IEO
Istituto Europeo di Oncologia

fondazione CNAO

Carbon ion radiotherapy: do we understand each other? How to compare different RBE-weighted dose systems in the clinical setting?

(P. Fossati)

Photons (and protons) make life easy

Table 1. Local Control in Early-Stage Non–Small-Cell Lung Cancer

Study	Year of Publication	Treatment	Local Control Rate (%)
North America/Europe			
Timmerman et al[10]	2006	20-22 Gy × 3	95 at 2+ years
Bauman et al[47]	2006	15 Gy × 3	80 at 3 years
Fritz et al[48]	2006	30 Gy × 1	80 at 3 years
Nyman et al[49]	2006	15 Gy × 3	80, crude
Zimmermann et al[50]	2005	12.5 Gy × 3	87 at 3 years
Timmerman et al,[45] McGarry et al[46]	2003, 2005	18-24 Gy × 3	90 at 2 years
Asia			
Xia et al[52]	2006	5 Gy × 10	95 at 3 years
Hara et al[53]	2006	30-34 Gy × 1	80 at 3 years
Nagata et al[54]	2005	12 Gy × 4	94 at 3 years

Timmerman et al JCO 2007

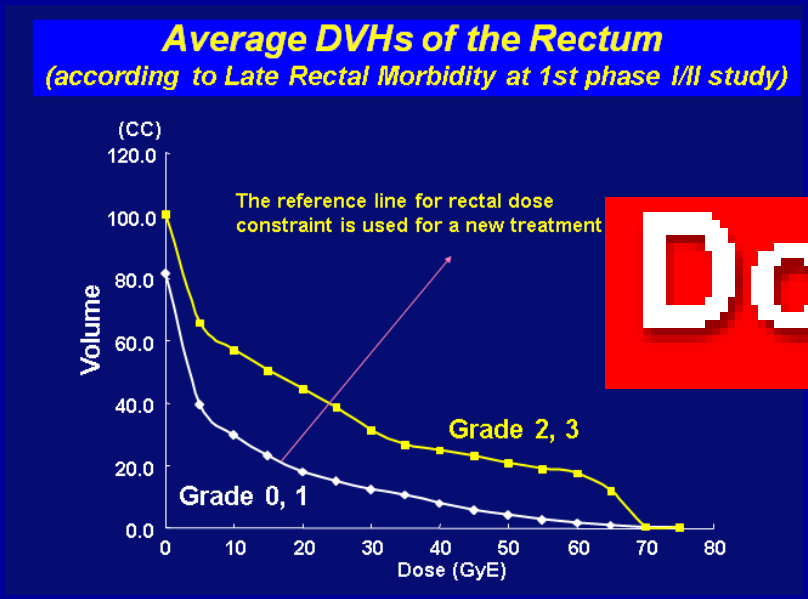
Dosimetric limits for thoracic organs at risk

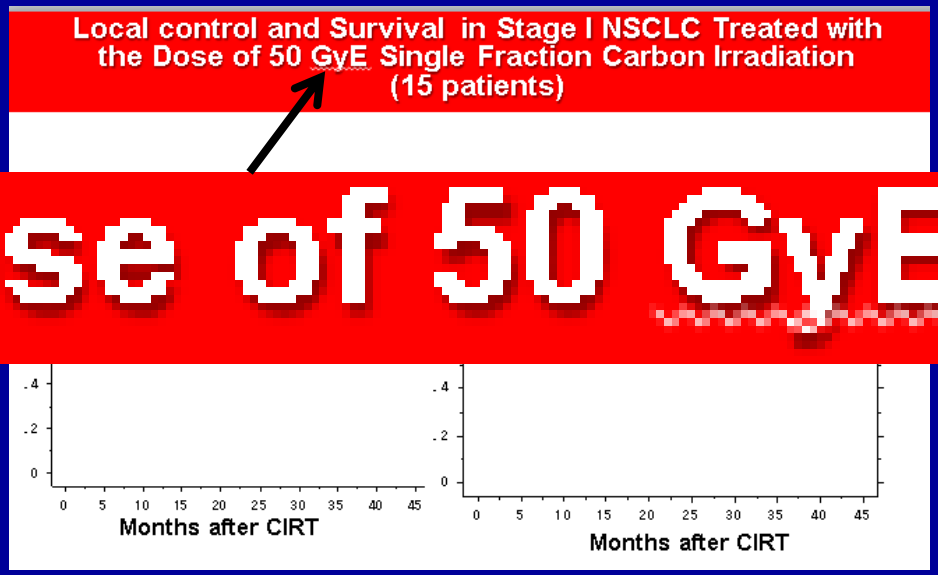
Dose limits for OARs	3D-CRT (RTOG 0617)	3D-CRT (RTOG 0972/CALGB 36050)	SBRT (RTOG 0618, 3 fx)	SBRT (ROSEL European trial, 3 or 5 fx)
Spinal cord (point dose)	Point dose ≤50.5 Gy	Any portion ≤50 Gy	≤18 Gy (6 Gy/fx)	18 Gy (3 fx) 25 Gy (5fx)
Lung	Mean lung dose ≤20 Gy, V_{20} ≤37%	V_{20} ≤35%	V_{20} ≤10%*	V_{20} <5–10%†
Esophagus	Mean dose ≤34 Gy	Not limited	≤27 Gy (9 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Brachial plexus (point dose)	≤66 Gy	Not limited	≤24 Gy (8 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Heart‡	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤30 Gy (10 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Trachea, bronchus	Not limited	Not limited	≤30 Gy (10 Gy/fx)	30 Gy (3 fx) 32 Gy (5 fx)
Ribs	Not limited	Not limited	Not limited§	Not limited
Skin	Not limited	Not limited	≤24 Gy (8 Gy/fx)	Not limited

Abbreviations: OARs = organs at risk; 3D-CRT =three-dimensional conformal radiotherapy; RTOG = Radiation Therapy Oncology Group; CALGB = Cancer and Leukemia Group B; SBRT = stereotactic body radiotherapy; ROSEL = *Radiosurgery Or Surgery for Early Lung Cancer*; fx = fraction; V20 = percentage of both lungs (without inclusion of gross tumor volume) receiving ≥20 Gy.

Kong et al IJROBP 2011

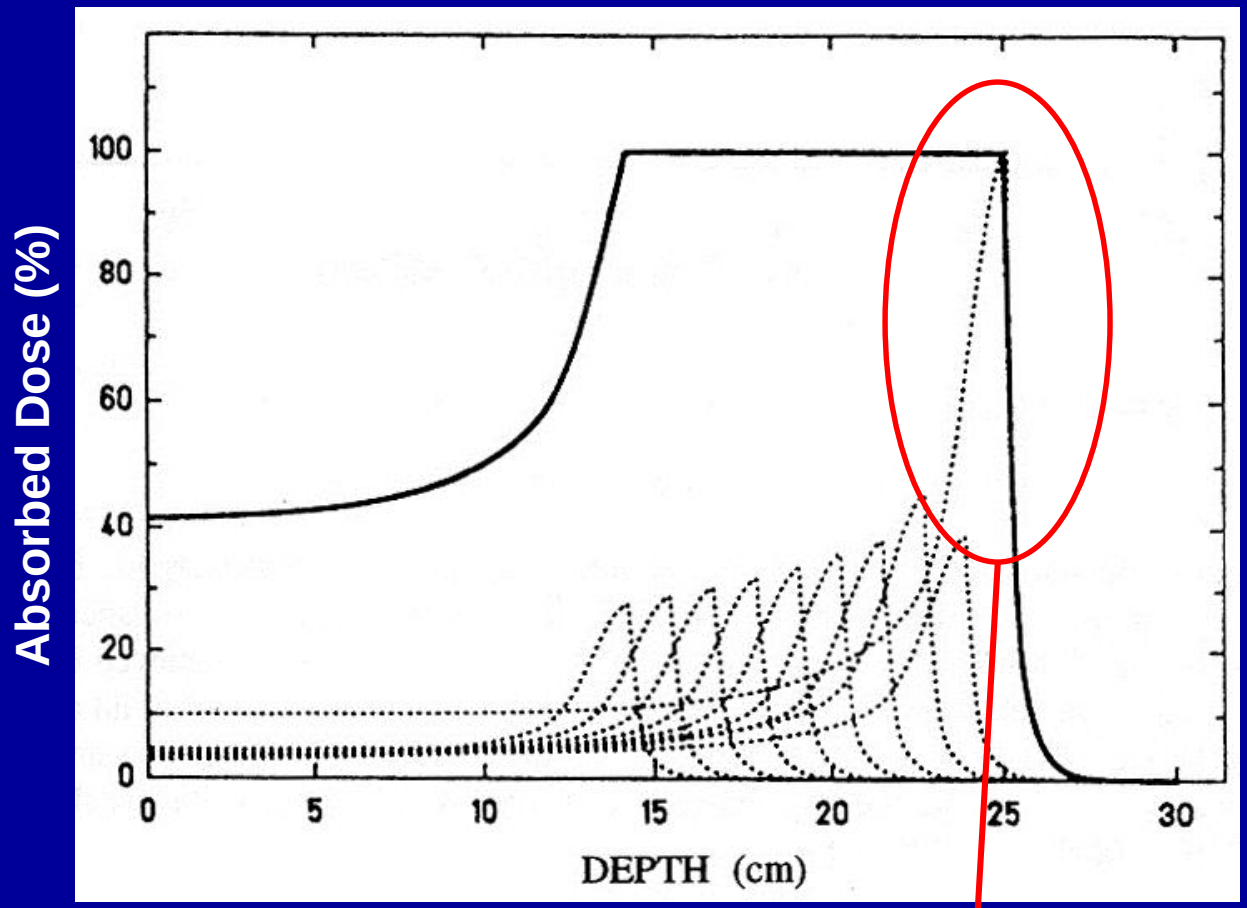
Can we do the same with carbon ions?





Courtesy of Dr. Kamada, NIRS

Carbon ions



→ higher biological effect whichever endpoint you choose

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

Contents lists available at ScienceDirect

Nuclear Instruments and Methods in Physics Research B

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

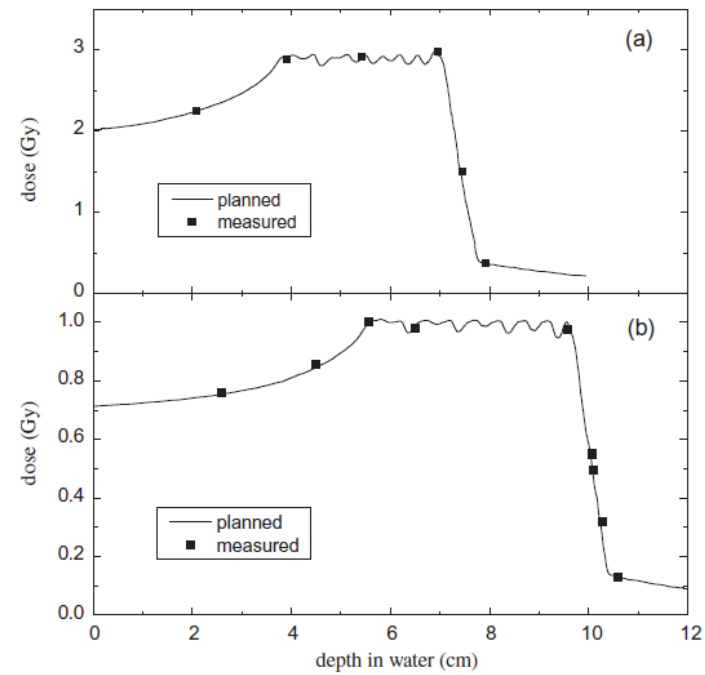


Fig. 3. Depth dose distributions for 195 (a) and 235 MeV/u (b) carbon-ion beams with 3 and 4 cm SOBPs generated by the mini-SOBP layer-stacking irradiation method respectively, where the planned depth-dose distributions were calculated using the current TPS at IMP.

