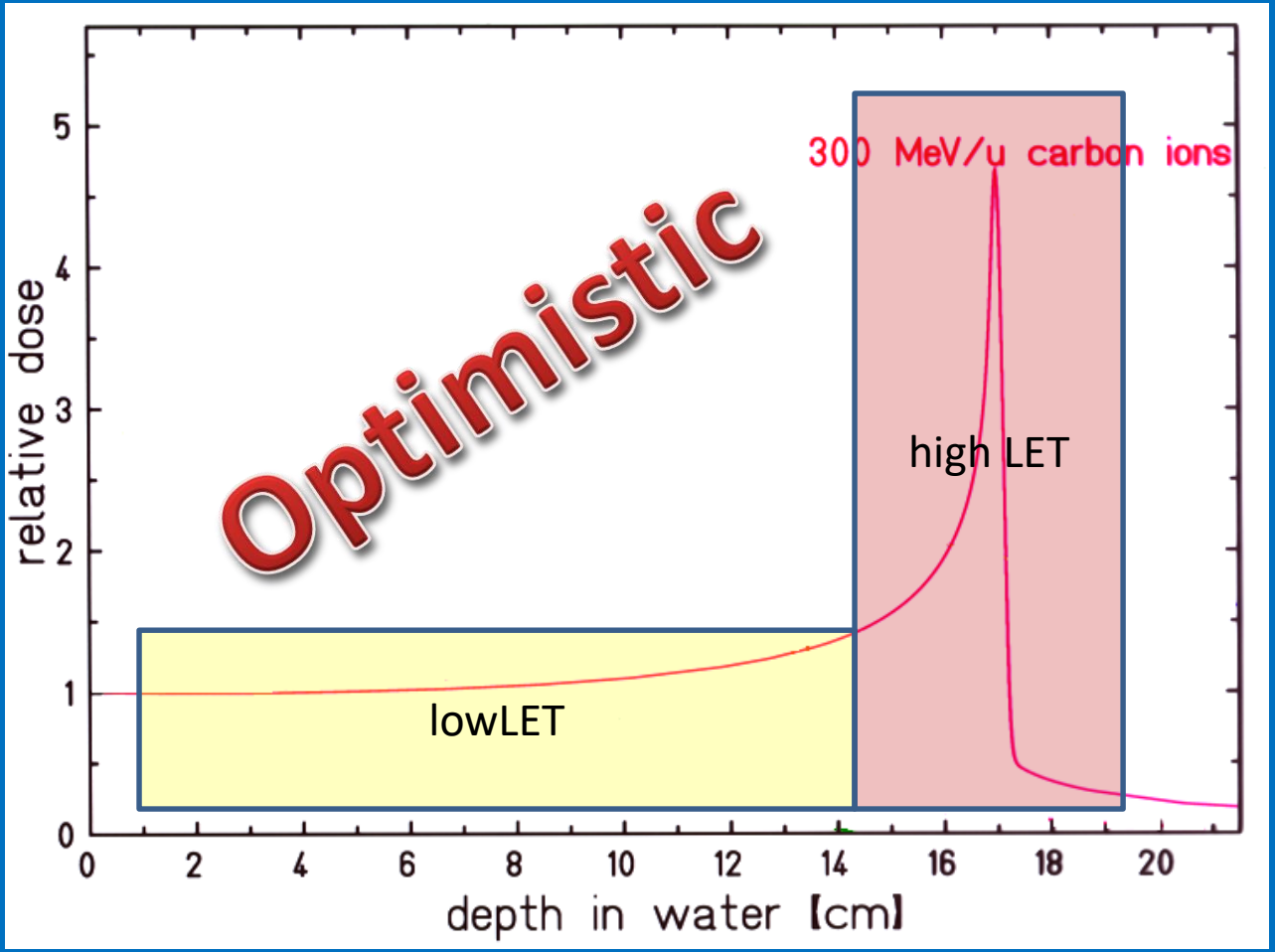


The effect of this dose equals an irradiation of the total volume to a uniform dose D_{eff}

$$D_{eff}^{1/n} = \sum_{i=1}^{N} \frac{\Delta V_i}{V_0} (D_i)^{1/n}$$

RBE models

Carbon Ions
high LET ?(only where you need it)



Short outline of

- Kanai Model
- LEM I model
- LEM IV model
- MKM model

KANAI Model

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 2, pp. 650–656, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.09.043

PHYSICS CONTRIBUTION

EXAMINATION OF GyE SYSTEM FOR HIMAC CARBON THERAPY

Tatsuaki Kanai, Ph.D.,* Naruhiro Matsufuji, Ph.D.,† Tadaaki Miyamoto, M.D.,‡ Junetsu Mizoe, M.D.,‡ Tadashi Kamada, M.D.,‡ Hiroshi Tsuji, M.D.,‡ Hirotoshi Kato, M.D.,‡ Masayuki Baba, M.D.,‡ and Hirohiko Tsujii, M.D.‡

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Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 1, pp. 201–210, 1999

0360-3016/99/$–see front matter

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PII S0360-3016(98)00544-6

PHYSICS CONTRIBUTION

BIOPHYSICAL CHARACTERISTICS OF HIMAC CLINICAL IRRADIATION SYSTEM FOR HEAVY-ION RADIATION THERAPY

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*Division of Accelerator Physics and Engineering, †Medical Physics and Engineering Office, ‡Division of Radiation Research, §Space and Particle Radiation Science Research Group, ‖Division of Planning and Coordination, National Institute of Radiation Sciences, Chiba, Japan

In the design of SOBP, we needed data concerning the LET dependence of the coefficients (α and β) in the LQ model of the survival curve for HSG, for the most common beam energy. The survival curves were experimentally investigated for various monoenergetic carbon beams in order to tabulate the coefficients.

It is regarded that cell survival for combined high- and low-LET beams could also be expressed by the LQ model, with new coefficients (α_{mix} and β_{mix}) for a mixed radiation field.

$$\alpha_{mix} = \sum f_i \alpha_i$$

$$\sqrt{\beta_{mix}} = \sum f_i \sqrt{\beta_i}$$

- Measure several survival curves in several position along a monochromatic bragg peak
- Describe the single monochromatic Bragg peak and the mixed field as Linear quadratic
- Use Zaider Rossi formula
- Manufacture a less “spiky” ridge filter

$$\alpha_{mix} = \sum f_i \alpha_i$$

$$\sqrt{\beta_{mix}} = \sum f_i \sqrt{\beta_i}$$

From this point the story becomes complicated

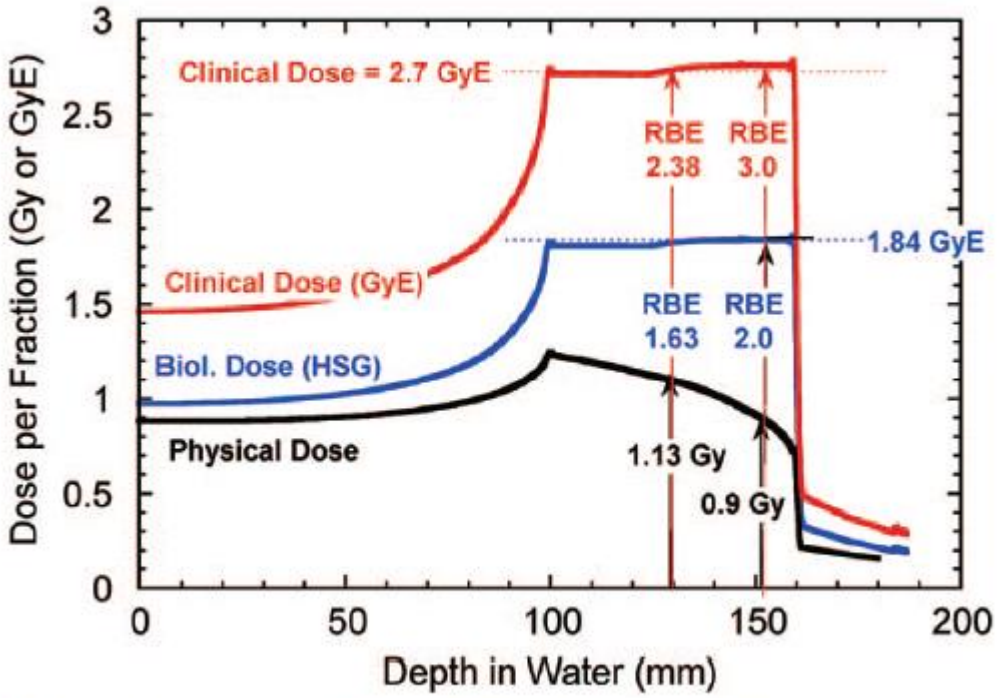


Fig. 5. Schematic method used to determine RBE at the center of SOBP for the clinical situation.

Why the red line ?

Why do we care about 80 KeV/µm ?

Multiple endpoints vs singkle endpoint ?

HSG surviival or pig skin reddening or clinical toxicity

80 KeV/µm was the LET of fast neutron used at NIRS

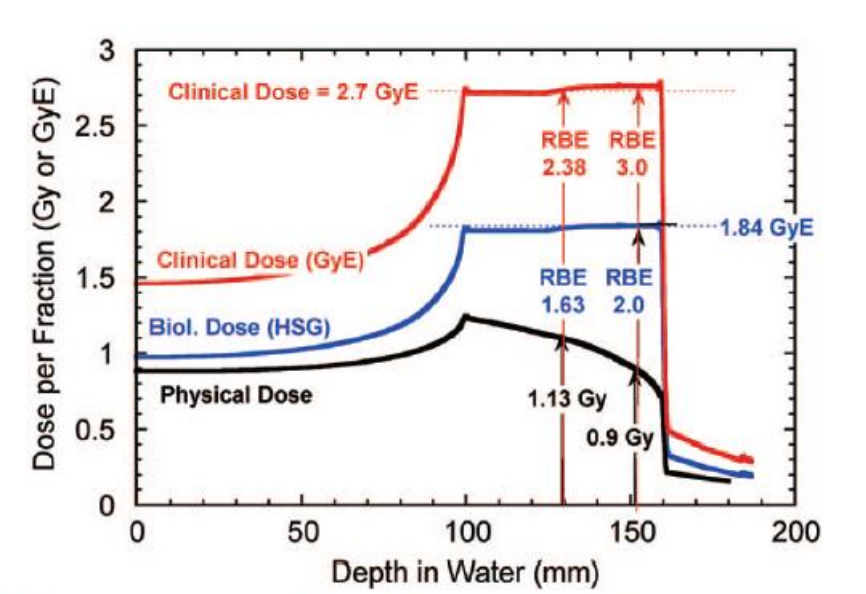


Fig. 5. Schematic method used to determine RBE at the center of SOBP for the clinical situation.

Gan No Rinsho. 1985 Sep;31(12):1552-9.

[Fast neutron radiotherapy at NIRS, indication and prospects].

[Article in Japanese]

Morita S, Nakano T, Gomi H, Aoki Y, Shibayama K, Kumagaya K, Arai T, Tsunemoto H, Ando K, Ishikawa T.

Abstract

Eleven hundred and seventy one patients, 921 previously untreated and 250 recurrent, have been treated with 30 MeV (d-Be) fast neutron beam between 1975 and 1984 at NIRS. Some trends have been identified: non-randomized results have been at least as good as those of photons in carcinomas such as: supraglottic carcinoma in the larynx, pancoast type tumor of the lung, malignant melanoma of the skin and so on. Randomized results with mixed beam studies for carcinoma of the uterine cervix have indicated no significant advantages against those of photons. Treatment technique for the beam concentration must be improved to demonstrate the merit of neutrons in the next step.

More than 1000 patients from 1975 to 1984

Melanoma, NSCLC, H&N SCC, Gynecological cancer

1. Neutron at NIRS were used with RBE 3
2. Carbon with the same LET **must** have the same RBE
3. Pig skin reddening agrees with neutrons and not with HSG survival
4. you do not get curves out of pig skin reddening or clinical experience

Solution:

Scale linearly the biological dose of HSG multipling by 1.5

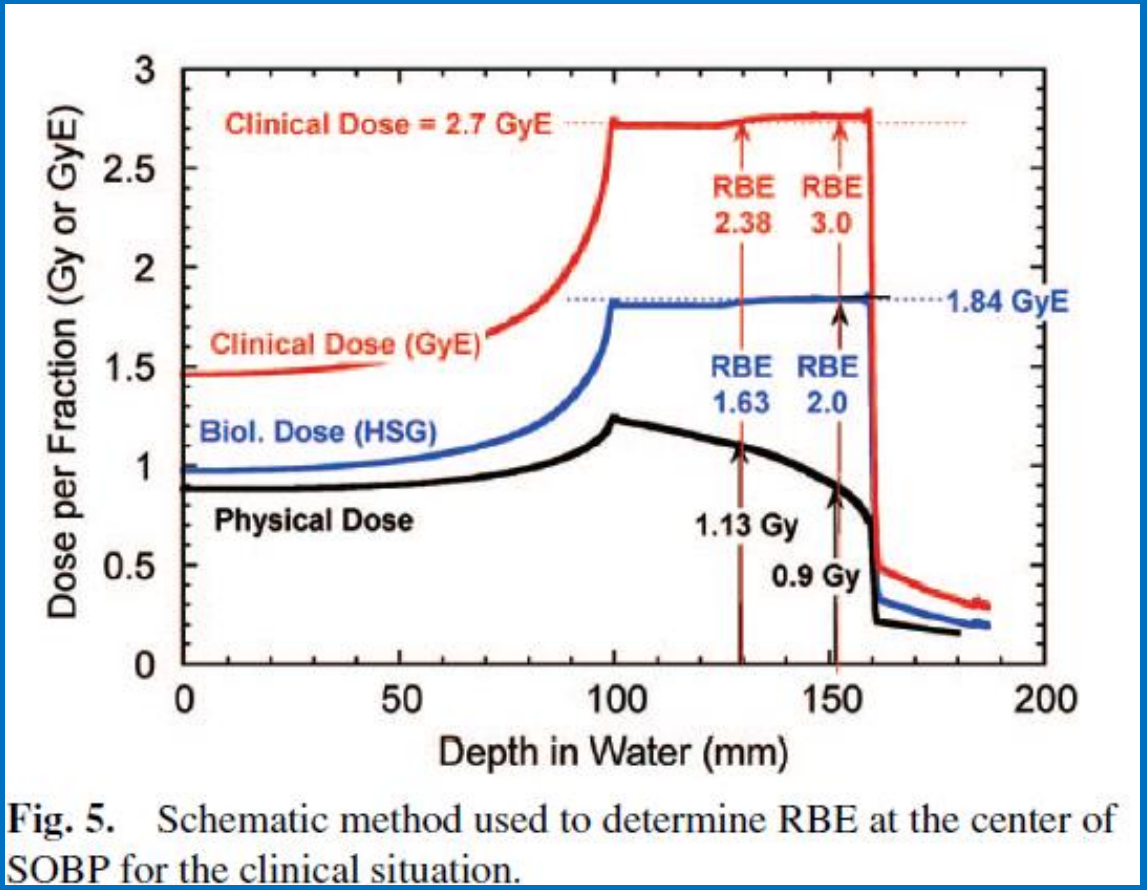


Fig. 5. Schematic method used to determine RBE at the center of SOBP for the clinical situation.

