RadioOnkologie

Behandeln
Forschen
Lehren

UniversitätsKlinikum Heidelberg

Point/Counterpoint:

The more important heavy charged particle RT of the future is more likely to be with heavy ions rather than protons

AAPM 55, Indianapolis

August 5th, 2013

Oliver Jäkel

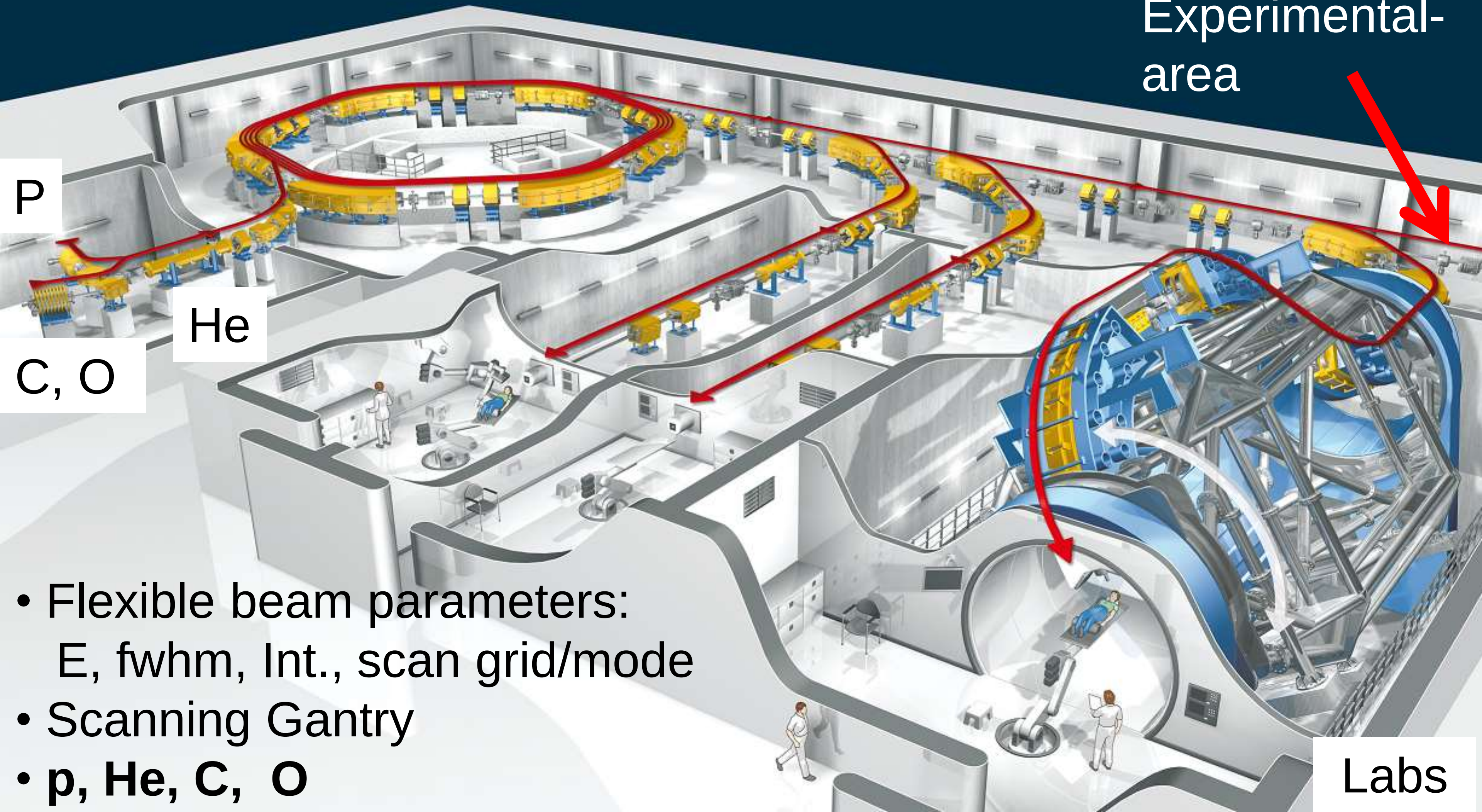
Heidelberger Ionenstrahl-Therapiezentrum

UniversitätsKlinikum Heidelberg
IonenStrahl TherapieZentrum

dkfz.

Heidelberg Ion Beam Therapy Center

November 2009: 1. patient treated
October 2012: Gantry treatment started
Today: > 2000 patients treated



- Flexible beam parameters:
  E, fwhm, Int., scan grid/mode
- Scanning Gantry
- **p, He, C, O**

Opening statement:

(I) With regard to Physics:

Everything that can be done with protons, can be done also with heavy ions, but in a better way.

(II) With regard to Radiobiology:

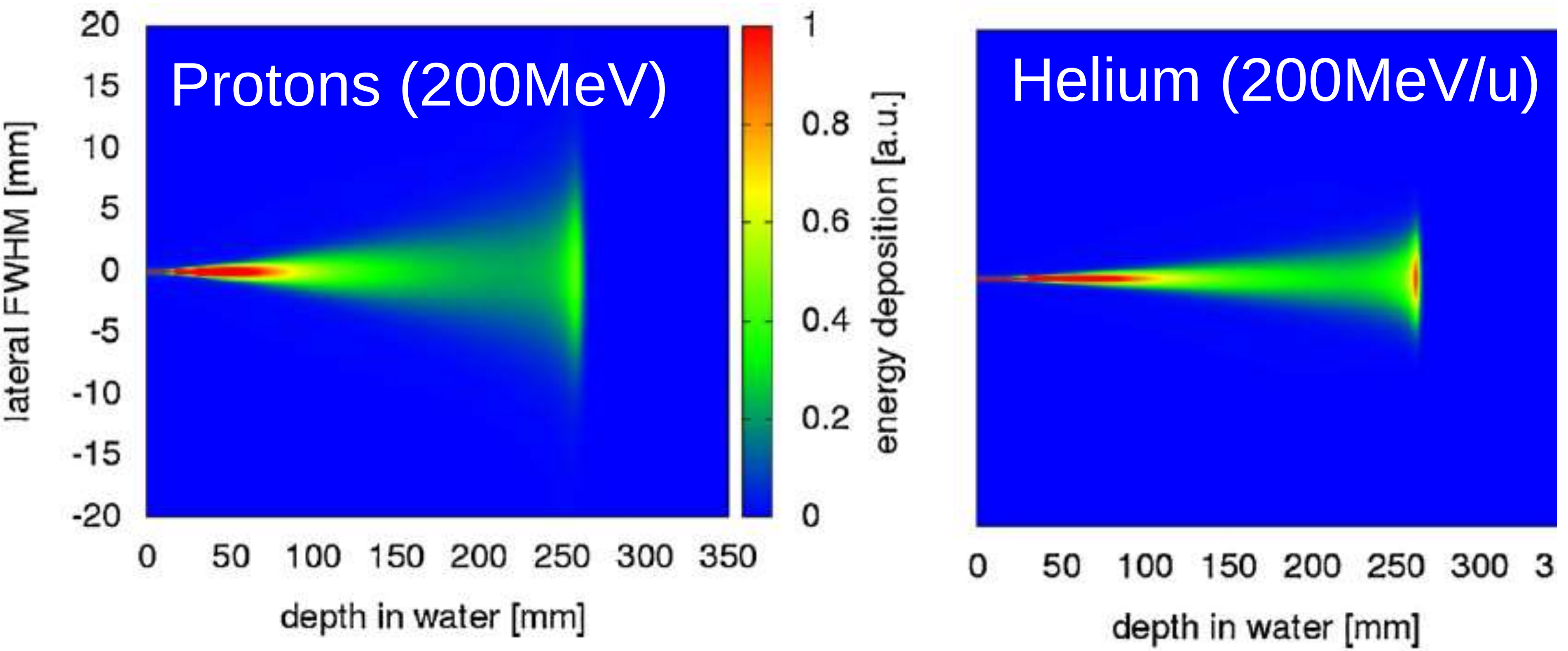
Heavier ions have the potential to significantly improve clinical results esp. for radioresistant tumors (e.g. Hypoxia, Heterogeneity, Genetic resistance …)

Physical advantages of heavier ions vs. protons

- Reduced angular scattering: sharper penumbra
- Reduced range straggling: sharper distal fall-off
- Better targeting due to better in-vivo monitoring
- There is a whole variety of heavy ions

Pencil beams for Protons vs. Helium

Ströbele et al., Z. Med. Phys. 2012

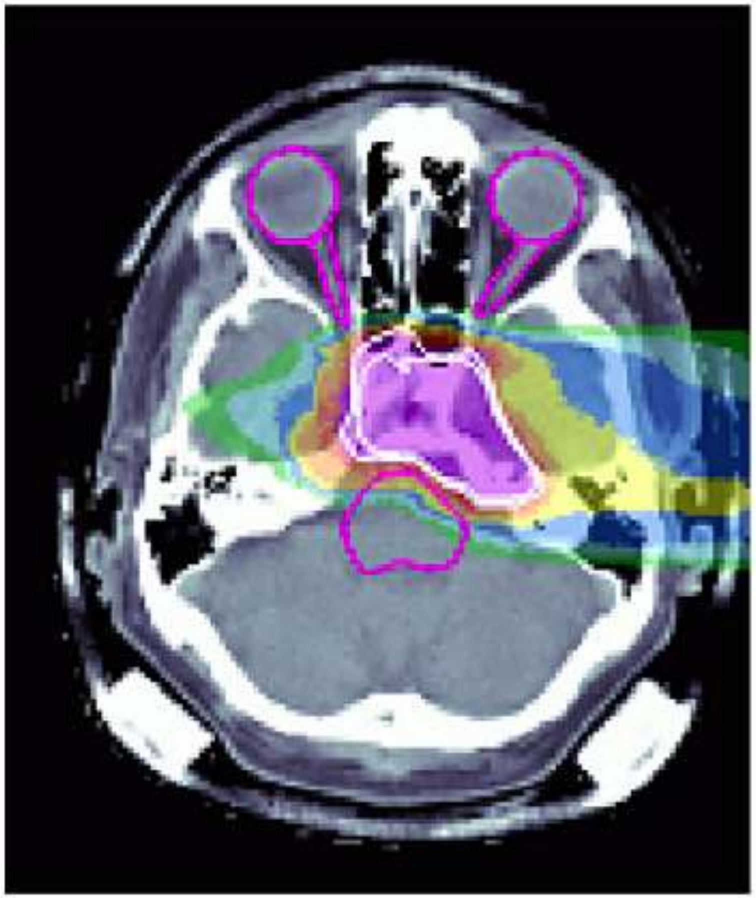


Improved peak to plateau ratio and reduced lateral penumbra for Helium

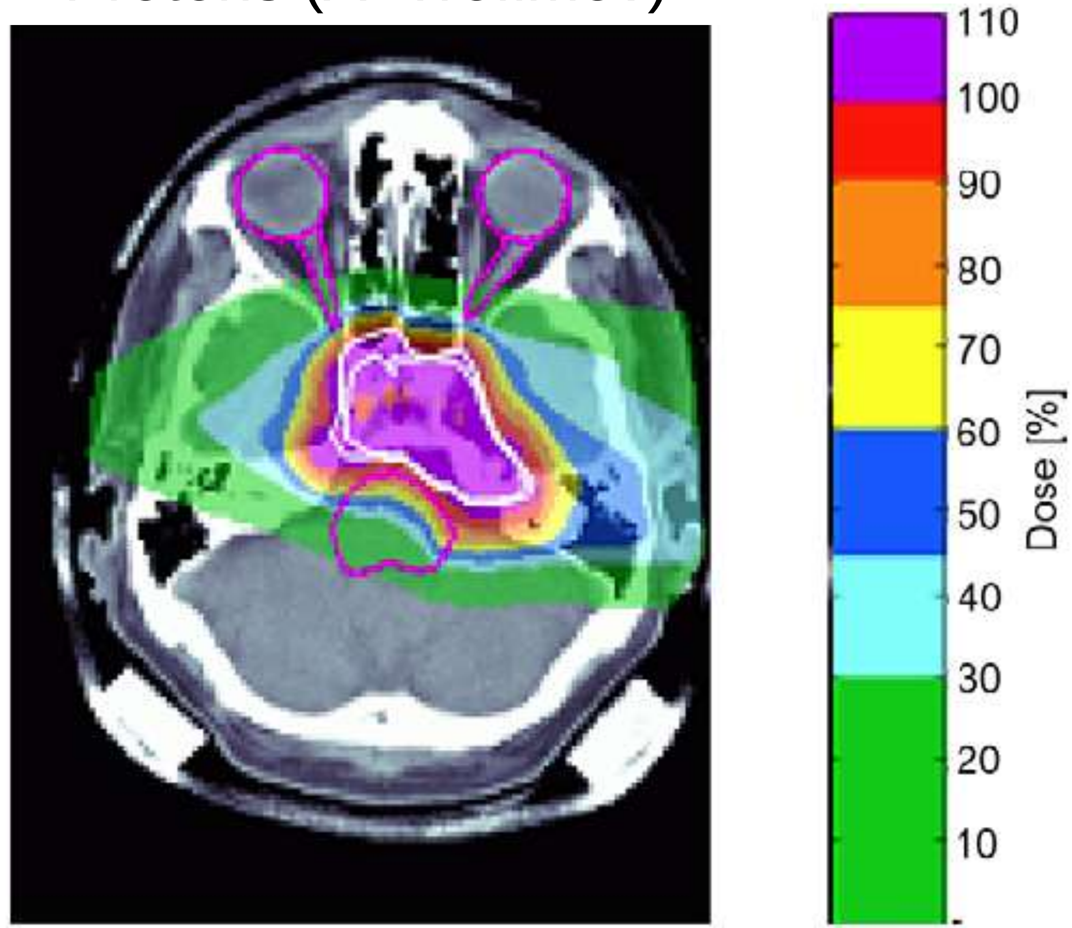
Helium offers excellent dose conformation, only slightly elevated RBE (~1.3); similar costs as p

Clinical relevance of lateral penumbra
TP for scanned beams

Carbon (O. Jäkel)



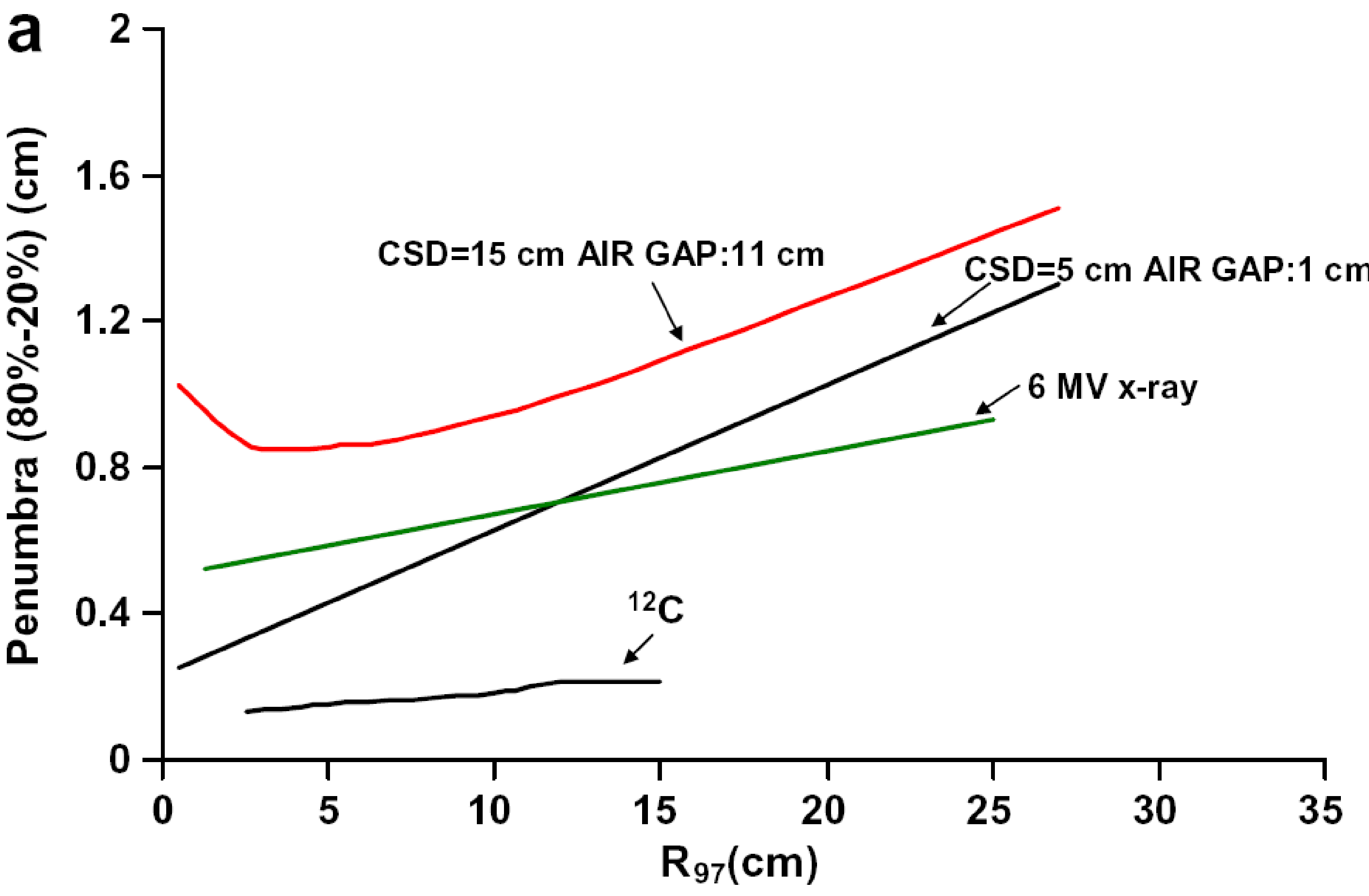
Protons (A. Trofimov)



