New challenges for biologically adapted ion beam treatment planning:

single and multi-ion approaches

Emanuele Scifoni, Michael Krämer,
Walter Tinganelli, Wilma Kraft-Weyrather, Andreas Maier
Ryochi Hirayama, Yoshiya Furusawa and Marco Durante

Biophysics Department, GSI, Darmstadt
IOL, NIRS, Chiba

Outline

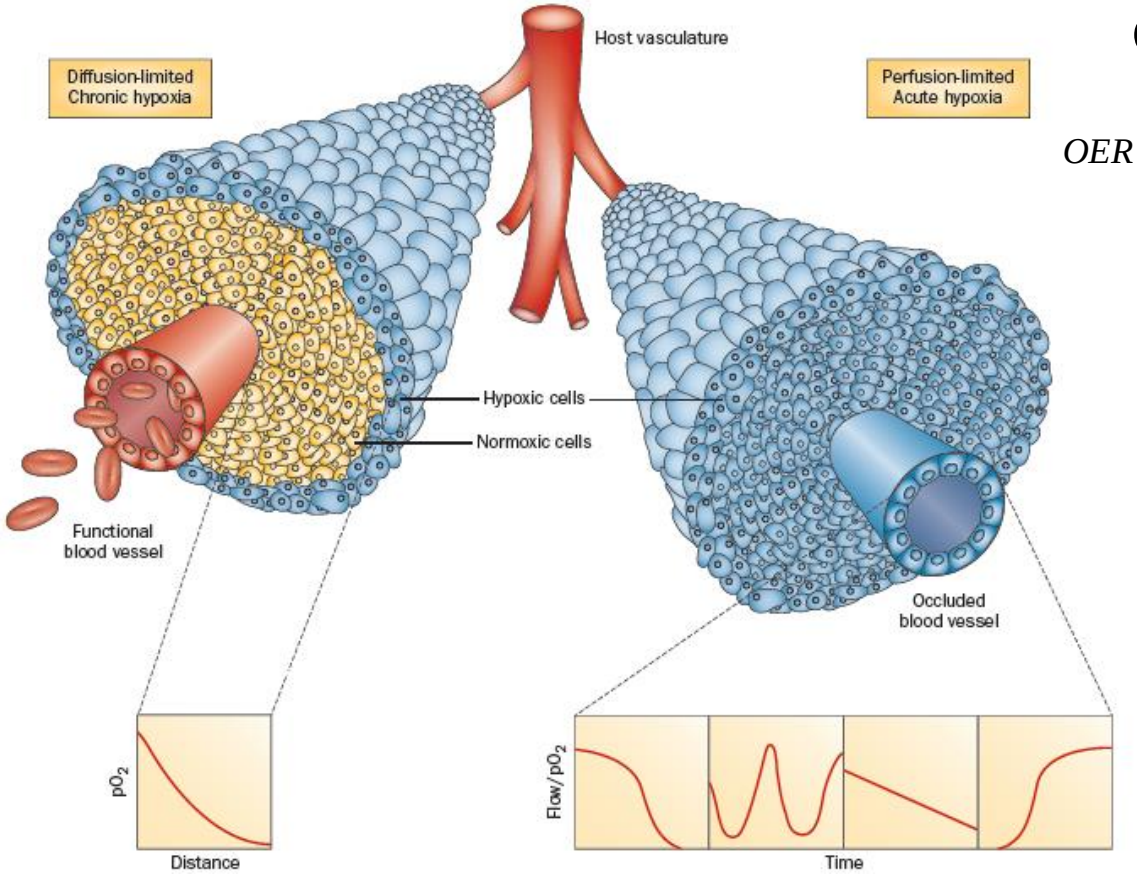
Introduction
- Hypoxia, Particle Therapy
- and related treatment planning (“painting”) strategies

TRiP98OER : “Killing Painting”
- OER modeling
- TP implementation
- Experimental verification

Alternative Ion species and perspectives

Summary & outlook

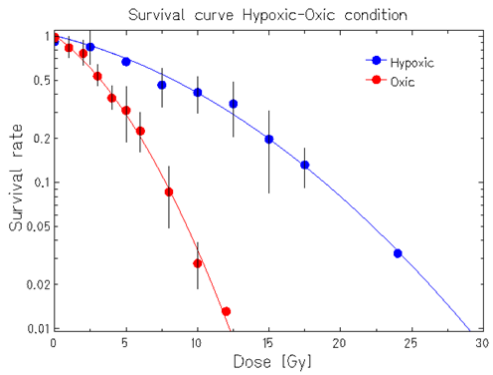
Contrasting Hypoxia

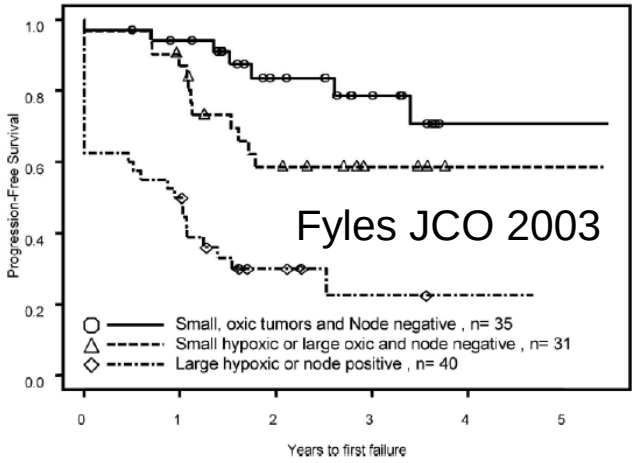


Horsman et al *Nat. Rev. Clin. Oncol.* (2012)