We have measured that for HSG it is equivalent to 1.84 Gy but we Believe taht for the patient it may be equivalent to 2.7 Gy

Even more complicated

1. Dose escalation trials have been carried out at NIRS escalating dose per fraction
2. SOBP shape has not been changed and RBE has been assumed to scale linearly

LEM I (Local Effect Model)

Phys Med Biol. 2000 Nov;45(11):3319-30.

Treatment planning for heavy-ion radiotherapy: calculation and optimization of biologically effective dose.

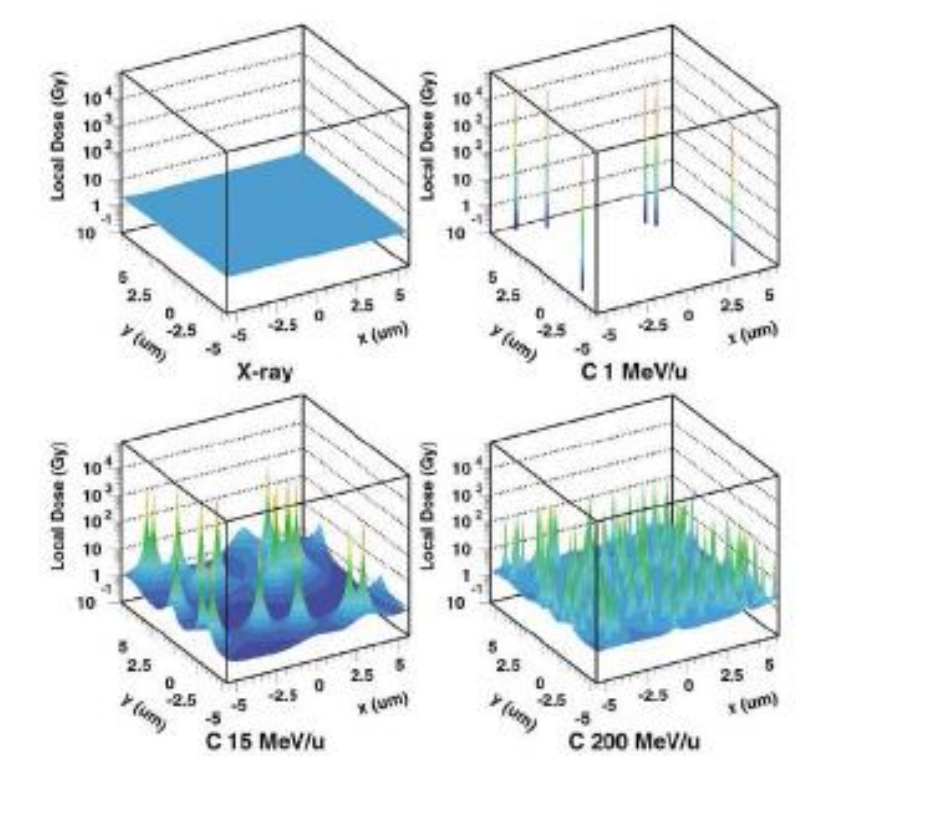
Krämer M, Scholz M.
GSI Biophysik, Darmstadt, Germany.

Abstract

We describe a novel approach to treatment planning for heavy-ion radiotherapy based on the local effect model (LEM) which allows us to calculate the biologically effective dose not only for the target region but also for the entire irradiation volume. LEM is ideally suited for use as an integral part of treatment planning code systems for active dose shaping devices like the GSI raster scan system. Thus it has been incorporated into our standard treatment planning system for ion therapy (TRiP). Single intensity modulated fields can be optimized with respect to a homogeneous biologically effective dose. The relative biological effectiveness (RBE) is calculated separately for each voxel of the patient CT. Our radiobiologically oriented code system has been used since 1995 for the planning of irradiation experiments with cell cultures and animals such as rats and minipigs. It has been in regular and successful use for patient treatment planning since 1997.

PMID: 11098906 [PubMed - indexed for MEDLINE]

LEM I (Local Effect Model)



The difference depends on microscopic pattern of dose deposition:
Photons are like spanking,
carbon like stabbing with a dagger

Photons survival curves are used

- Survival means zero lethal events
- Probability of lethal events for a cell is derived from survival curves with Poisson statistics

$$N_{lethal}(D) = -\ln[S(D)]$$

- Lethal events are assumed uniformly spaced in the nucleus for photons

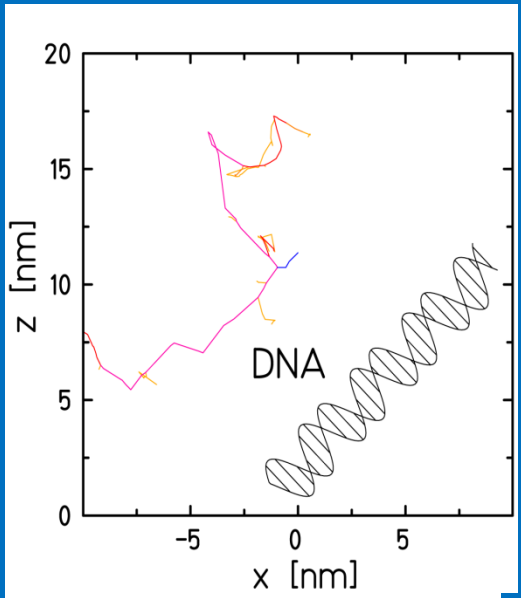
The fundamental assumption of the LEM is that the local biological effect is determined by the local dose, but is independent of the particular radiation type leading to a given local dose

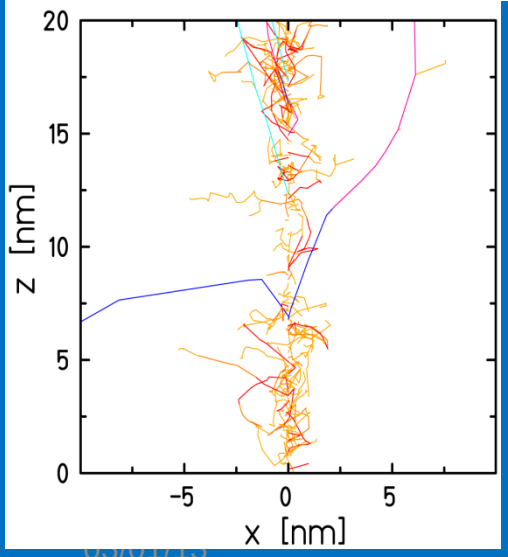
- For carbon ions number of lethal events is integrated over the nucleus and local probability is derived from photons global curves

$$N_{lethal} = \iiint_{V_N} -\frac{\ln[S_X(D(r))]}{V_N} dr$$

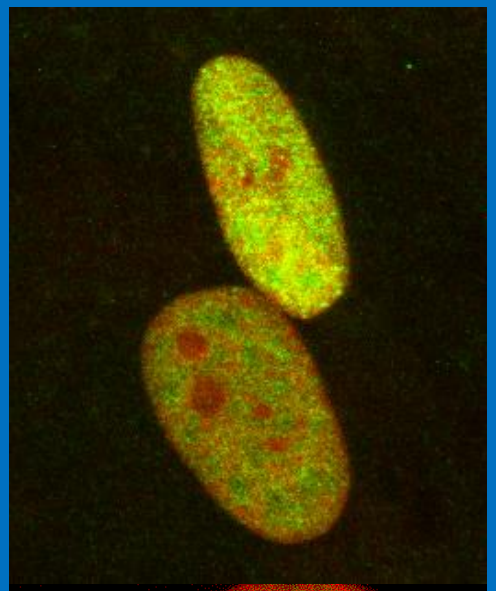
- Local dose is calculated based on the amorphous track
- There are some free parameters

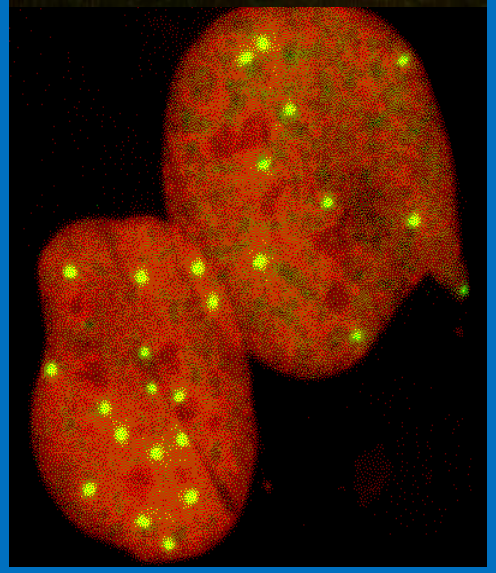
Ionization tracks





Damage in nucleus





Low LET

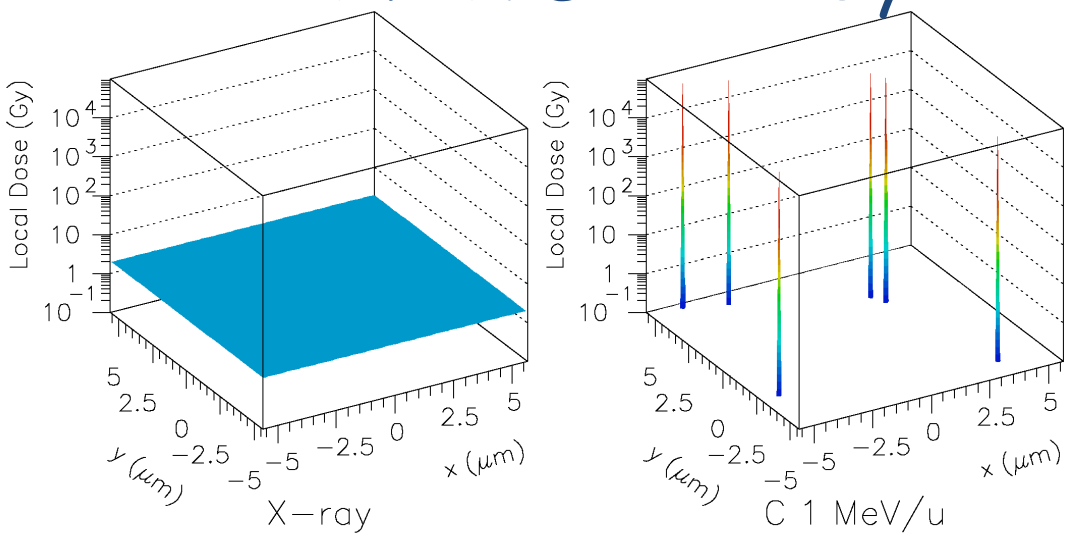
Homogeneous deposition of dose

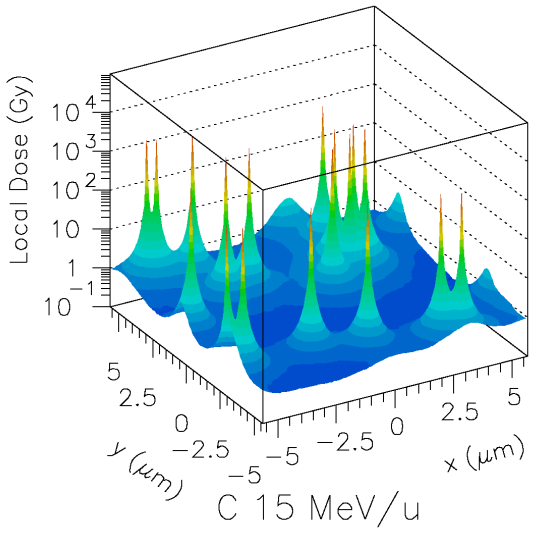
High LET

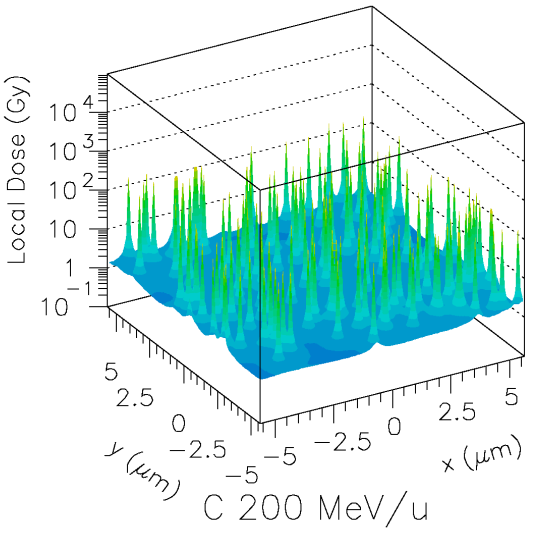
Local deposition of high doses

M. Scholz et al.
Rad. Res. 2001

Mean Dose: 2 Gy







Courtesy of O. Jaekel

The most critical free parameter is Transition dose from linear quadratic to linear

- Local doses can exceed 1000 Gy
- It is not possible to assume LQ relation between dose and survival, survival curves are linearized at a given dose

LEM model

- You can apply it to any mixed field of particles
- OK for spot scanning
- OK for inverse planning
- Predicts cell survival for complex beam arrangements
- You can change the reference cell line easily

Microdosimetric Kinetic Model (MKM)

RADIATION RESEARCH **166**, 629–638 (2006)
0033-7587/06 $15.00

Microdosimetric Measurements and Estimation of Human Cell Survival for Heavy-Ion Beams

Yuki Kase,[a,1] Tatsuaki Kanai,[a,b] Yoshitaka Matsumoto,[b] Yoshiya Furusawa,[b] Hiroyuki Okamoto,[a] Toru Asaba,[a] Makoto Sakama[a] and Hiroshi Shinoda[a]

[a] *Tokyo Institute of Technology, 4259, Nagatsuta-cho, Midori-ku, Yokohama 226-8502, Japan; and* [b] *National Institute of Radiological Sciences, 4-9-1, Anagawa, Inage-ku, Chiba 263-8555, Japan*

IOP PUBLISHING — PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. **55** (2010) 6721–6737 — doi:10.1088/0031-9155/55/22/008

Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model

Taku Inaniwa, Takuji Furukawa, Yuki Kase, Naruhiro Matsufuji, Toshiyuki Toshito, Yoshitaka Matsumoto, Yoshiya Furusawa and Koji Noda

Medical Physics Research Group, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

E-mail: taku@nirs.go.jp

The basic idea is not so much different from LEM

- Expected number of lethal event in a cell is obtained by summation of expected number of lethal events in a small “domains”
- Instead of integrating points over a volume a finite number of small domains is added.
- This allows to directly measure relvant radiation parameters down in the microscopic domain

MKM

- Once again a lot of dose clustered in a small volume is predict to create more damage
- Once again there is linear quadratic dependence
- The model is less of a black box respect to LEM as many of its parameters can be derived form microdismetric measurments

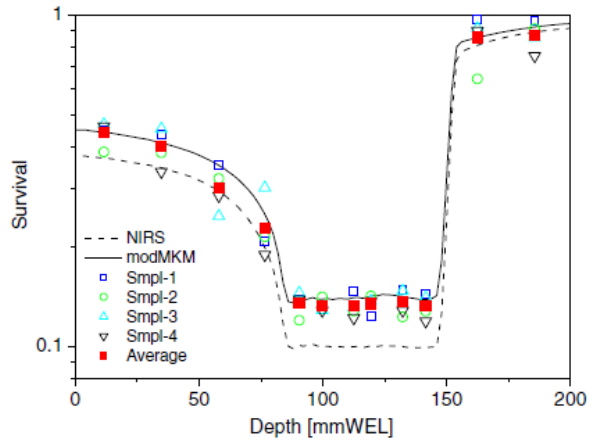


Figure 13. Measured survival values (symbols) are compared with the planned survival curve (dashed curve) based on the NIRS radio-biological model (Kanai *et al* 1999) using the response of the 'old' HSG tumor cells. The recalculated survival curve (solid curve) based on the modified MKM in which the current response of the HSG tumor cells was reflected through the value of α_0.