H. Suit et al, Radiat. Oncol. 2010

Lateral penumbra alone may justify to use heavier ions

Reduced lateral penumbra



protons

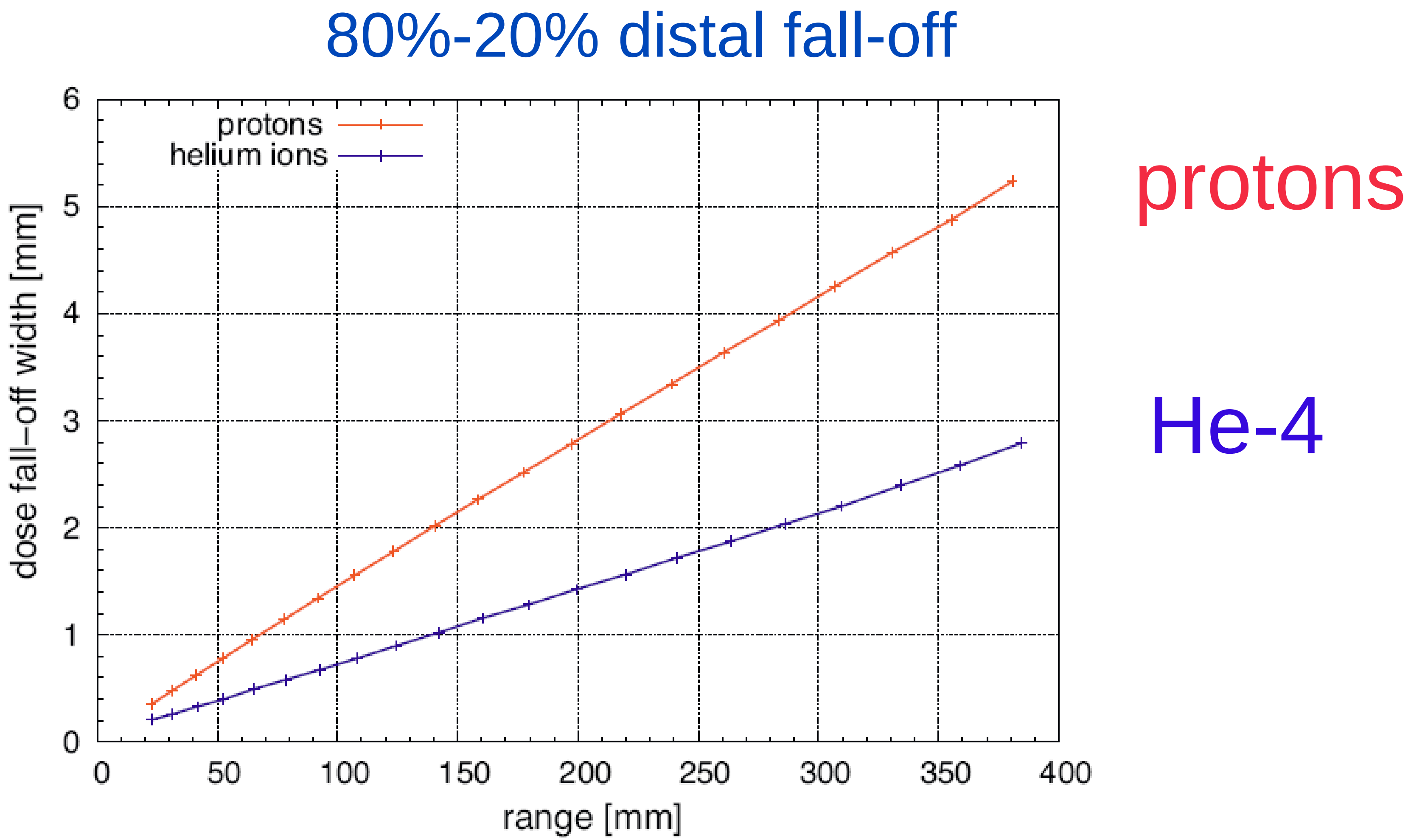
X-rays

C-12

H. Suit et al, Radiat. Oncol. 2010

The penumbra of protons is worse than for photons at larger depth

Reduced energy straggling



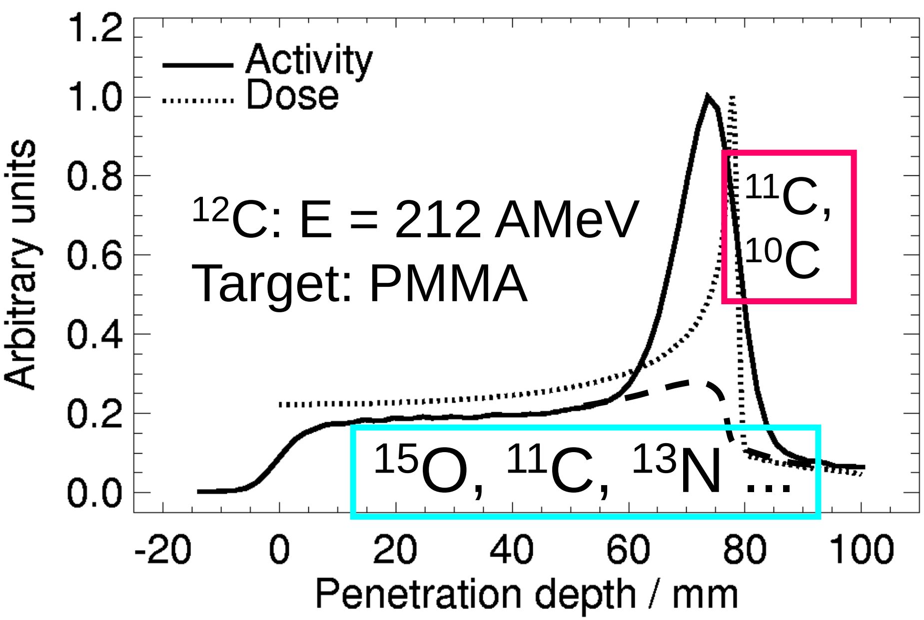
Ströbele et al., Z. Med. Phys. 2012

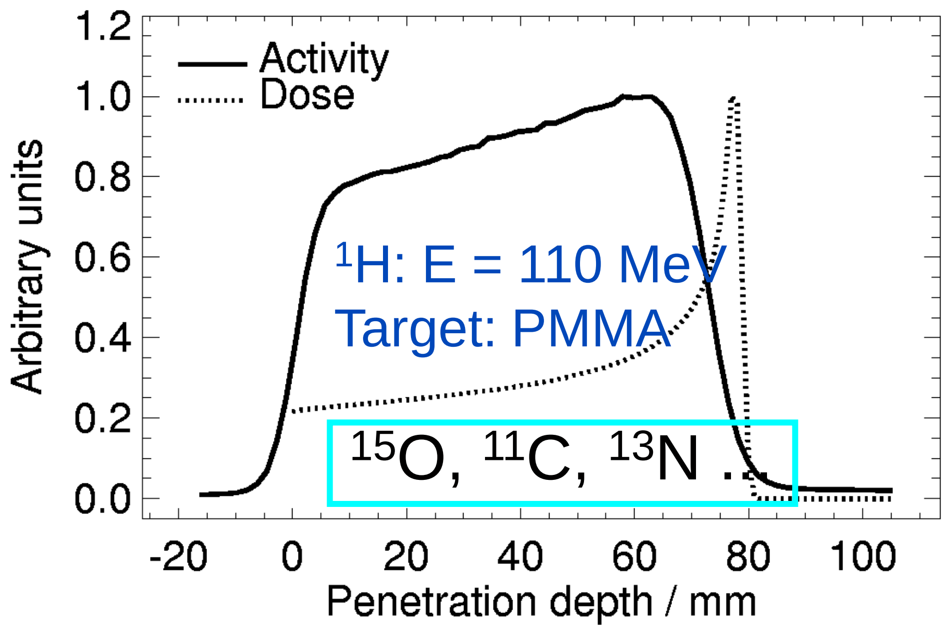
PET Imaging with ion beams

Peripheral nucleus-nucleus-collisions, low momentum transfer

Z ≥ 6 Target fragments | Projectile fragments

Z < 6 Target fragments

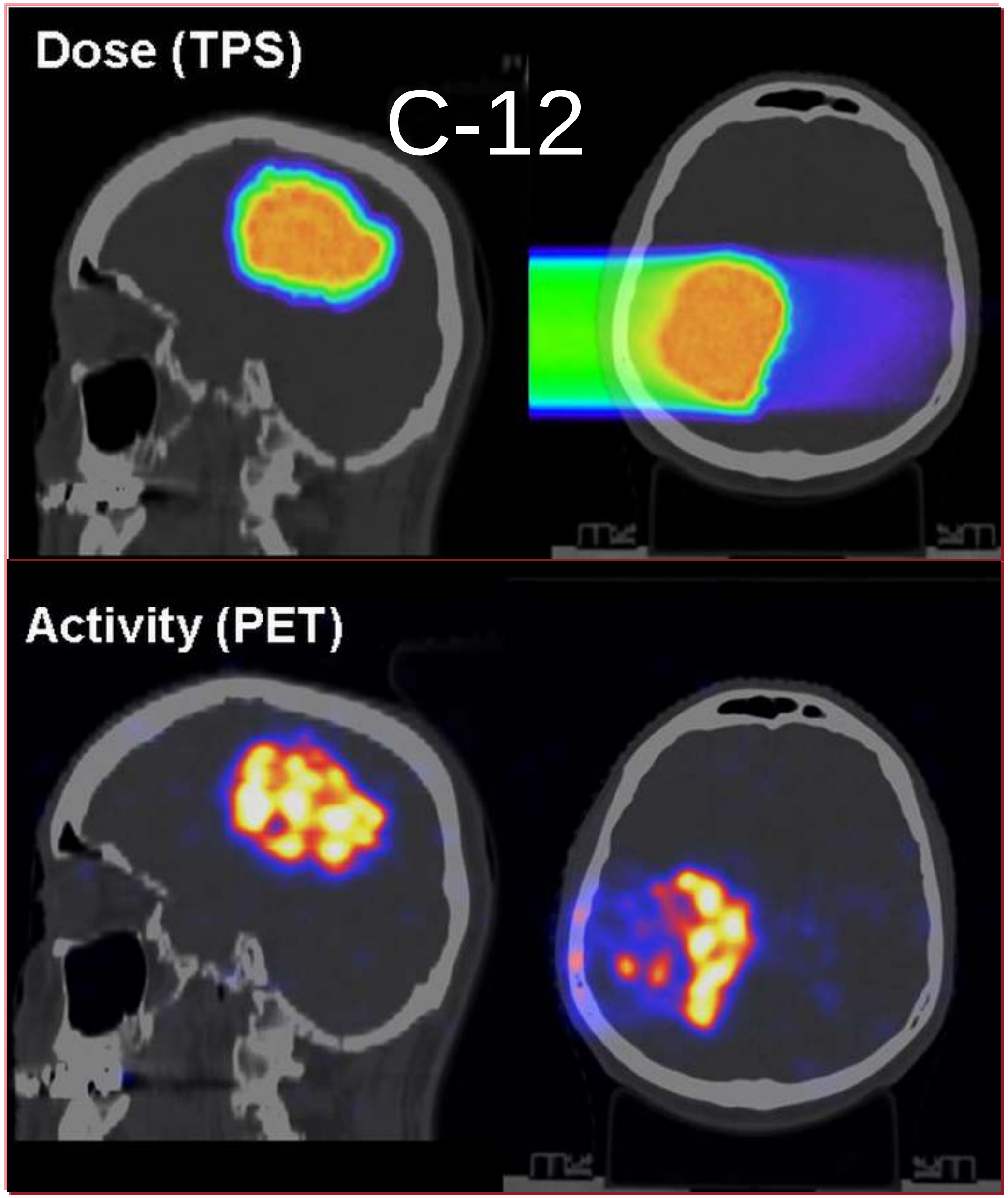


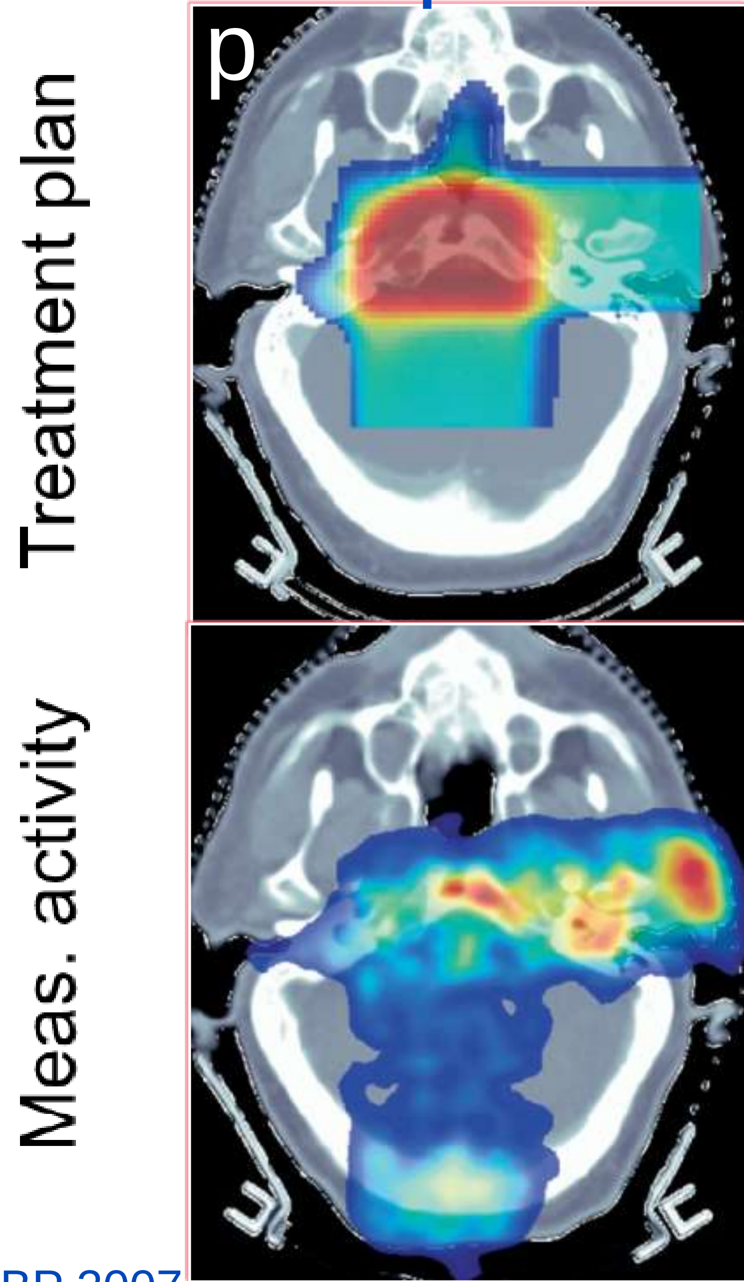


Courtesy of W. Enghardt

Potential range probing with radioactive beams: C11,Ne19

In vivo PET Monitoring in C-12 vs. p-RT

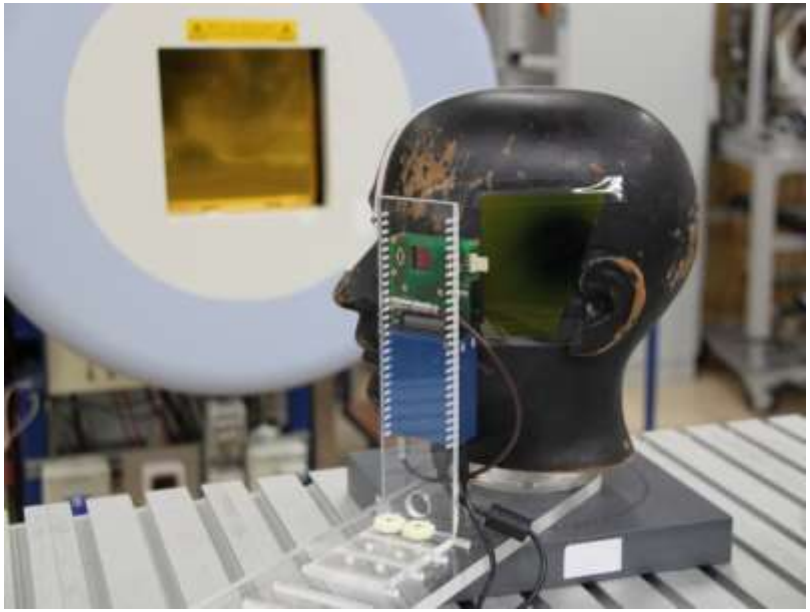


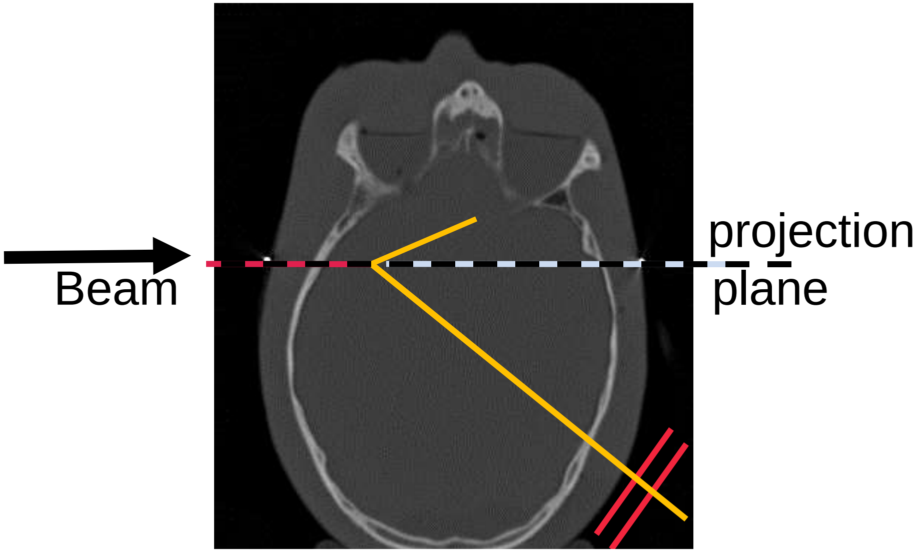


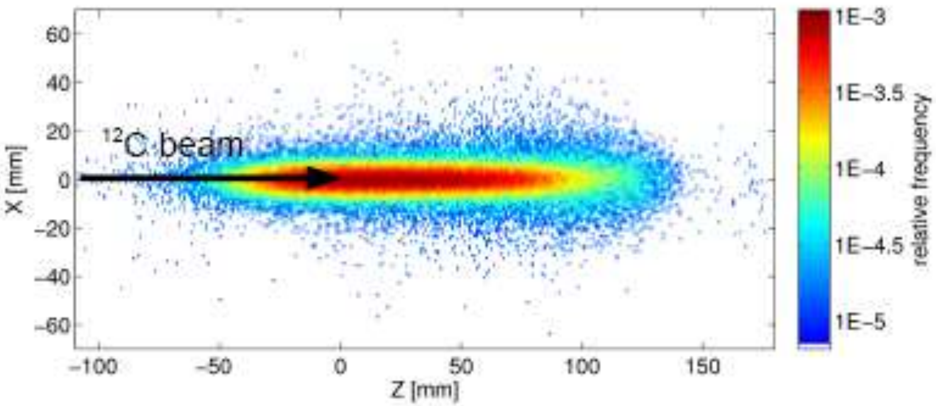
Combs BMC Cancer 2012

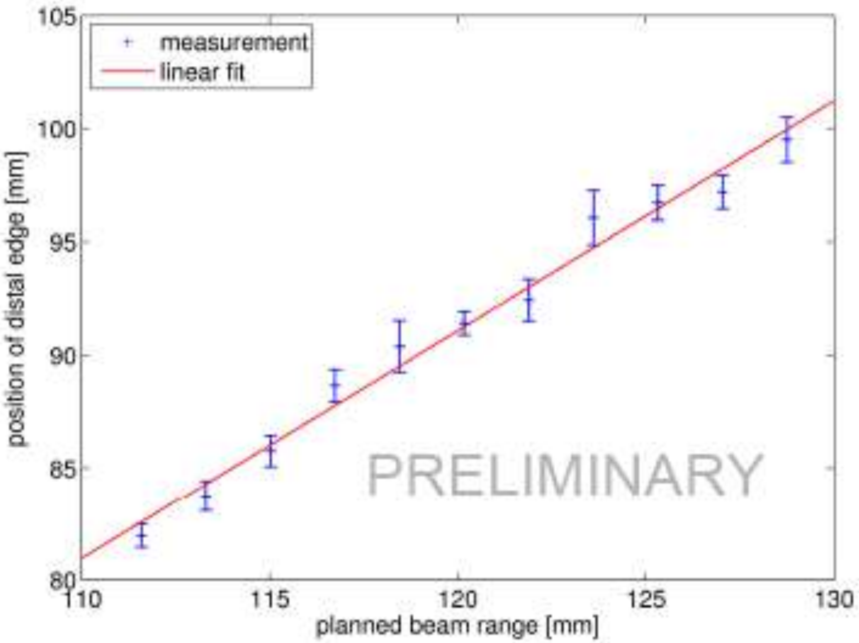
Parodi et al IJROBP 2007

Tracking of prompt protons from a Carbon beam





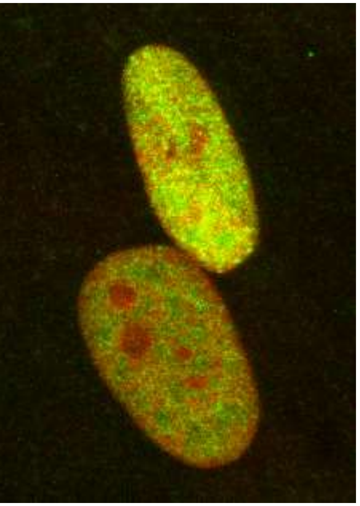




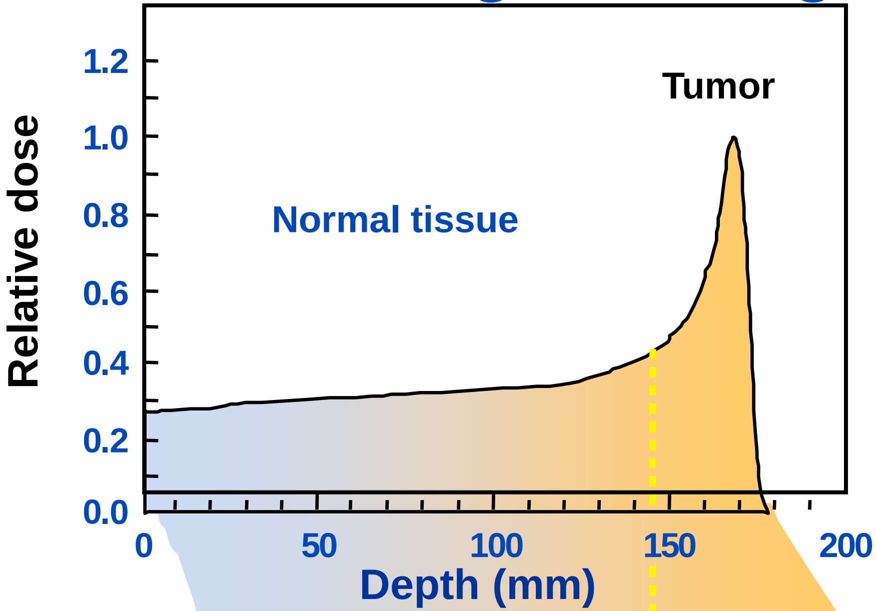
Gwosch et.al, PMB 2013

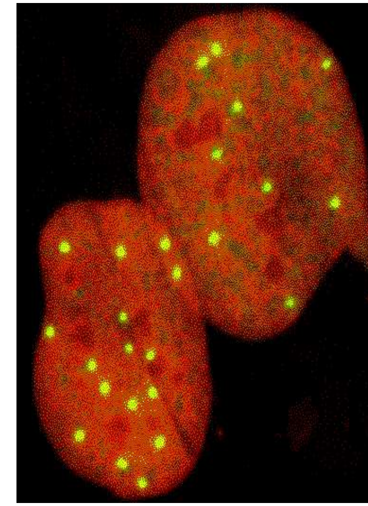
Measurement of peak position, beam width with 1mm resolution

Biological Advantages of high LET RT



Low LET dose





Carbon tracks in nucleus

Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3

Tumor dose >> normal tissue

Effective for radioresistant tumors

Effective in hypoxic tumor cells

Durante, Loeffler, *Nature Rev Clin Oncol* 2010

Which tumors might be better treated by Ions ?