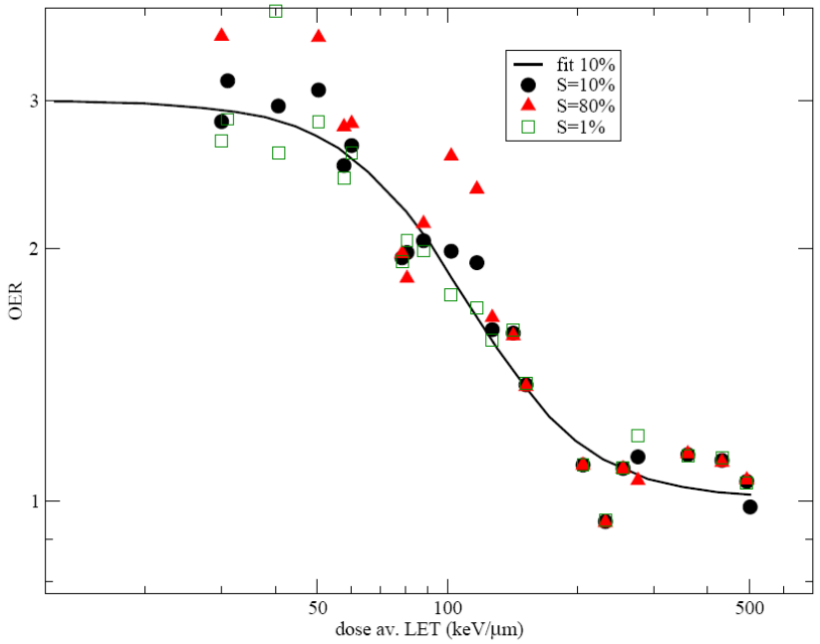
Oxygen Enhancement Ratio

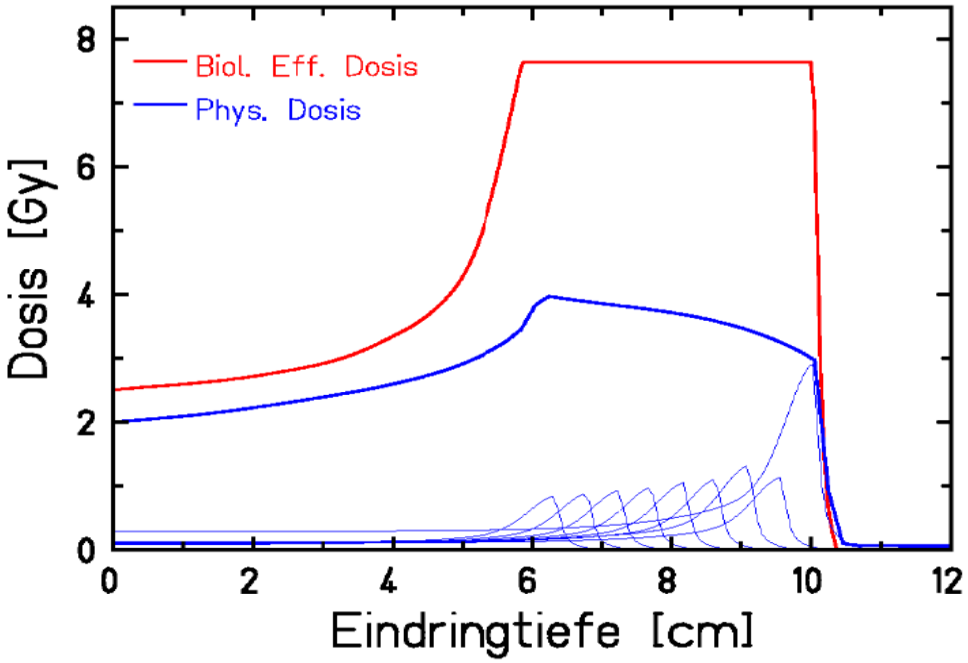
$$OER = \left.\frac{D_{hypoxic}}{D_{normoxic}}\right|_{same\,effect} \quad ; \quad OER(p) = \left.\frac{D(p)}{D_{normoxic}}\right|_{same\,effect}$$





Is this problem solved for high LET radiation?



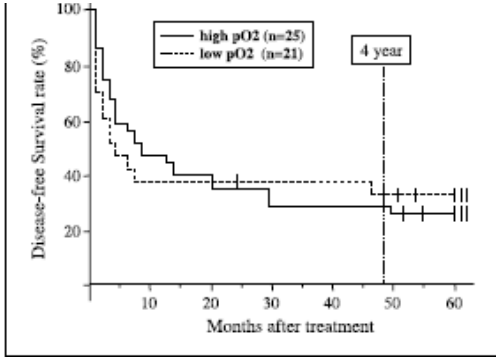


Furusawa et al., Radiat. Res. 2000

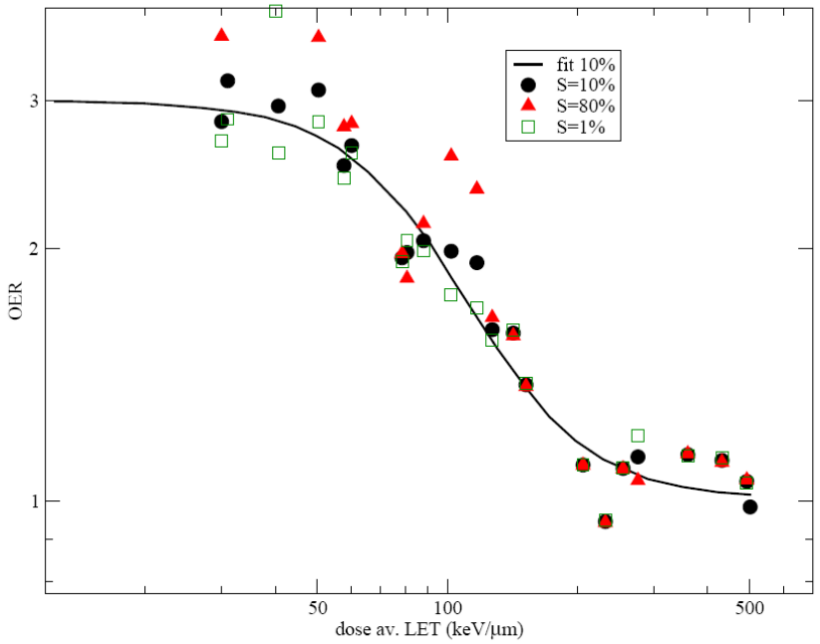
Carbon Beam Therapy Overcomes the Radiation Resistance of Uterine Cervical Cancer Originating from Hypoxia

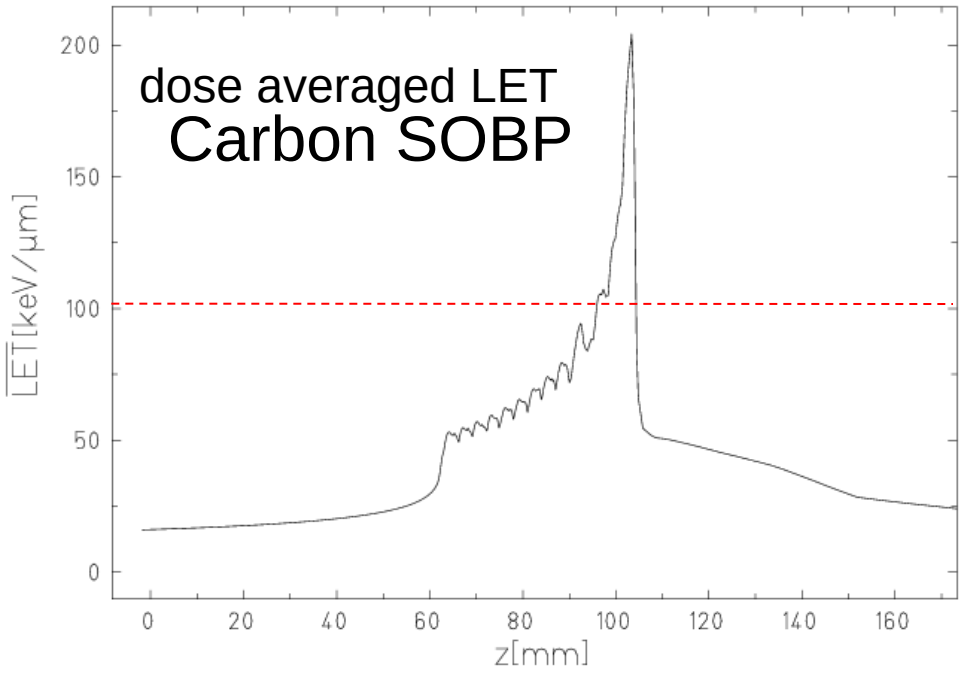
Takashi Nakano, Yoshiyuki Suzuki, Tatsuya Ohno, et al.

Clin Cancer Res 2006;12:2185-2190. Published online April 11, 2006.



Is this problem solved for high LET radiation?



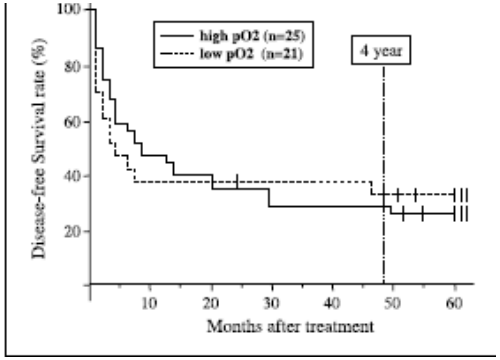


Furusawa et al., Radiat. Res. 2000

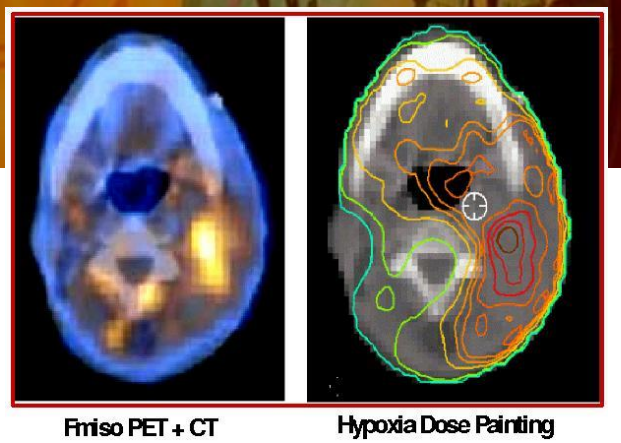
Carbon Beam Therapy Overcomes the Radiation Resistance of Uterine Cervical Cancer Originating from Hypoxia

Takashi Nakano, Yoshiyuki Suzuki, Tatsuya Ohno, et al.