Good fit of in vitro data

Nasty mathematics

$$
\begin{aligned}
(z^{*}_{1D\,\mathrm{mix}})_i &= \frac{\sum_{j=1}^{N_{\mathrm{spot}}} w_j \cdot \int_0^{\infty} (F(z))_{ij}\,\mathrm{d}z \cdot \int_0^{\infty} z_{\mathrm{sat}} z\,(f(z))_{ij}\,\mathrm{d}z}{\sum_{j=1}^{N_{\mathrm{spot}}} w_j \cdot \int_0^{\infty} (F(z))_{ij}\,\mathrm{d}z \cdot \int_0^{\infty} z\,(f(z))_{ij}\,\mathrm{d}z} \\
&= \frac{\sum_{j=1}^{N_{\mathrm{spot}}} w_j \cdot \int_0^{\infty} (F(z))_{ij}\,\mathrm{d}z \cdot \int_0^{\infty} z\,(f(z))_{ij}\,\mathrm{d}z \cdot \frac{\int_0^{\infty} z_{\mathrm{sat}} z(f(z))_{ij}\,\mathrm{d}z}{\int_0^{\infty} z(f(z))_{ij}\,\mathrm{d}z}}{\sum_{j=1}^{N_{\mathrm{spot}}} w_j \cdot \int_0^{\infty} (F(z))_{ij}\,\mathrm{d}z \cdot \int_0^{\infty} z\,(f(z))_{ij}\,\mathrm{d}z} \\
&= \frac{\sum_{j=1}^{N_{\mathrm{spot}}} w_j \cdot \int_0^{\infty} (F(z))_{ij}\,\mathrm{d}z \cdot z_{F_{ij}} \cdot \frac{\int_0^{\infty} z_{\mathrm{sat}} z(f(z))_{ij}\,\mathrm{d}z}{\int_0^{\infty} z(f(z))_{ij}\,\mathrm{d}z}}{\sum_{j=1}^{N_{\mathrm{spot}}} w_j \cdot \int_0^{\infty} (F(z))_{ij}\,\mathrm{d}z \cdot z_{F_{ij}}},
\end{aligned}
\qquad (A.4)
$$

It is used in Japan for spot scanning, however it was designed to be compatible with the old Kanai model

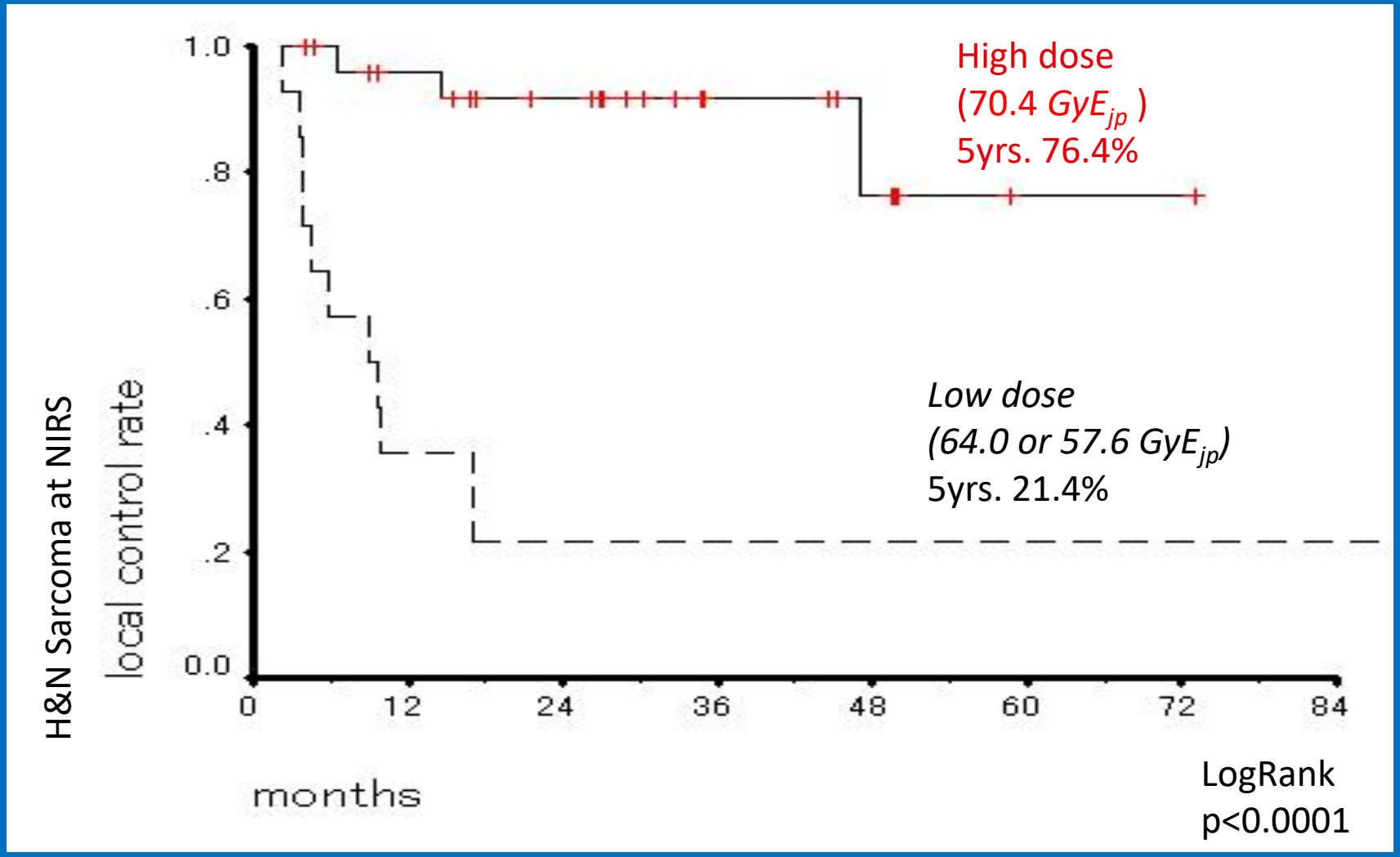
Different way to prescribe carbon ion RT

- Everyone agree qualitatively but there is quantitative disagreement
- No one is right as there are many relevant endpoints and all are difficult to measure

BUT

- We risk not to understand each other
- Kanai vs. LEM one is a clinically relevant conversion
- The shape wil be different but we want to avoid systematic errors

10% difference is clinically relevant



Is it relevant ?

Radiotherapy and Oncology 173 (2022) 223–230

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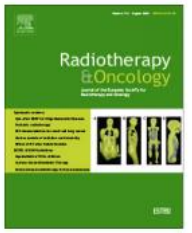
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



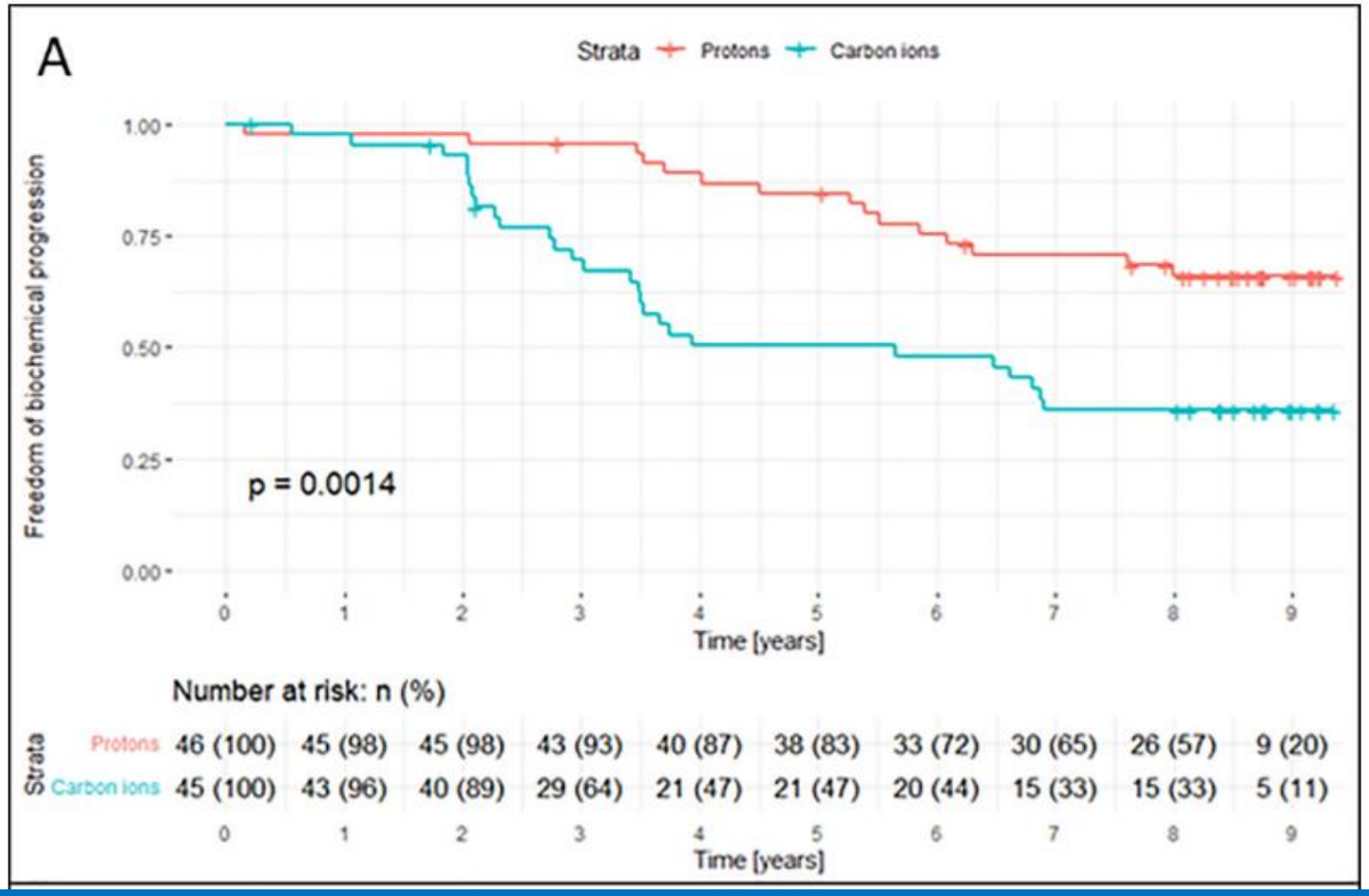
Original Article

Results of a prospective randomized trial on long-term effectiveness of protons and carbon ions in prostate cancer: LEM I and α/β = 2 Gy overestimates the RBE