Tumors, which are refractory to low LET irradiation

Radioresistance

Genetic alterations

upregulated oncogenes
mutated tumor suppresor genes
disregulated apoptosis

Intratumoral micromilieu

Deprivation of oxygen
Up-regulated defense system
High angiogenic potential

Proliferation status

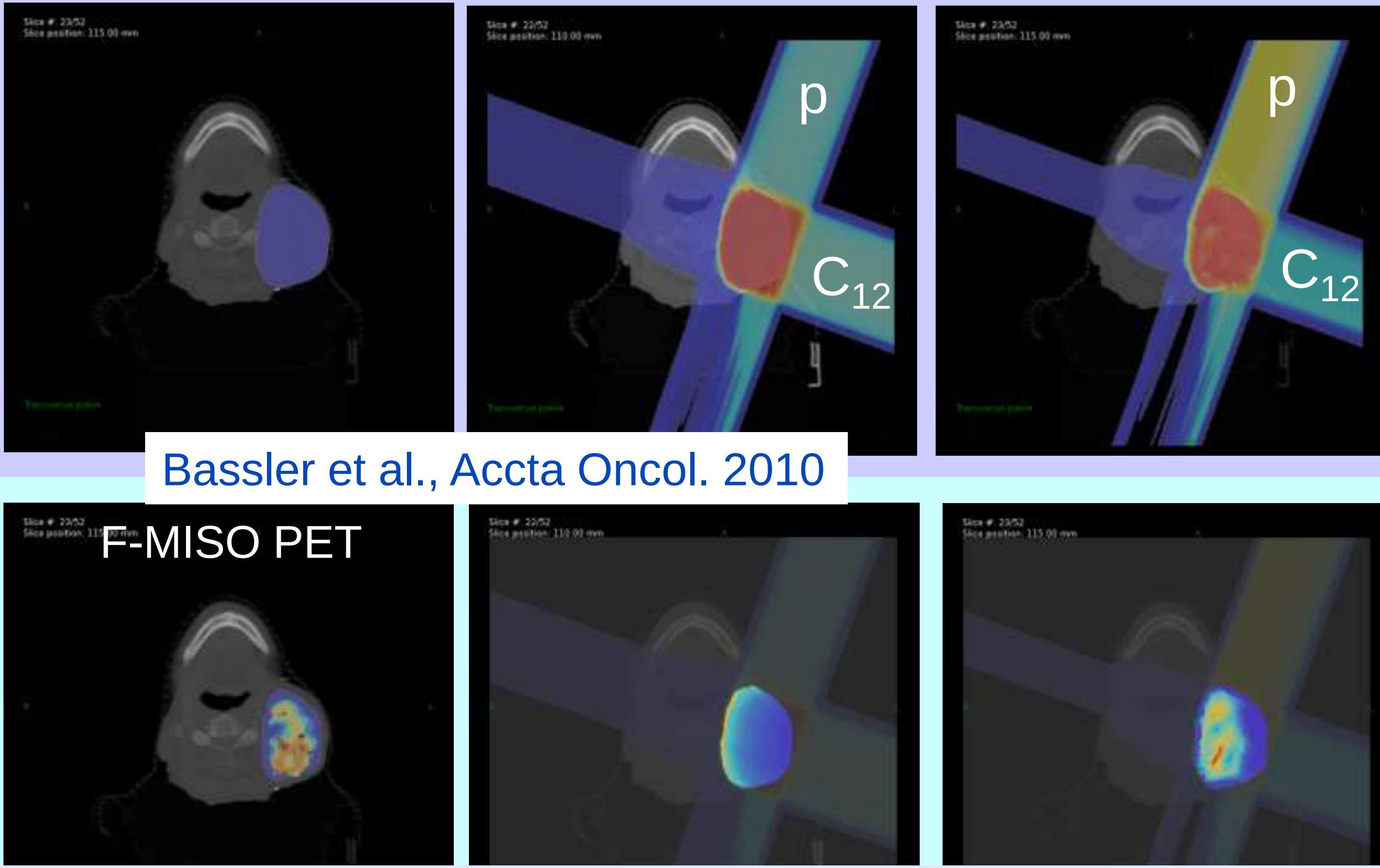
High content of quiescent cell clones
Slow proliferation activity

LET Painting for hypoxic tumors

Planned target | SFUD | LET-Painting

DOSE

LET



Bassler et al., Accta Oncol. 2010

Scanning and IMPT offers additional degrees of freedom for adapting high LET to hypoxic areas

Clinical Trials at HIT

see www.clinicaltrials.gov

1. SB Chordome: H1 vs. C12 recruting
2. SB Chondrosarkome: H1 vs. C12 recruting
3. CLEOPATRA (H1 vs. C12 im Boost; prim. Glioblastom) recruting
4. CINDERELLA (C12 bei Gliobastom Rezidiv) recruting
5. MARCIE (C12 Boost bei malignen Meningeomen) recruting
6. COSMIC (C12 Boost bei Speicheldrüsen Ca) finished
7. TPF-C HIT (Kopf-Hals-Tumor RChT mit C12 Boost) recruting
8. IMRT HIT-SNT (Sinu-nasale Tumore, IMRT mit C12 Boost) recruting
9. ACCEPT (C12 + Erbitux bei ACC) BFS cleared
10. PROMETHEUS (C12 bei primärem HCC) recruting
11. OSCAR (inoperables Osteosarkom) recruting
12. PANDORA (C12 bei Rektum Ca Lokalrezidiv) BFS cleared
13. IPI (C12/H1 bei Prostata Ca) BFS cleared

Carbon + GEM for loc. adv. Pancreatic Cancer

S. Yamada, NIRS, Rochester May 2nd, 2013

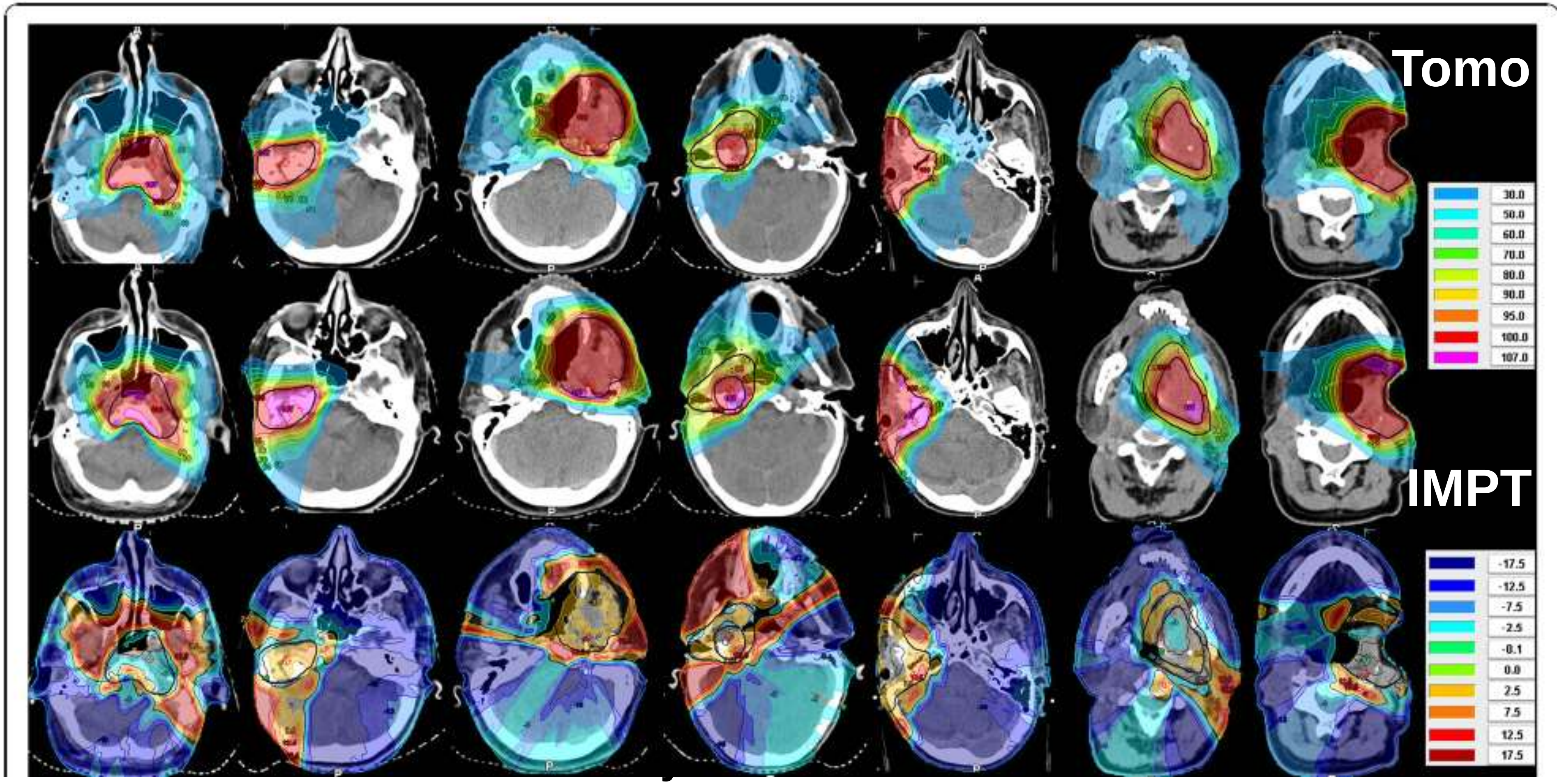
	Year	n	Treatment	Dose	Survival 1yr	Survival 2yr
ECOG	2008	34	GEM+RT	50.4Gy	50%	12%
		37	GEM	-	32%	4%
Ishii	2010	50	GEM	-	64%	14%
Sudo	2011	34	S-1+RT	50.4Gy	71%	25%
Small	2011	28	GEM+BZ*+ RT	36Gy/15fr.	45%	17%
Schellenberg	2011	20	GEM+SBRT	25Gy/1fr.	50%	20%
NIRS		**47**	**GEM+CIRT**	**45.6-55.2 GyE**	**74%**	**54%**

*Bevacizumab

Incidence (Mortality) of pancreatic Ca. 2012 (US): 43 920 (37 390)

Protons are not per se superior to modern IMRT

Tomotherapy vs. IMPT (Stuschke, Radiother. Oncol, 2013)



Excess dose of IMPT in RED

Modern IMRT has come close to IMPT

The small benefit may not justify higher price for protons

Clinical potential for ion beams

- Clinical data from prospective phase I/II and phase II trials support the strong potential of heavy ions
- Randomized studies are underway
- Radiobiological research will be crucial for patient selection and targeting
- Protons offer limited benefit compared to X-rays
- Why should be stop the development with the easiest and least beneficial ion, i.e. protons?

Heavier ions will be more important than protons

… maybe not in the next few years

… maybe not in the US

“If we are satisfied,
we are lost”

William J. Mayo, MD
1935

Treatment costs

Costs for p-RT in the US:
Av. Reimbursement by CMS: $35,917
Upper range for pediatric patients up to 250 000 $

Carbon RT is reimbursed in the EU with 19k€

Investment costs account for < 50% treatment costs!

Hypofractionation will change these numbers:
C-12 for lung tumors at NIRS: 10‘040 €

Cost-effectiveness is more relevant than costs!

Technical develoment and hypo-Fx will reduce costs

Carbon therapy in Heidelberg plus extras is cheaper than p-RT in the US …

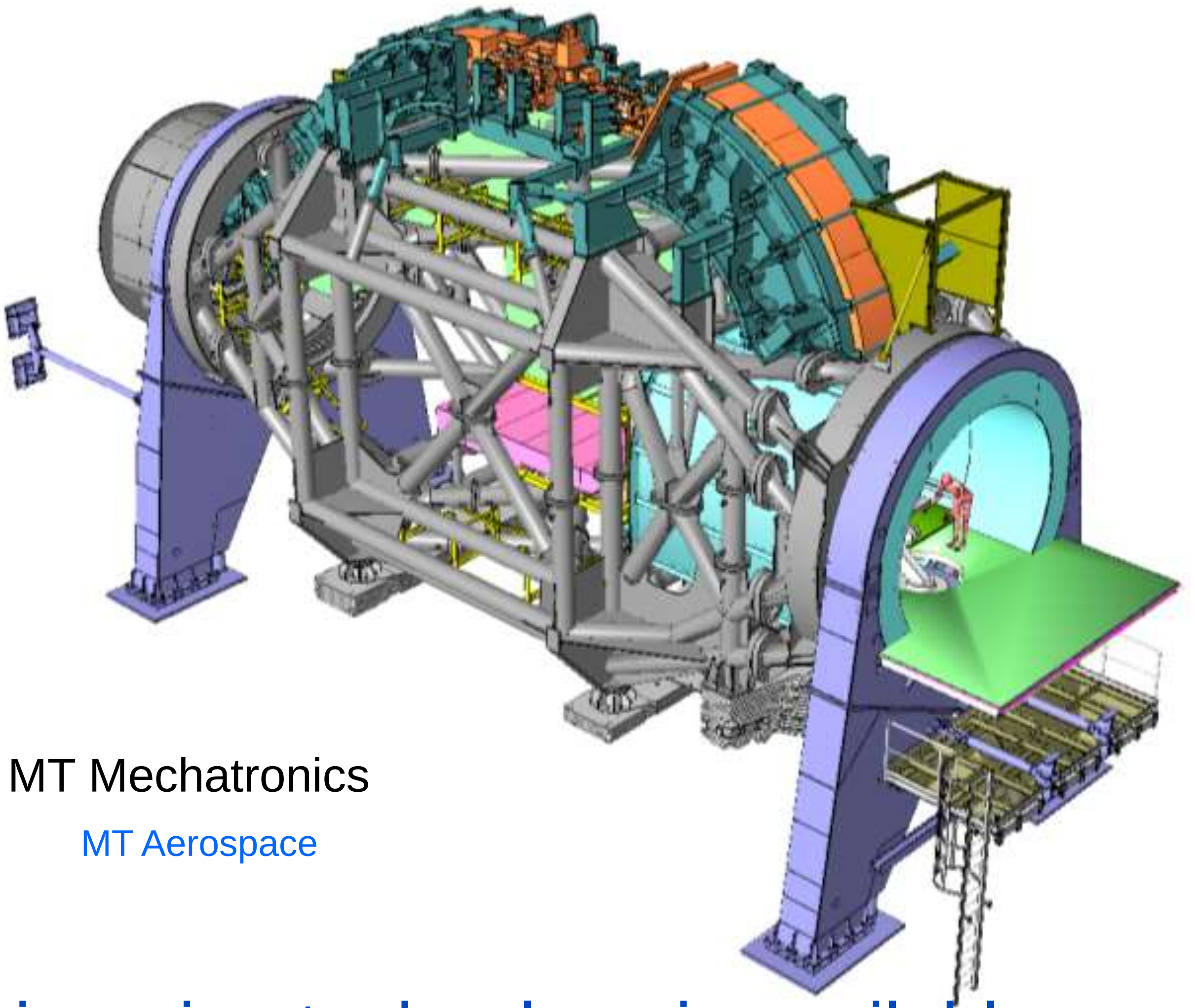
Carbon Gantry in clinical operation

world-wide first
ion gantry

2D parallel scanning

± 180^o rotation
3^o / second

13m diameter
25m length
600 to rotating
(145 to magnets)



MT Mechatronics

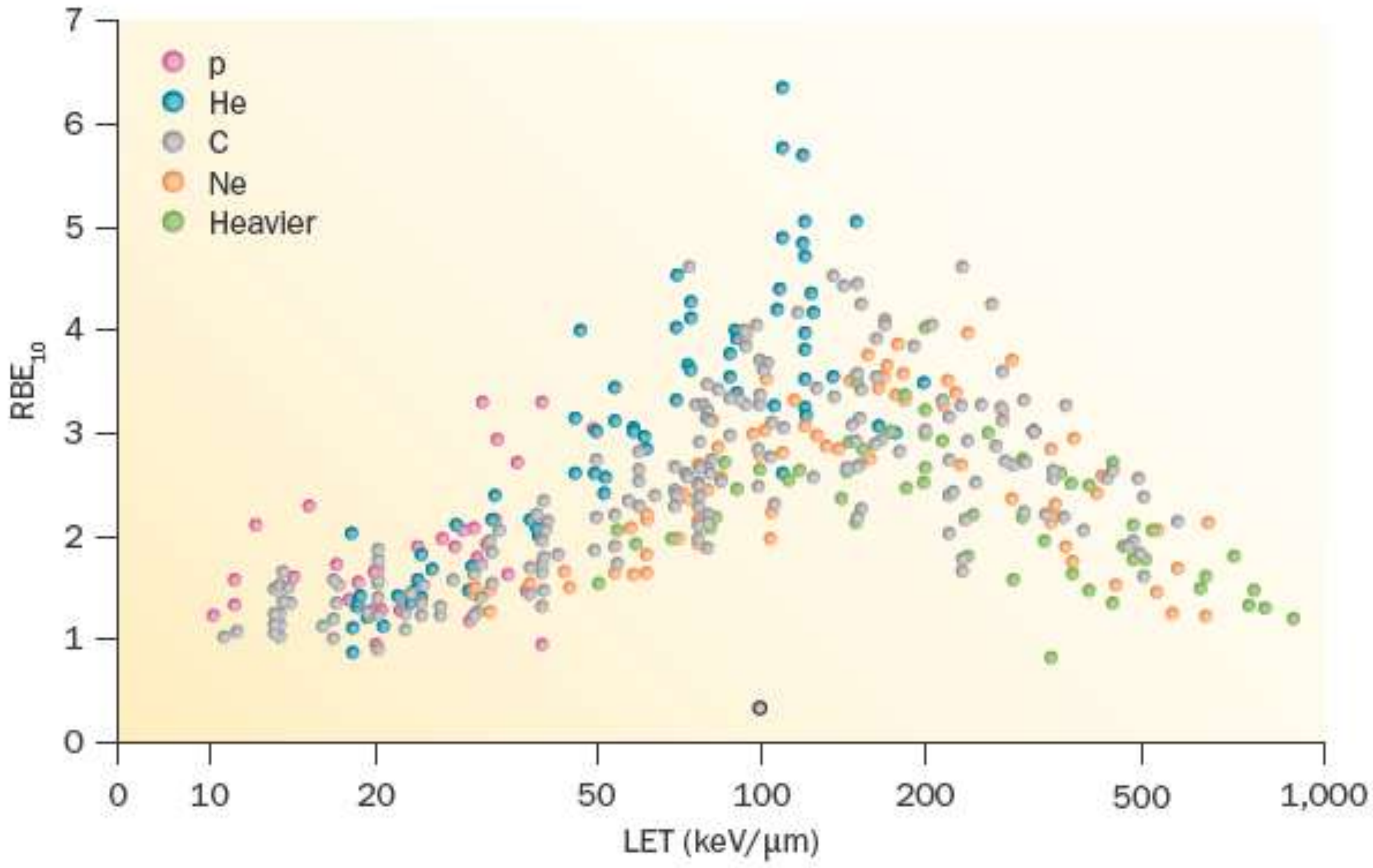
MT Aerospace

Required engineering technology is available

Btw: some providers for p-RT offer fixed beamlines ?!