Clin Cancer Res 2006;12:2185-2190. Published online April 11, 2006.

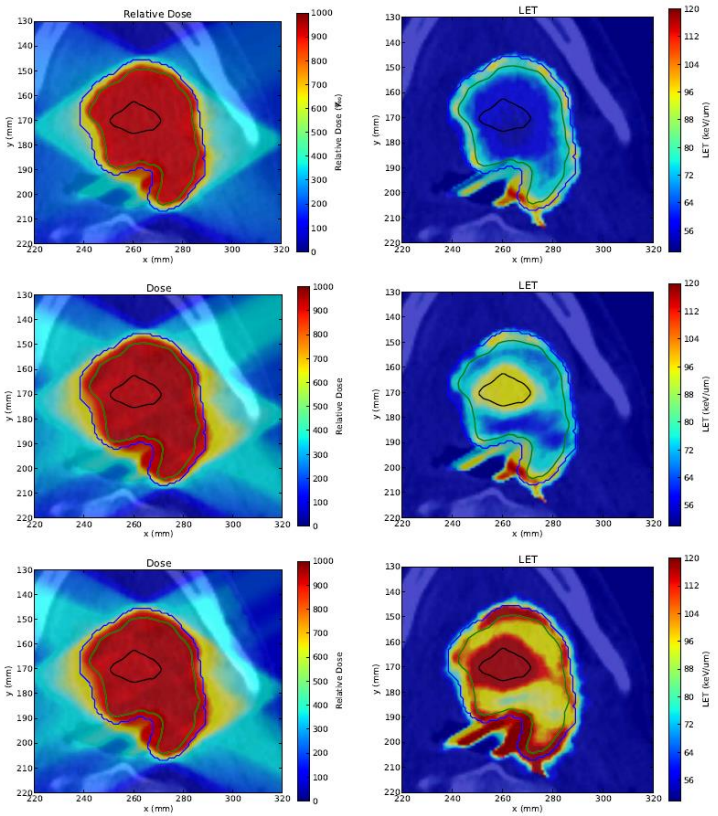


Painting Strategies



Thorwarth et al.2010

- Dose painting by contours
  - Boost dose in defined iso-uptake contours
- Dose painting by numbers
  - voxel-based prescription function
- LET painting
  - Redistribution of LET, to be maximized
    in the target volume
    also using dose ramps

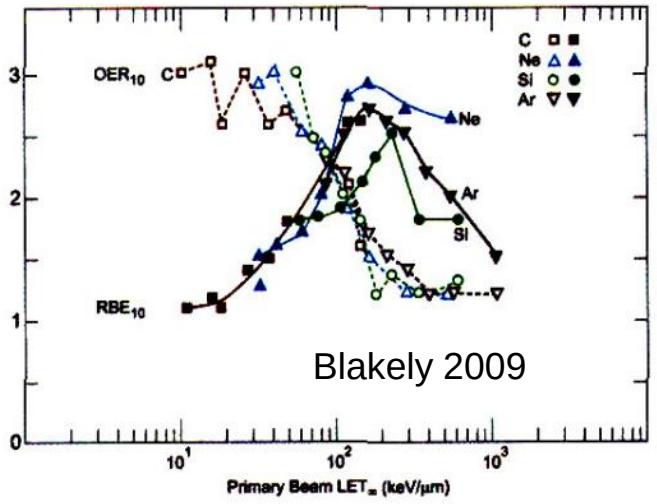


*see **N. Bassler** talk on Thu*

Bassler, et al. Acta Oncol 2013

“Killing” painting

- Restoring a prescribed survival level in the target volume, independently on the oxygenation level of different regions
- Taking fully into account the potential of ion beam active scanning dose delivery
- Close connection of RBE and OER
  - Maximum slope in the same LET range



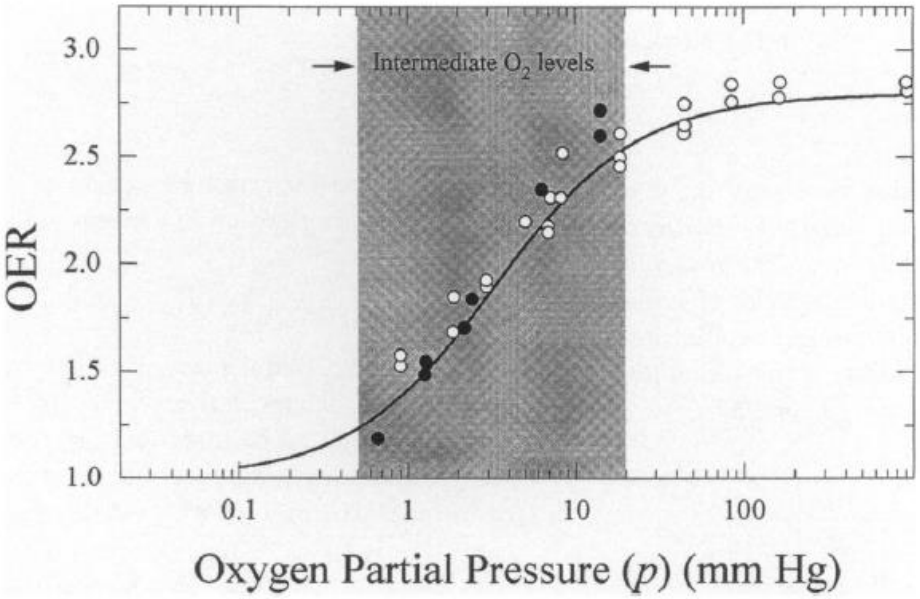
Blakely 2009

- LET and pO_2 dependence at the same time

Oxygenation level (X-rays only)

Cells at Intermediate Oxygen Levels Can Be More Important Than the "Hypoxic Fraction" in Determining Tumor Response to Fractionated Radiotherapy

Bradly G. Wouters and J. Martin Brown



Radiat. Res. 1997

Alper formula

$$\frac{S_{10\%}(pO_2)}{S_{10\%}^{N_2}} = \frac{m \cdot pO_2 + K}{pO_2 + K}$$

Alper and Howard-Flanders, *Nature* 1956

m=maximum relative sensitivity

K=ratio of the rate constants for chemical repair and oxygen fixation

OER(pO_2, LET) model for adaptive particle treatment planning

$$OER(pO_2, \overline{LET}) = \frac{b(Ma + \overline{LET}^{\alpha})/(\overline{LET}^{\alpha} + a) + pO_2}{b + pO_2}$$