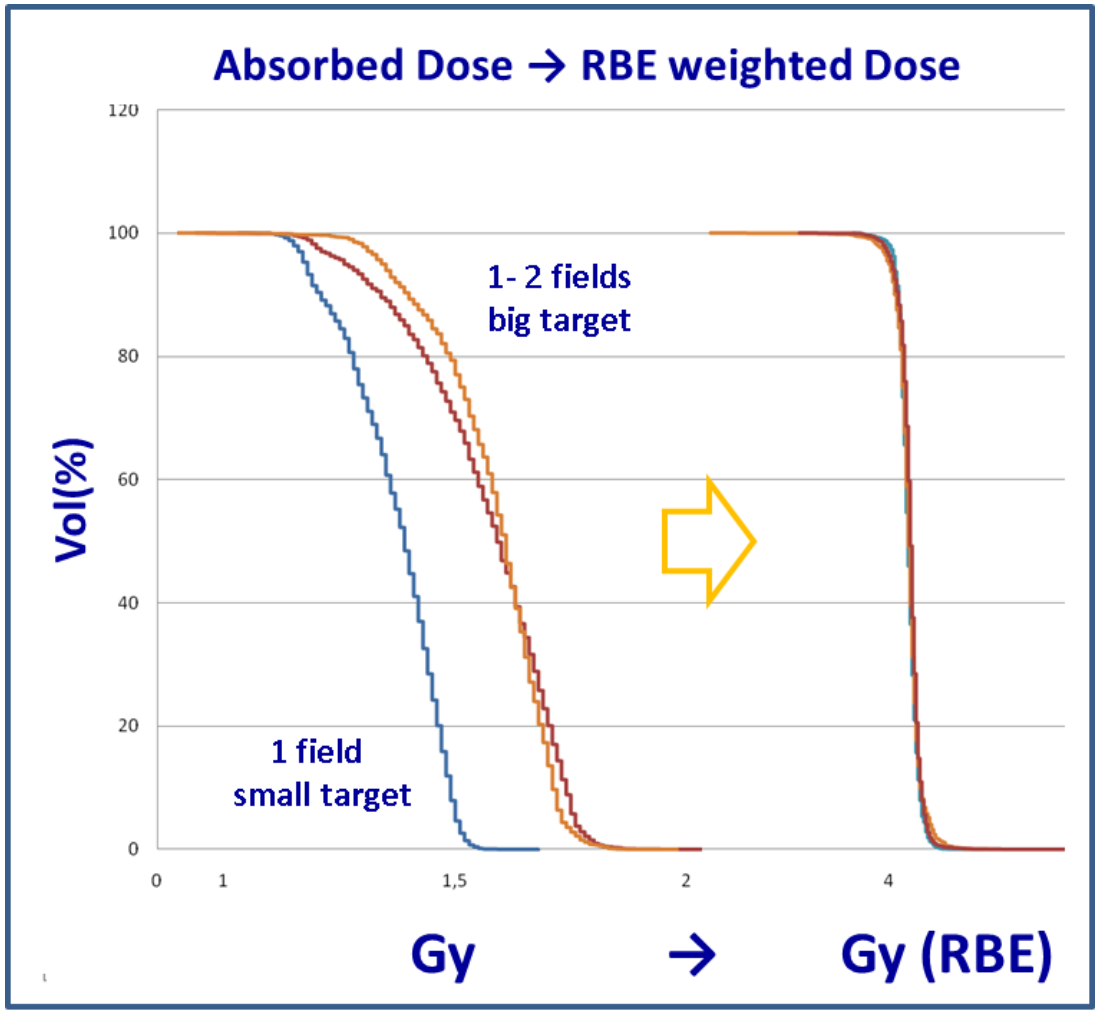
Tanja Eichkorn [a,b,c,e,*], Christian P. Karger [b,g], Stephan Brons [b], Stefan Alexander Koerber [a,b,c,e], Thomas Mielke [a,e], Thomas Haberer [b,e], Juergen Debus [a,b,c,d,e,f], Klaus Herfarth [a,b,c,e]

[a] *Department of Radiation Oncology, Heidelberg University Hospital, Germany;* [b] *National Center for Radiation Oncology (NCRO), Heidelberg Institute for Radiation Oncology (HIRO);* [c] *National Center for Tumor Diseases (NCT), Heidelberg;* [d] *Clinical Cooperation Unit Radiation Oncology (E050), German Cancer Research Center (DKFZ), Heidelberg;* [e] *Heidelberg Ion Beam Therapy Center (HIT), Heidelberg;* [f] *German Cancer Consortium (DKTK), Partner Site Heidelberg, German Cancer Research Center (DKFZ); and* [g] *Dept. of Medical Physics in Radiation Oncology, German Cancer Research Center, Heidelberg, Germany*

Results of a prospective randomized trial on long-term effectiveness



Can we compare physical dose?



→ Different physical dose DVH

RBE comparison

Possible solution (1)

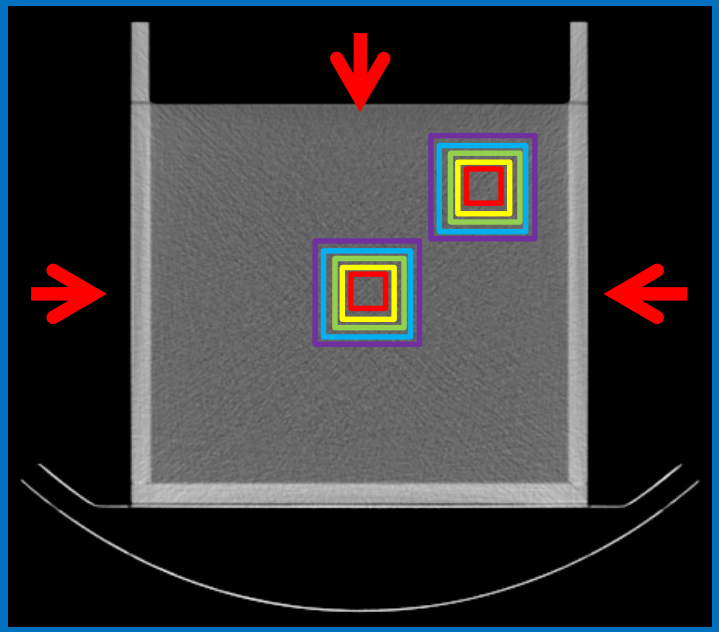
Compare physical dose fixing “reference conditions”

→ Homogeneous conditions - Water phantom

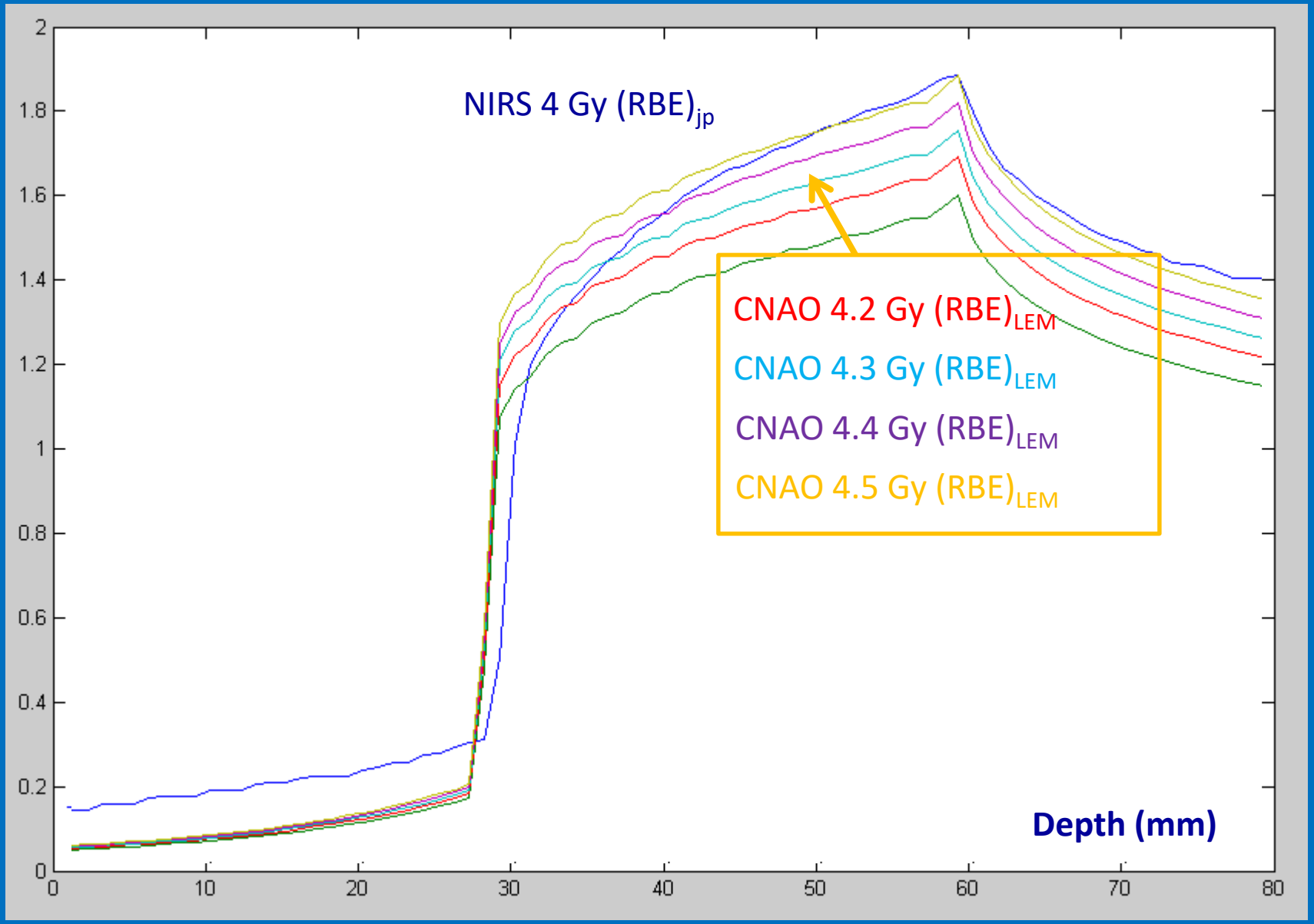
→ **Same volumes** - 5 Cubes: (4, 6, 8, 10, 12 cm)

→ **Same number of fields** - low energy (290 MeV/u) and high energy (400 MeV/u)

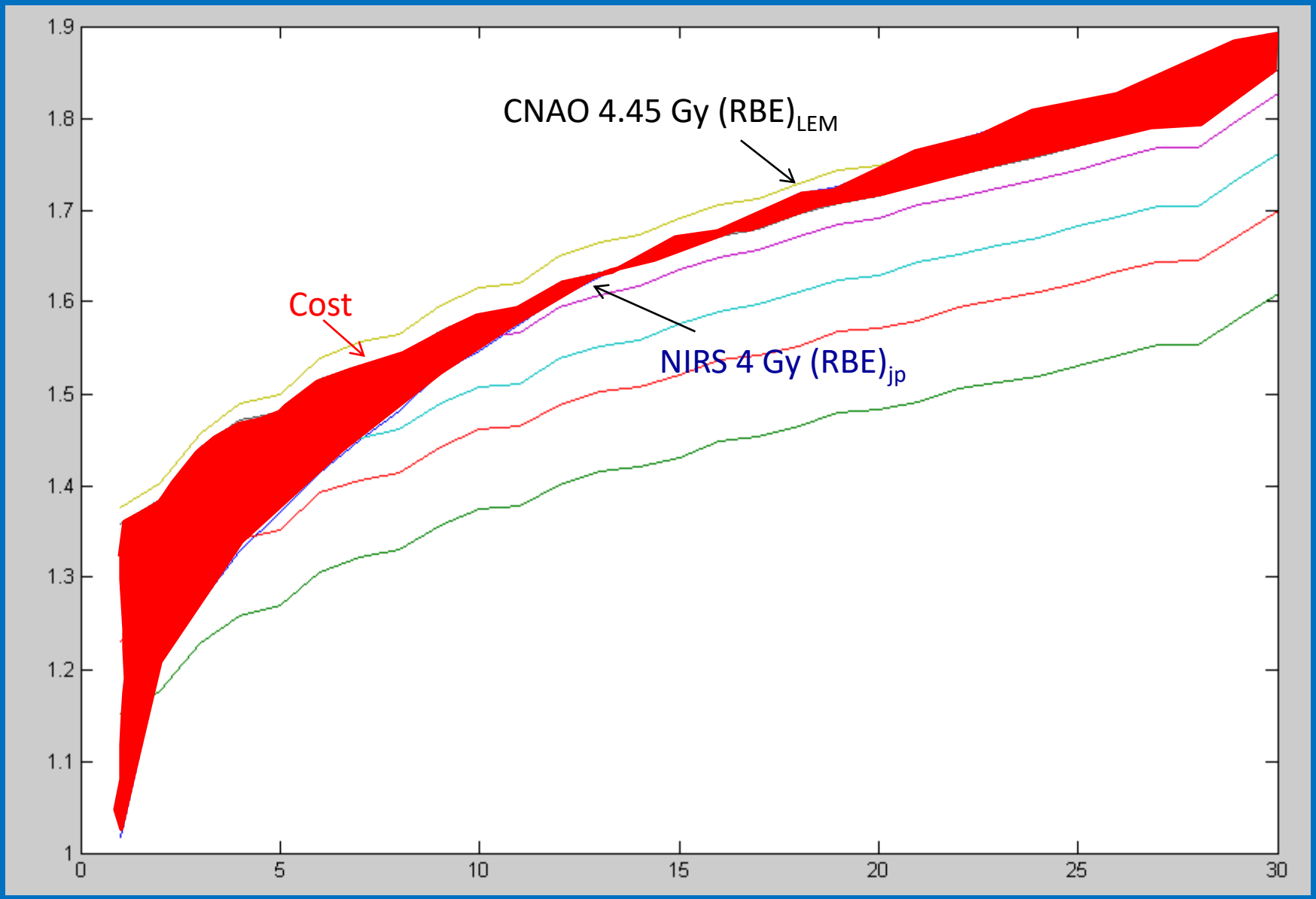
→ **Same field orientation** – single, 2 orthogonal, 2 opposed



NIRS physical dose - 6 cm SOBP (4 Gy $(RBE)_{jp}$)



Minimize physical dose difference in the SOBP



Final results

Prescription doses (GyE)

(16 fractions, 4 fractions per week)

Indication	NIRS dose	CNAO dose						
		Opposed ports		Orthogonal ports		Single port		
		quadratic errors		quadratic errors		quadratic errors		MC
		Cubes	Spheres	Cubes	Spheres	Cubes	Spheres	Spheres
Head and neck non mesenchymal cancer	3.60	4.20	4.15	4.20	4.15	4.20	4.15	4.19
Skull base chordoma and hondrosarcoma	3.80	4.35	4.30	4.35	4.30	4.35	4.30	4.33
Head and neck non mesenchymal cancer	4.00	4.50	4.40	4.50	4.45	4.50	4.45	4.47
Spinal chordoma and chondrosarcoma	4.20	4.65	4.60	4.70	4.60	4.70	4.60	4.64
Head and neck sarcoma	4.40	4.80	4.70	4.80	4.70	4.80	4.70	4.75
Bone and soft tissue sarcoma	4.40	4.80	4.75	4.80	4.75	4.80	4.75	4.78

H&N

64 Gy $(RBE)_{jp}$ → 71.2 Gy $(RBE)_{LEM}$

Retroperitoneal sarcoma

70.4 Gy $(RBE)_{jp}$ → 76 Gy $(RBE)_{LEM}$

IOP Publishing — Physics in Medicine and Biology

Phys. Med. Biol. 57 (2012) 7543–7554 doi:10.1088/0031-9155/57/22/7543

Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy

Piero Fossati[1,2,4,5], Silvia Molinelli[1], Naruhiru Matsufuji[3], Mario Ciocca[1], Alfredo Mirandola[1], Andrea Mairani[1], Junetsu Mizoe[1,3], Azusa Hasegawa[3], Reiko Imai[3], Tadashi Kamada[3], Roberto Orecchia[1,2,4] and Hirohiko Tsujii[3]

Indipendent calculation similar results

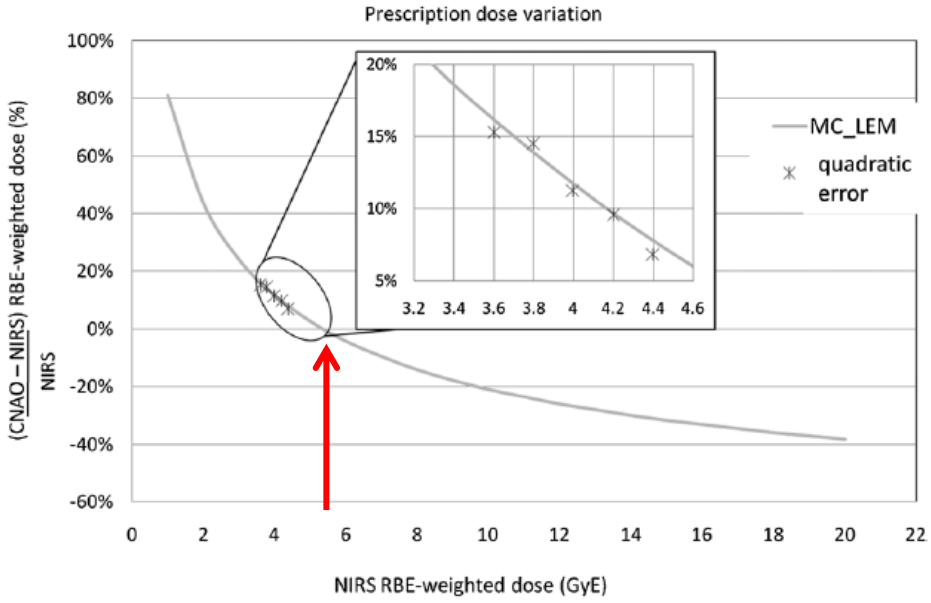


Figure 4. RBE-weighted dose percentage differences between LEM-based GyE and NIRS-based GyE systems, as a function of NIRS prescription doses: comparison between the quadratic deviation metric (single port, sphere model, shallow isocenter) and Monte Carlo simulations.

Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy. Fossati P et al. Phys Med Biol. 2012 57(22)

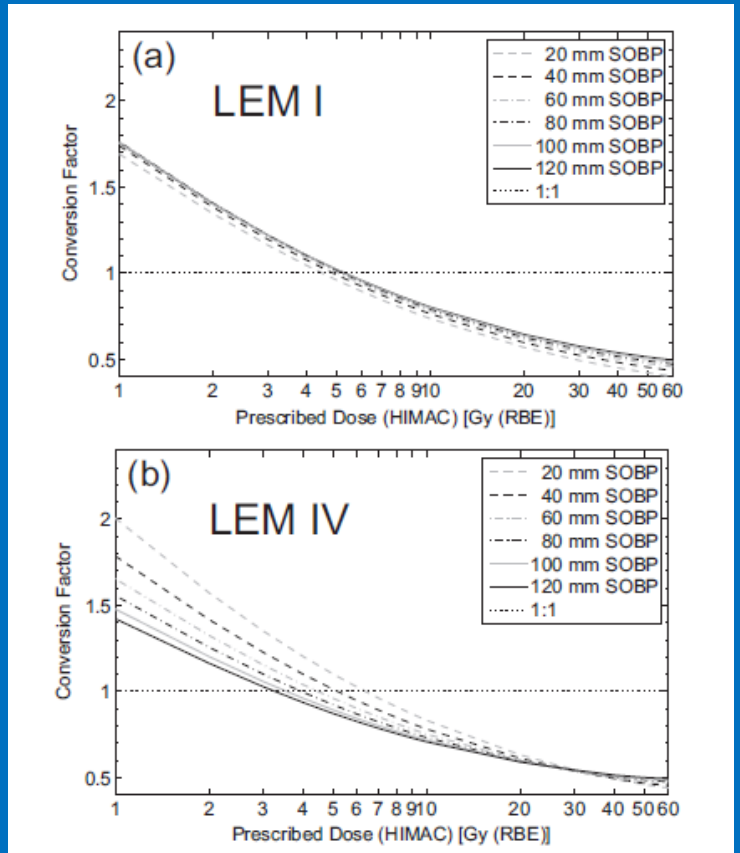


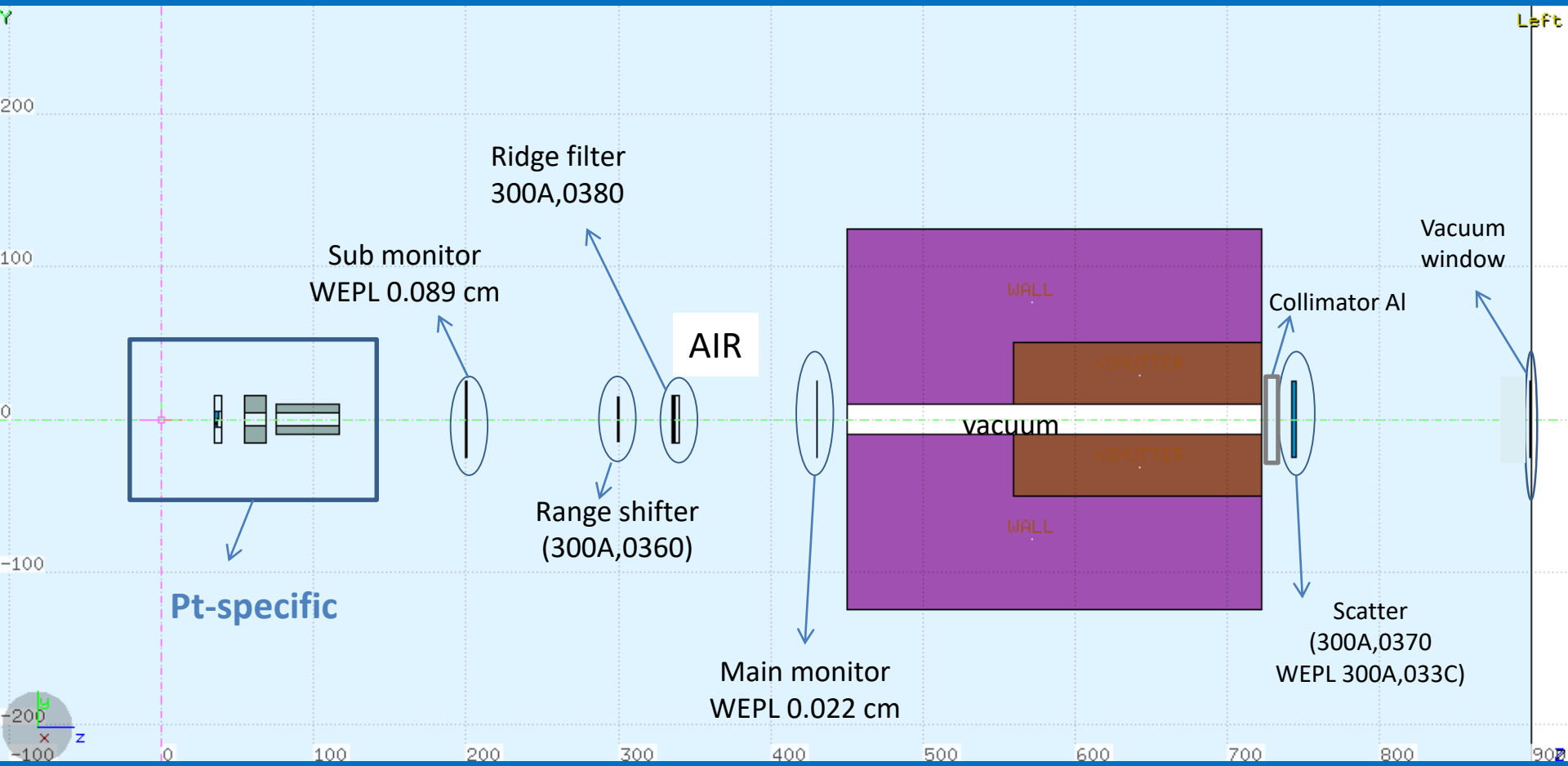
Fig. 4. Conversion factors, $d_{presc}^{LEM}/d_{presc}^{HIMAC}$, in dependence of d_{presc}^{HIMAC} for SOBPs from 20 to 120 mm (depth as in Fig. 1b) for carbon ions. a, results for LEM I; b, results for LEM IV. The $d_{presc}^{LEM} = d_{presc}^{HIMAC}$ relation is marked as dotted line. LEM = Local Effect Model (versions I and IV); SOBP = spread-out Bragg peak.

Mapping of RBE-weighted doses between HIMAC- and LEM-Based treatment planning systems for carbon ion therapy. Steinsträter O et al. Int J Radiat Oncol Biol Phys. 2012;84(3)

Possible solution (2)

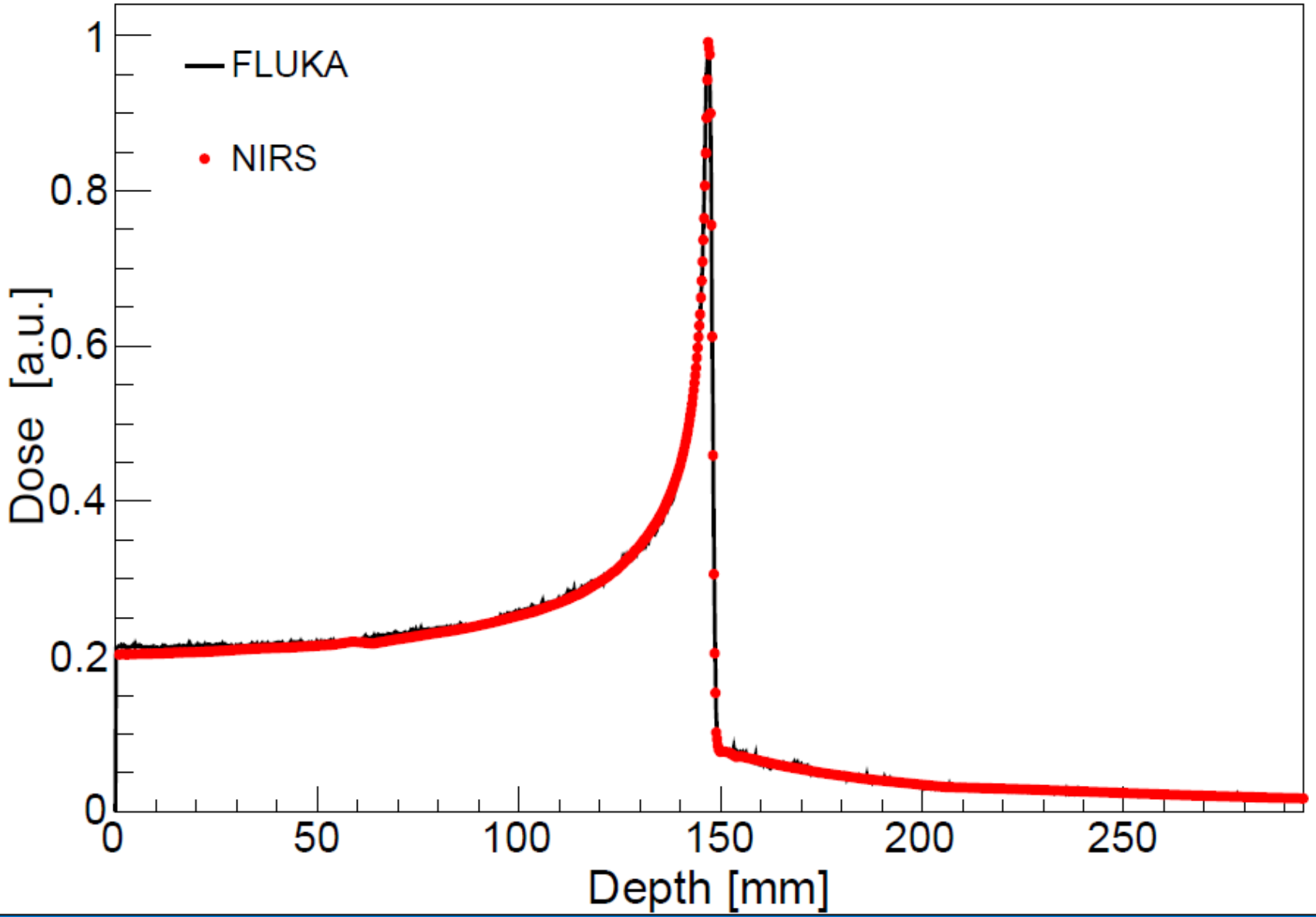
- Modeling of NIRS beamlines
- Beamline validation
  - mono-energetic depth dose profiles in water
  - ridge filter SOBP in water
- MC simulation of NIRS physical doses (clinical data)
- NIRS biological dose according to LEM I
  (Mairani A et al . Phys Med Biol. 2010)
- Comparison with Syngo optimized RT Plan