Dependence of RBE on LET

855 survival curves



Durante, Loeffler,

Nature Rev Clin Oncol 2010

The spread reflects the cell types but also uncertainty of RBE

Uncertainty of RBE

RBE(p)= 1.1 ??

There is not a single determination of RBE(p) from clinical data

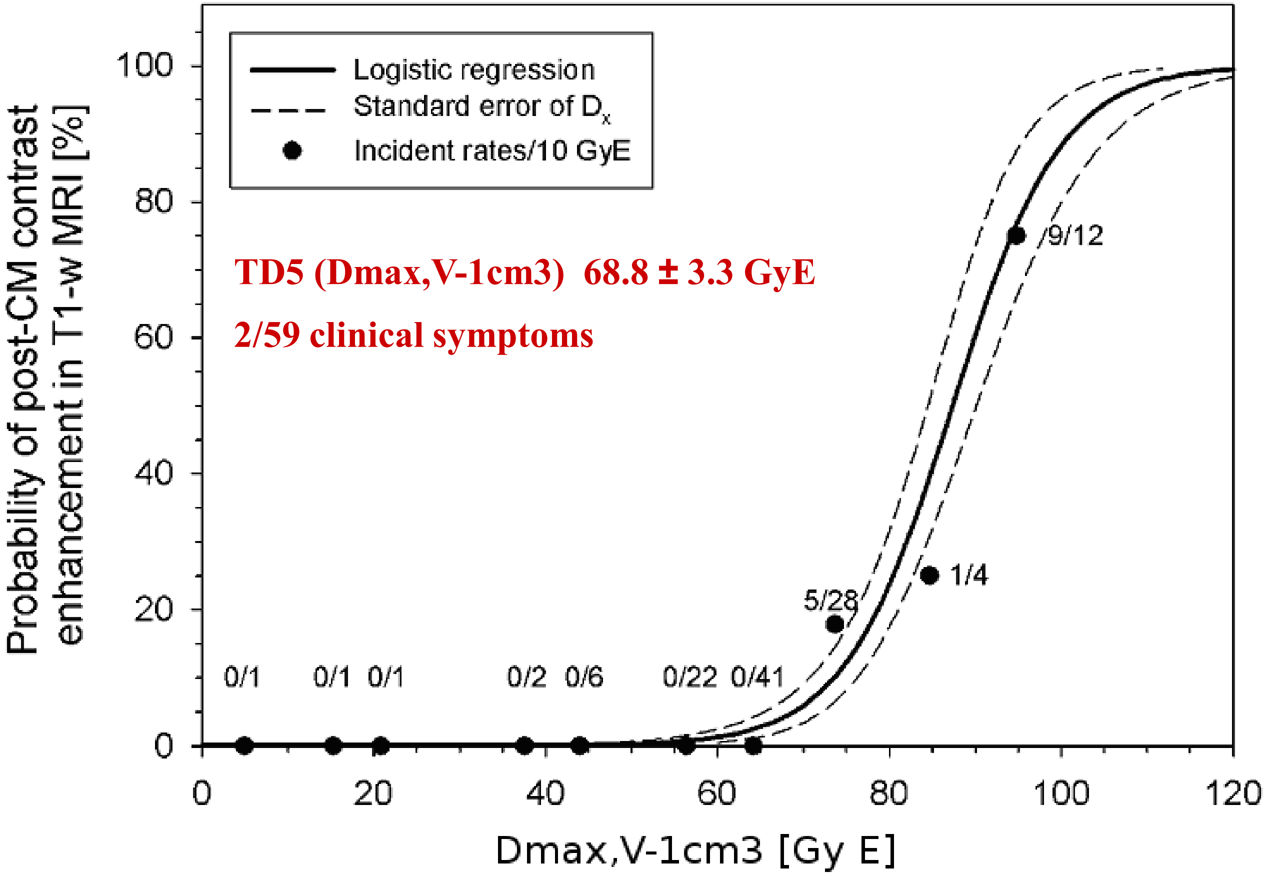
RBE(p) may have an uncertainty of ~ 20-30%

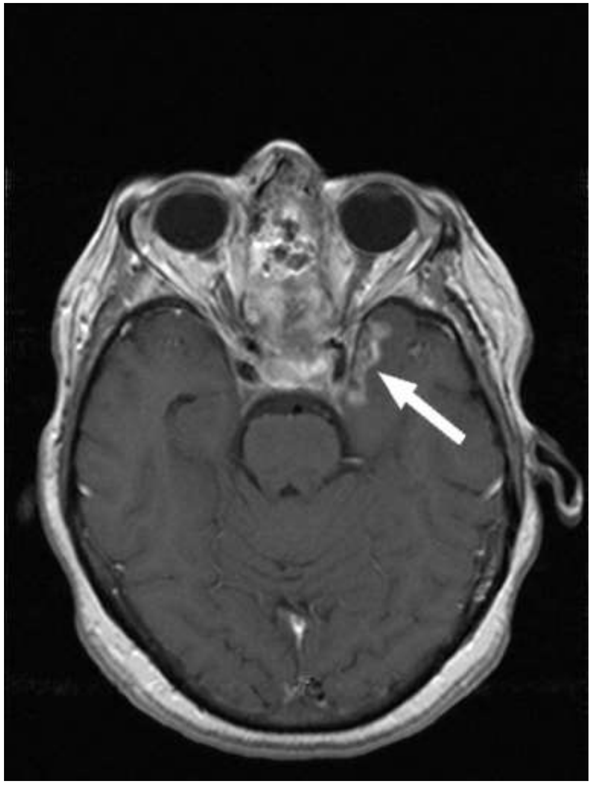
Using a model helps to reduce the uncertainty. Using a fixed RBE does not.

Normal tissue damage after carbon RT:

dose response for contrast enhancement in the temporal lobes

n=59, 2002-2003, FU 2,5 years





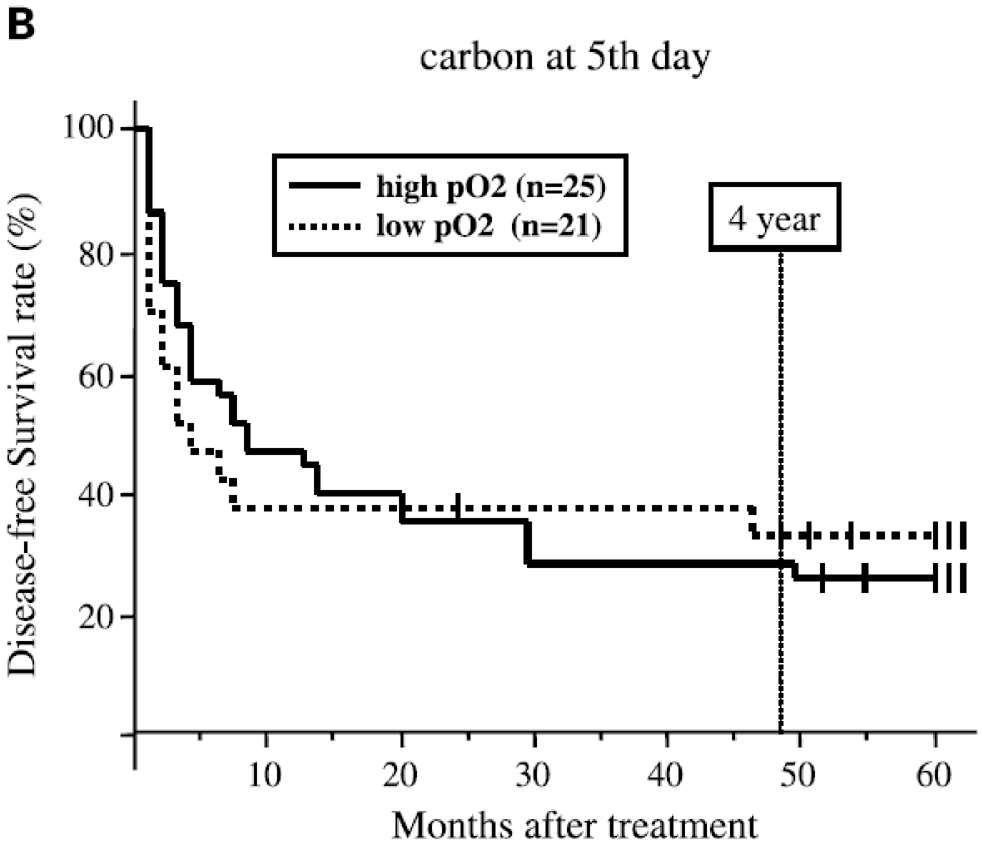
Schlampp et al., Int J Radiat Oncol Biol Phys, (2011) 80: 815ff

No signs of any increased normal tissue damage

Clinical evidence for OER effect in C-RT

Nakano et al: Clin. Cancer Rev. 2000

Patients w. uterine cervical cancer

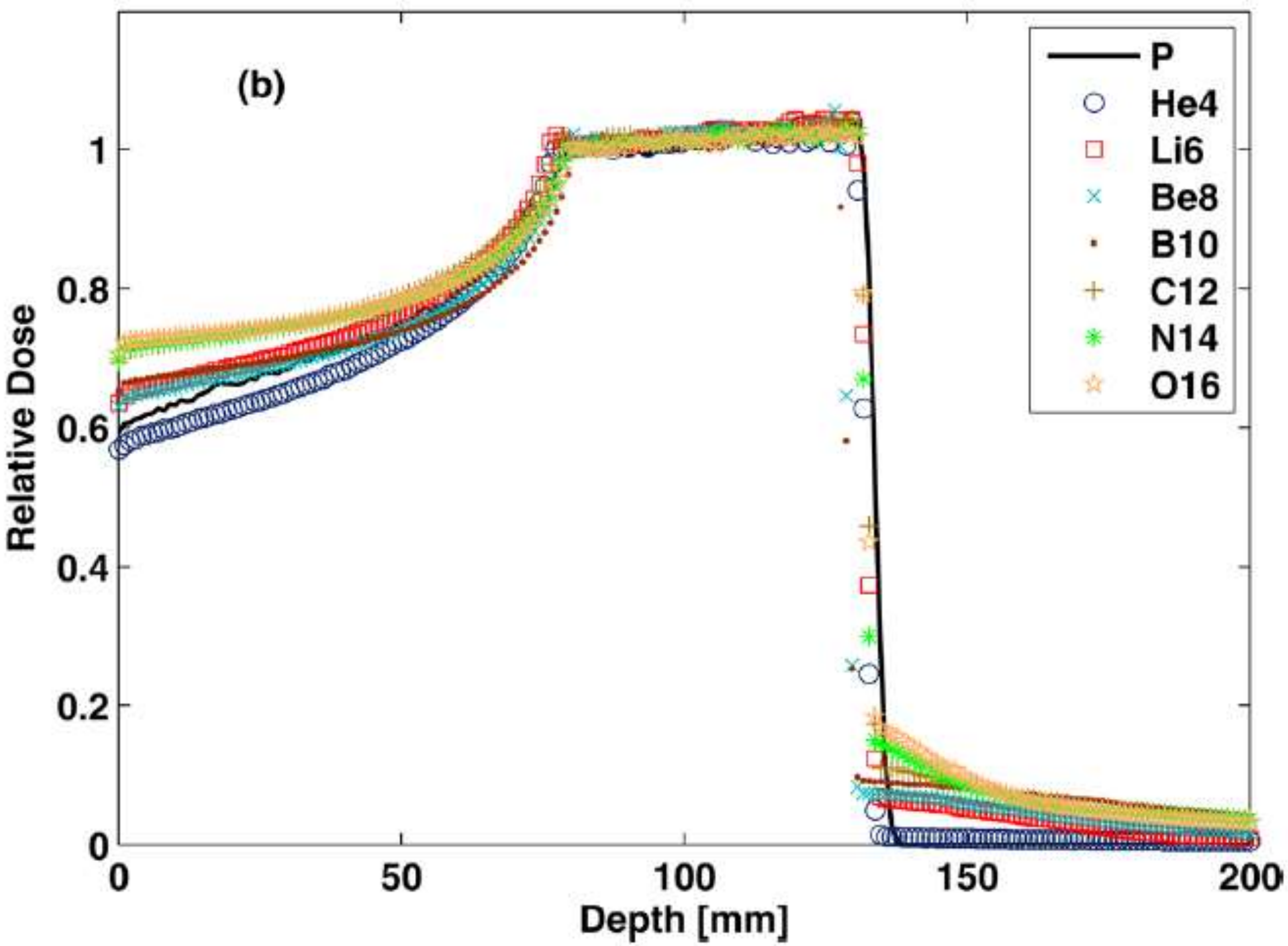


Carbon

Reoxygenation is less important in high LET

Hypofractionated proton-RT will reduce this effect

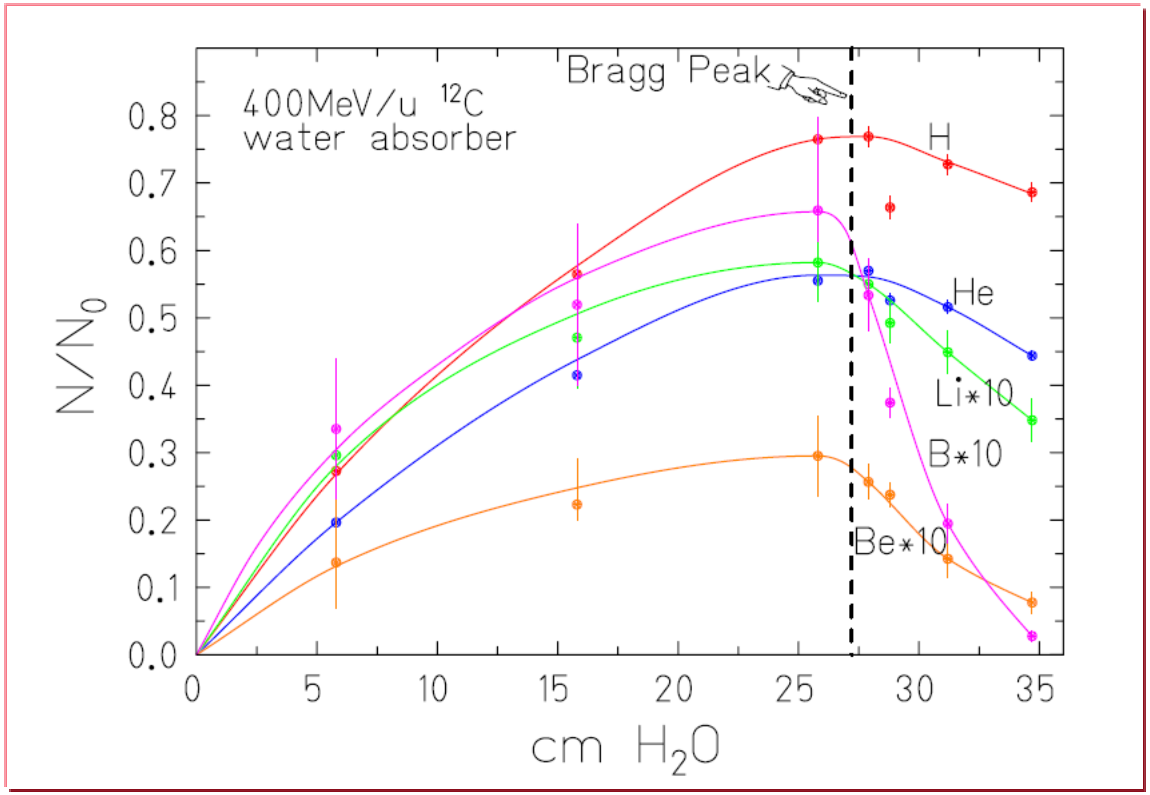
Depth dose curves for various ions



Kantemiris
Med Phys 38,
2011

There is no tail for Helium
The dose in the tail is 10-20%

Fragmentation of Carbon ions
400MeV/u in water



Most of the particles in the tail are protons!
Dose and RBE are included in the TPS
No clinical observation questioning this approach

Clinical evidence for protons

For brain tumors, despite reduced integral doses, no reduction of adverse events could be demonstrated.

S. E. Combs, N. Laperriere, M. Brada, Semin. Radiat. Oncol. 2013.

There are only a few sites potentially to benefit from the use of Proton Beam Therapy.

The report of ASTRO's emerging technology committee: A*n evidence based review of* proton beam therapy"

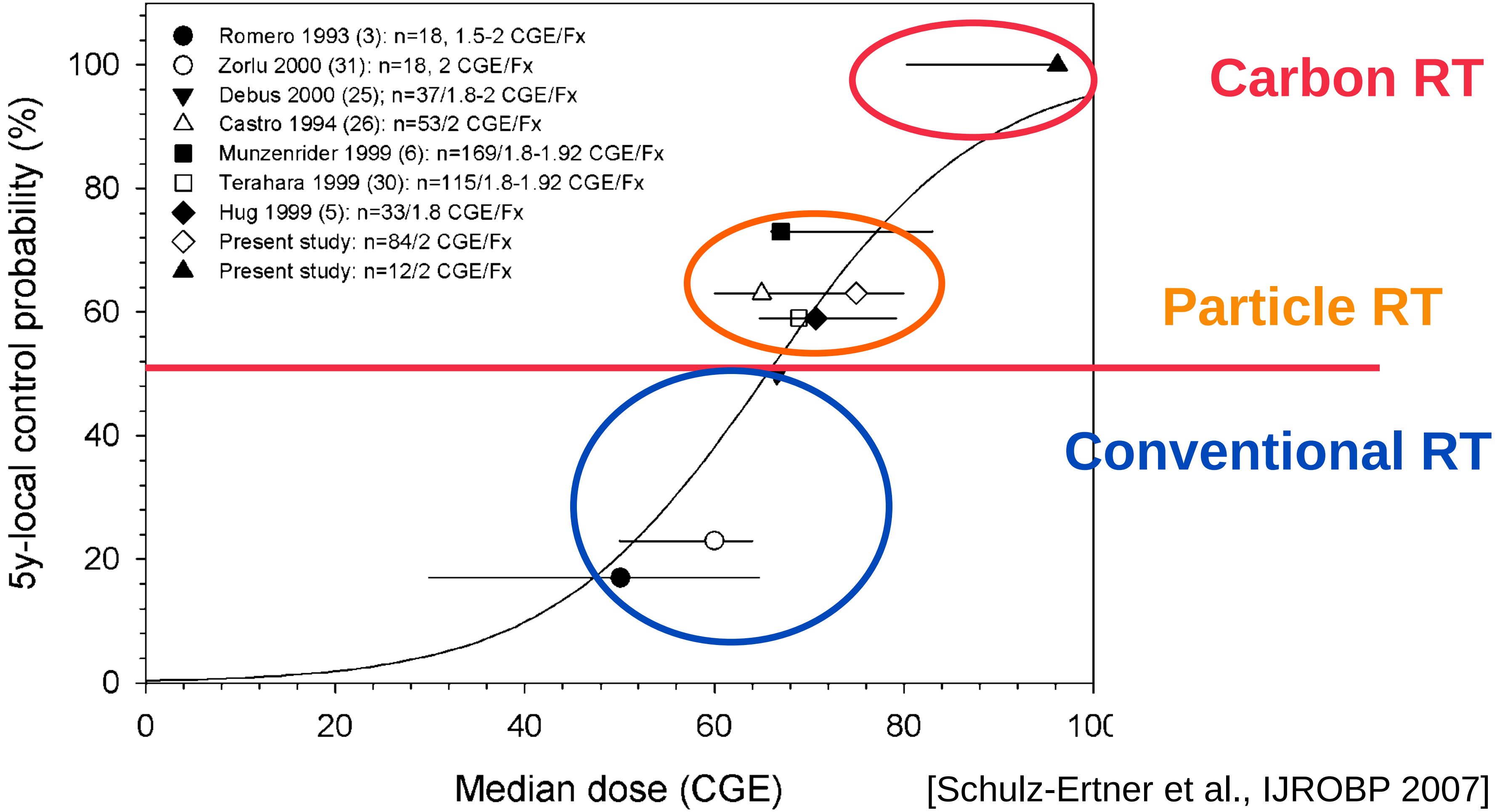
Proton Beam Therapy is not associated with an increased risk for secondary malignancies"

Chung et al. IJROBP 2013 Incidence of 2nd malignancies of patients treated with p and photons

There is little clinical evidence for protons
Are they cost-effective ??