→ 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**

All clinical results from Europe (GSI, HIT and CNAO) 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)

Different ways to prescribe carbon ion RT

- No easy way to compare carbon ion RT plans obtained with different models
- Everyone agree qualitatively but there is quantitative disagreement
- No one is right as there are many relevant endpoints and all are difficult to measure

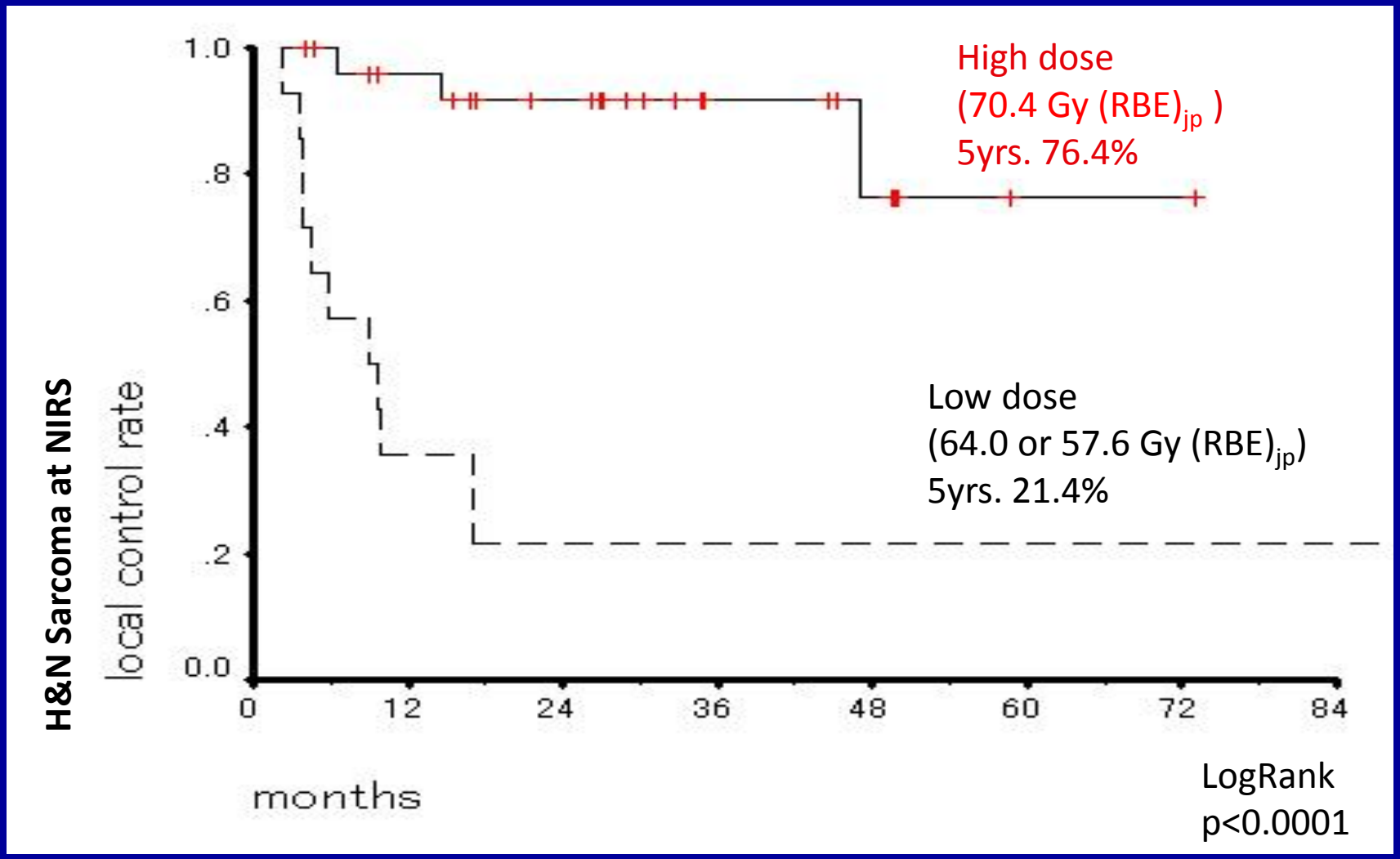
BUT

→ We risk **not** to understand each other

→ Kanai vs. LEM I is a clinically relevant difference

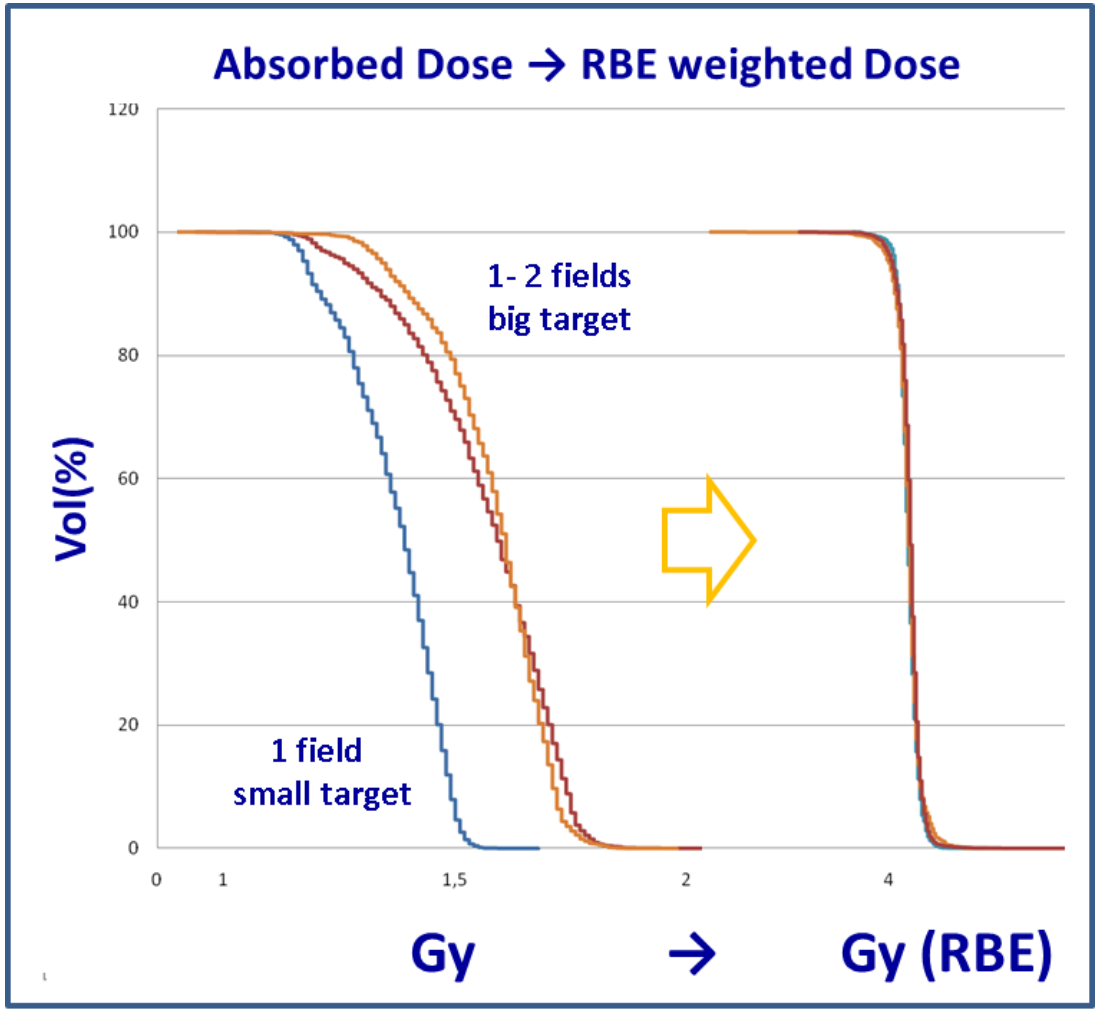
→ The physical dose shape will always be different, but we need to avoid systematic errors

10% difference is clinically relevant



Courtesy of Dr. Hasegawa, NIRS

Can we compare physical dose?



→ Different physical dose DVH

Possible solution (1)

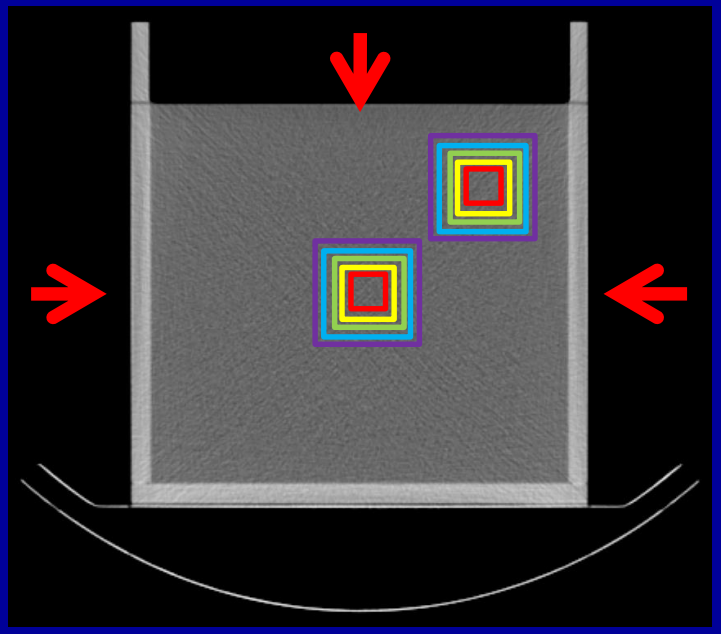
Compare physical dose fixing “reference conditions”

→ Homogeneous conditions - Water phantom

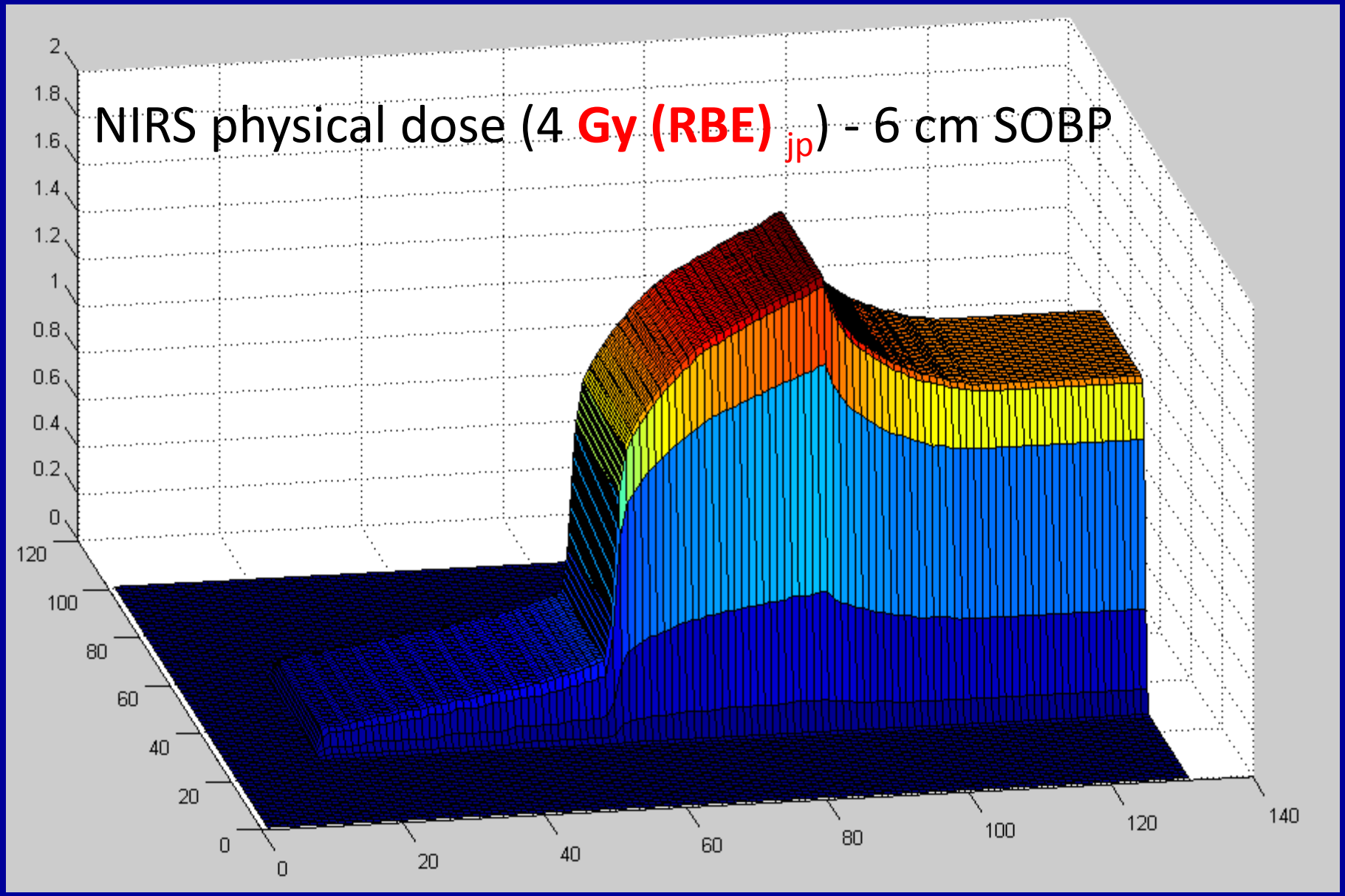
→ **Same volumes** - 5 Cubes: (4, 6, 8, 10, 12 cm)