Horizontal line



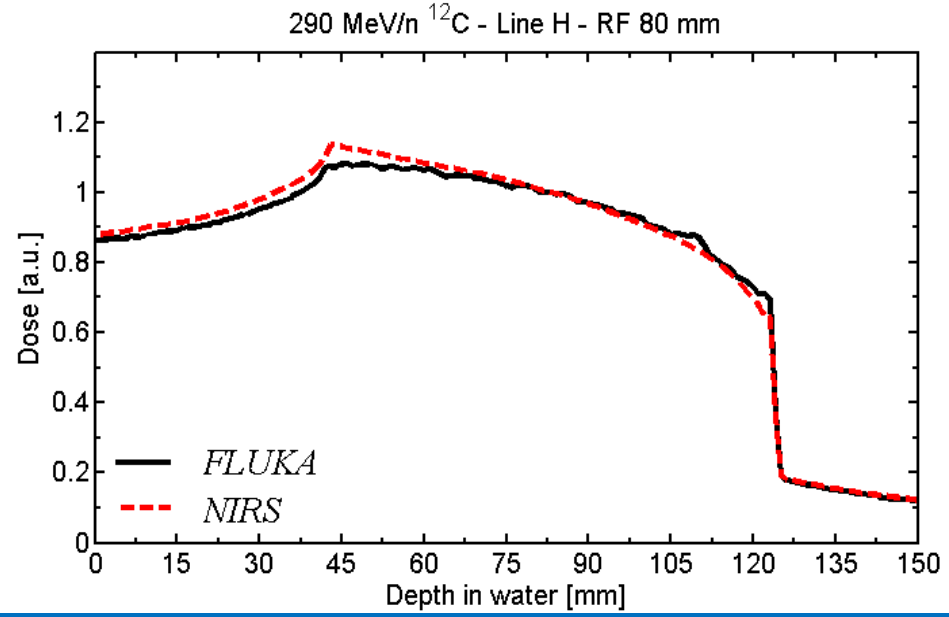
Horizontal line – 290 MeV/u

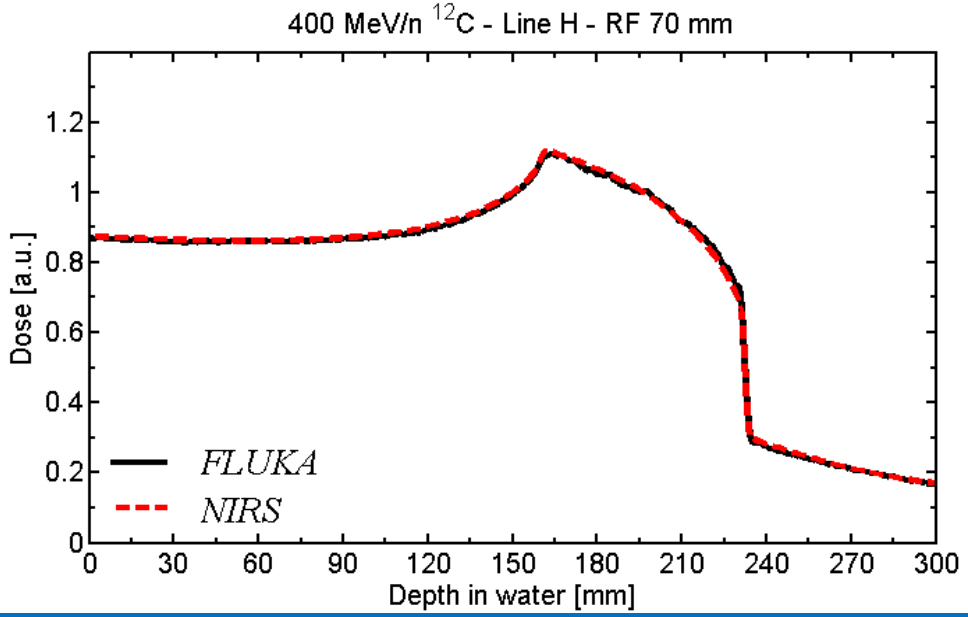
Basic beamline model validation



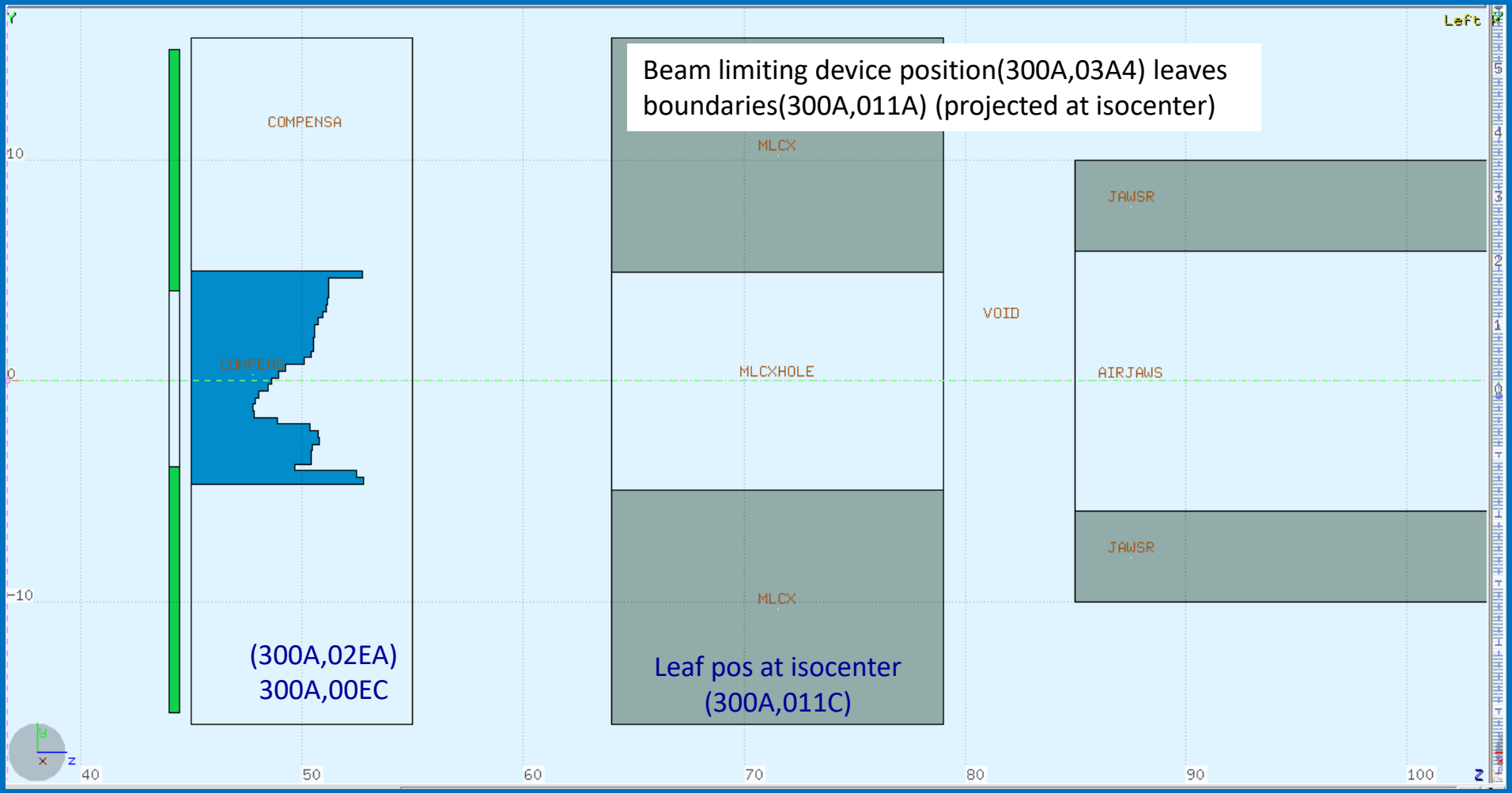
Ridge filter model validation

SOBP in a water phantom





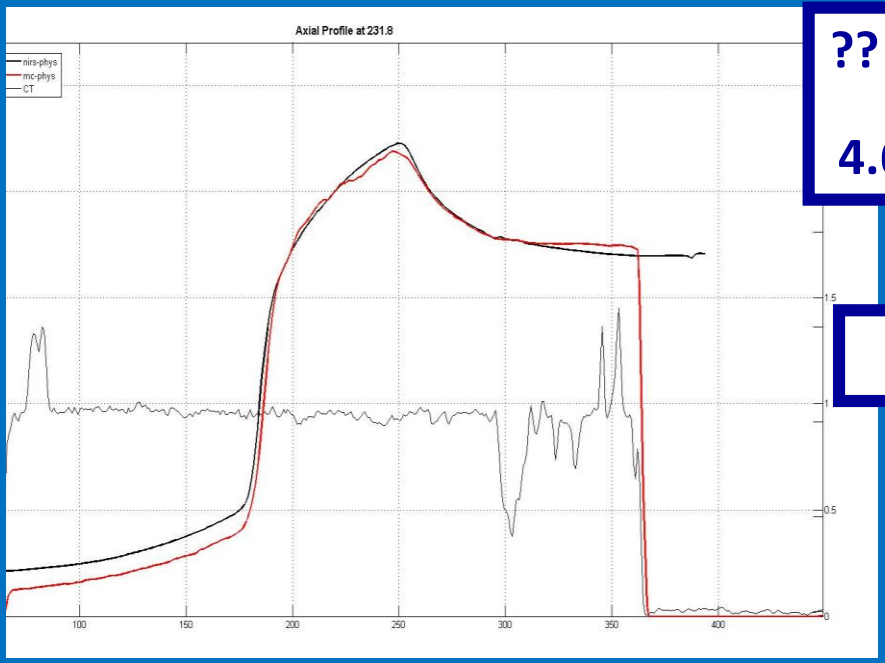
Horizontal line – 400 MeV/u – Pt specific



Pancreas Pt – BVC 400MeV/u - 4.6 Gy $(RBE)_{jp}$

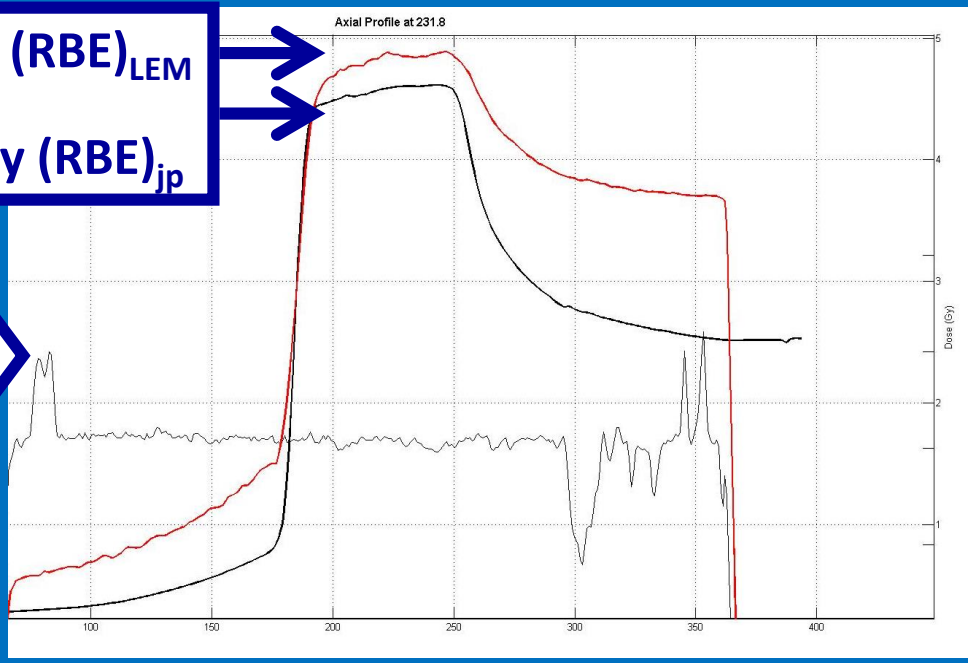
Physical dose
NIRS DICOM data vs FLUKA MC code

Biological dose
NIRS DICOM data vs FLUKA MC code & MyLEM



?? Gy $(RBE)_{LEM}$

4.6 Gy $(RBE)_{jp}$



Carbon ions Gy (RBE) – 3D Radiobiological Model

Step 2
(2016)

Target median RBE-weighted dose difference Japanese vs European RBE adopted models

RBE-weighted dose differences can range from 15% to 4% depending on the dose level

Radiotherapy and Oncology 120 (2016) 307–3

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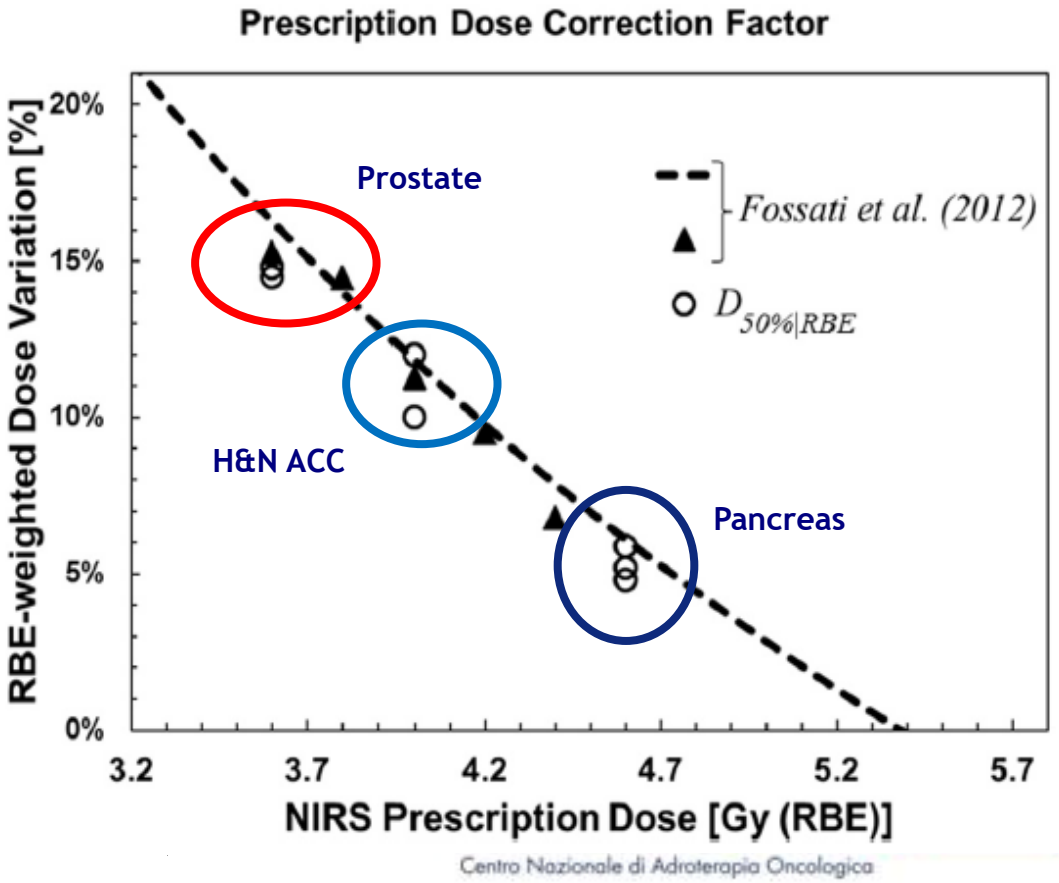
RBE-weighted dose calculation

Dose prescription in carbon ion radiotherapy: How different RBE-weighted dose calculation systems