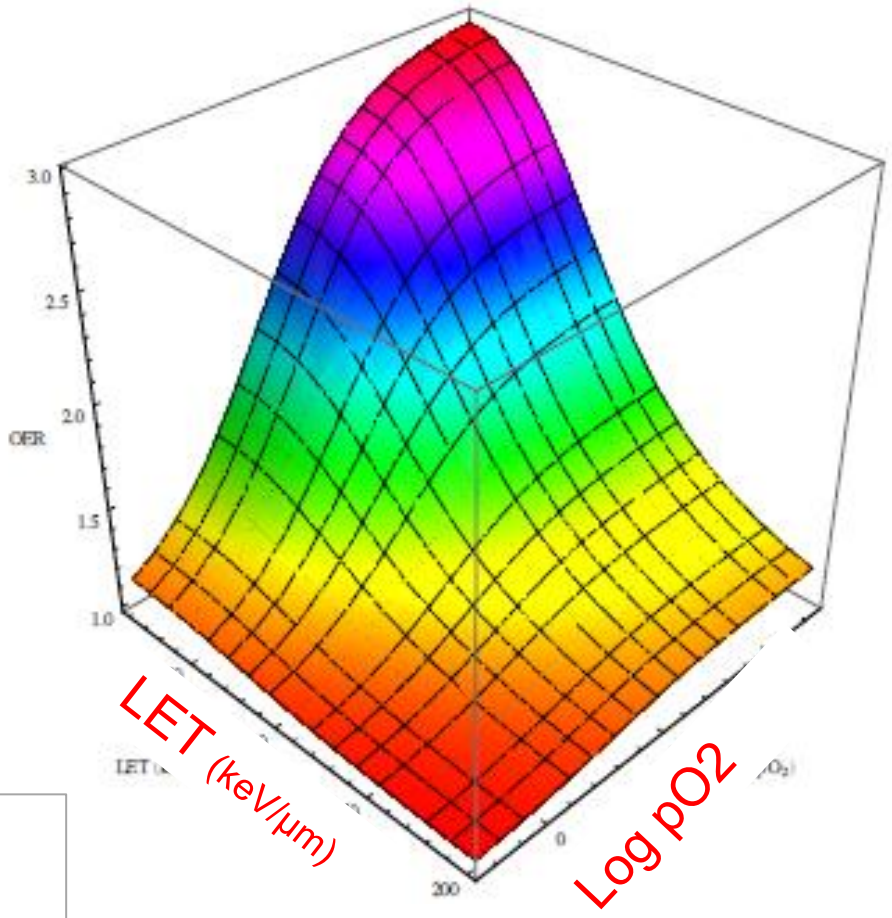
Scifoni *et al., Phys. Med. Biol.* 2013

$$D^{i}_{bio}(\vec{N}) = \sqrt{\frac{\alpha_i \cdot \vec{c}_i^{T} \cdot \vec{N} + \beta_i \cdot (\vec{c}_i^{T} \cdot \vec{N})^2}{\beta_x} + \left(\frac{\alpha_x}{2\beta_x}\right)^2} - \frac{\alpha_x}{2\beta_x} \quad ;$$

Krämer & Scholz, *Phys. Med. Biol. 2006*

$$\alpha'_i(\bar{L}_i, p_i) = \alpha_i / OER(\bar{L}_i, p_i)$$

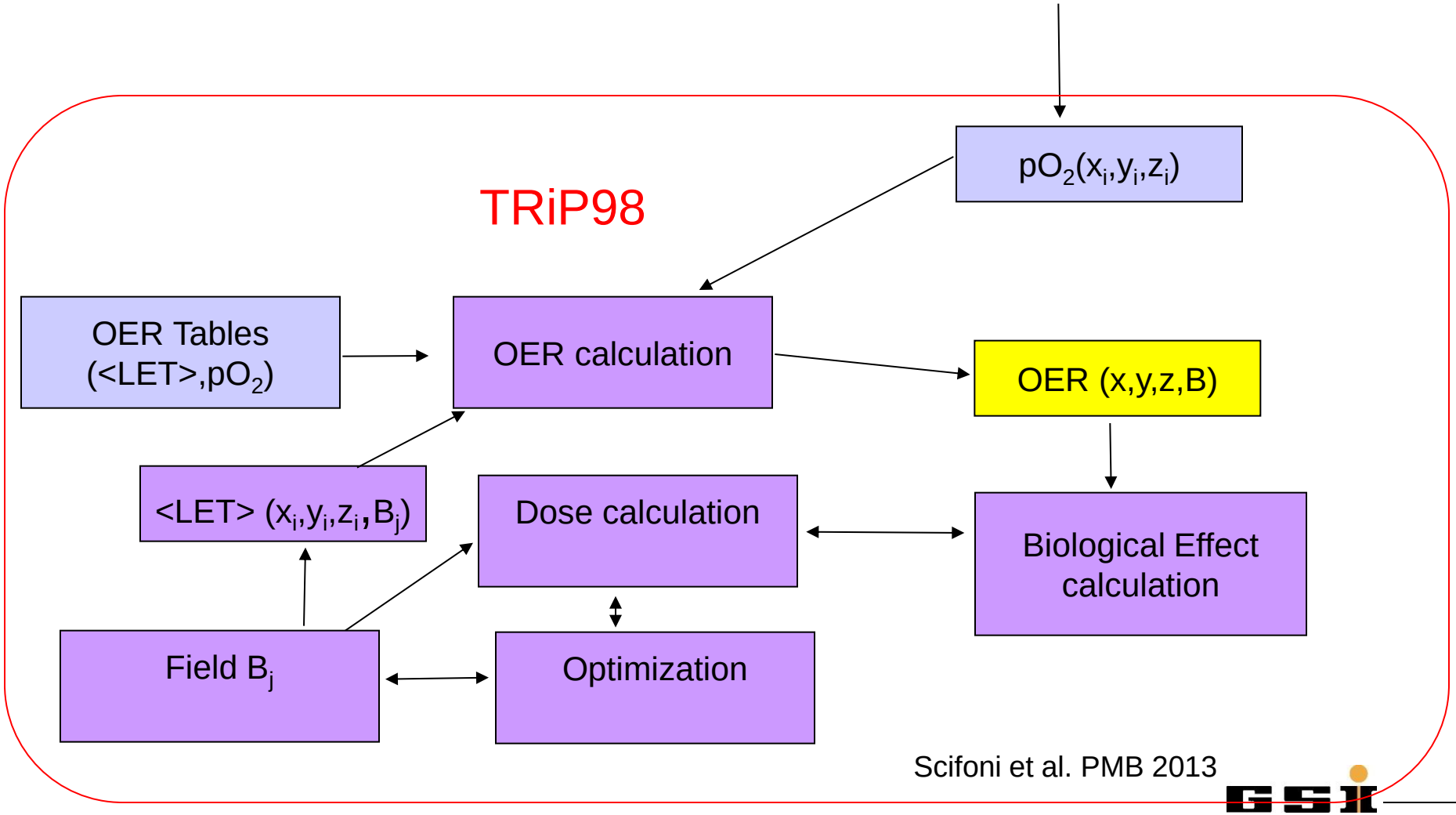
$$\sqrt{\beta'}_i(\bar{L}_i, p_i) = \sqrt{\beta_i} / OER(\bar{L}_i, p_i)$$



Validation Measurements
OER vs. LET for different pO2 values
@GSI-NIRS International Open Laboratory

Tinganelli, et al. in prep.