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

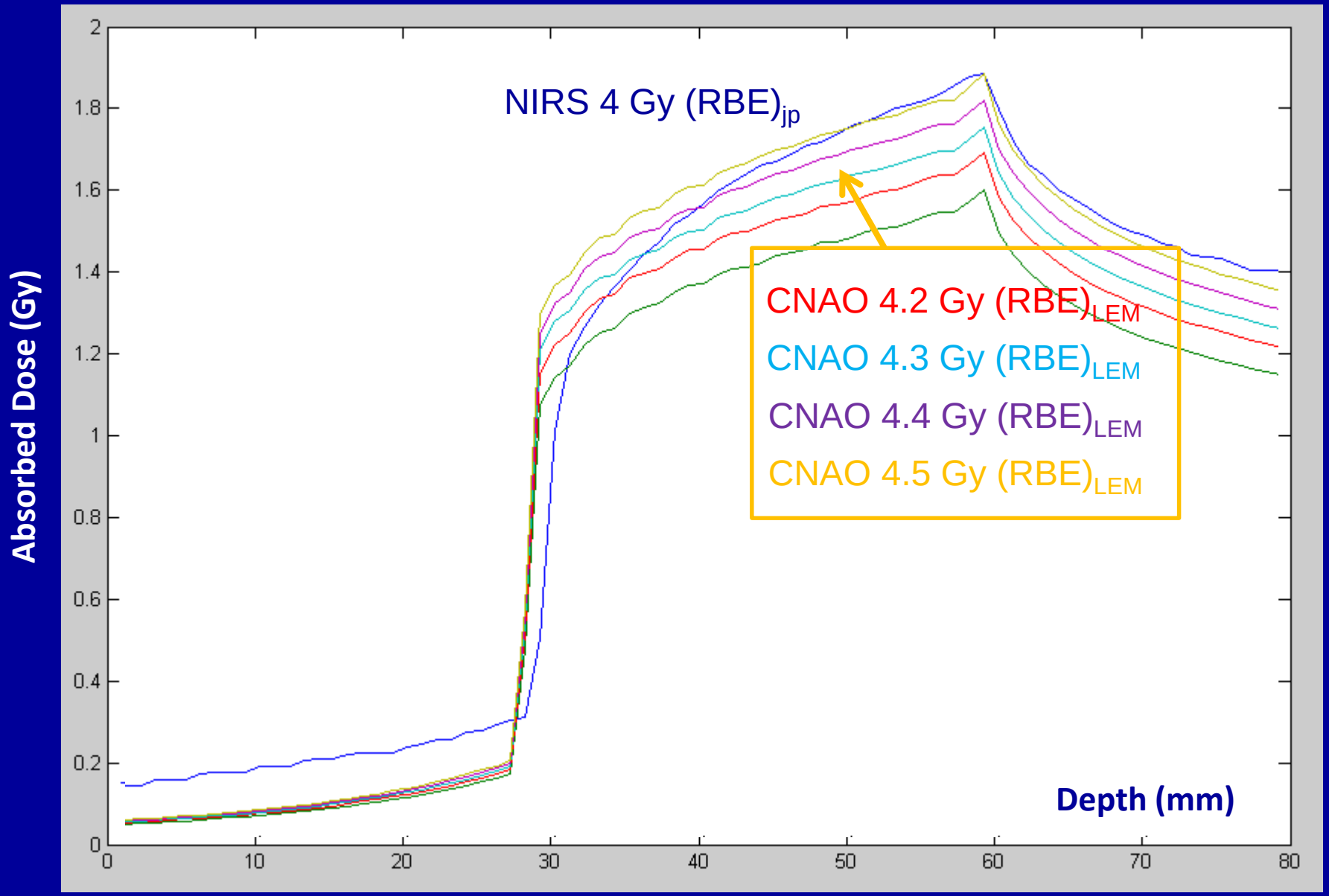
→ **Same field orientation** – single, 2 orthogonal, 2 opposed



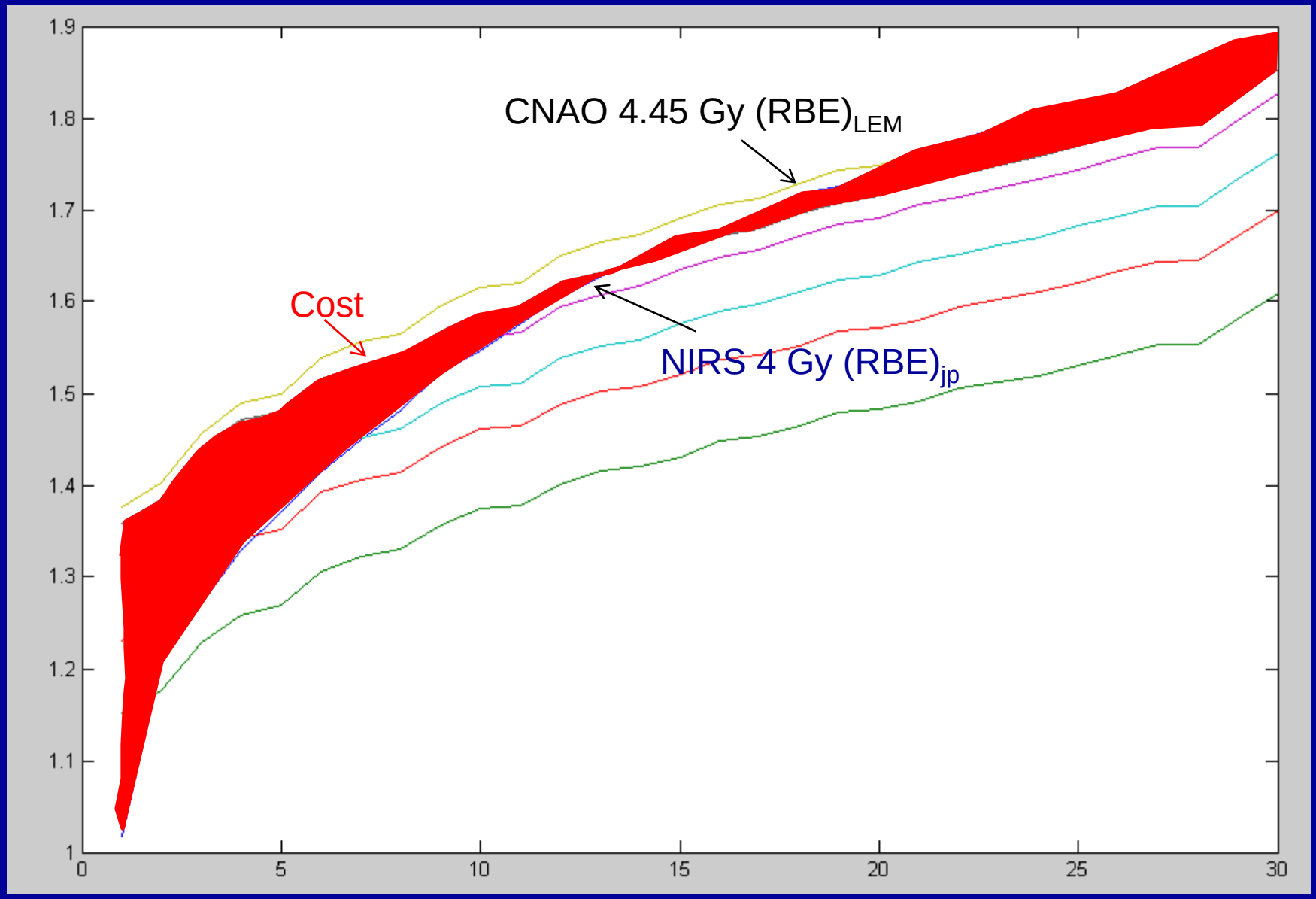
NIRS physical dose (4 **Gy (RBE)** $_{jp}$) - 6 cm SOBP



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



Minimize physical dose difference in the SOBP



Optimal dose is size dependant!

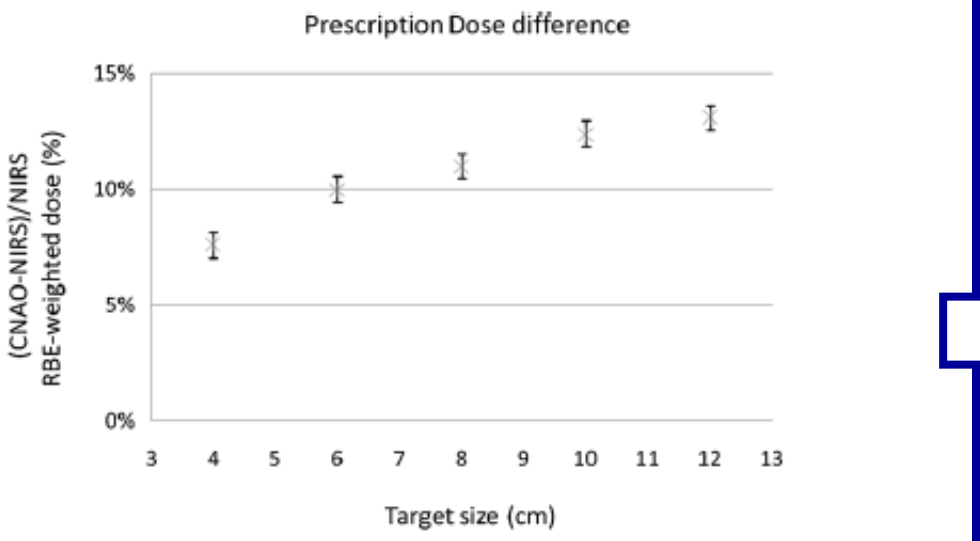
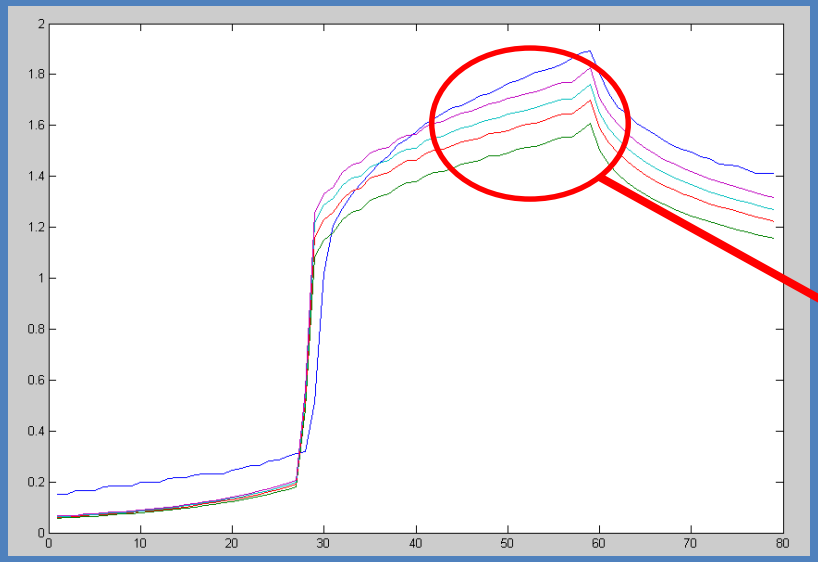
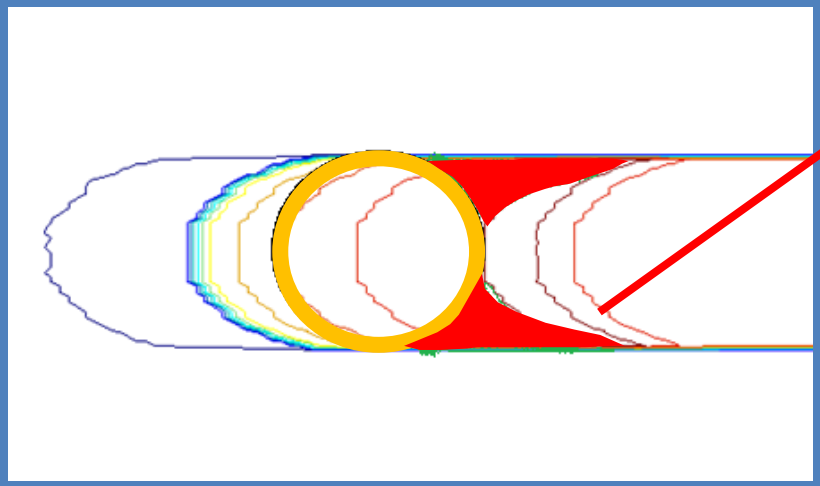


Figure 2. RBE-weighted dose percentage differences between LEM-based GyE and NIRS-based GyE systems, as a function of spherical target size. The percentage dose difference reported is averaged over all prescription dose level, isocenter position and beam configuration cases. The crosses represent the mean values, error bars represent standard deviations.

Sizes are weigthed according to real tumor size distributions, based on NIRS experience

Cubes, spheres or patients?