Silvia Molinelli [a,*], Giuseppe Magro [a], Andrea Mairani [a,b], Naruhiro



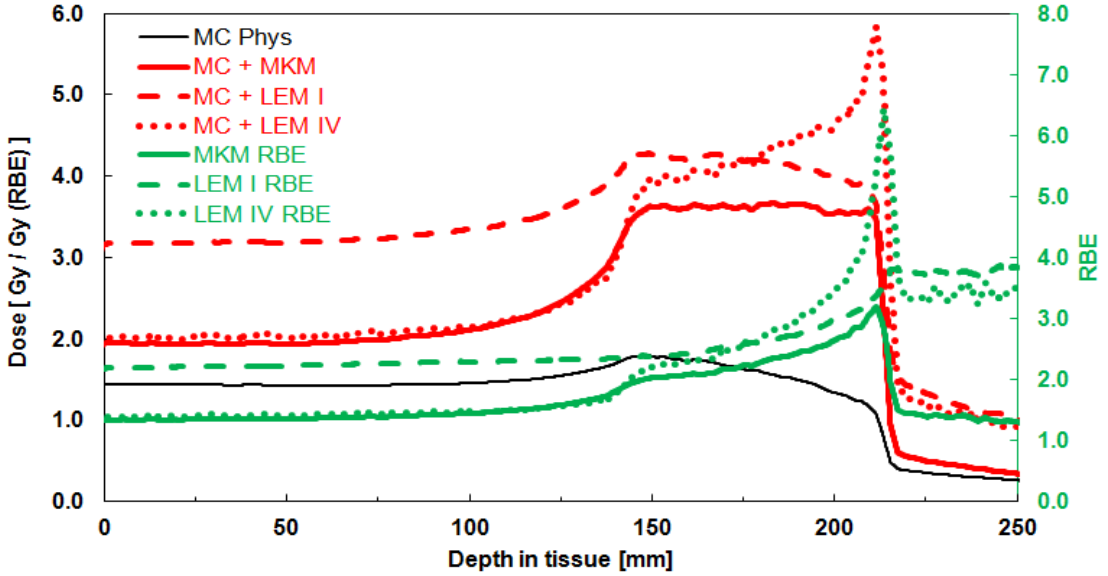
Step 3 (2017)

MKM implementation coupled with Fluka MC

Phys. Med. Biol. **62** (2017) 3814–3827 https://doi.org/10.1088/1361-6560/aa642b

The FLUKA Monte Carlo code coupled with the NIRS approach for clinical dose calculations in carbon ion therapy

G Magro[1], T J Dahle[2], S Molinelli[1], M Ciocca[1], P Fossati[1,3], A Ferrari[4], T Inaniwa[5], N Matsufuji[5], K S Ytre-Hauge[2] and A Mairani[1,6]



Step 4 (2019)

Radiotherapy and Oncology 140 (2019) 175–181

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journal homepage: www.thegreenjournal.com

Original Article

Optic nerve constraints for carbon ion RT at CNAO – Reporting and relating outcome to European and Japanese RBE

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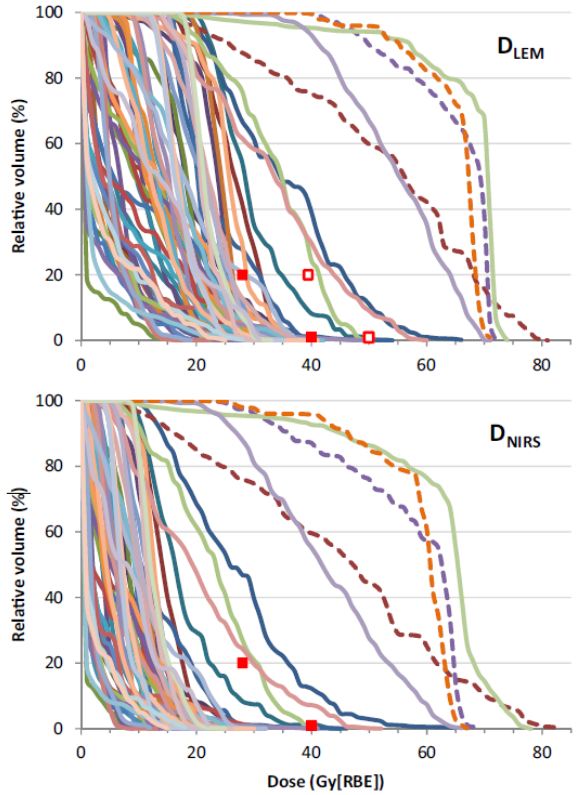


Fig. 1. Cumulative DVH of all 65 ONs in D_{LEM} (upper panel) and D_{NIRS} (lower panel). Dashed DVH-lines represent optic nerves that developed RION. Red, filled squares indicate the current dose constraints of $D_{1\%}$ ≤40 Gy(RBE) and $D_{20\%}$ ≤28 Gy(RBE). Red, open squares in upper panel represent possible new D_{LEM} constraints for CNAO based on RBE-weighted dose translation.

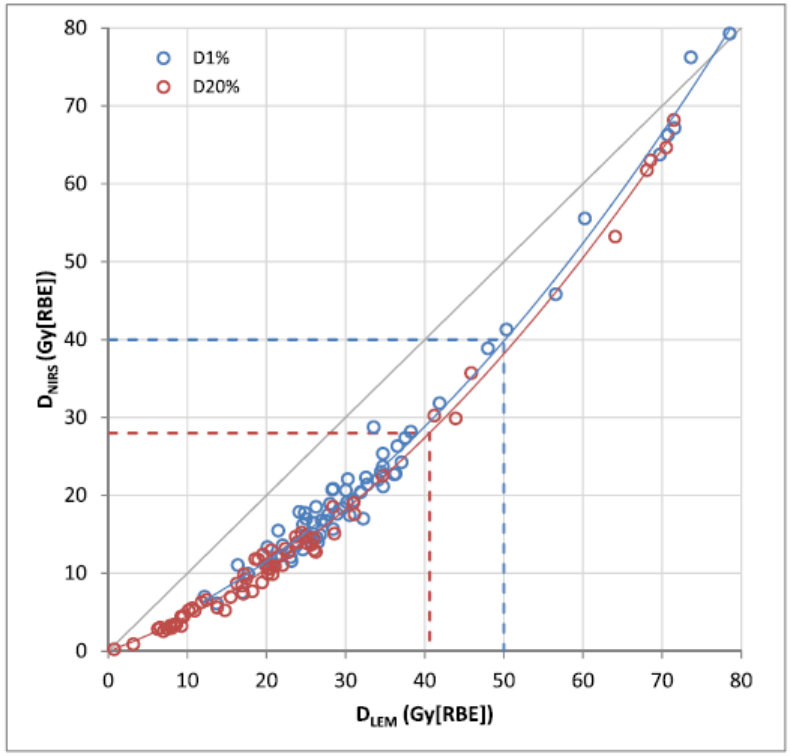
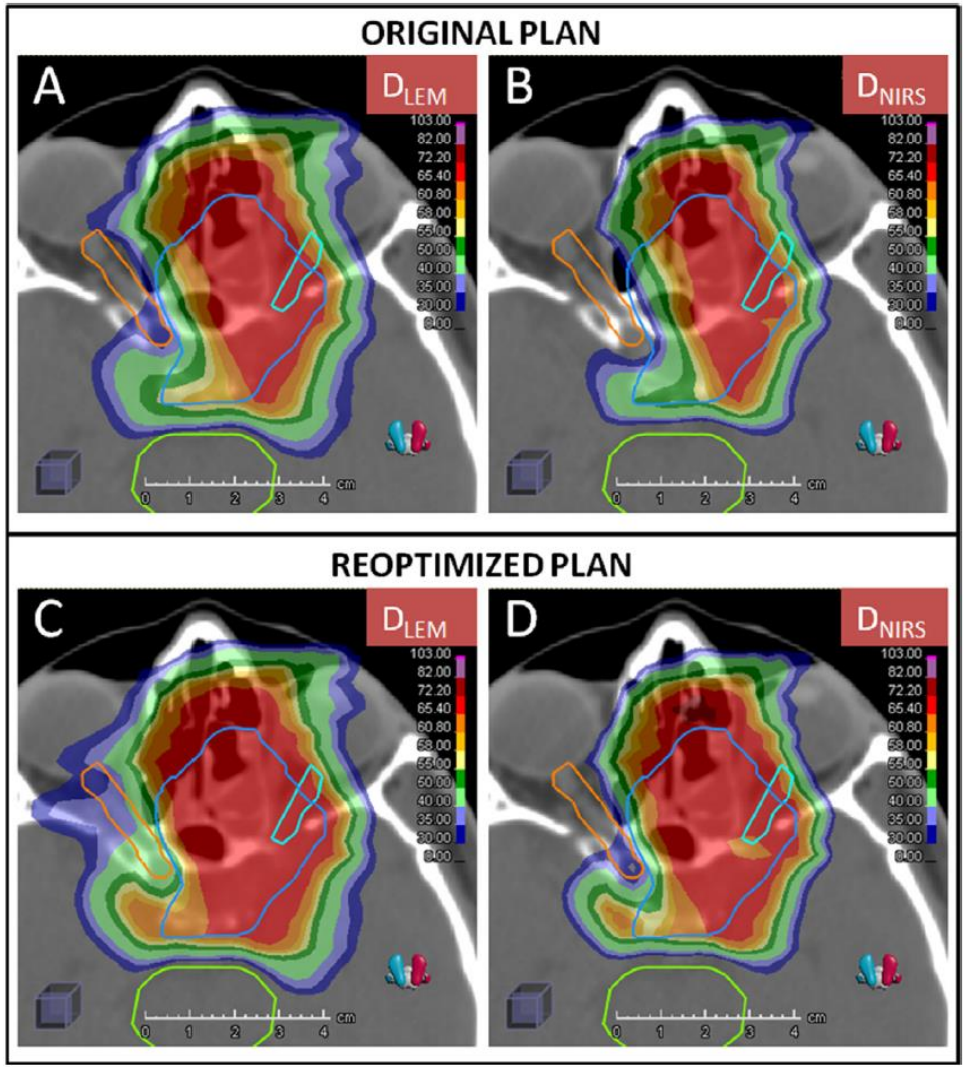


Fig. 2. Relationship of D_{NIRS} and D_{LEM} for $D_{1\%}$ (blue circles) and $D_{20\%}$ (red circles) with corresponding trend lines. Dashed lines represent translation from D_{NIRS} to D_{LEM} for constraint $D_{1\%}$ (blue) and $D_{20\%}$ (red).

Step 4 (2020)


ORIGINAL PLAN
A
D_{LEM}
B
D_{NIRS}
REOPTIMIZED PLAN
C
D_{LEM}
D
D_{NIRS}
103.00
82.00
72.20
65.40
60.80
58.00
55.00
50.00
40.00
35.00
20.00
8.00
cm
0 1 2 3 4

	constraint employed by Japanese Institutions	translated to LEM-I and employed at MedAustron	constraints employed at MedAustron	
Brainstem	D(RBE, 0,1cc) < 40 Gy RBE, D(RBE, 0,7 cc) < 30 Gy RBE	D(RBE, 0,1 cc) < 46 Gy RBE, D (RBE, 0,7cc) < 38 Gy RBE	D(RBE, 0,01 cc) < 54 Gy RBE, D (RBE, 2%) < 50 Gy RBE	
Spinal cord	D(RBE, 0,1cc) < 40 Gy RBE, D(RBE, 0,7cc) < 30 Gy RBE	D (RBE, 0,1cc) < 46 Gy RBE, D (RBE, 0,7cc) < 38 Gy RBE	D(RBE, 0,01cc) < 54 Gy RBE, D (RBE, 2%) < 50 Gy RBE	Same constraints as for Brainstem
Optic nerve and chiasm	D (RBE, 1%) < 35 Gy RBE, D (RBE, 20%) < 30 Gy RBE	D (RBE, 1%) < 45 Gy , D (RBE, 20%) < 38 Gy	D (RBE, 0,01cc) < 50 Gy RBE	The LEM-I constraint of 45 Gy RBE can be increased to 50 Gy RBE on one side
Brain (endpoint necrosis)	Optimal D(RBE, 5cc) < 50 Gy RBE Acceptable D(RBE, 5cc) < 60 Gy RBE	Optimal D RBE, 5cc) < 54 Gy RBE Acceptable D(RBE, 5cc) < 64 Gy RBE	Optimal D(RBE, 1cc)< 56,7 Gy RBE Acceptable D (RBE, 1cc) < 59 Gy RBE	Brain and temporal lobe data have been pooled together

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Carbon ion irradiation

Dose–volume histogram analysis of brainstem necrosis in head and neck tumors treated using carbon-ion radiotherapy

Katsuyuki Shirai [a,*], Kyohei Fukata [a], Akiko Adachi [a], Jun-ichi Saitoh [a], Atsushi Musha [a,b], Takanori Abe [a], Tatsuaki Kanai [a], Daijiro Kobayashi [a], Yuka Shigeta [a], Satoshi Yokoo [b], Kazuaki Chikamatsu [c], Tatsuya Ohno [a], Takashi Nakano [a]

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Table 2
Optimal cut-off values based on the receiver operating characteristic curve analysis.

	Cut-off value	2-year brainstem necrosis rate (%)	*P*-value
Maximum dose	≥48 Gy (RBE)	40	<0.001
	<48 Gy (RBE)	0	
D1 cm^3	≥27 Gy (RBE)	33	<0.001
	<27 Gy (RBE)	0	
V40 Gy (RBE)	≥0.1 cm^3	40	<0.001
	<0.1 cm^3	0	
V30 Gy (RBE)	≥0.7 cm^3	33	<0.001
	<0.7 cm^3	0	
V20 Gy (RBE)	≥1.4 cm^3	28	<0.001
	<1.4 cm^3	0	

RBE: relative biological effectiveness.