TRiP98-OER

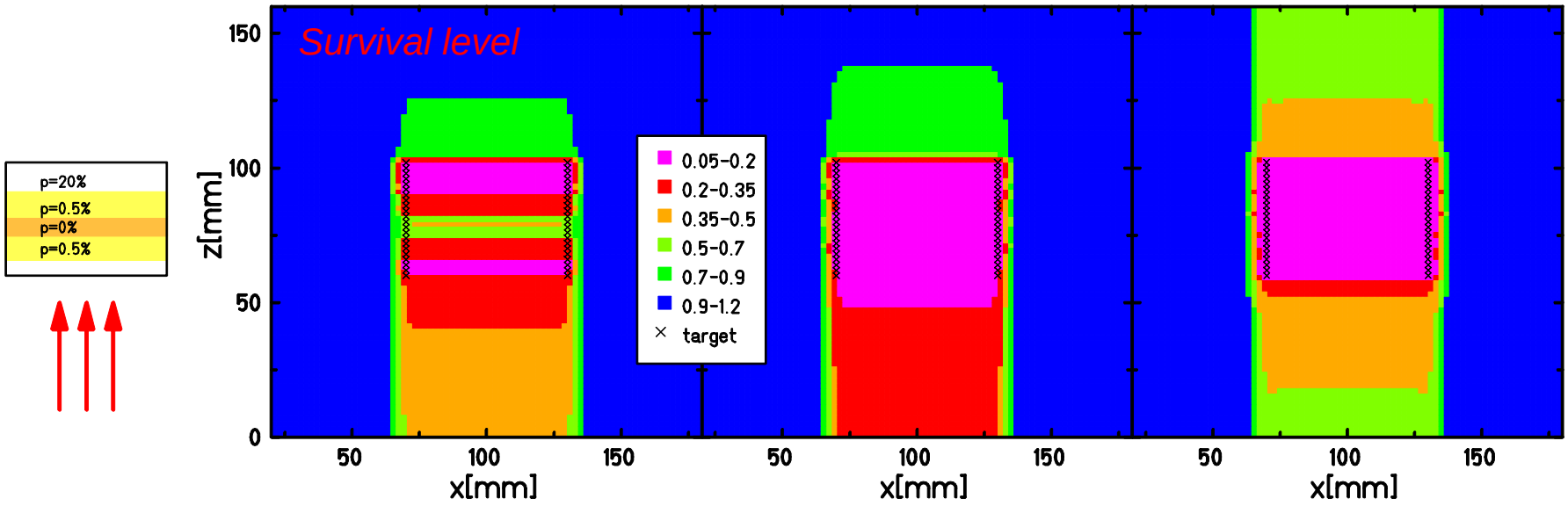


Scifoni et al. PMB 2013

Optimized plans with dose compensation

•*normoxic plan* •*OER-optimized, 1Field* •*OER-optimized, 2 fields*

Multiple Field Optimization

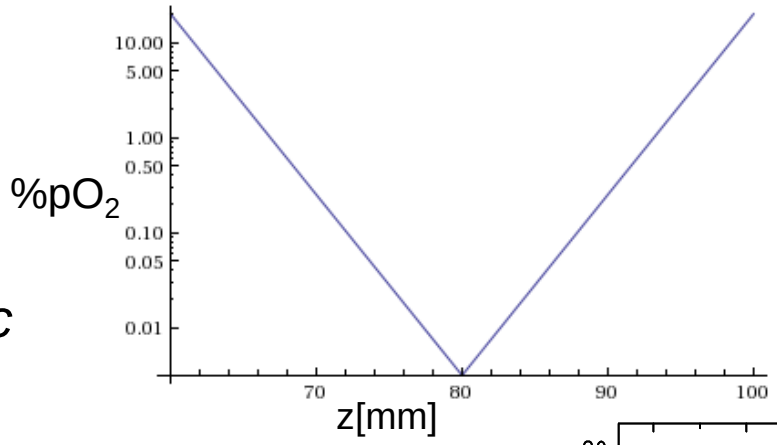


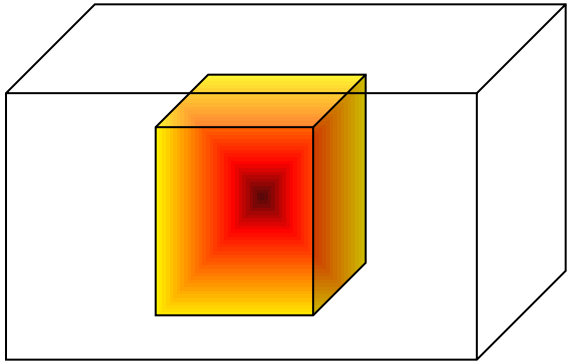
Optimization “decides” contribution of different fields according to hypoxia distribution

Scifoni et al. PMB 2013

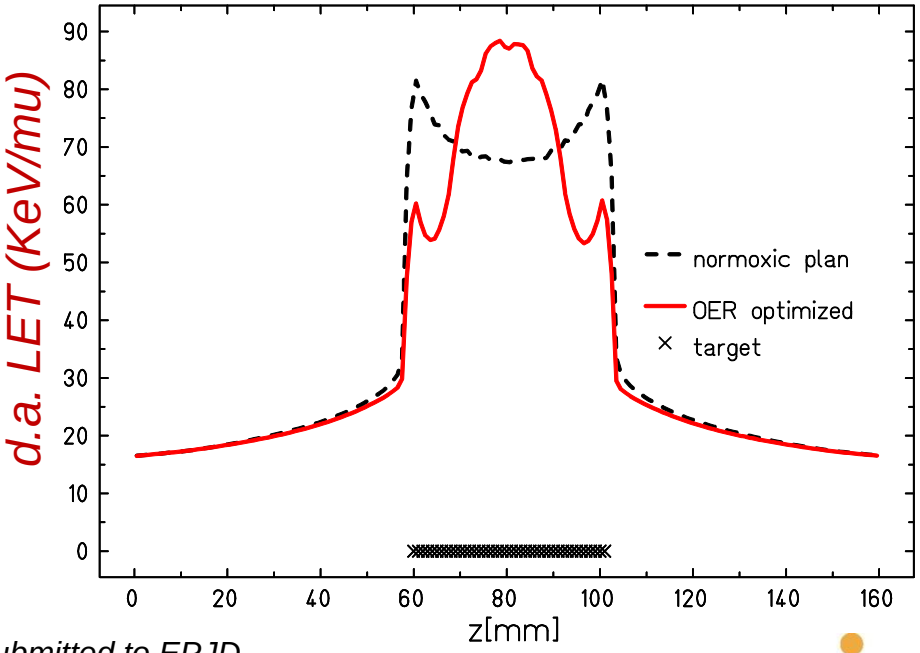
Realistic pO_2 distributions

Smooth pO_2 *gradient from a central anoxic core*





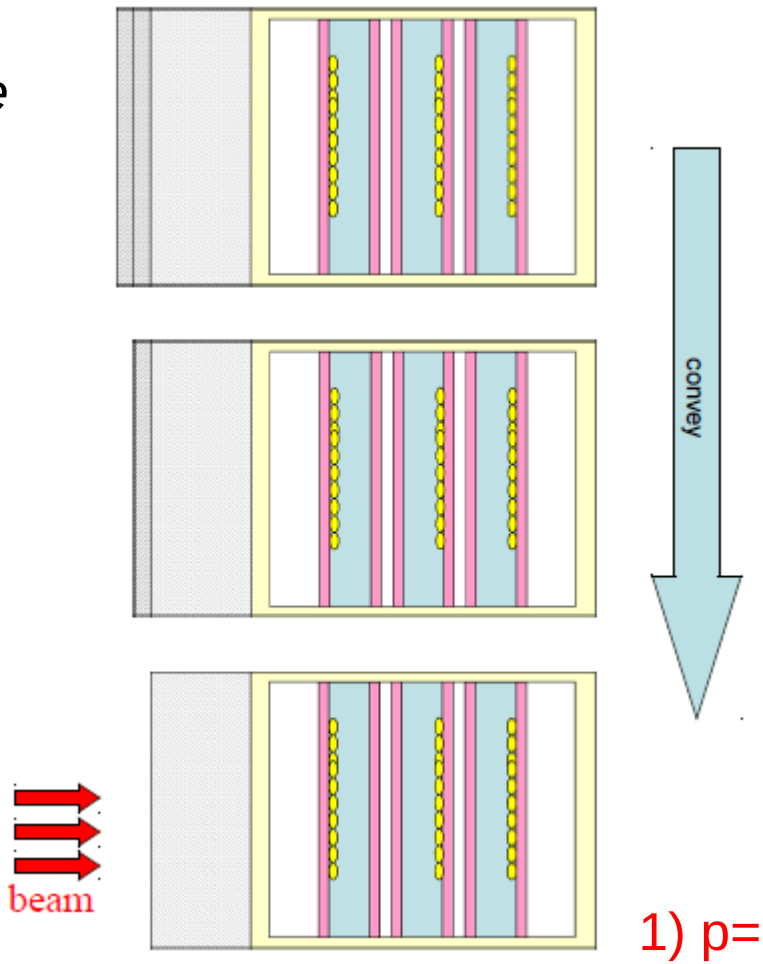
LET distribution automatically adjusted from the optimization through the "hypoxic gradients" to the oxygen distribution