Tails of “wasted” SOBP were LEM is planning a lower physical dose
→ higher distal SOBP contribution
→ If we treat **spheres** we should give slightly lower dose

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

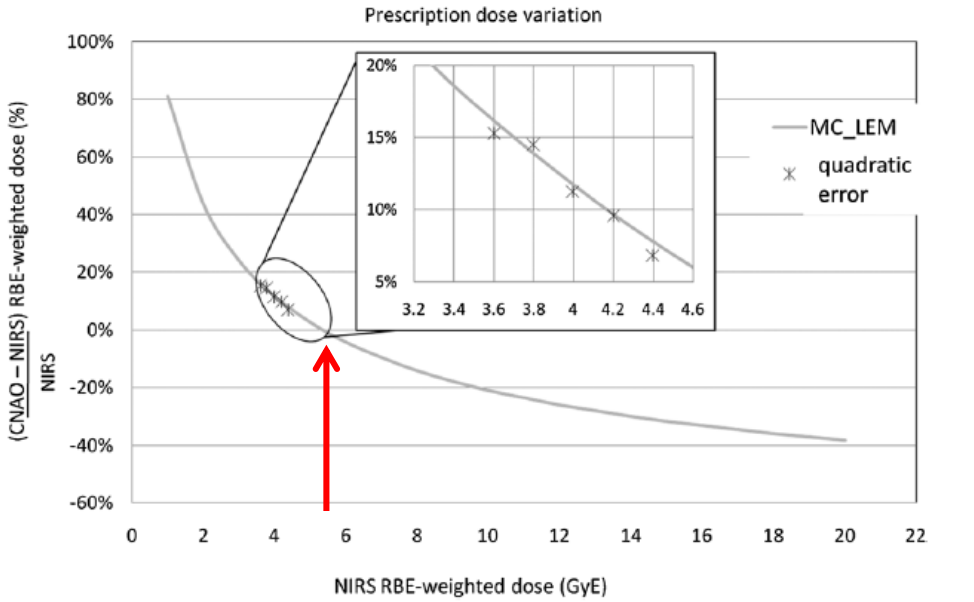


Figure 4. RBE-weighted dose percentage differences between LEM-based GyE and NIRS-based GyE systems, as a function of NIRS prescription doses: comparison between the quadratic deviation metric (single port, sphere model, shallow isocenter) and Monte Carlo simulations.

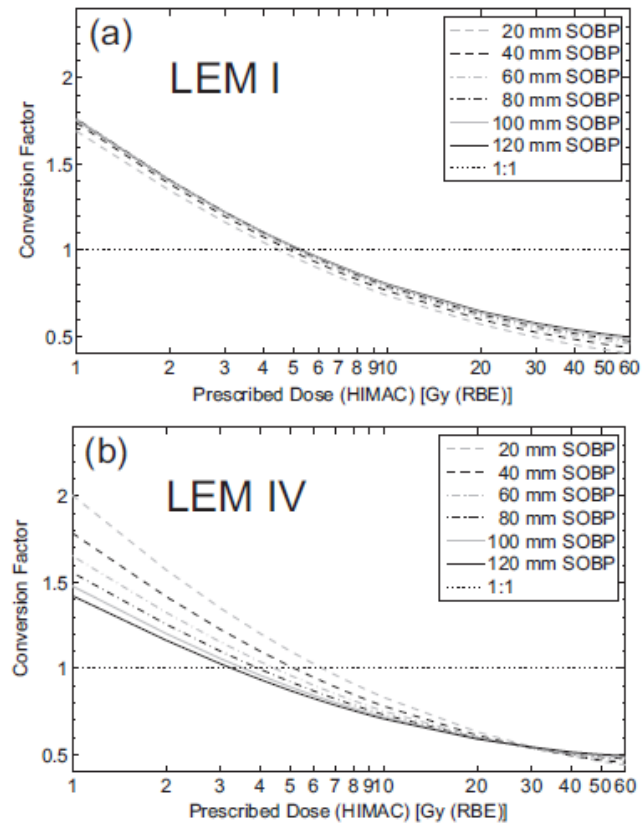


Fig. 4. Conversion factors, $d_{presc}^{LEM}/d_{presc}^{HIMAC}$, in dependence of d_{presc}^{HIMAC} for SOBPs from 20 to 120 mm (depth as in Fig. 1b) for carbon ions. a, results for LEM I; b, results for LEM IV. The $d_{presc}^{LEM} = d_{presc}^{HIMAC}$ relation is marked as dotted line. LEM = Local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

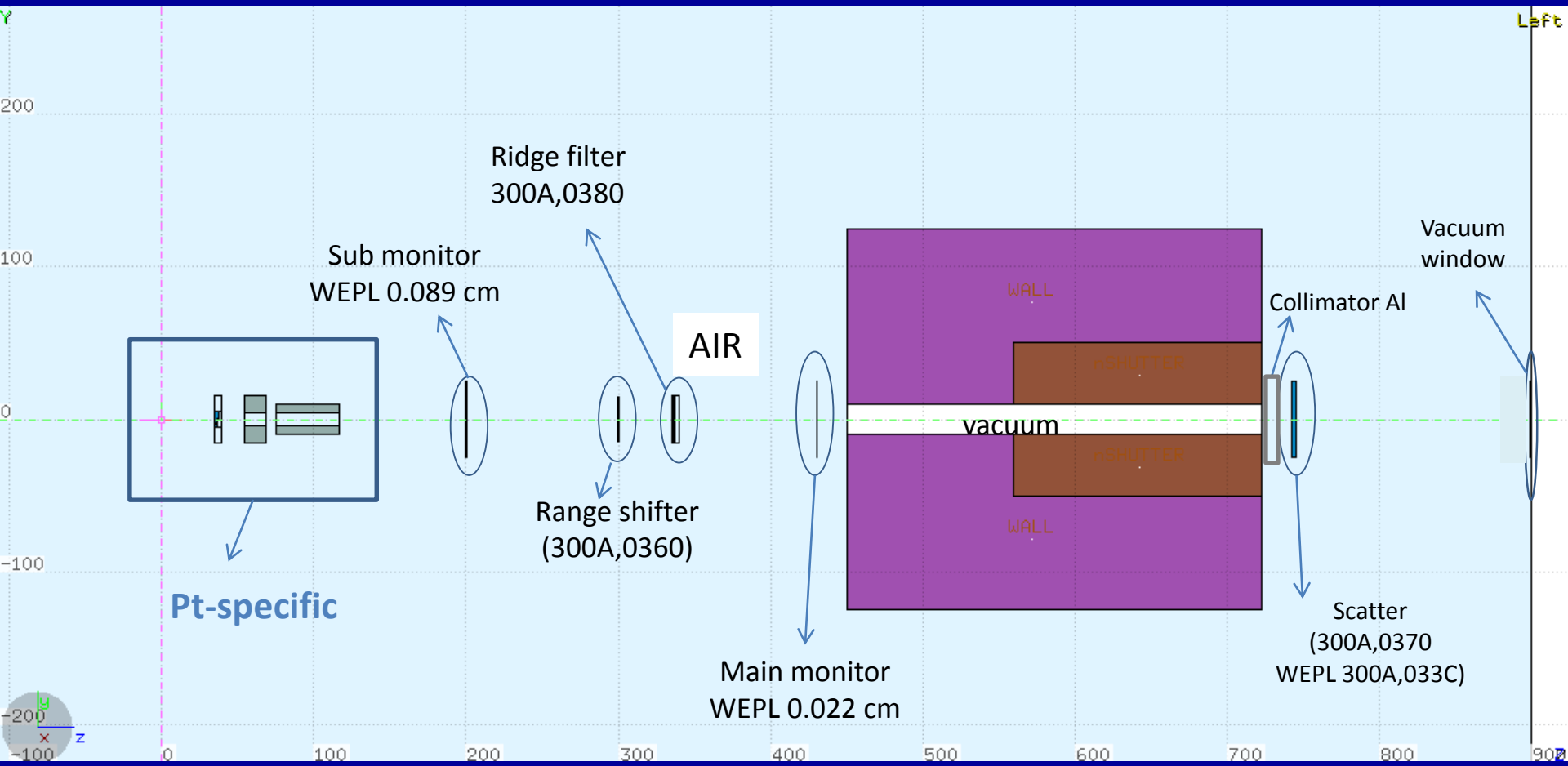
Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy. Fossati P et al. Phys Med Biol. 2012 57(22)

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)

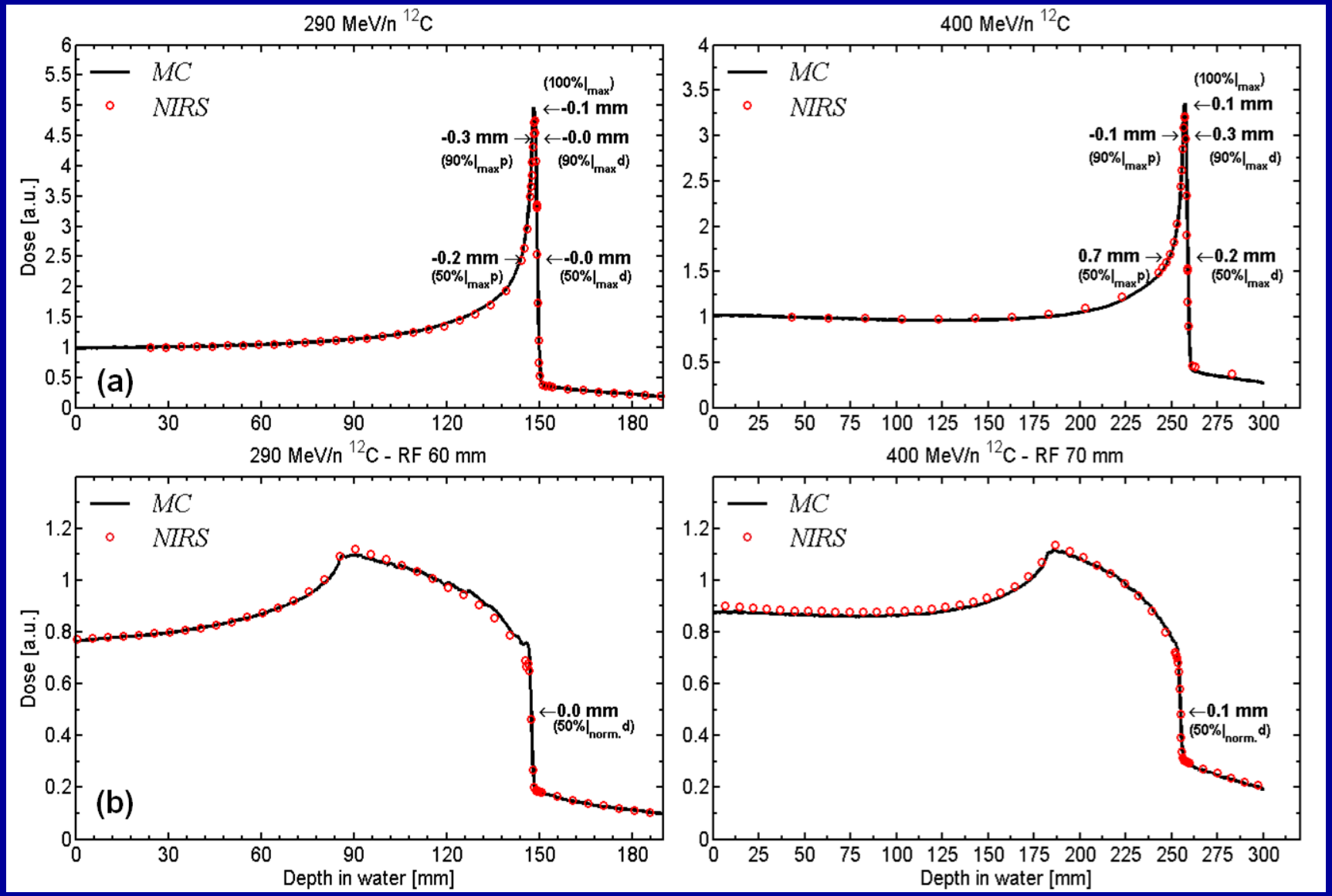
- Modeling of NIRS beamlines
- Beamline validation
  - mono-energetic depth dose profiles in water
  - ridge filter SOBP in water
- MC simulation of NIRS physical doses (clinical data)
- NIRS biological dose according to LEM I
  (Mairani A et al . Phys Med Biol. 2010)
- Comparison with Syngo optimized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