Clinical evidence for Carbon ions
Skull base chordoma

C12 as *primary* RT: 60-70 Gye in 20 Fx



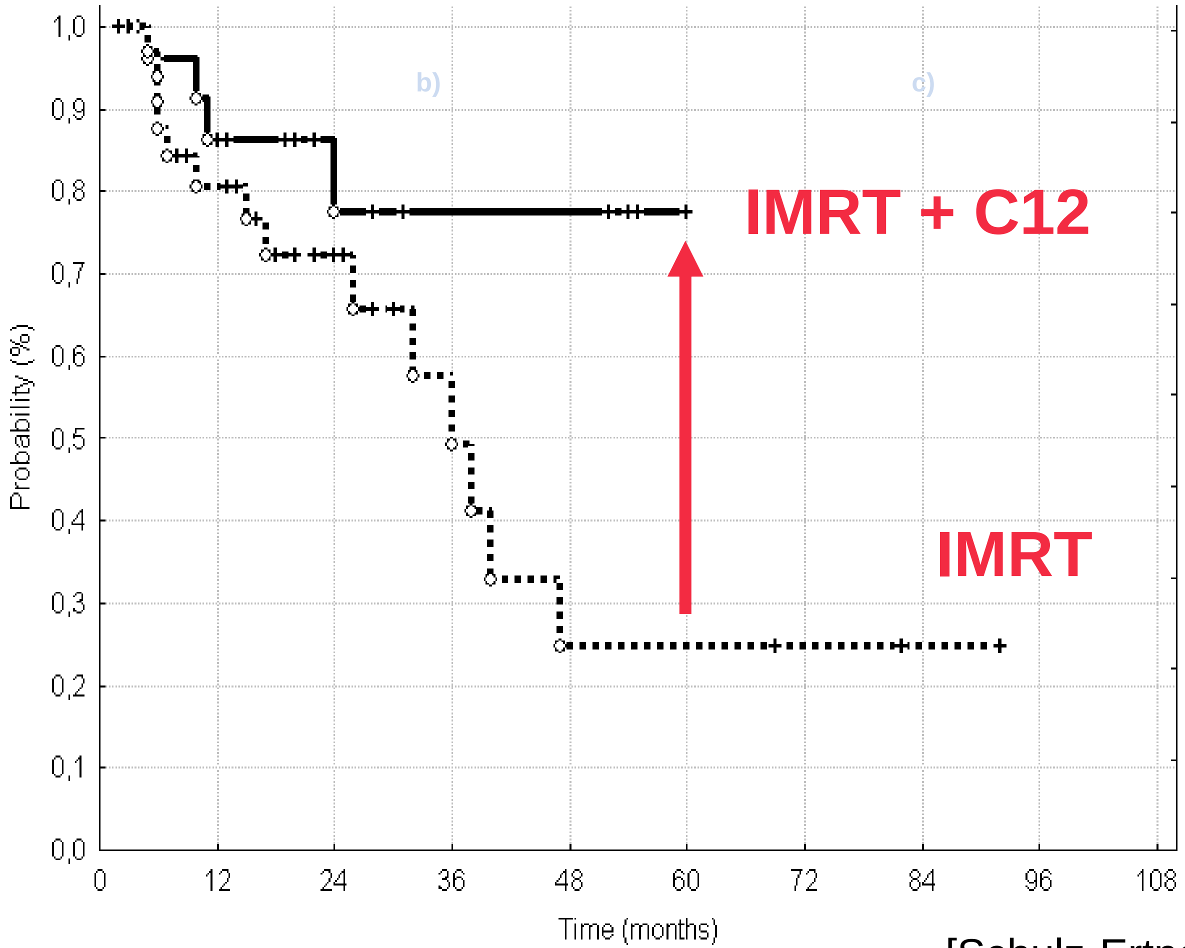
[Schulz-Ertner et al., IJROBP 2007]

Open question: high LET or high conformity?

Clinical evidence for Carbon ions

Adenoid cystic carcinoma

Local Control Rate after IMRT vs. IMRT+C12 (54Gy+ 18 Gye)

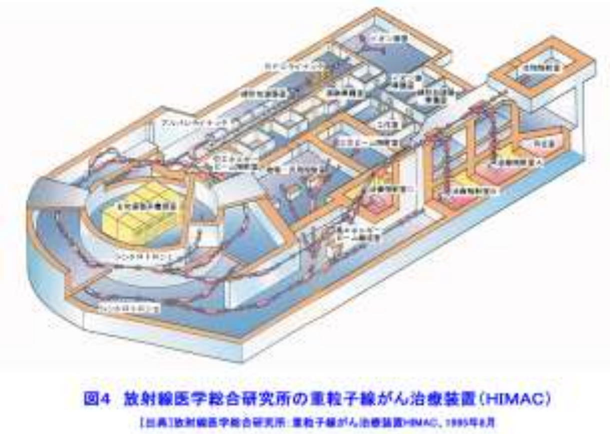


[Schulz-Ertner et al., Cancer 2004]

Open question: can Chemo-RT reduce distant metastasis ?

Ion beam Therapy worldwide in 2013

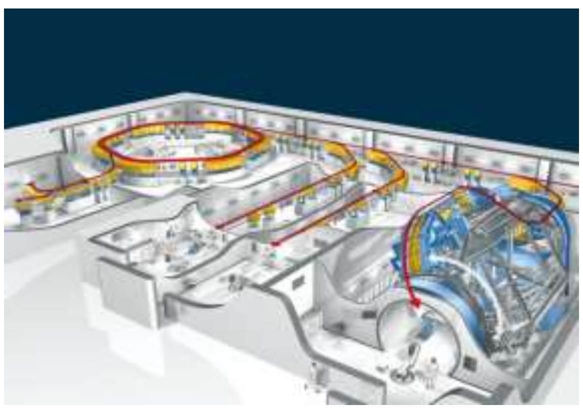
HIMAC, Chiba



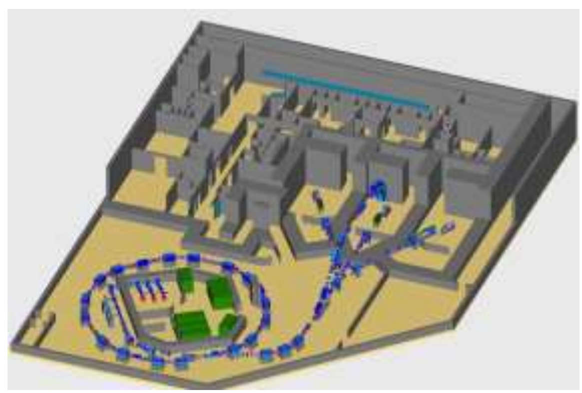
HIBC, Hyogo

HIMC, Gunma

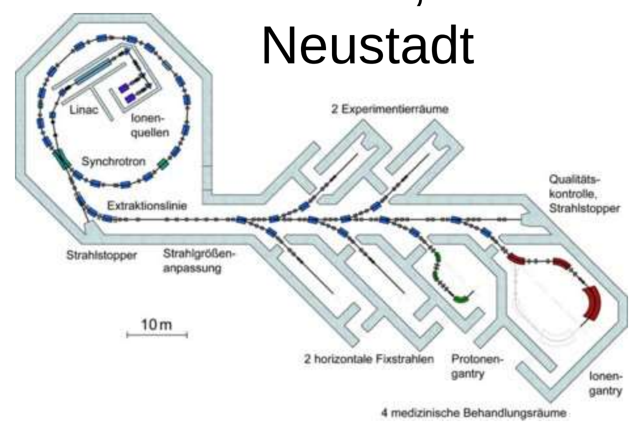
HIT, Heidelberg



CNAO, Pavia



MedAustron, Wiener Neustadt

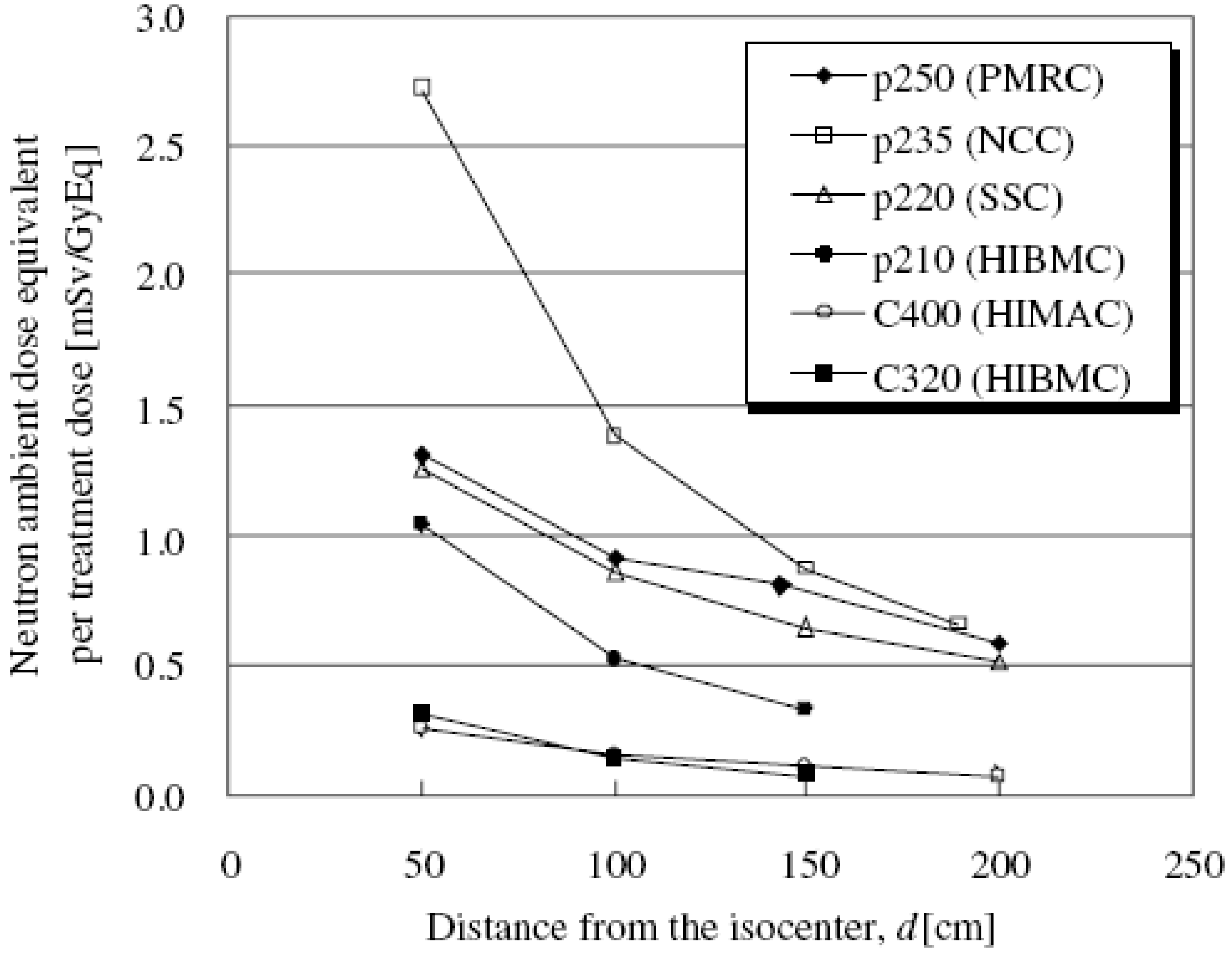


Japan: Tokyo Bay, Yokohama, Obu-City
France, China (2), South Korea, Thailand, Russia

Availability of Ion Beam RT is increasing worldwide

HIT in the middle of a unique campus

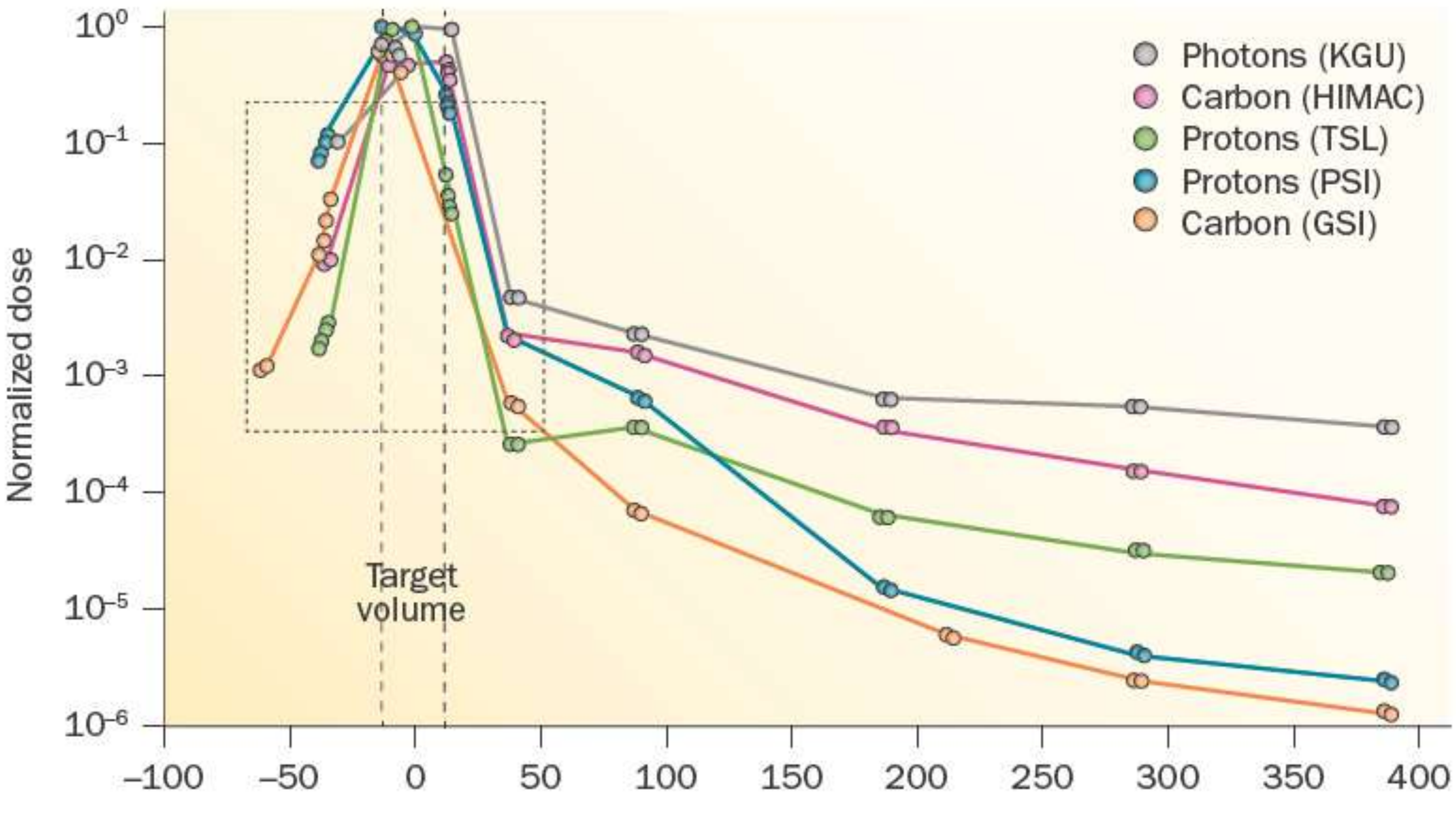
Neutron production Carbon vs. protons



H. Tsuji et al. Rev. Accel. Sci. Technol. 2009

At the same beam line, n-doses are lower for Carbon

Out of field dose

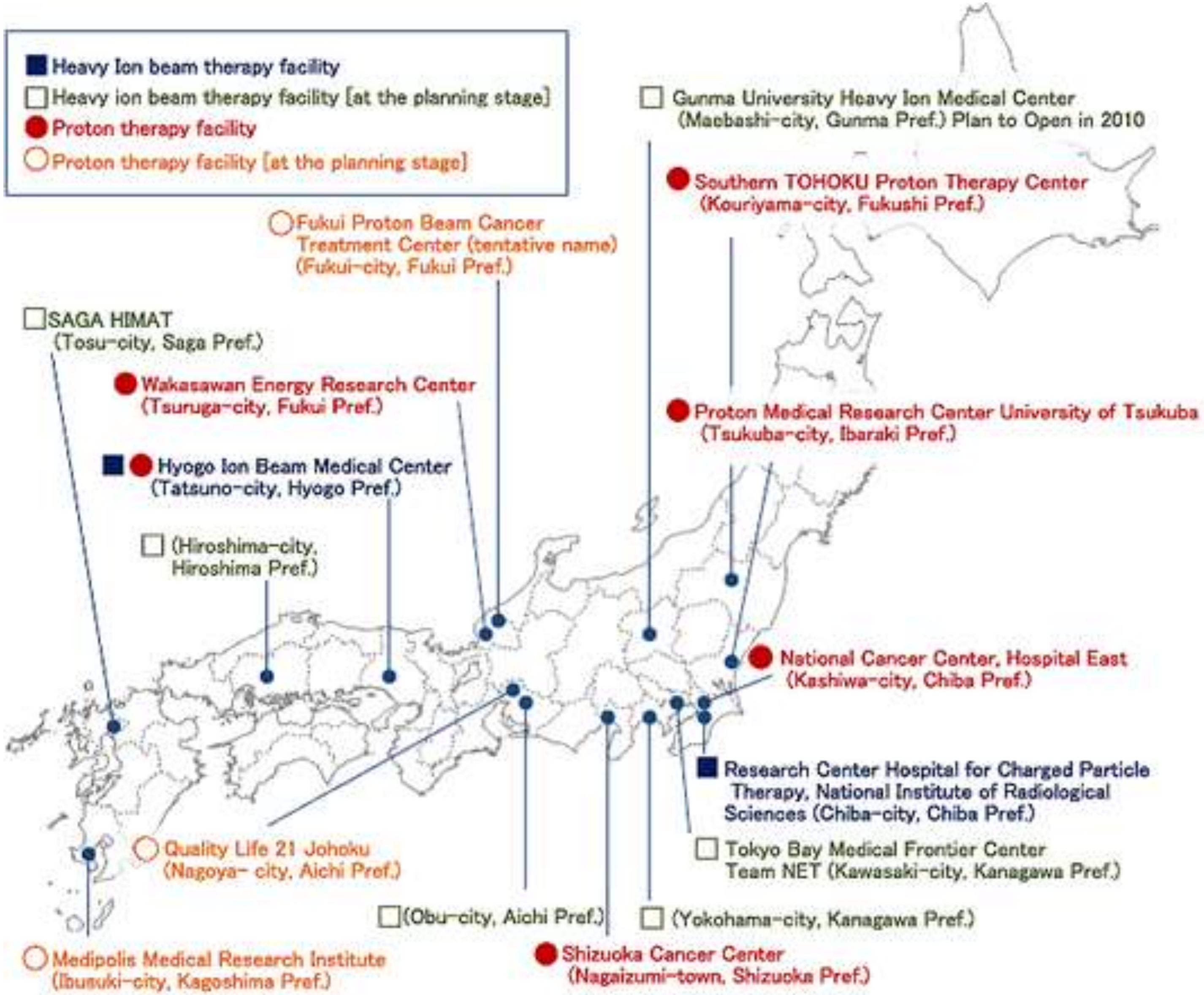


Photons
Pass. C
Pass. P
Act. P
Act. C

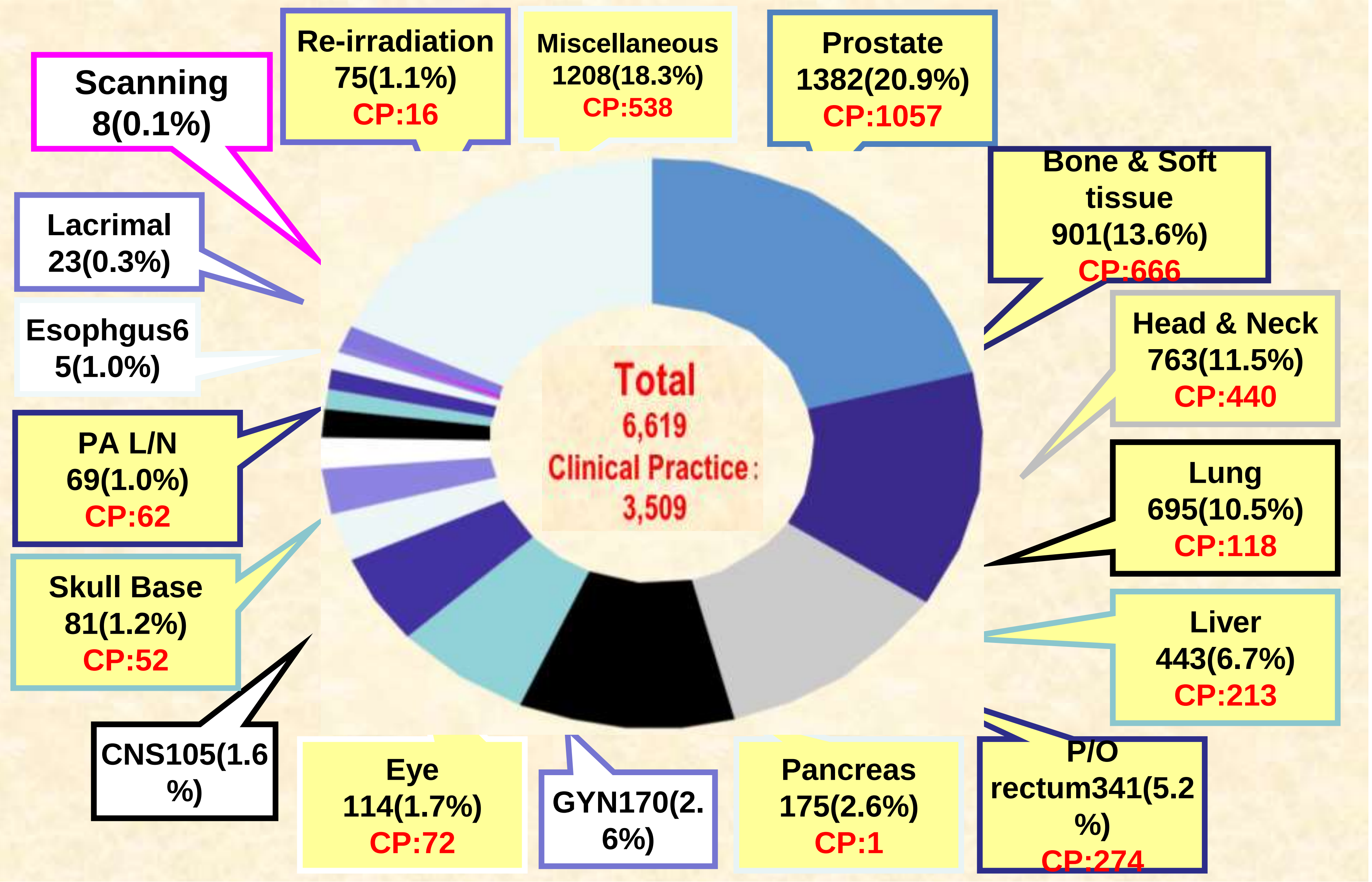
Loeffler and Durante, Nat. Rev. Clin. Oncol, 2013