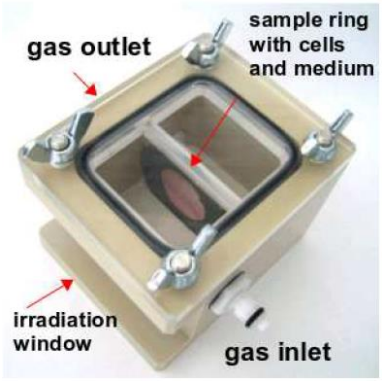


Krämer, Scifoni, ,Schmitz, Sokol, Durante, *submitted to EPJD*

Experimental verification

• *Densely sampling the last cm, zooming on the region of maximum LET effect*

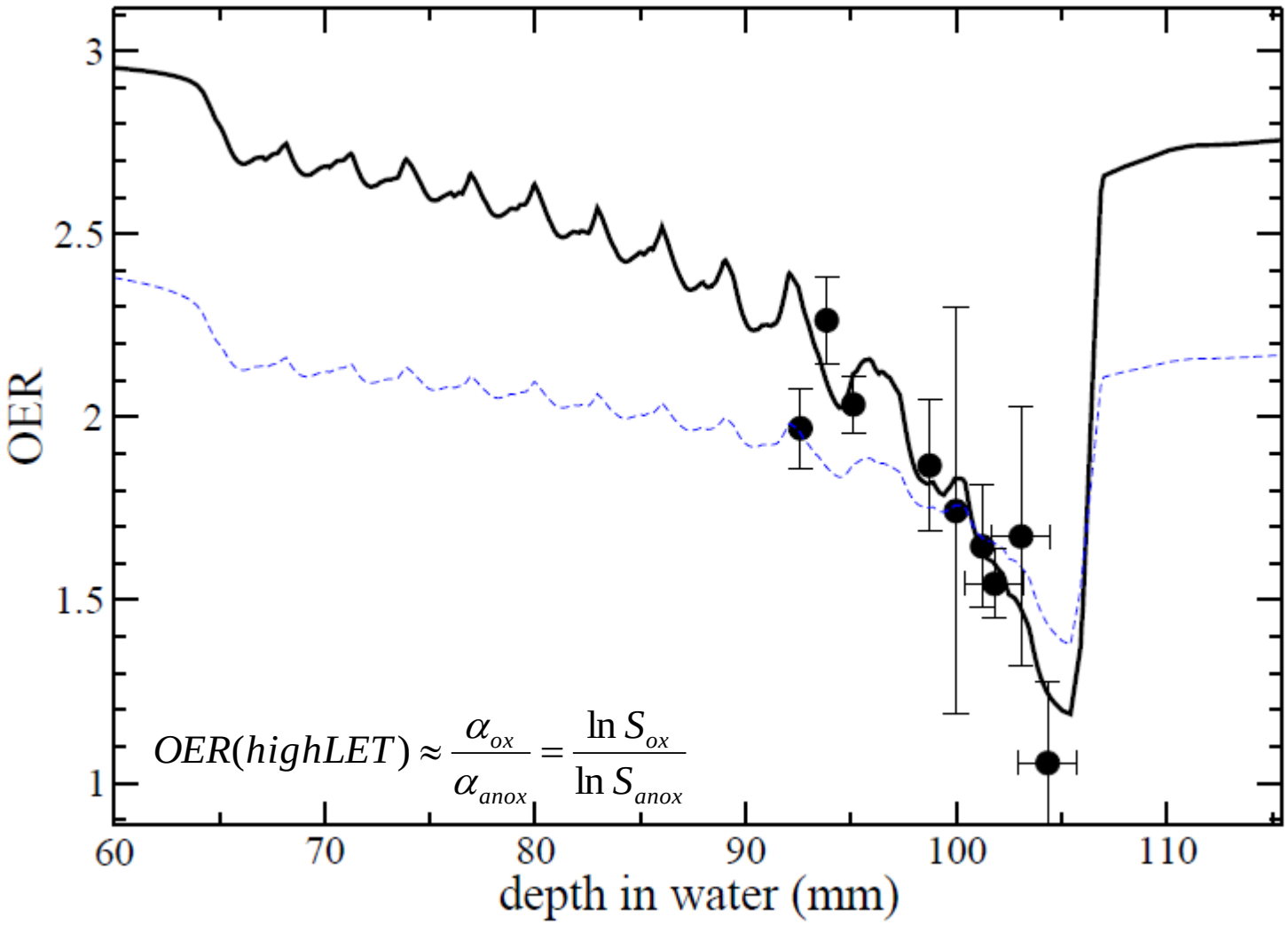




1) p=0

2) Normoxic

OER(z), experimental

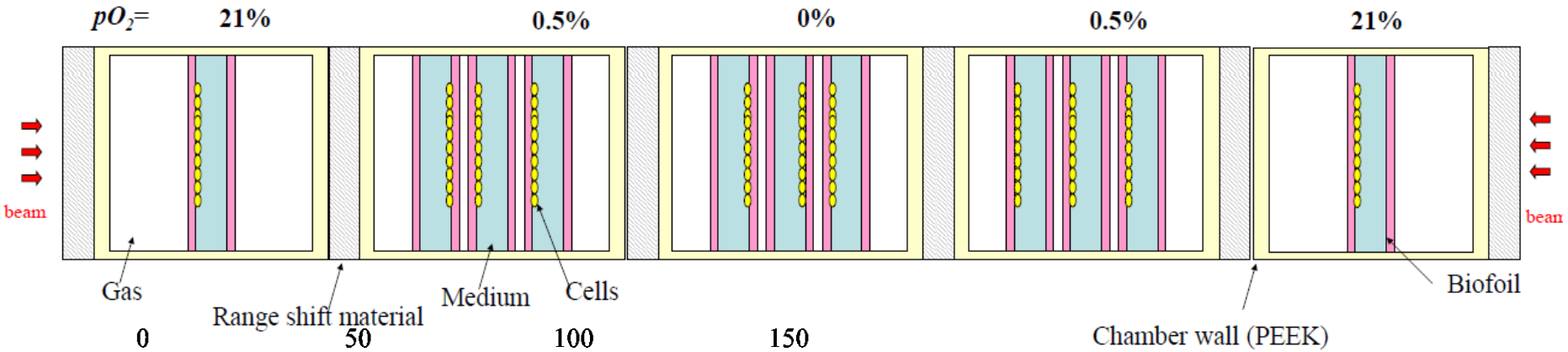


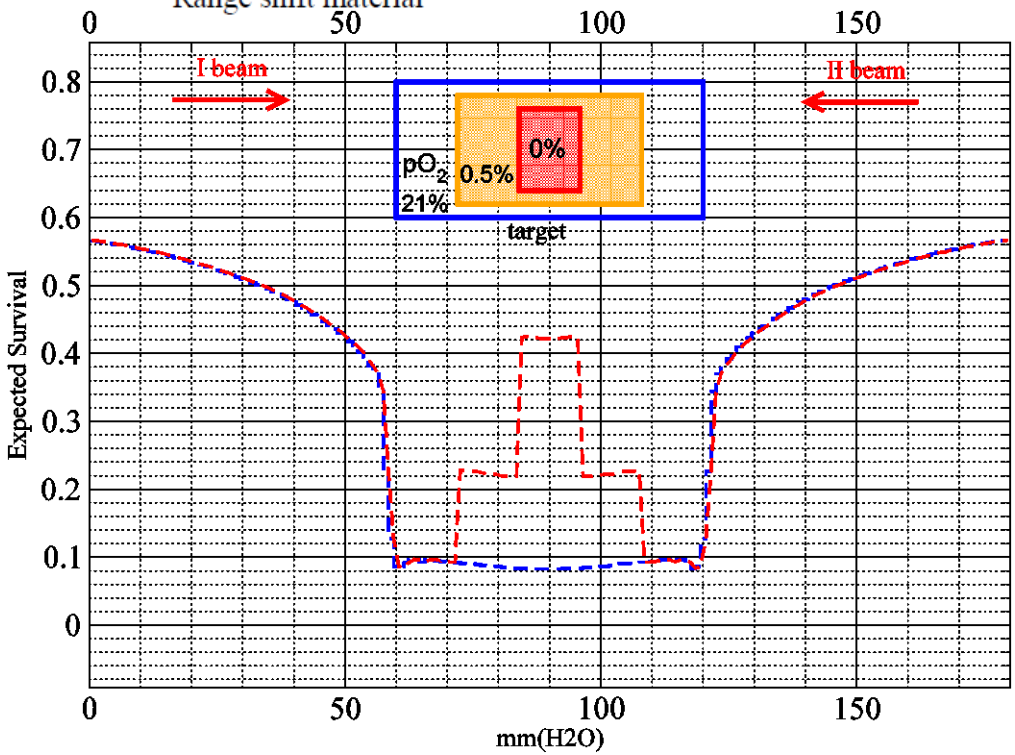
- TRiP-OER+ present model tables
- TRiP-OER+ model tables from Wenzl&Wilkens 2011

Scifoni, Tinganelli, Weyrather, Durante, Krämer, Phys. Med. Biol. 58 (2013) 3871–3895