Horizontal line

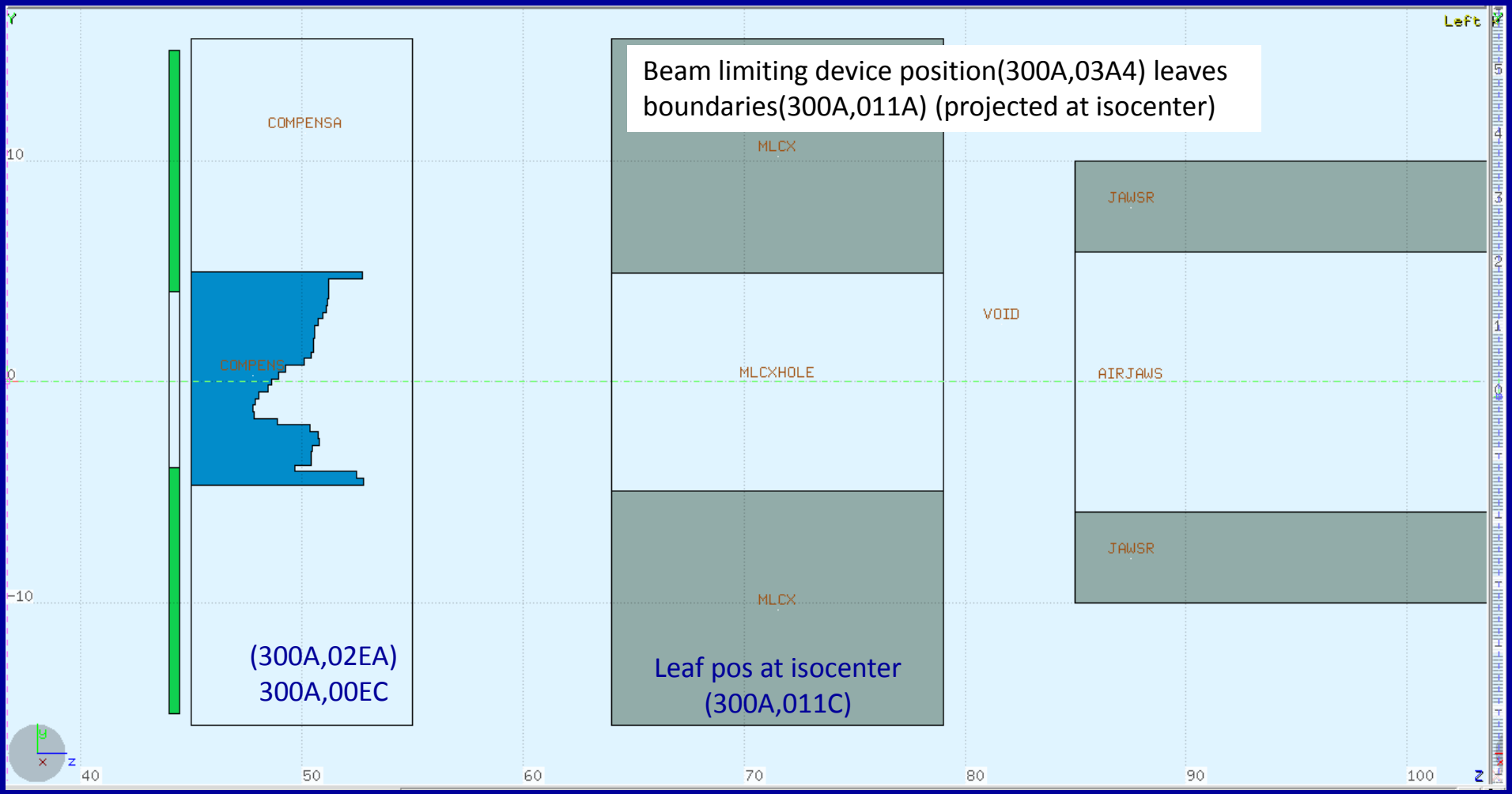


Horizontal line – 290 MeV/u

Basic beamline model validation



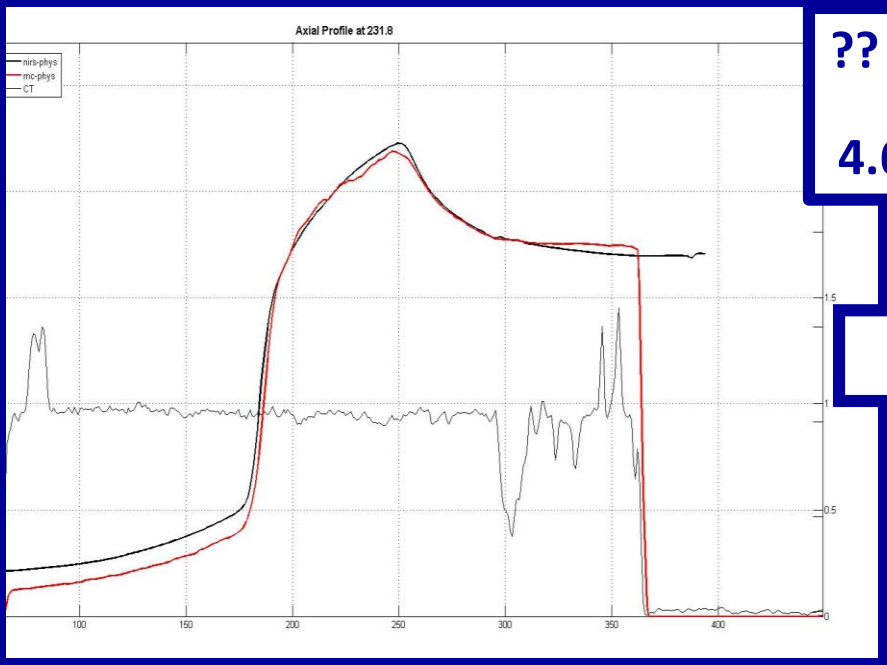
Horizontal line – 400 MeV/u – Pt specific



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

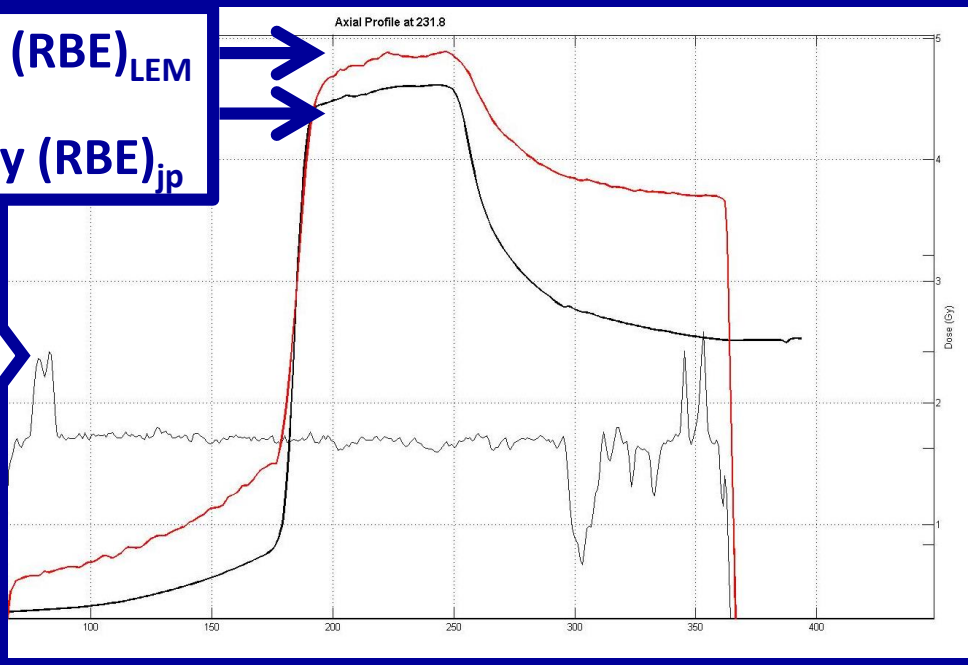
Physical dose
NIRS DICOM data vs FLUKA MC code