Scanned Carbon offers lowest out-of-field dose

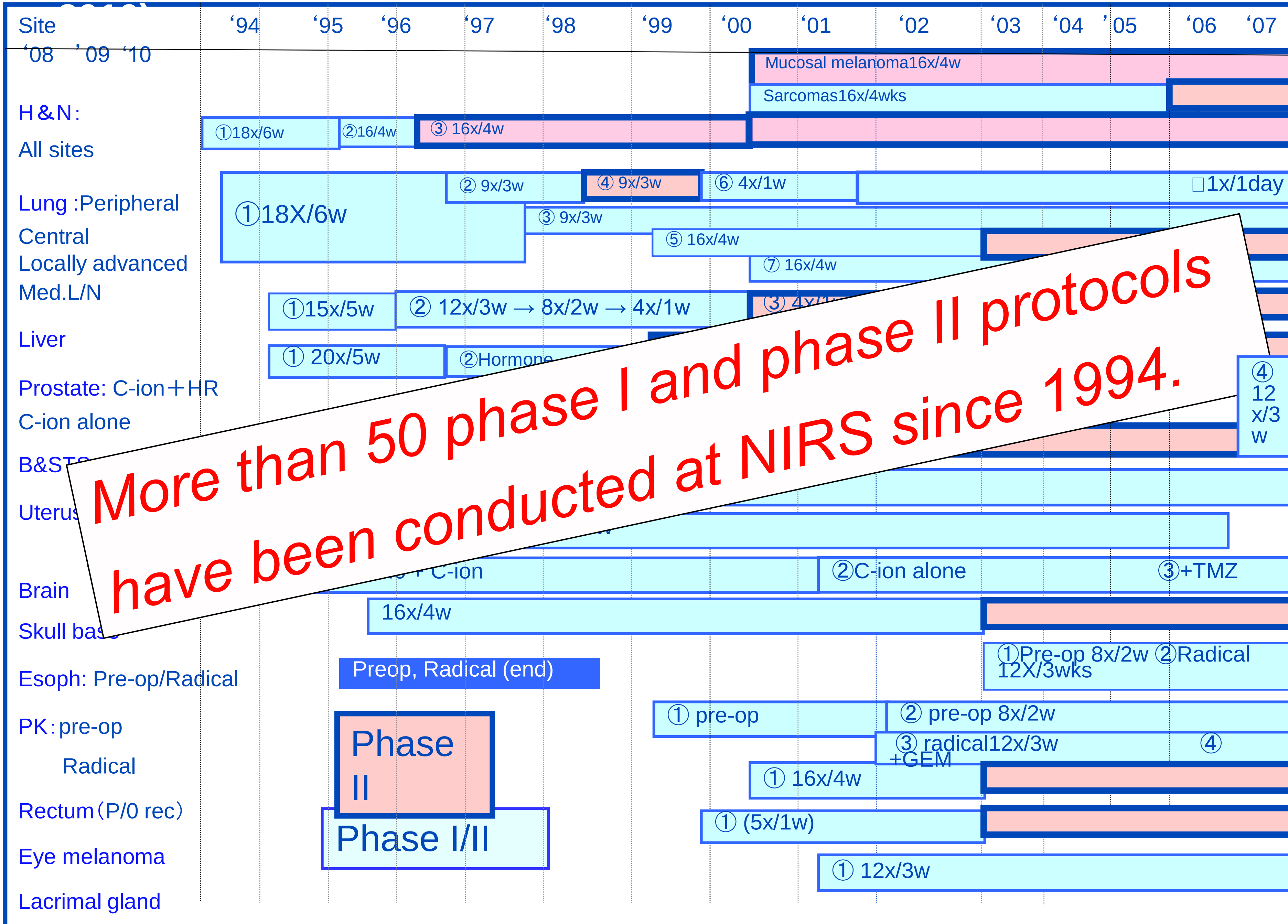
Ion beam Therapy in Japan



Patient Distribution Enrolled in Carbon Ion Therapy at NIRS (Treatment: June 1994～July 2011)



Protocols and Time Line of Carbon Ion Clinical Trials (1994-



More than 50 phase I and phase II protocols have been conducted at NIRS since 1994.

Depth dose profile of a Neon beam

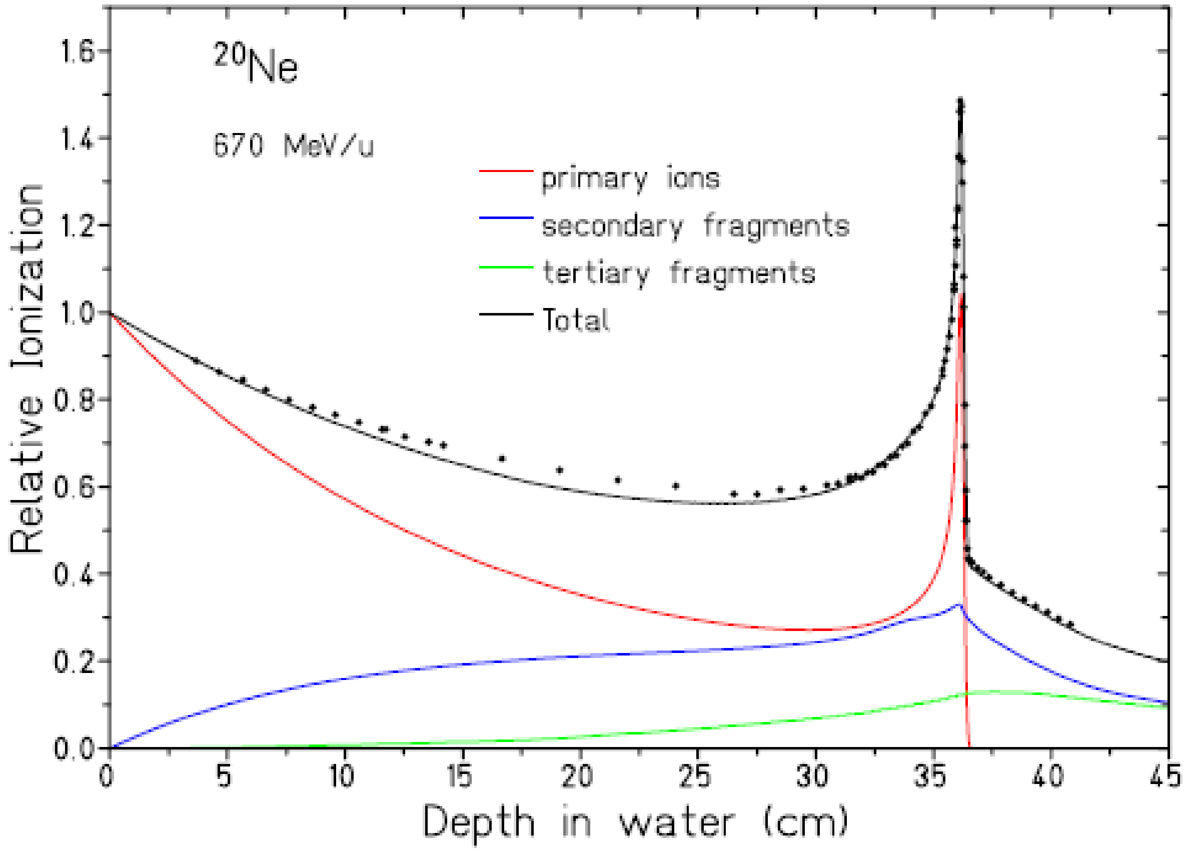
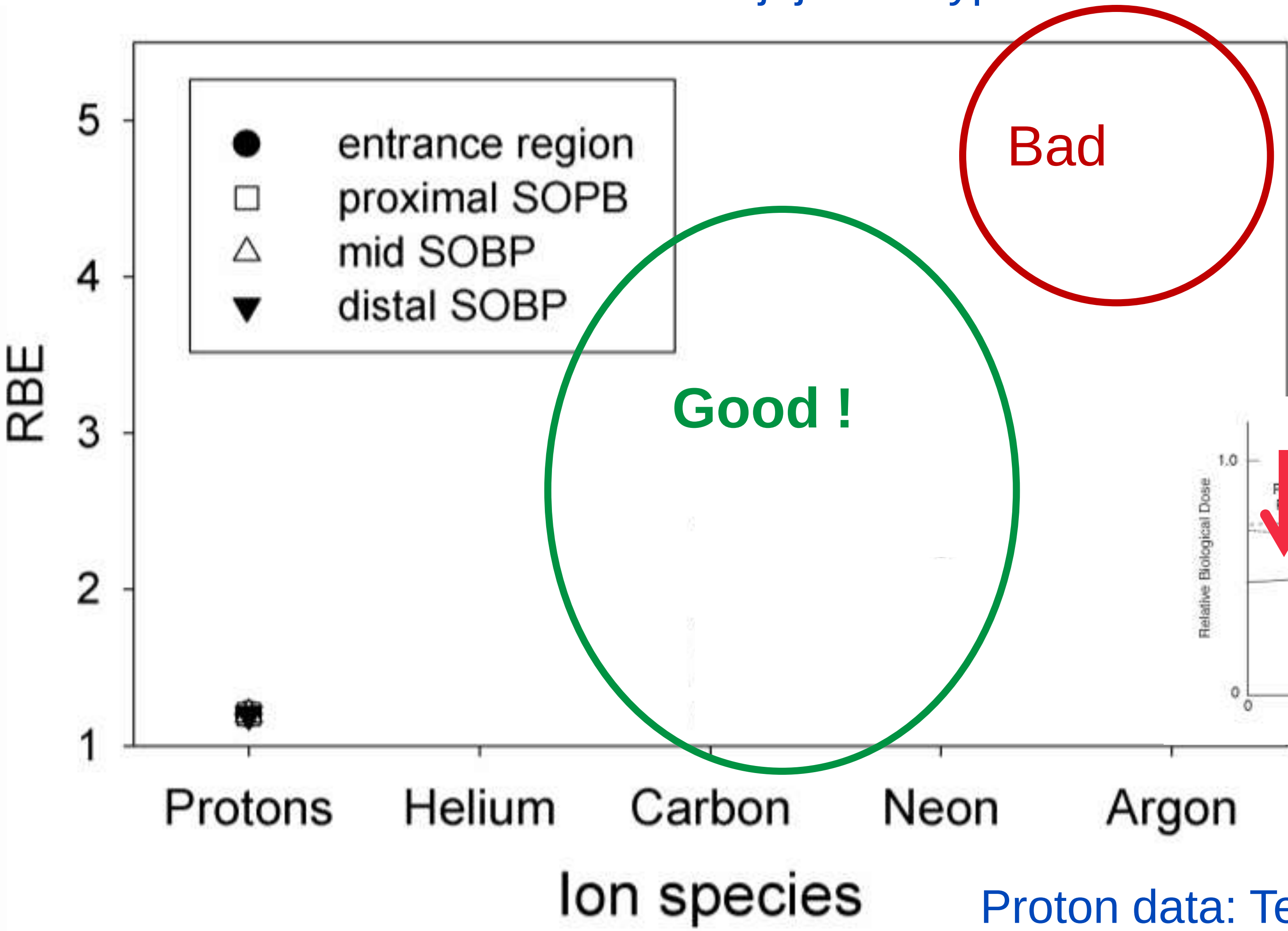


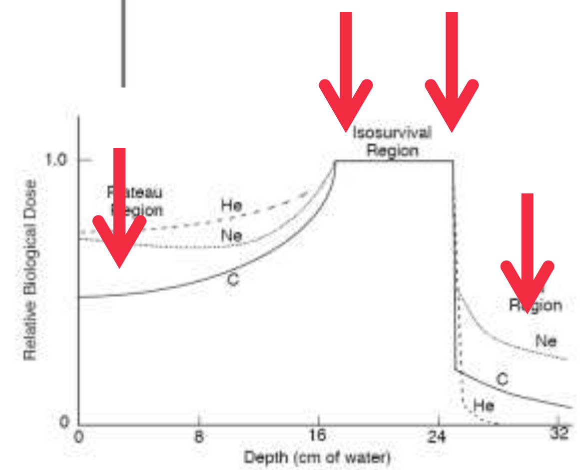
FIG. 9. (Color online) Bragg curve for 670 MeV/u ^{20}Ne ions in water measured at GSI (circles) and calculated contributions of primary ions, secondary and tertiary fragments. Adapted from Sihver *et al.* (1998).

No conformation of high LET to the target region

Which is the best ion for RT ?

RBE for a fractionated irradiation of jejunal crypt cells of mice (SOBP of 8 cm)





Proton data: Tepper et al 1977,
Ion data: Goldstein et al. 1981.

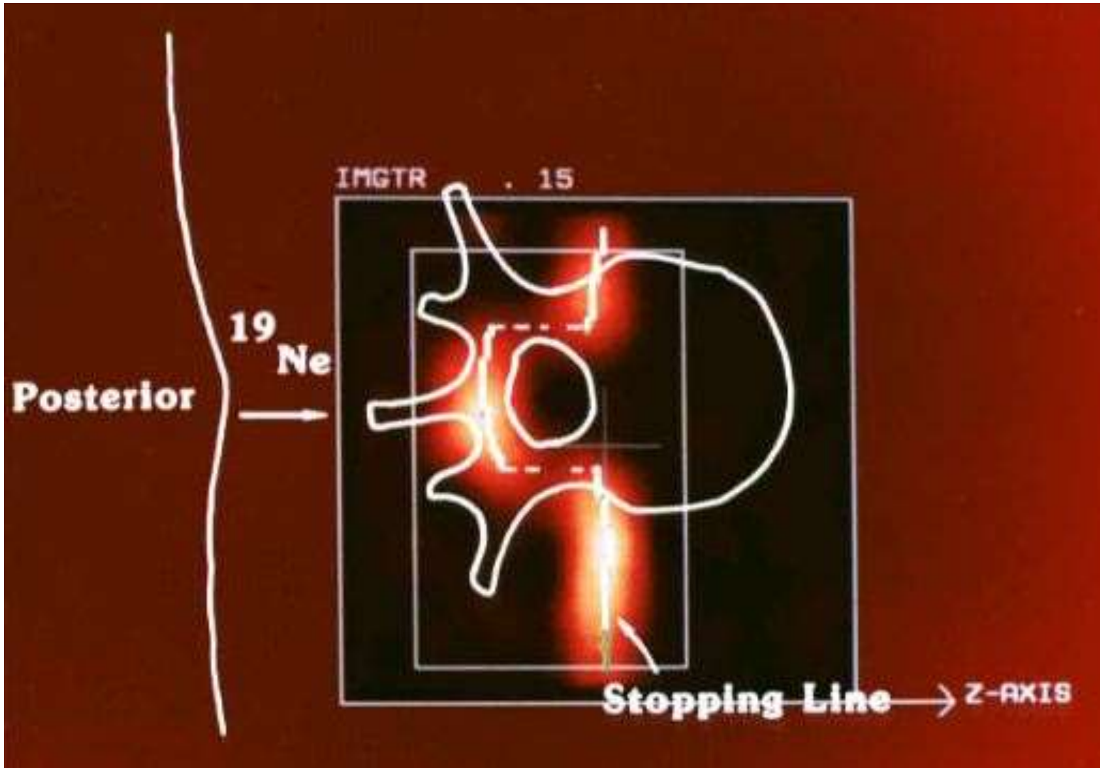
The differential RBE peak/plateau is optimal for Li…O

Radioactive beams: Pet imaging with Ne-19

Idea:

- Use Ne-19 for range probing
- Use Ne-20 for treatment

Images: Courtesy of Bill Chu, Berkeley



Stopping Region Determined by PEBA

Scattering at inhomogeneities

Scattered dose behind an inhomogeneity (bone) in water

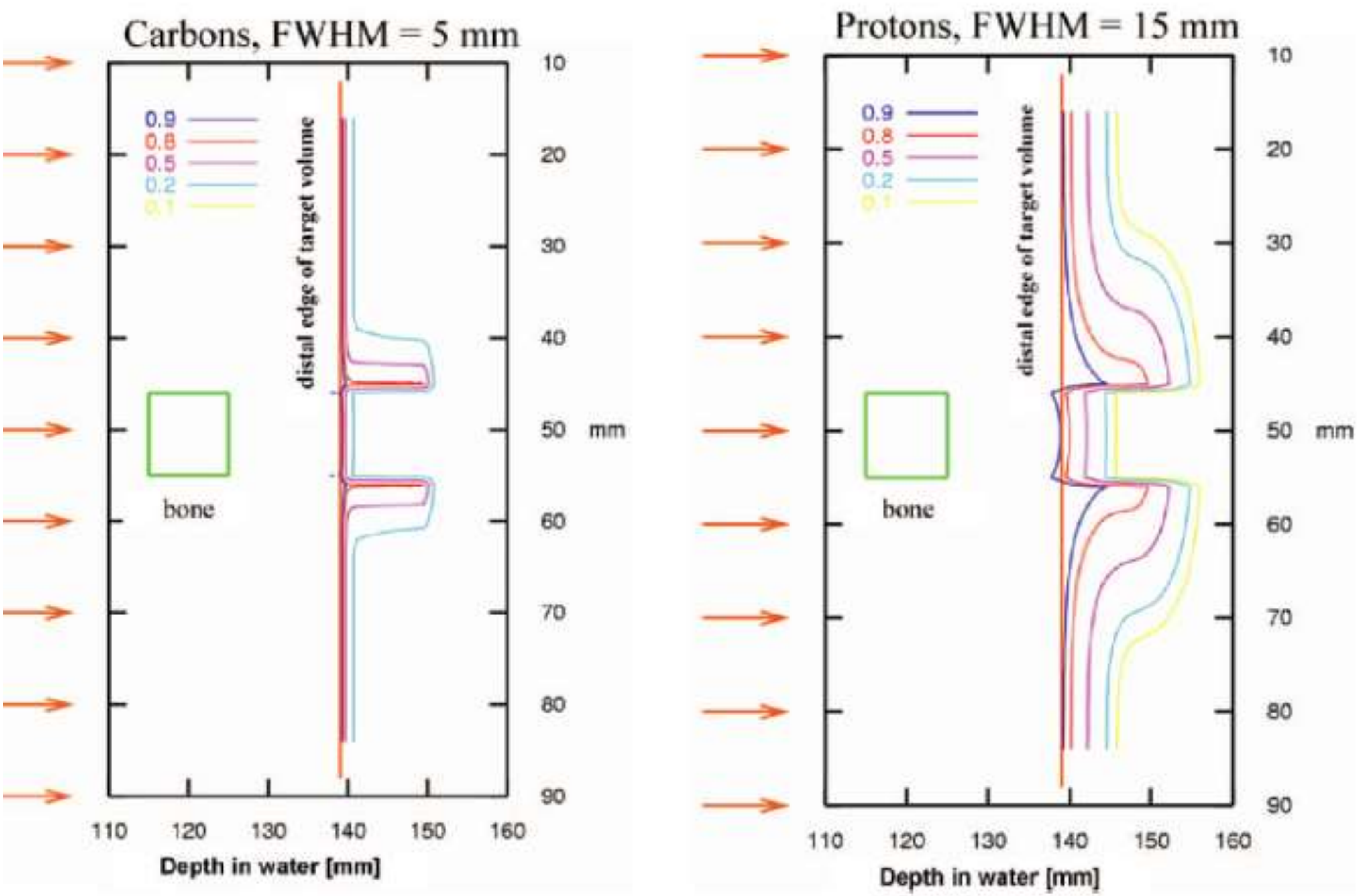


Image: Weber 2009

Mayo Clinic
Light Ion Therapy Program – Phase II

Structure


Today@Colorado State
Friday, July 26, 2013

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Currently: 75°F

Veterinary Medicine

New Frontiers: Making the case for bringing carbon ion radiation therapy to American cancer patients

April 4, 2012

Join us April 26-27 for New Frontiers in Cancer Treatment: A Focus on Photon and Carbon Ion Radiation Therapy. The symposium, hosted by CSU and the College of Veterinary Medicine and Biomedical Sciences, will be held in Fort Collins at the Hilton Hotel.