Extended target irradiation

- validation of TRiP-OER, 2 Fields, 3 different O_2

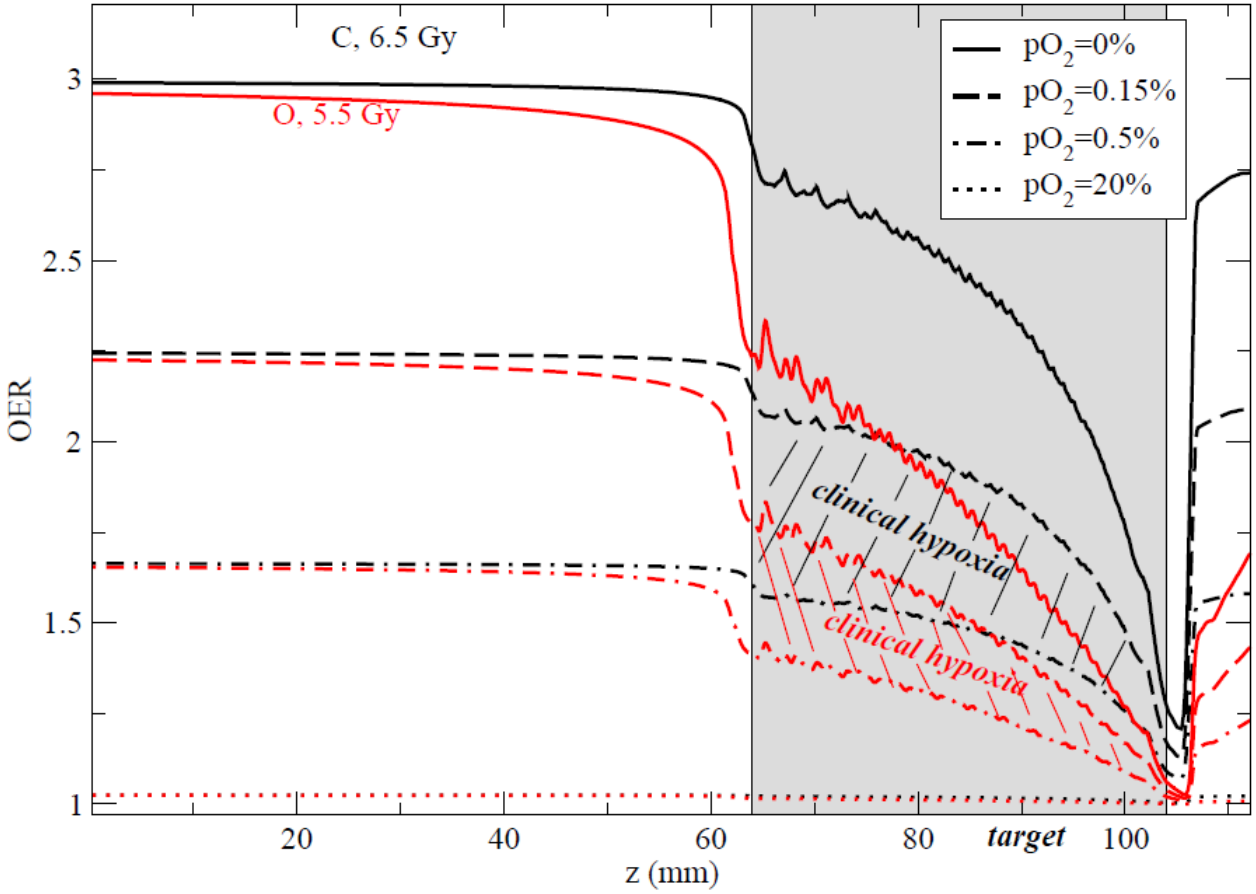




- *November BT @HIMAC preliminary test with 2 passive fields Cfr with expected survival predicted by TRiP-OER*

- *March BT @GSI including OER-optimization (restoring uniform survival)*

Using different ions: Oxygen vs Carbon beam

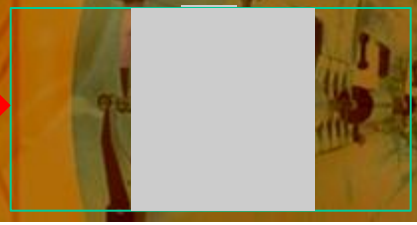


- C, O, p and soon He available @HIT
- Joining OER driven and Multiion modality in next TRiP release