Biological dose
NIRS DICOM data vs FLUKA MC code & MyLEM

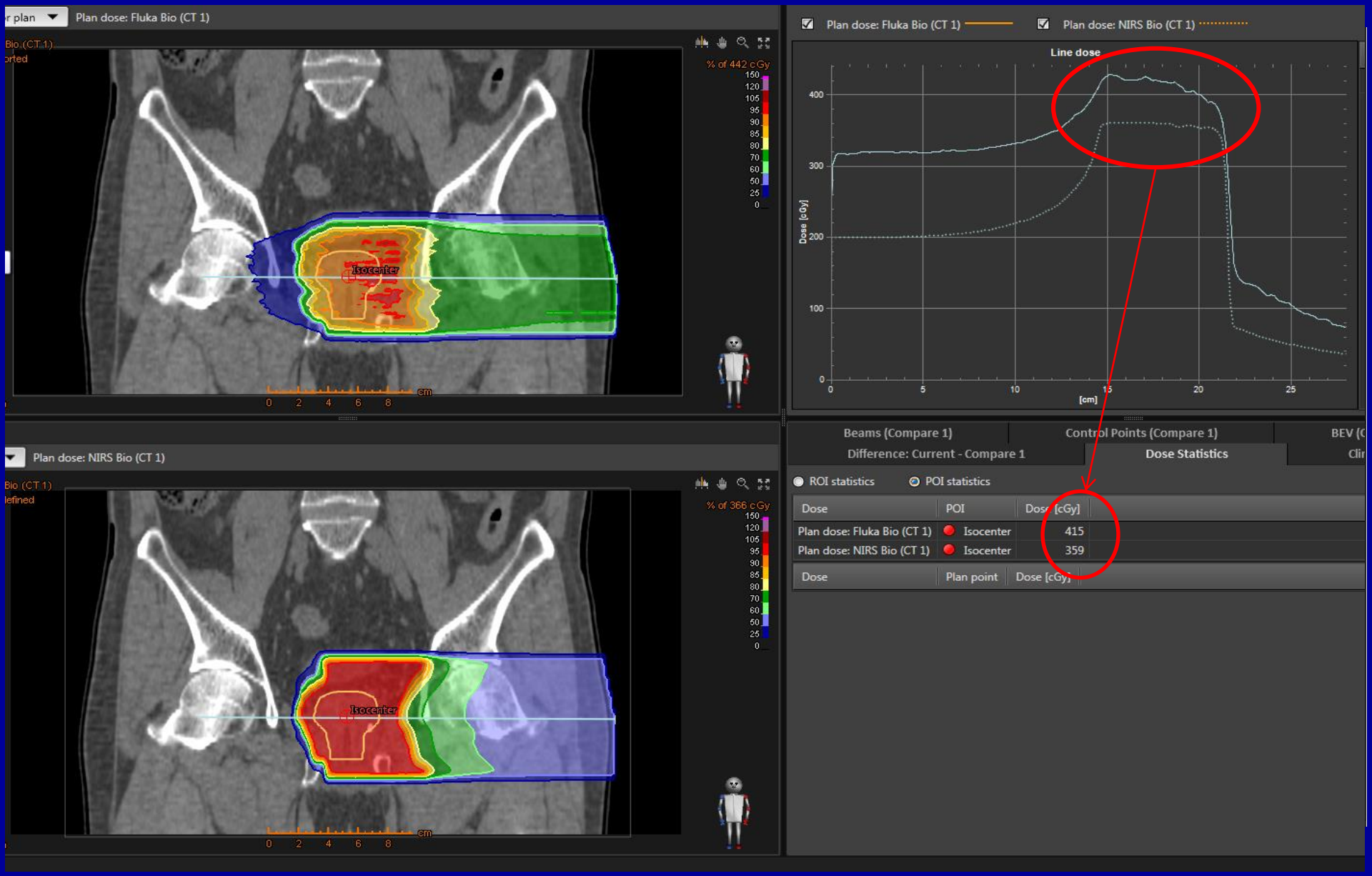


?? Gy $(RBE)_{LEM}$

4.6 Gy $(RBE)_{jp}$

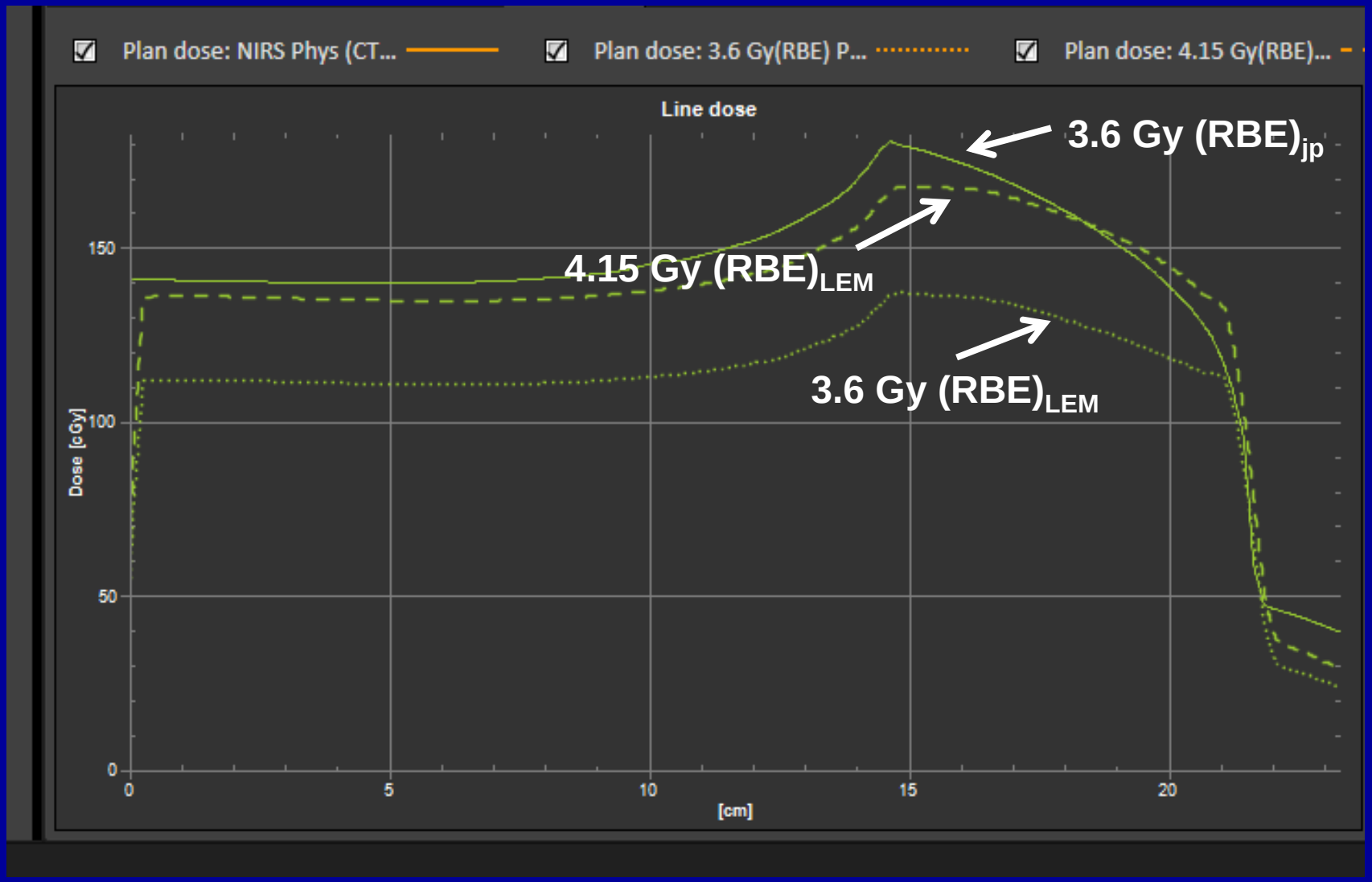


Prostate Pt – BHC 400MeV/u - 3.6 Gy $(RBE)_{jp}$

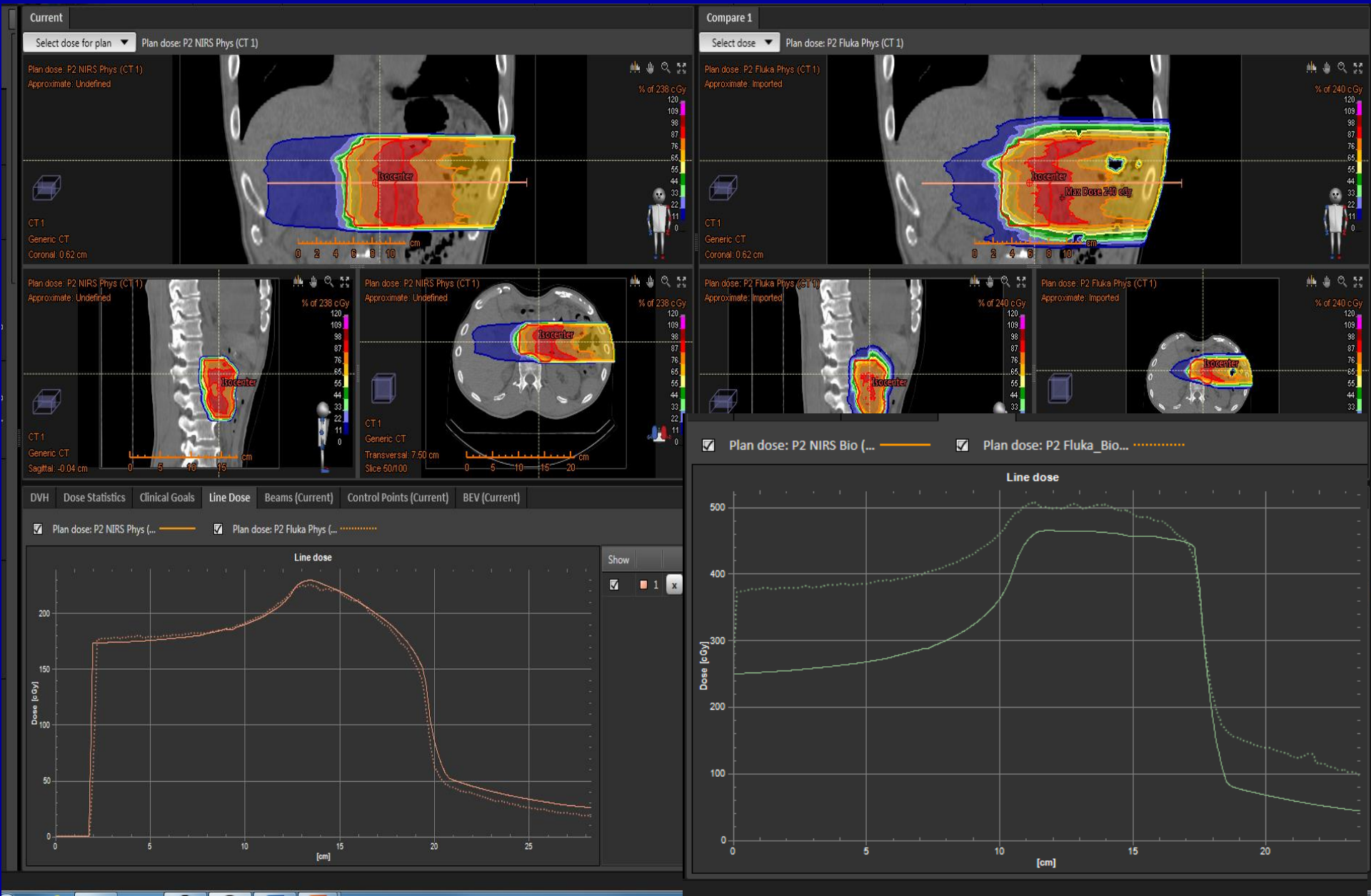


Prostate Pt – BHC 400MeV/u - 3.6 Gy $(RBE)_{jp}$

NIRS vs CNAO prescription Dose – Absorbed Dose comparison



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



Disease	prescription dose (Gy[RBE]nirs)	Energy (MeV/u)	RF (mm)		mean difference **in RBEweighte dose**
Prostate	3.6	400	70		-1,1%
Prostate	3.6	400	70		-0,8%
H&N ACC	4	290	80		-0,2%
H&N SCC	4	290	70		0,5%
Pancreas	4.6	400	70		0,9%
Pancreas	4.6	400	90		1,6%
Pancreas	4.6	400	80		-0,2%

Clinical results comparison

ACC

NIRS

- 57.6 – 64 GyE

Adenoid cystic carcinoma

CNAO clinical

- 68.8 GyE

Adenoid cystic carcinoma

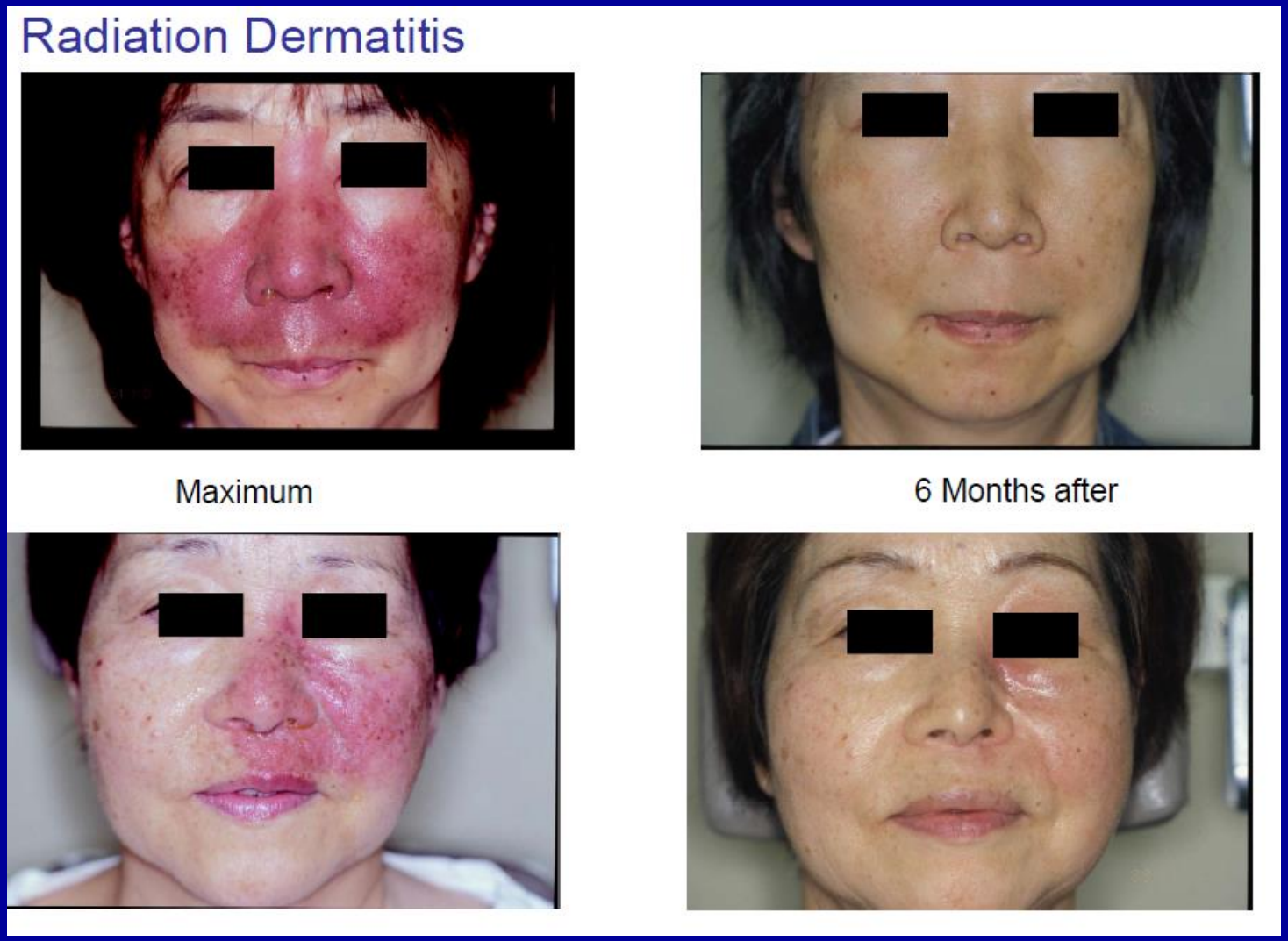
CNAO translated

- 66.4 GyE - 71,2 GyE

Adenoid cystic carcinoma

Skin toxicity - NIRS

G3



G1/0

Courtesy of Dr Mizoe J.