There are three in Japan, one in China and one in Germany. In the next five years, Japan will add two more, China will add two more, Italy had just completed construction on one, two are under construction in Germany, and one is under

Inside This Edition

- Recycled Military Parachute exhibit
- Fun in the summer: Downtown!
- Office of Greek Life changes its name
- Students: Recognize and avoid employment scams
- Team receives $2 million NSF grant to research biofuel through photosynthesis
- Michael Pagliassotti assumes

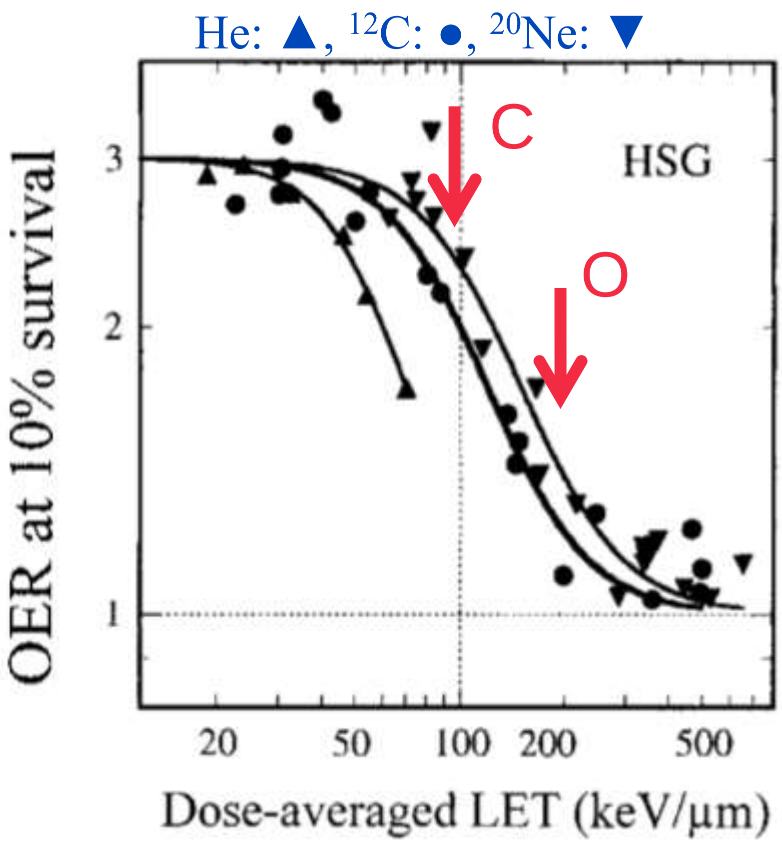
Mayo Clinic
Light Ion Therapy Program – Phase II

Technical Specifications

- **Ions** – Protons, Carbon, (He? Li? O?)
- **Beam** – Pencil beam scanning, 50-450 MeV/nucleon
- **Range** – from 1 g/cm^2 to 30 g/cm^2 in H_20
- **Field size** – 30x30 cm^2
- **Rooms** – Three rooms with robotic patient positioners, two with fixed horizontal and oblique angle beams and single room with a small field, fixed horizontal beam. (New gantry technology?)

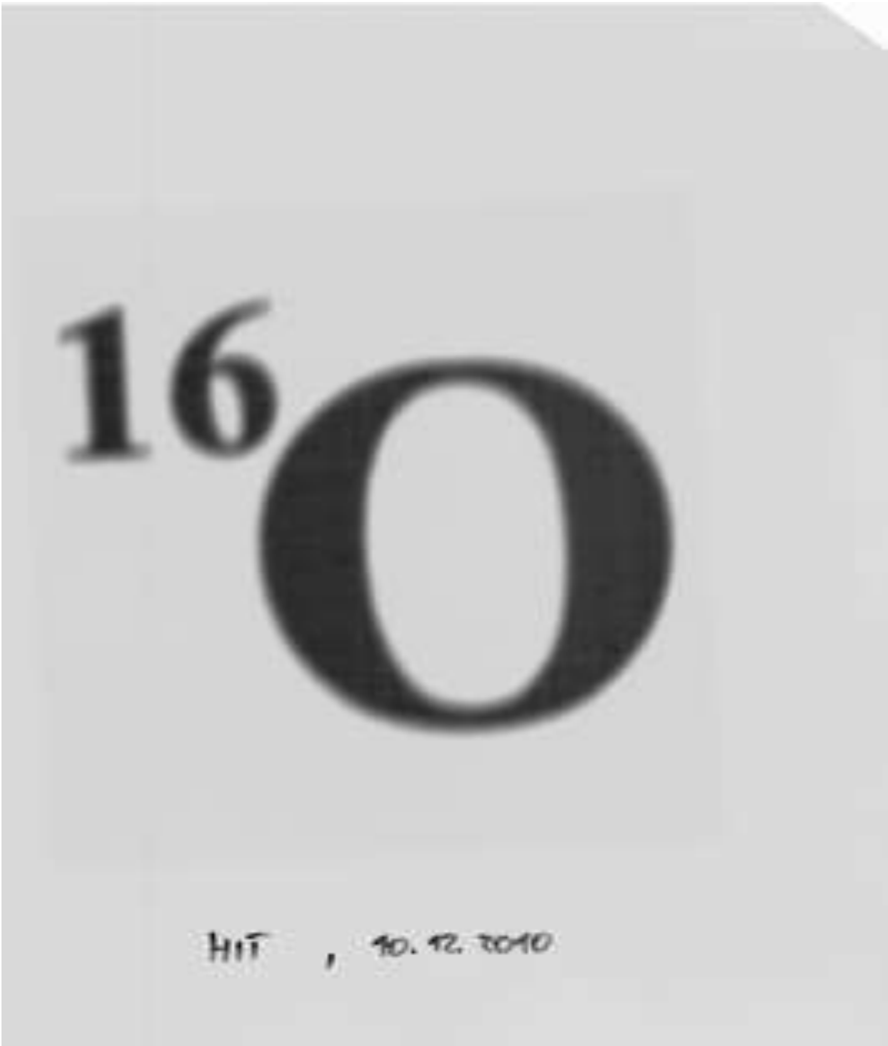
The Rationale for Oxygene: OER

OER as function of LET



Furusawa et al Rad. Res. (2000)

Rasterscan @ HIT-R+D-Room



Oxygen maybe more used for hypoxic areas

Re-oxygenation

- Will not work for hypo-fractionated Tx
- Less important for Carbon (increased vascular damage; antiangiogenetic effects, decreased latency)
- Other factors also important intratumor heterogeneity (stem cells, highly repairing subpopulations enhanced metabolism)

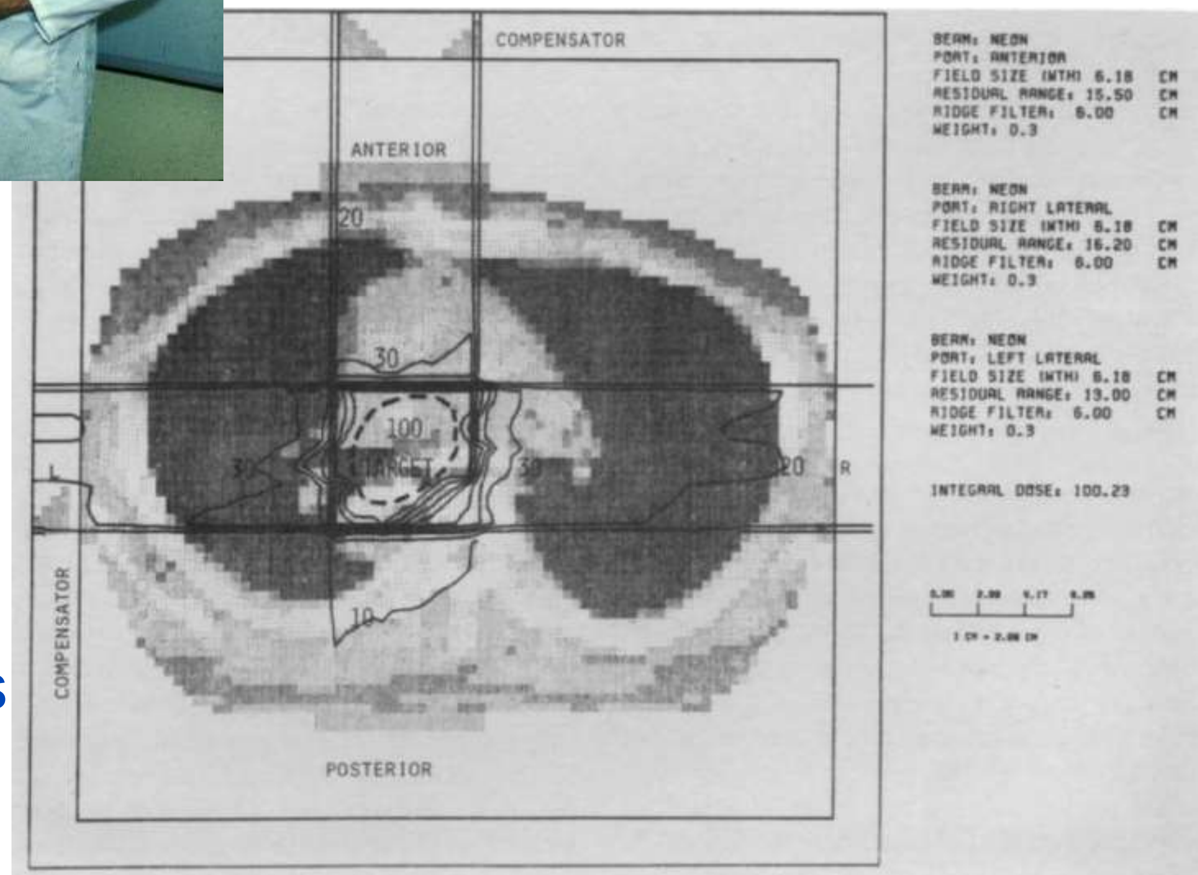
Thank you !

Check out our online Master program: **http://www.apmr.uni-hd.de**

The Past: Pioneering work at LBNL-UCSF, 1975–1992

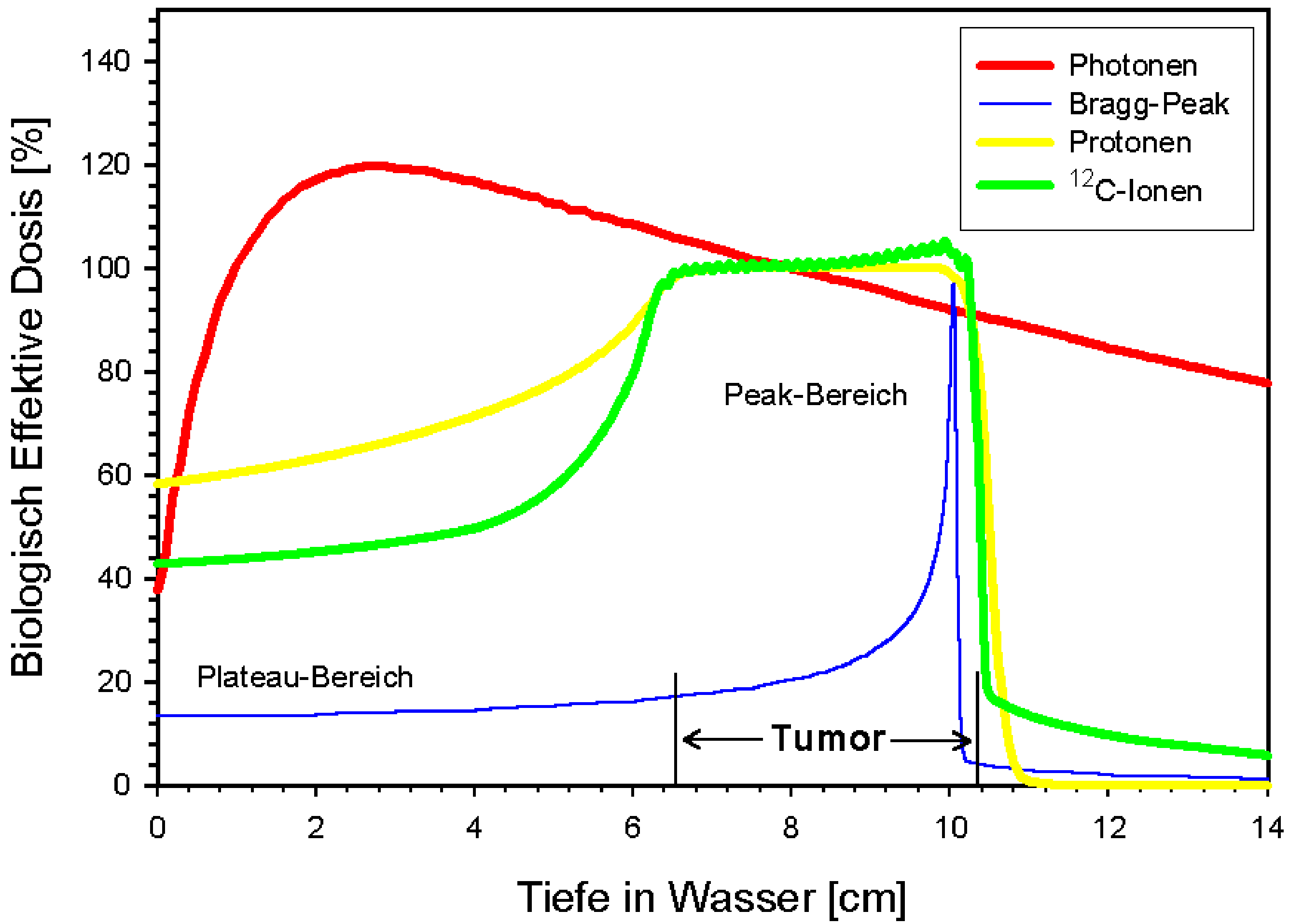
Courtesy of Bill Chu, Berkeley

Joseph Castro, MD, UCSF Radiation Oncologist, who conducted the LBNL clinical trials.



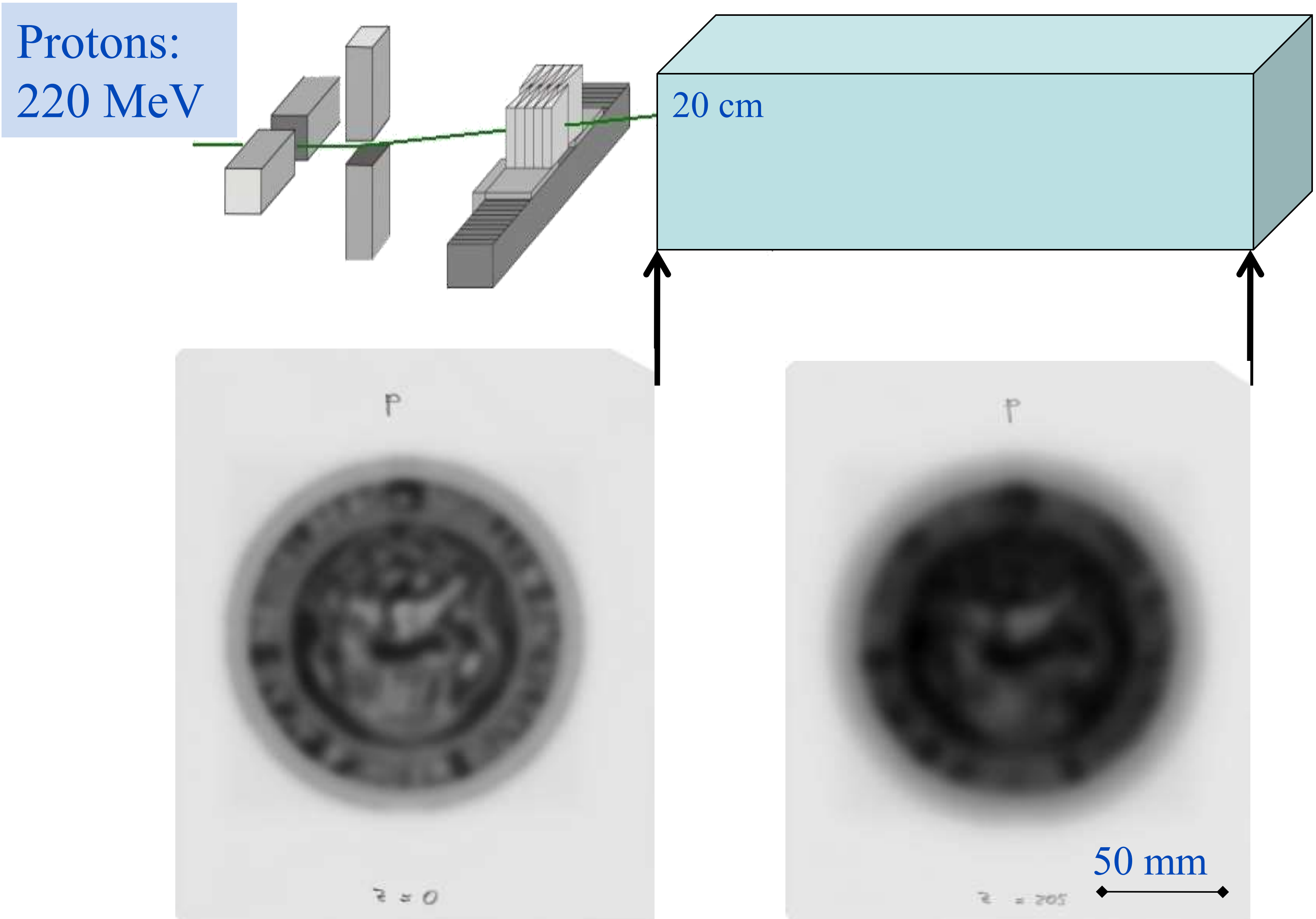
Treatment plan for a lesion in the Esophagus using Neon beams (Chen,IJROBP 1979)