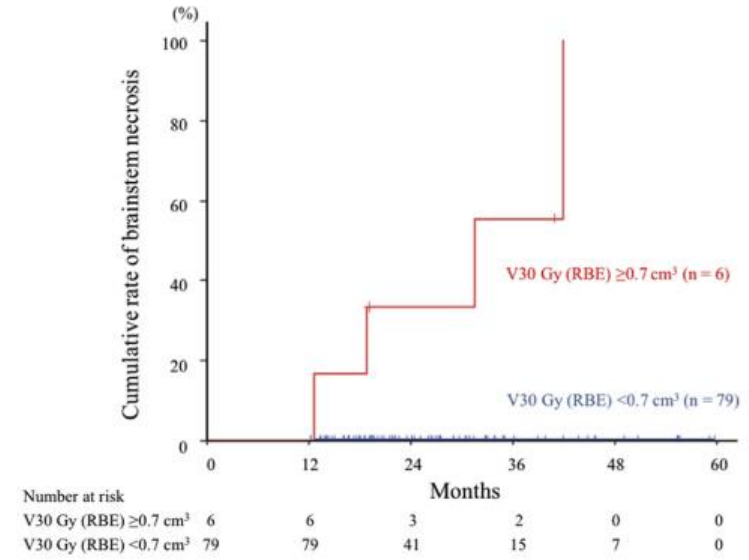
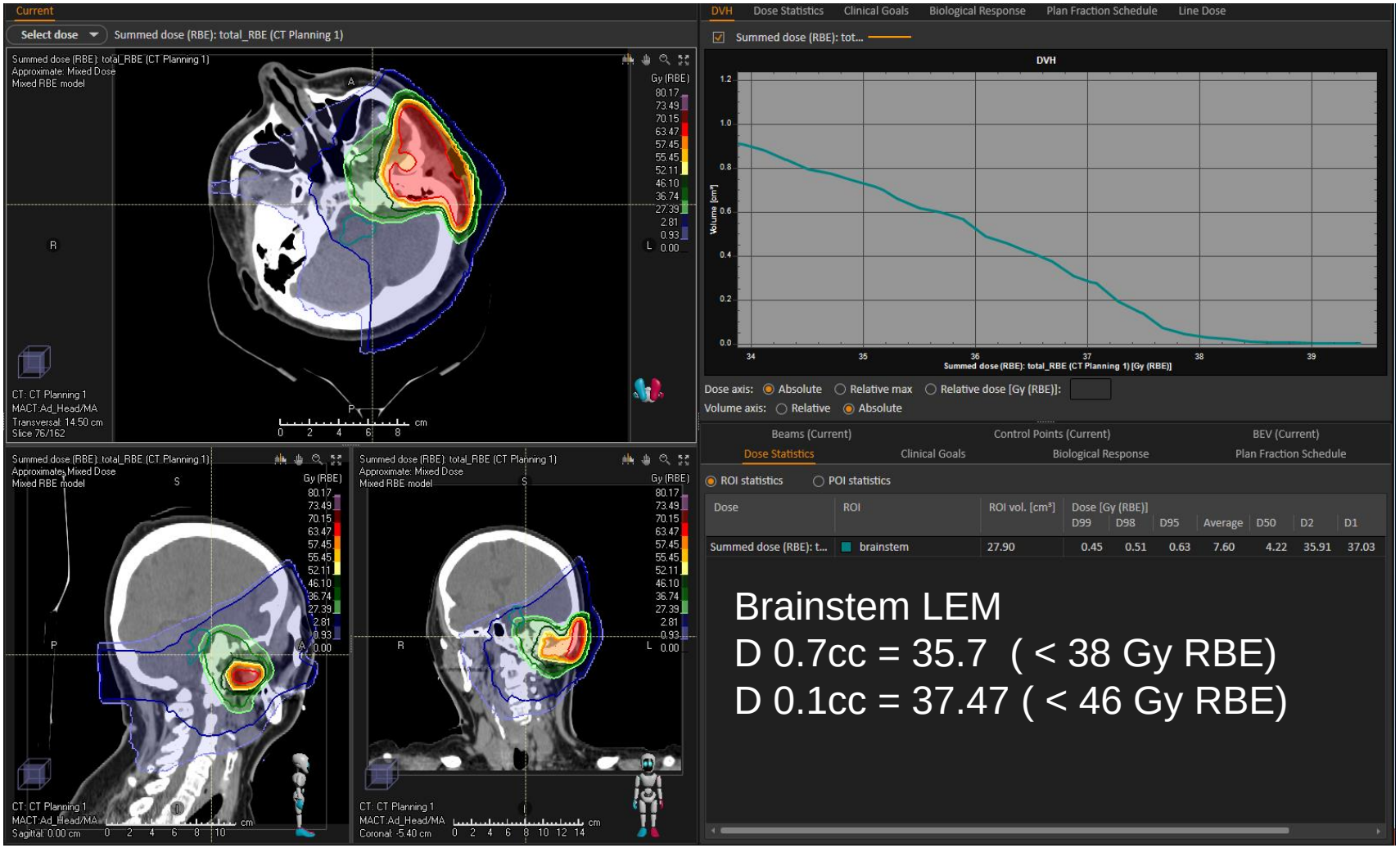


Fig. 3. The cumulative rates of brainstem necrosis according to V30 Gy (RBE) of ≥0.7 cm^3 ($n = 7$) and V30 Gy (RBE) of <0.7 cm^3 ($n = 79$). The 2-year cumulative brainstem necrosis rates for the higher and lower dose groups were 33% and 0%, respectively ($p < 0.001$).

First CIRT patient LEM plan



Brainstem LEM

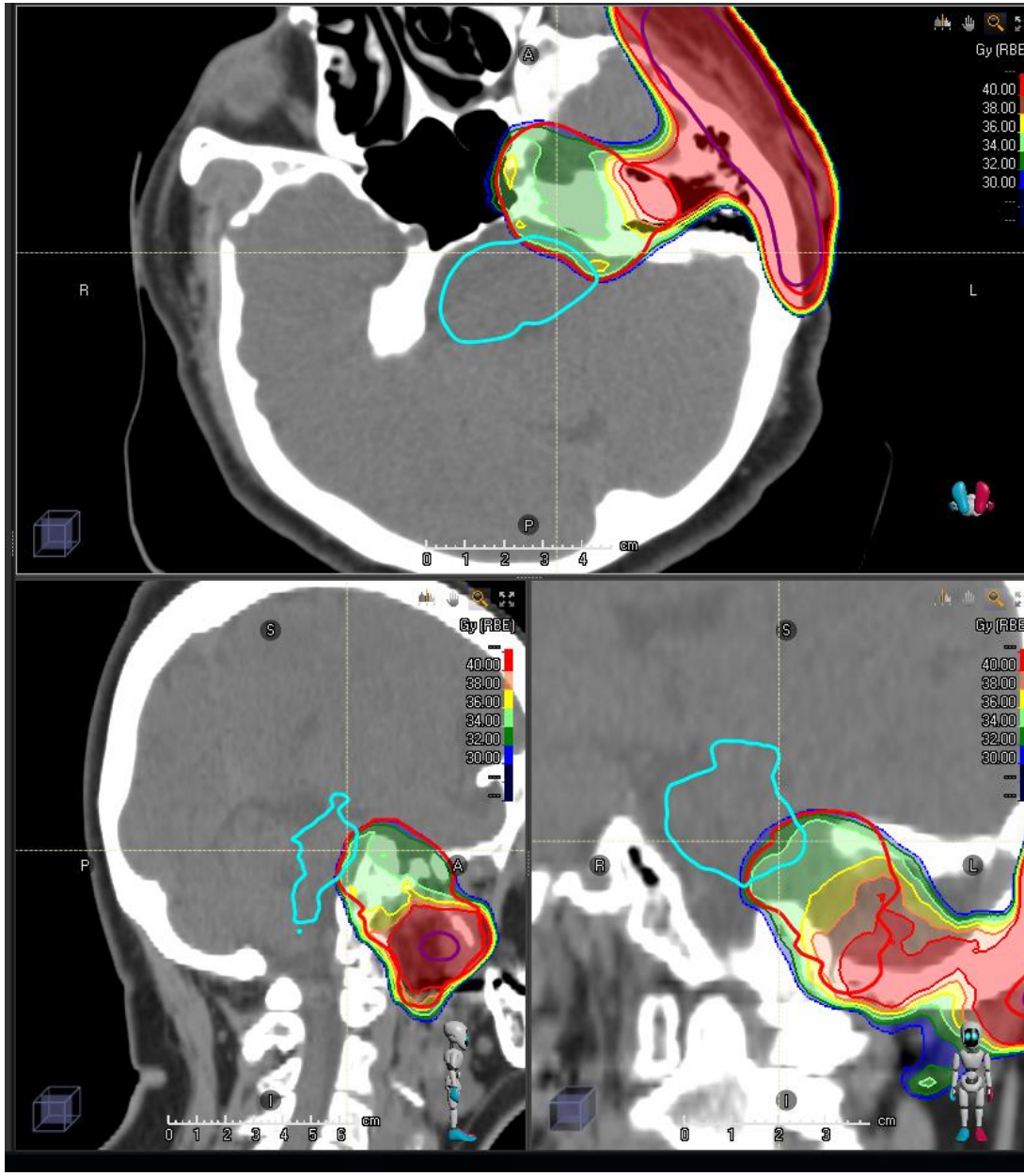
D 0.7cc = 35.7 (< 38 Gy RBE)

D 0.1cc = 37.47 (< 46 Gy RBE)

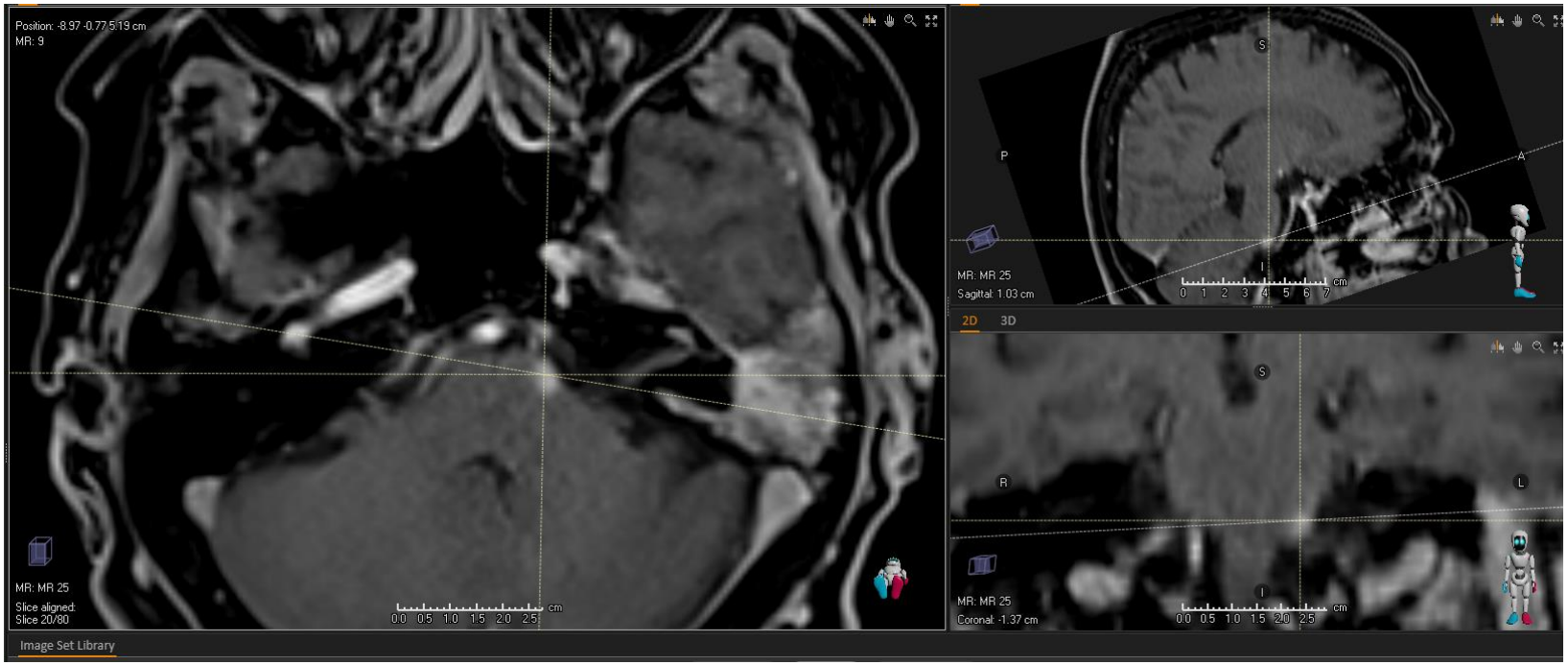
Recomputed
MKM dose

Brainstem LEM
D0.7cc = 35.7 (< 38 Gy RBE)
D0.1cc = 37.47 (< 46 Gy RBE)

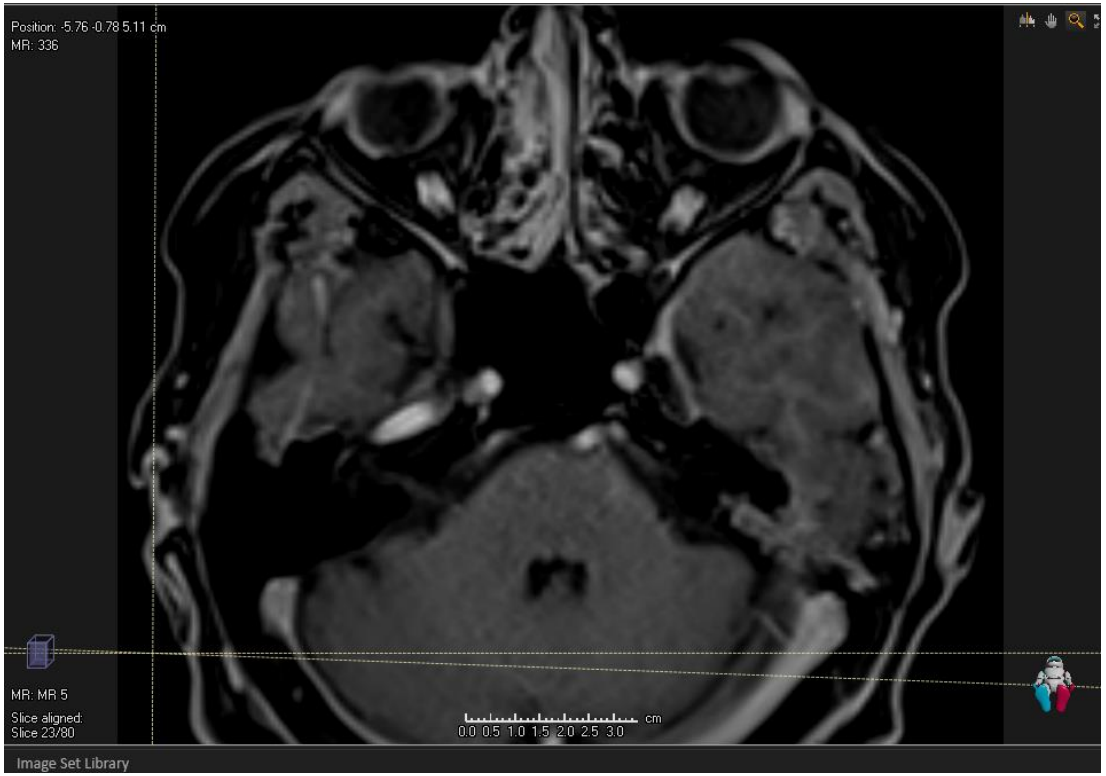
Brainstem MKM
D0.7cc = 32.68 (> 30 Gy RBE)
D0.1cc = 35.4 (< 40 Gy RBE)



9 months after CIRT asymptomatic CE



After 20 Mo. Without symptoms and without therapy



Step 5 (today at MedAustron)

- Examine simultaneously both LEM and MKM plans
- Respect OARs dose constraints and target coverage in both RBE sistems (with different values)

Step 6 (Future)

- Have a TPS that performs simultaneous multi Rbe optimization

Vielen Dank für ihre Aufmerksamkeit