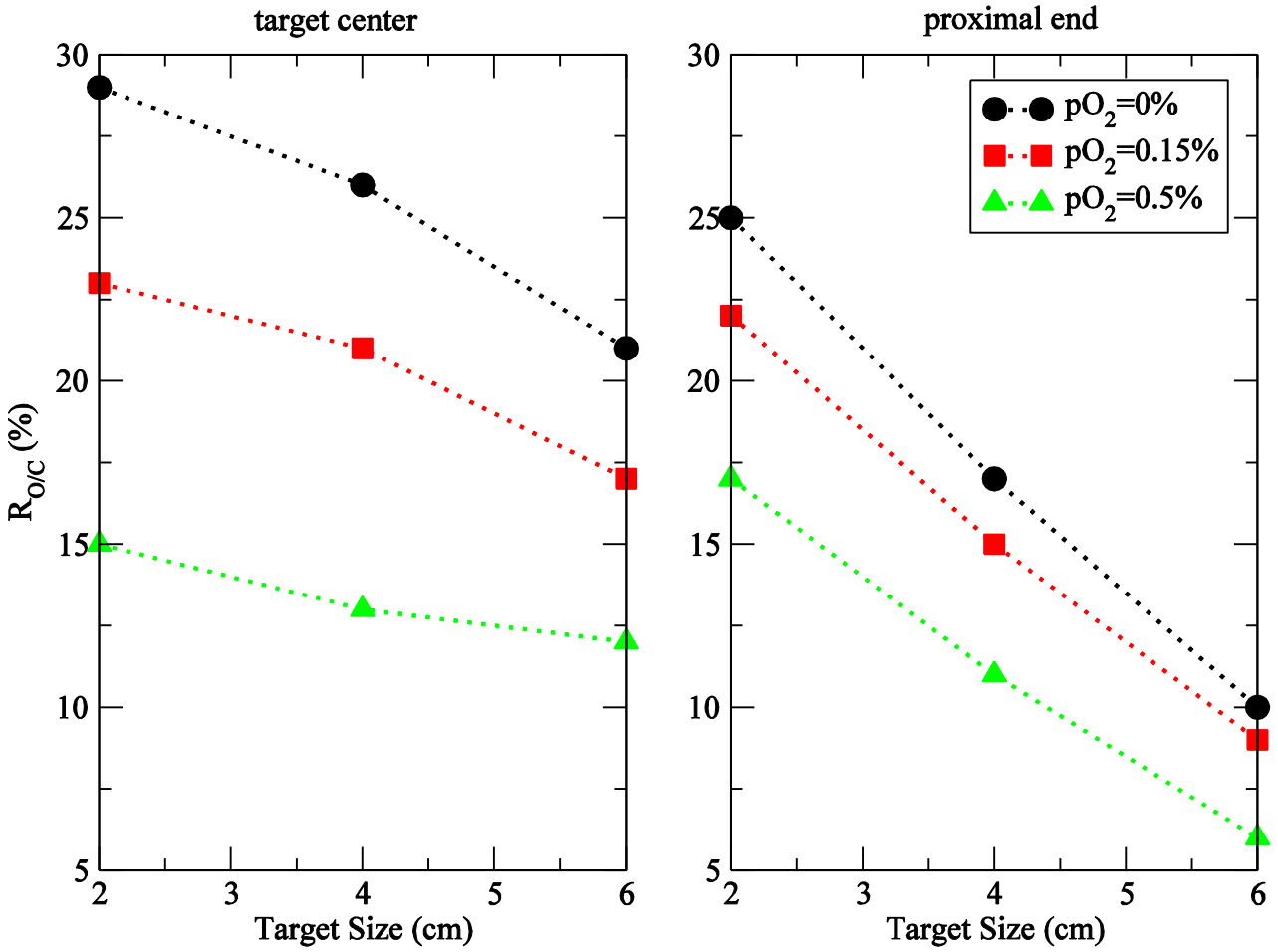
Krämer, Scifoni, Waelzlein, Durante JPCS 2012

Scifoni et al PMB 2013

O vs C for different tumor sizes

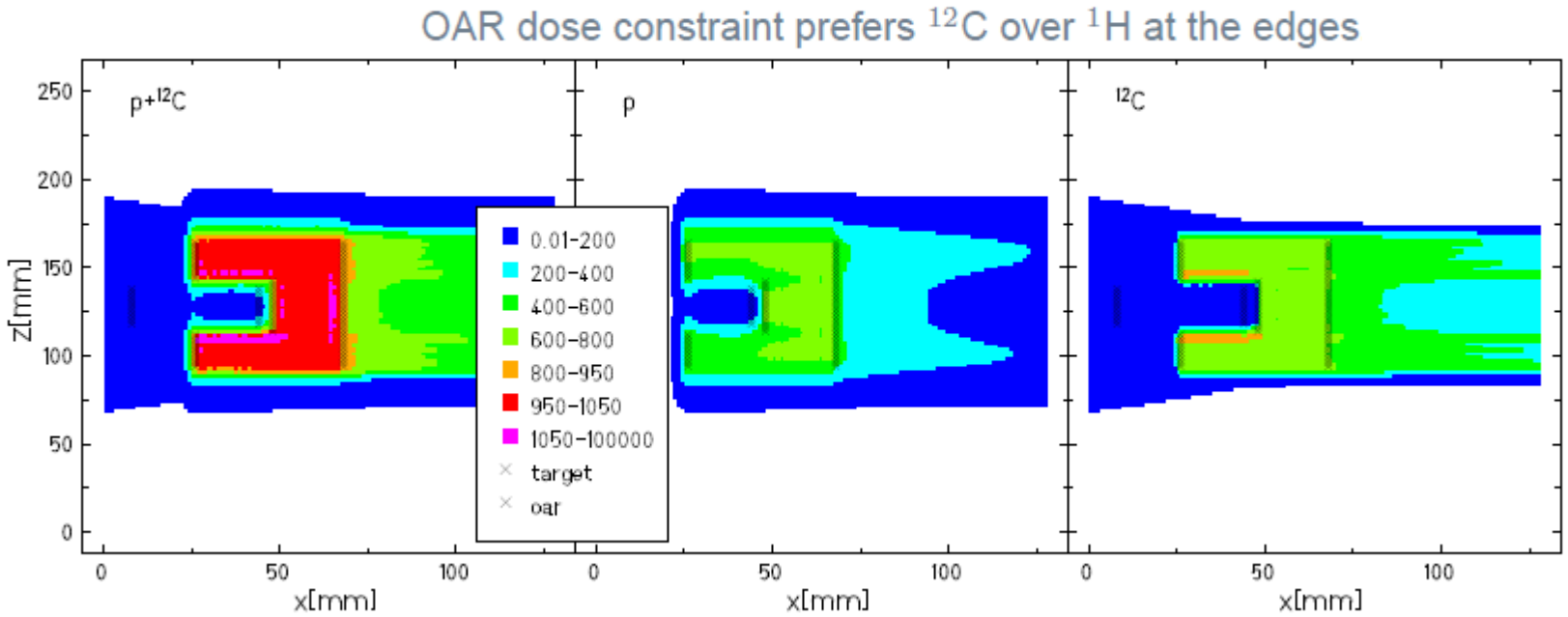


Relative OER reduction $R_{O/C} = (\mathrm{OER}_C - \mathrm{OER}_O)/\mathrm{OER}_C$



Multi-ion treatment planning

- TRiP version for a biologically optimised multi-ion treatment plan
- TPS enhanced to handle more than one ion beam modality at once (e.g. $^{12}C+^{16}O$, $p+^{12}C$)



Krämer, Scifoni, ,Schmitz, Sokol, Durante, *submitted to EPJD*

Summary

- Intratumor Heterogeneity (hypoxia) can be tackled from particle therapy

- First TPS for particles implemented to account for OER and to optimize on iso-survival differently oxygenated areas: *Killing optimization*
- LET redistribution and dose compensation intrinsic by the multiple field optimization

- Carbon Ion beams can be optimized for hypoxic tumors – moderate effect
- Use of larger LET ions (^{16}O) quantitatively assessed and encouraged for boosts or multimodal plans
- Experimental biological dosimetry on extended target irradiation returns agreement with TRiP98 OER predictions

WIP / Outlook

- Tests with clinical PET data (coll. with Aarhus)
- OER optimized + multi-ion
- Acute/Chronic hypoxia distinction
- Experimental verification of dose compensation and refined optimization approaches, also for O and mixed beam
- Impact of fractionation and reoxygenation (especially for SBRT and HDSF regimes)
- Application to other types of intratumour heterogeneity

Thanks to

- Michael Kraemer, Walter Tinganelli, Marco Durante

and to

- W. Kraft-Weyrather, A. Maier, M. Horcicka, T. Friedrich, M. Scholz (GSI)
- Y.Furusawa, R. Hirayama, M. Ozaki (NIRS)
- N. Bassler, J. Petersen, J. Toftegaard (Aarhus)

And…

Funding:

Helmholtz Portfolio Technology&Medicine

International Open Laboratory

ULICE
Union of Light Ion Centres in Europe

GSI