Depth dose distributions of RT beams

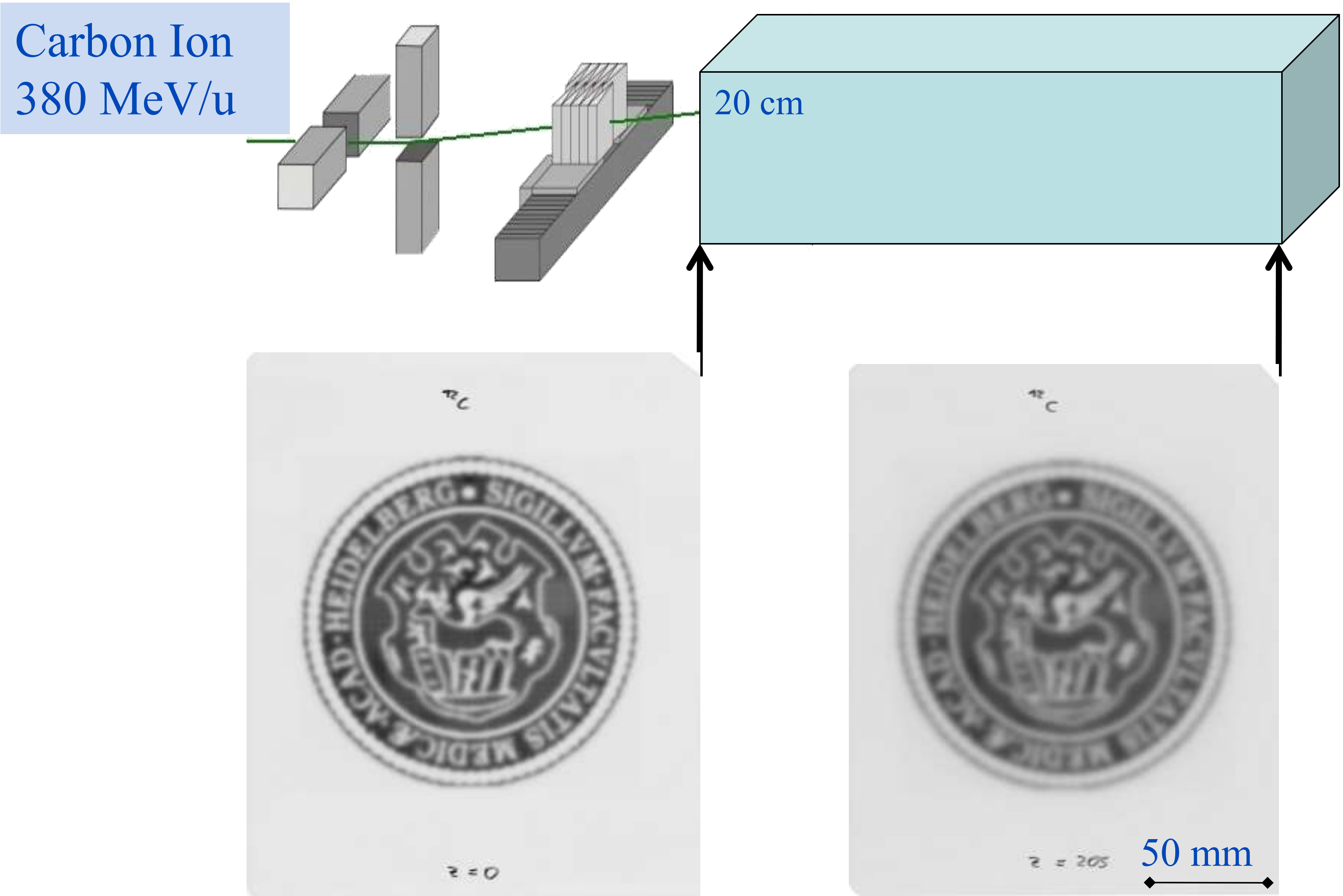


- Similar absorbed dose for protons ad Carbon
- Lower biological effective doe for Carbon
- Small tail of fragents behind the BP of Carbon

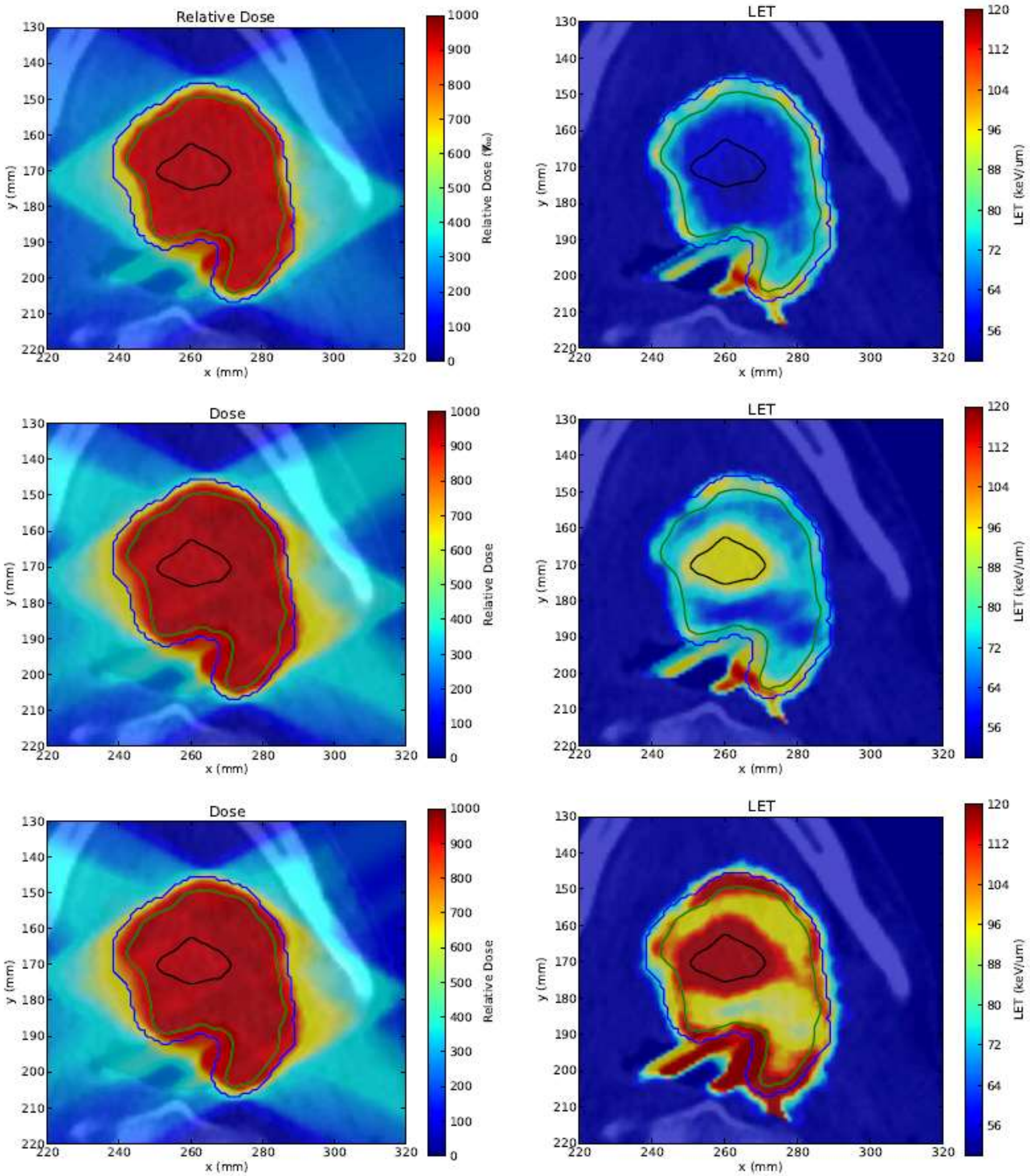
Influence of Scattering in Tissue



Influence of Scattering in Tissue



LET Painting for hypoxic tumors



C-12 dose optimized

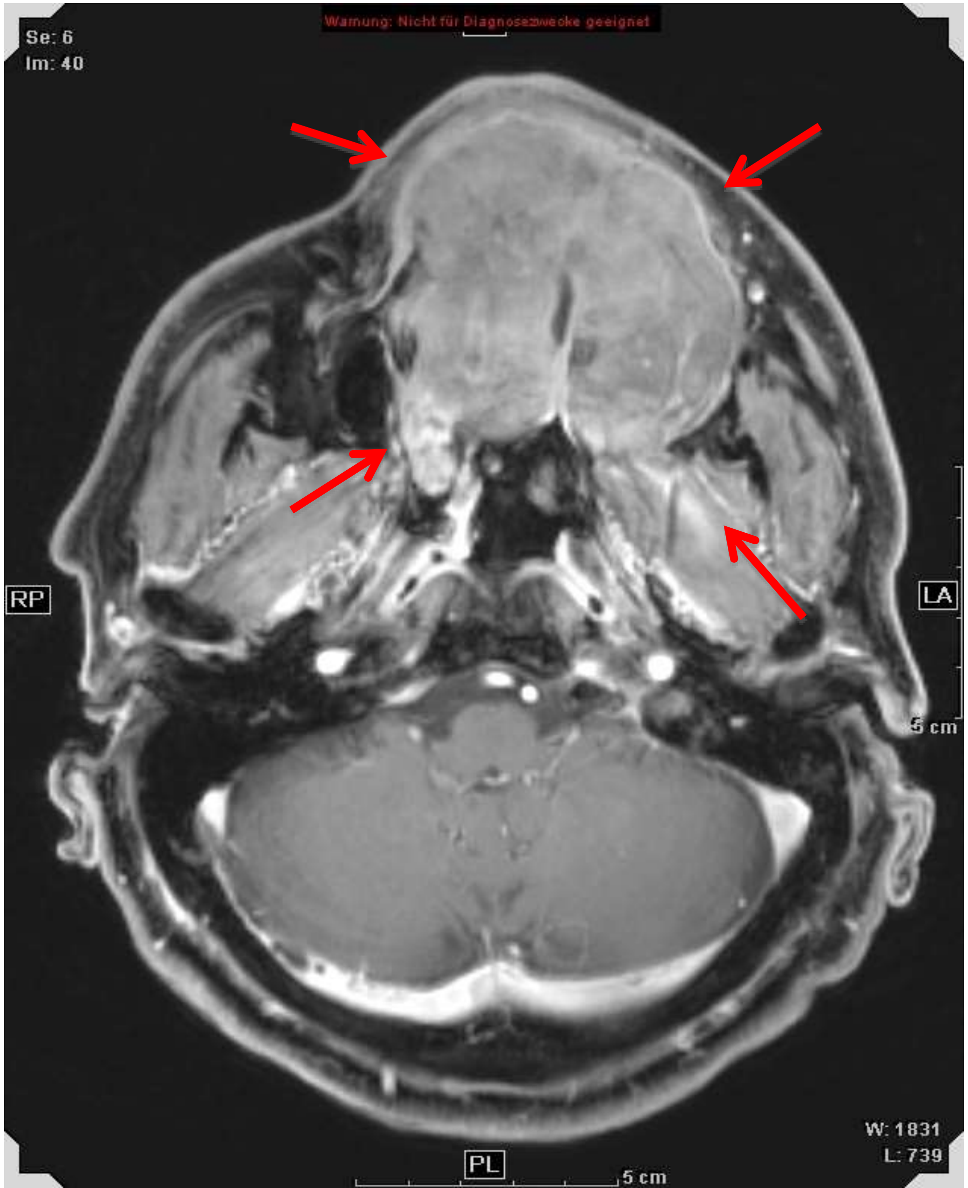
C-12 w. LET painting

O-16 w. LET painting

Bassler et al. *LET painting increases TCP n hypoxic tumors*. Acta Oncol 2013

COSMIC Study: Response

At treatment planning

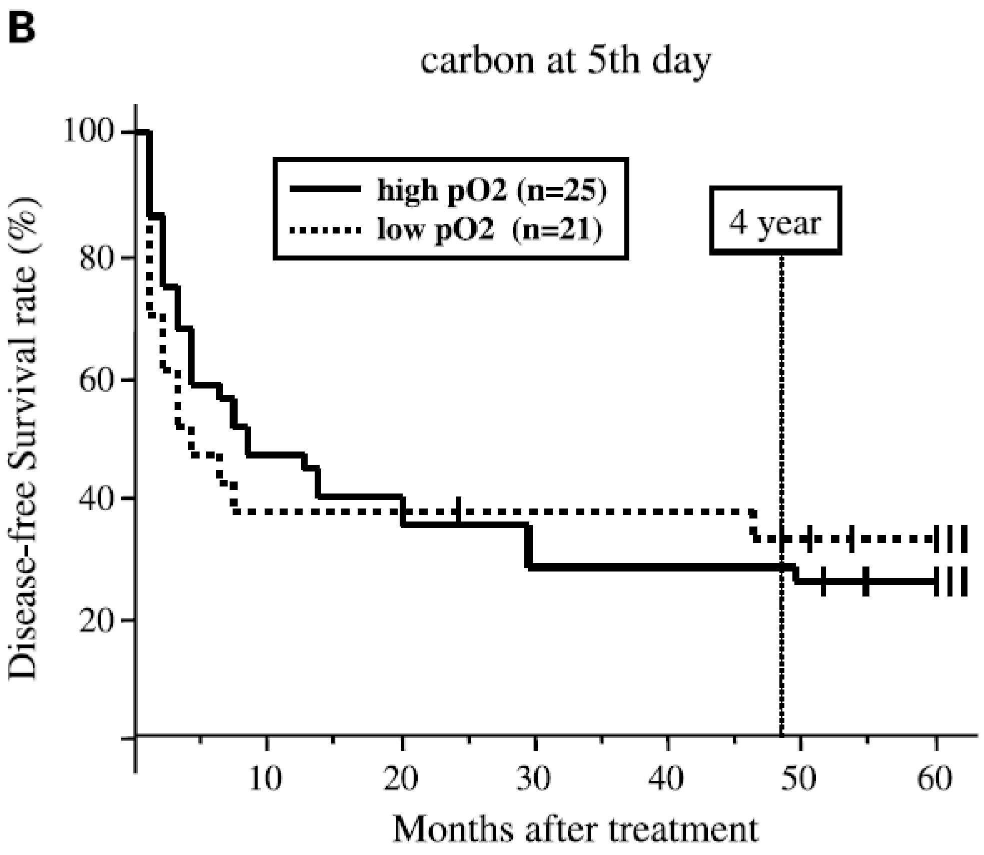


FU @ 6 weeks after C12

Clinical evidence for OER effect in C-RT

Nakano et al: Clin. Cancer Rev. 2000

Patients w. uterine cervical cancer



Carbon

Reoxygenation is less important in high LET

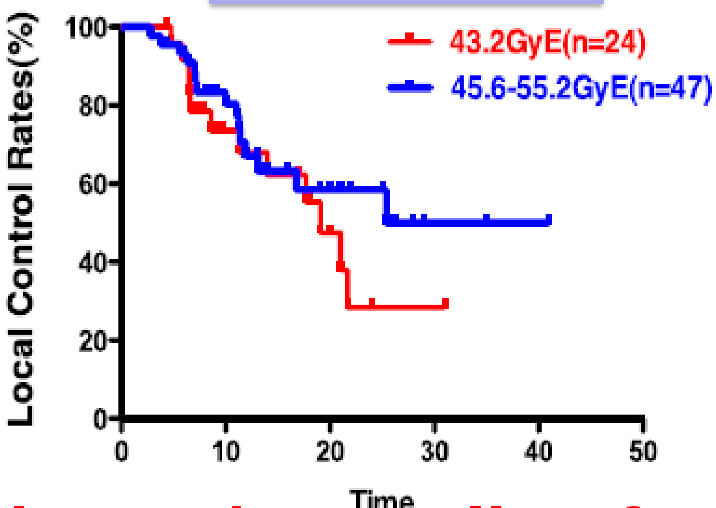
Hypofractionated proton-RT will reduce this effect

S. Yamada, NIRS, Rochester May 2nd, 2013

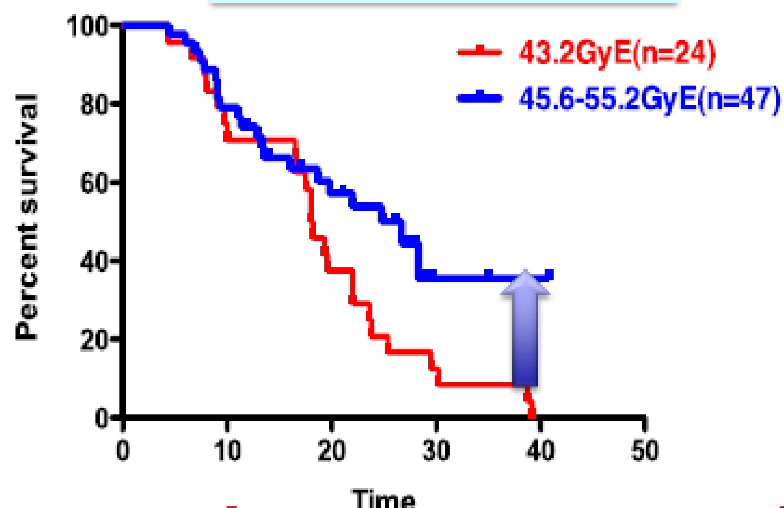
GEM + CIRT for locally advanced Pancreatic Cancer

	Total dose	n	12mo	24mo
Local Control	45.6GyE<	47	67%	58%
	43.2GyE	24	68%	28%
Overall Survival	45.6GyE<	47	74%	54%
	43.2GyE	24	71%	21%

Local Control



Overall Survival



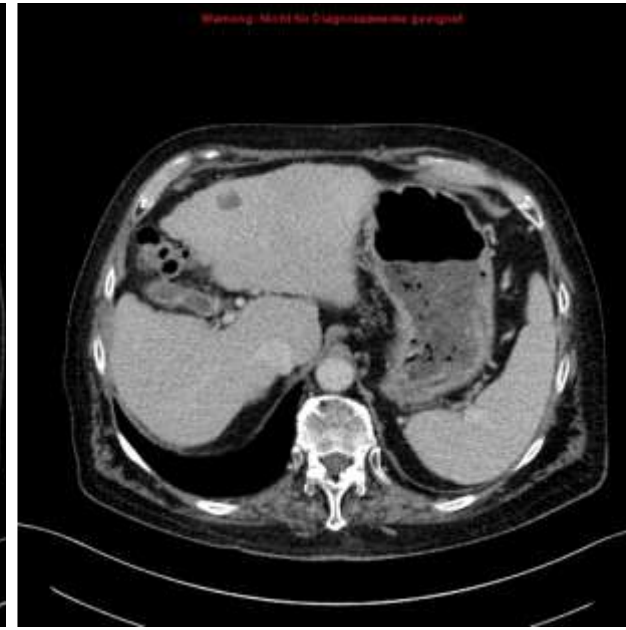
Incidence / Mortaliy of pancreatic tumors 2012 (US): 43 920 / 37 390

Treatment verification for gated Tx

Initial TP

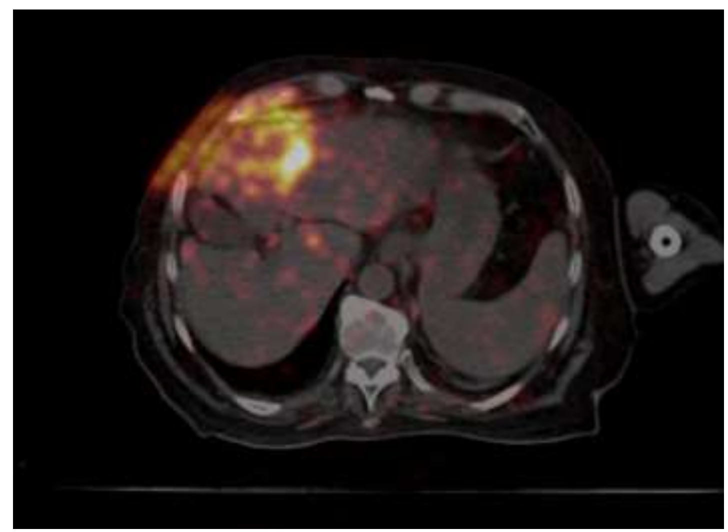
4 weeks after RT

12 weeks after RT



D. Habermehl

RT: 4 x 10Gy (RBE)
Prometheus study



Activation study Using PET-CT @ HIT
(J. Bauer)

Arguments against protons

Proton RT is less robust as photon plans and may lead to worse coverage in reality

Photon RT has made great progress, so that the benefit of proton becomes less important

Given the higher price, protons may not offer enough benefit for the higher price

Cheap single room, passive beam facilites may yield sub-optimal results