Skin toxicity - CNAO

G1

Skin toxicity

During treatment

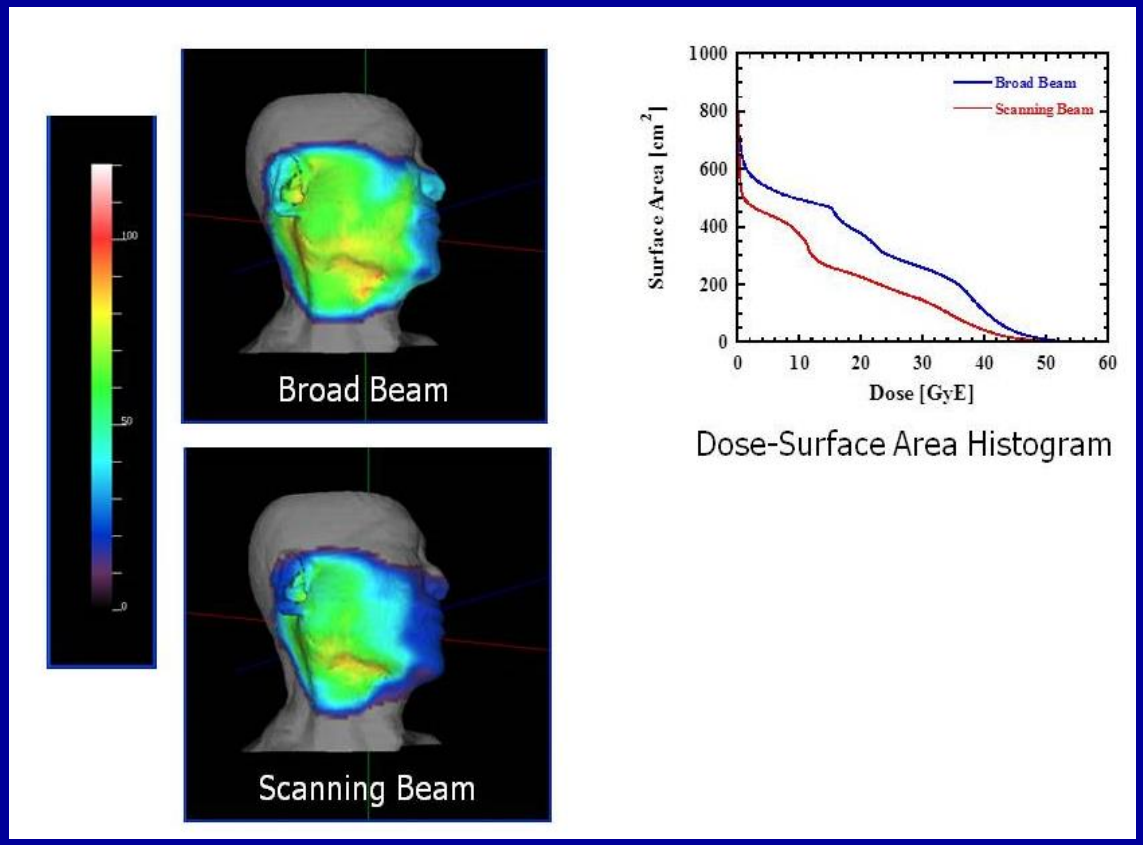
End of treatment

6 months after RT

Skin toxicity

Acute Skin toxicity

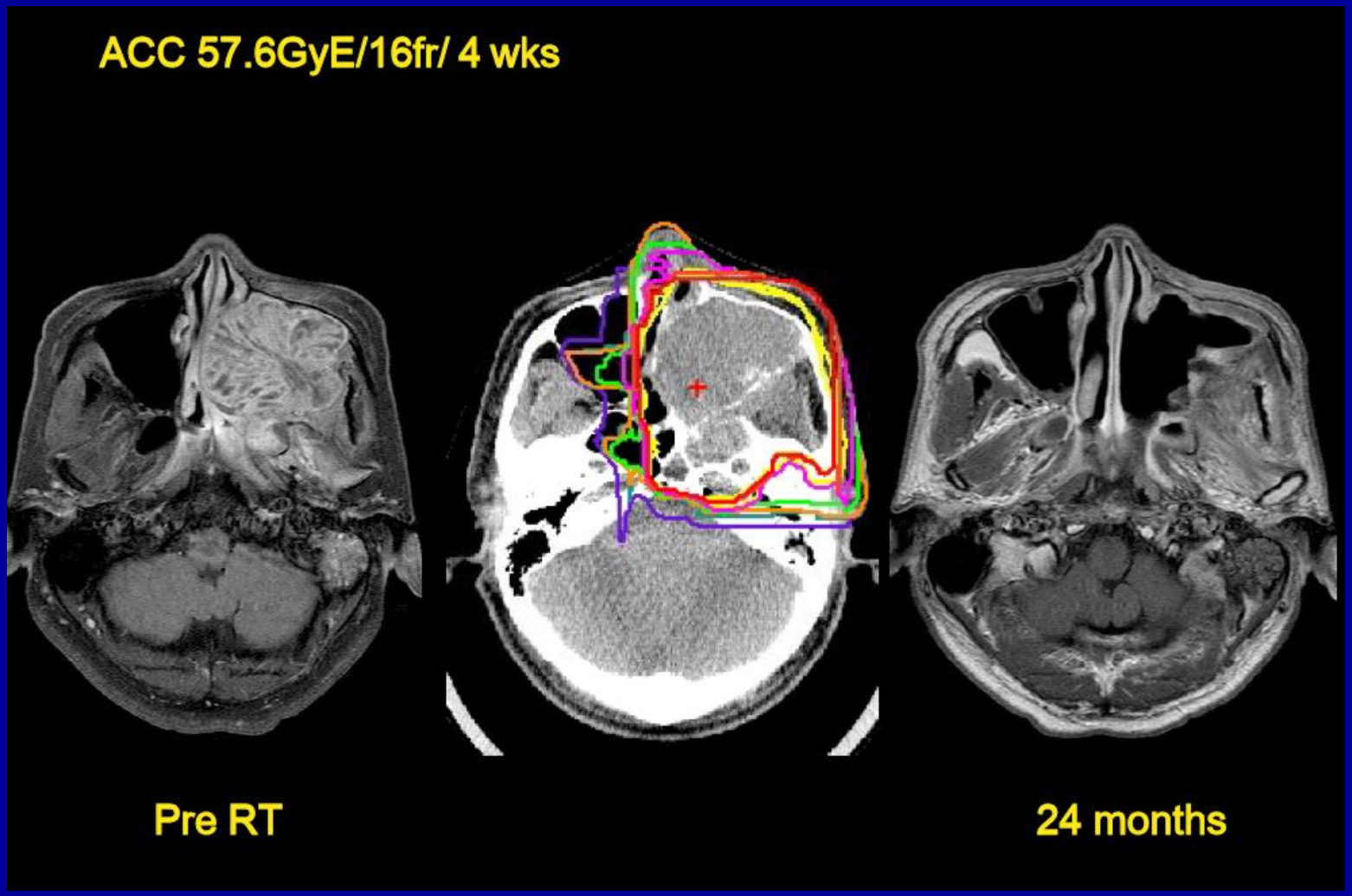
	NIRS	CNAO
• G2	28%	10%
• G3	4%	0%



CNAO Skin reaction looked milder with respect to NIRS experience
→ it may reflect the use of active scanning vs passive scattering

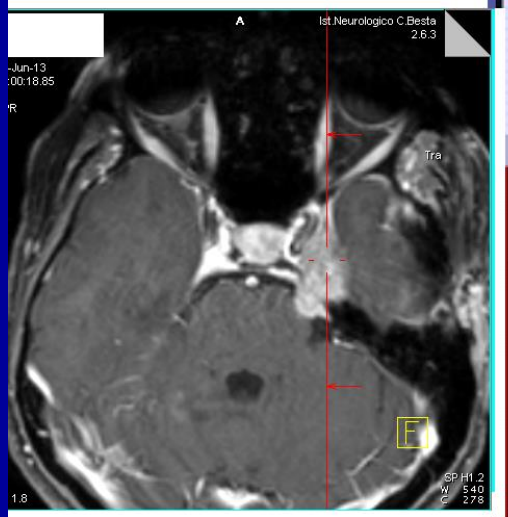
Courtesy of Dr Mizoe J.

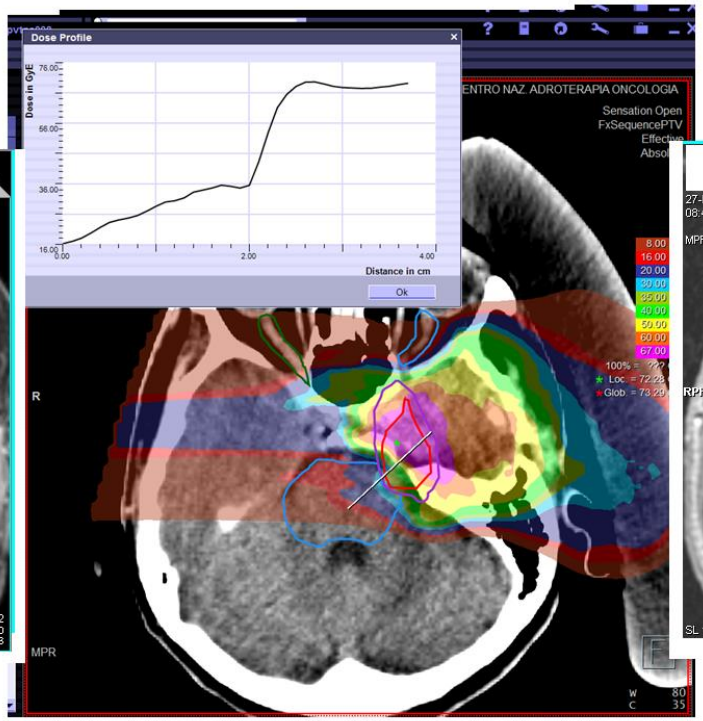
ACC NIRS

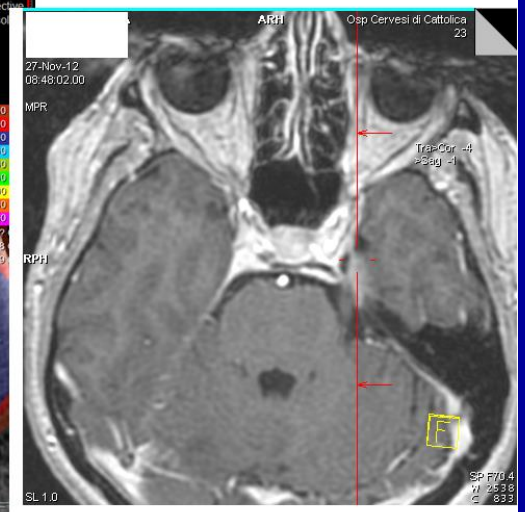


Courtesy of Dr Mizoe J.

ACC CNAO







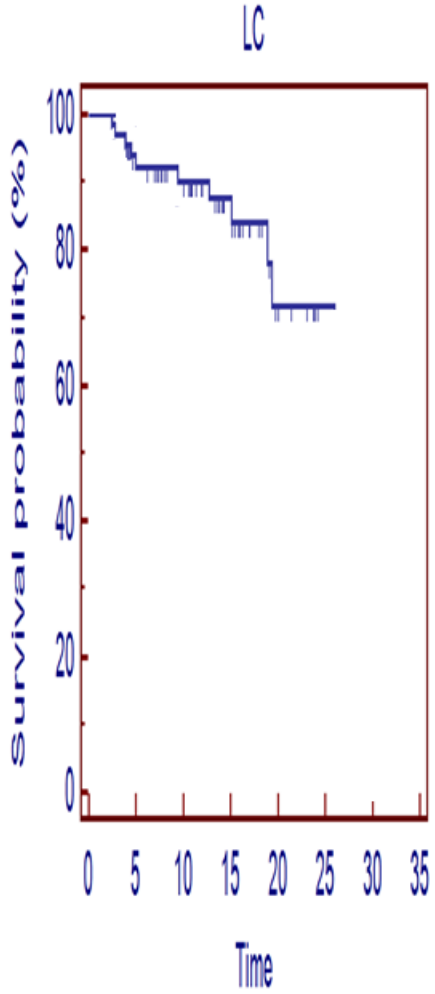
Before RT

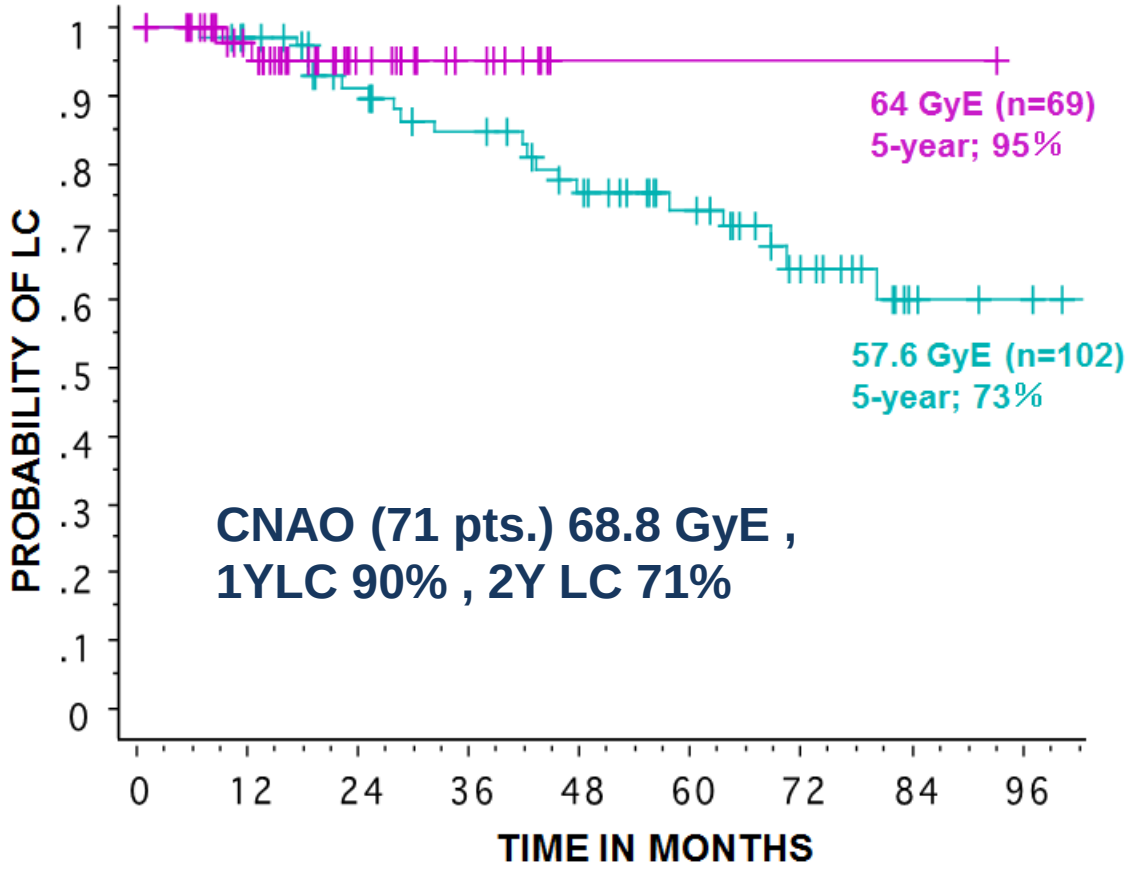
4.3 Gy $(RBE)_{LEM}$ x 16 fx
68.8 Gy $(RBE)_{LEM}$

9 months after RT

Phase II (9602) for Malignant Head-and-Neck Tumors

Local Control of ACC (n=171) according to Carbon ion





TIME IN MONTHS

Courtesy of Dr. Kamada, NIRS

Conclusion

- It is possible to compare Gy $(RBE)_{jp}$ with Gy $(RBE)_{LEM}$ but a dedicated effirt is needed
- CNAO approach can be considered a benchmark for moderately hypofractionated treatments
- Extreme hypofractionation should be studied separately
- Dose constraints deserve a separate, cooperative, study

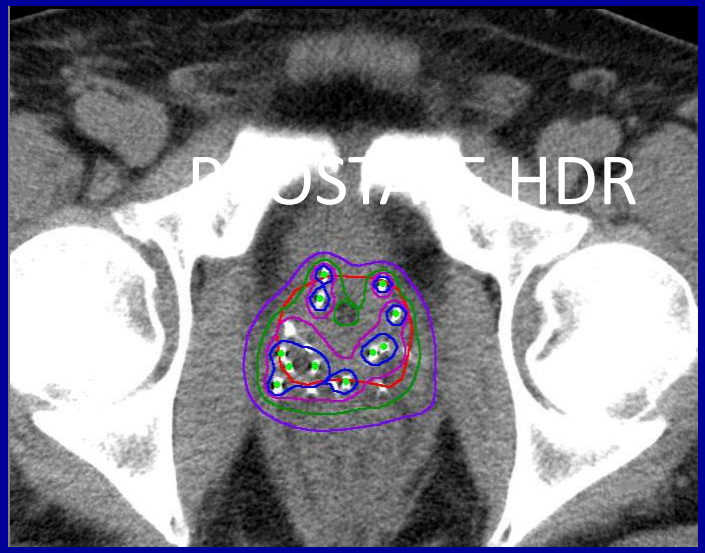
Optimal dose distribution ?

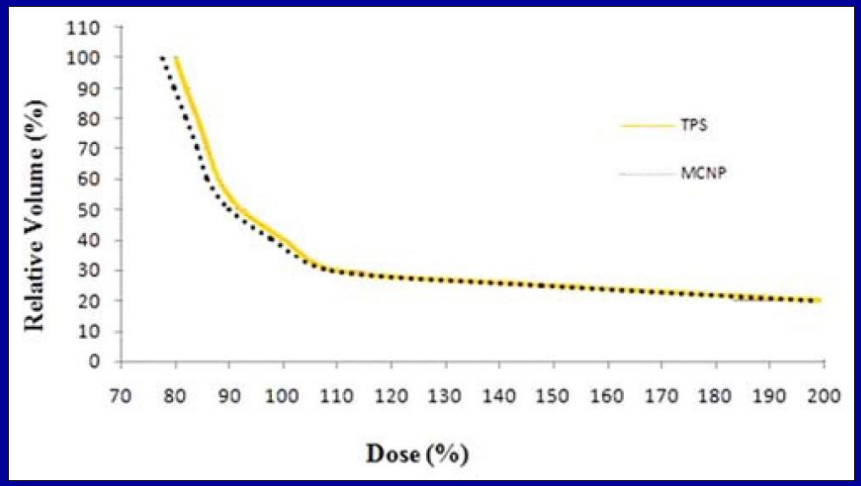
- Should we really try so hard to do the same as a uniform field of photons ?

Using carbon to mimick a uniform dose of photons…

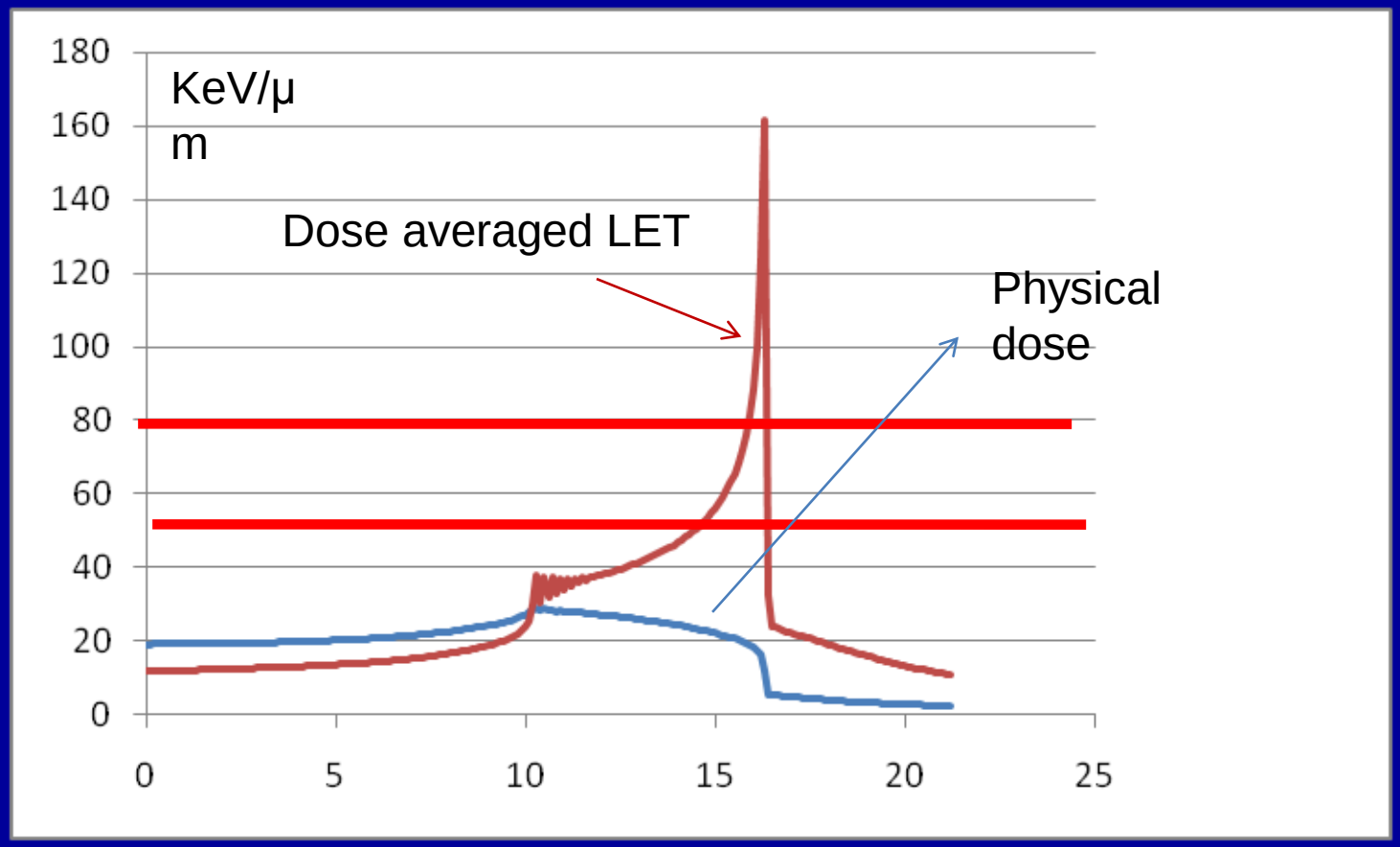
BAD DOSE NON-UNIFORMITY ?

- TECHNICALLY DRIVEN:
  - BRACHYTHERAPY
  - CYBERKNIFE
  - GAMMAKNIFE
  - SBRT





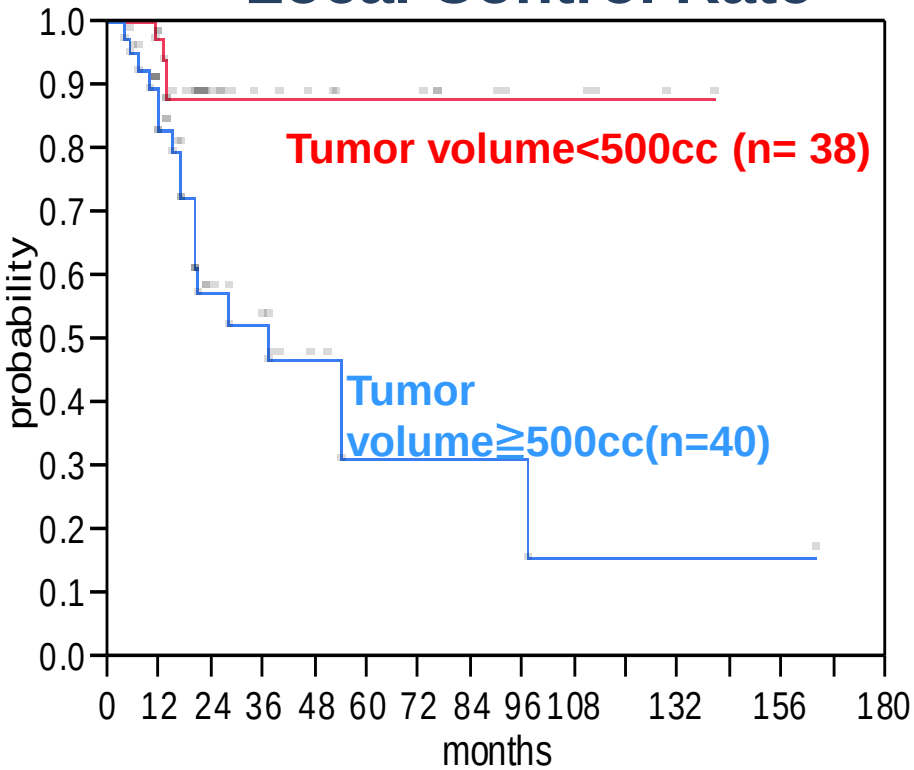
Carbon ion treatment is not high LET RT, not even in the target



NIRS, physical dose and dose averaged LET for 1 field
Courtesy of Dr. Matsufuji

Osteosarcoma of the Trunk
Result By Tumor Volume

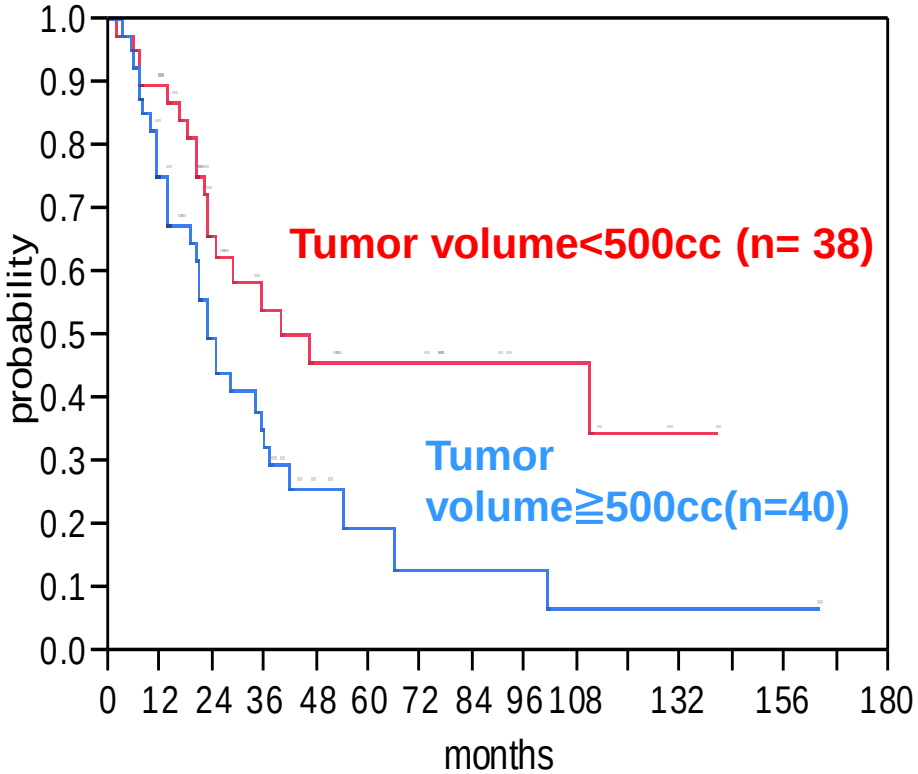
Local Control Rate



	2y	5y
＜500cc	87%	87%
≧ 500cc	57%	31%

Logrank p=0.0006

Overall Survival Rate



	2y	5y
＜ 500cc	65%	46%
≧ 500cc	50%	19%

Logrank p=0.015

Courtesy of Dr. Kamada, NIRS

Uniform RBE weighted dose or LET painting