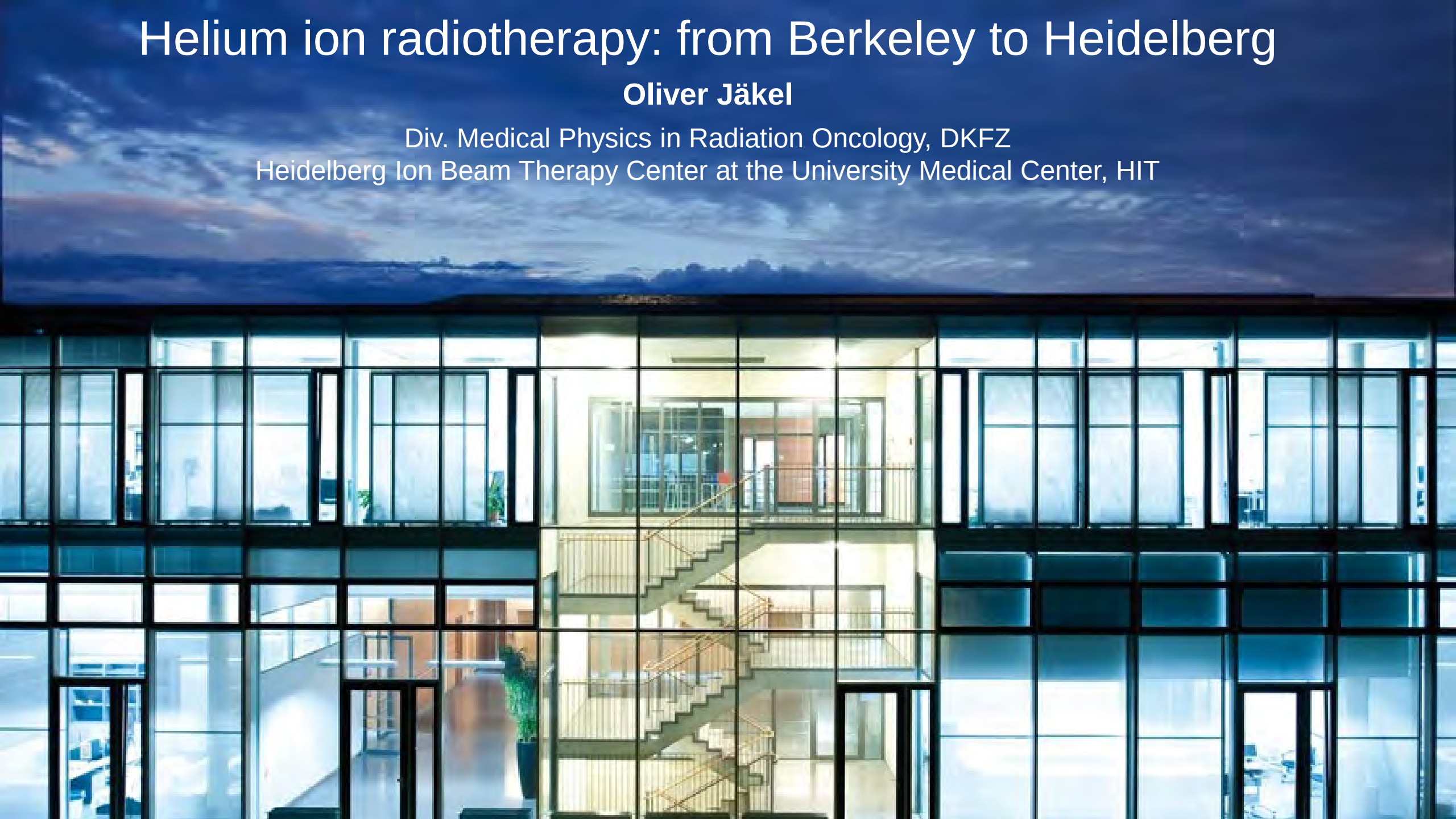
Helium ion radiotherapy: from Berkeley to Heidelberg

Oliver Jäkel

Div. Medical Physics in Radiation Oncology, DKFZ
Heidelberg Ion Beam Therapy Center at the University Medical Center, HIT



The Lawrence Berkeley National Laboratory (LBNL)

Located in the Berkeley Hills, overlooking UC Berkeley

Established in 1931 by UCB, sponsored by DOE

Founded by Ernest Lawrence

Directed by Lawrence until 1958

Ernest Lawrence (1901-1959)

1928 Position at UC Berkeley

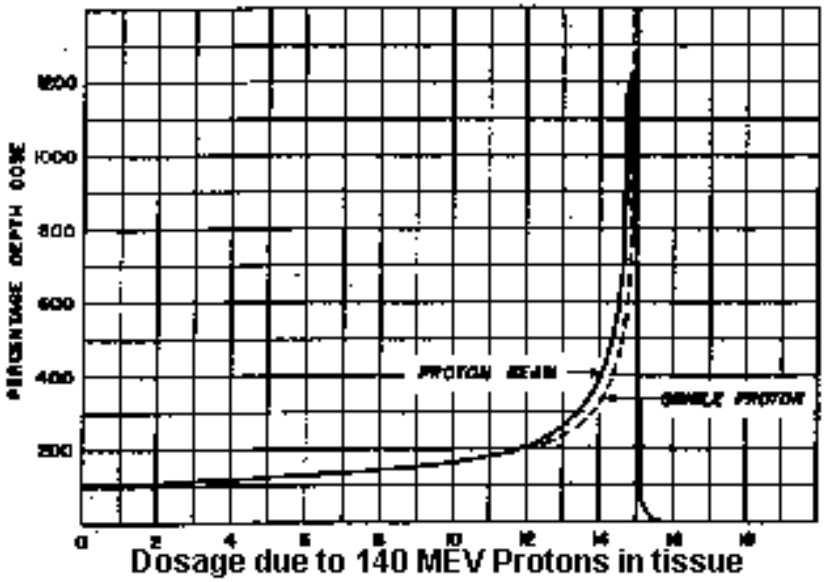
1929 Invention of the cyclotron

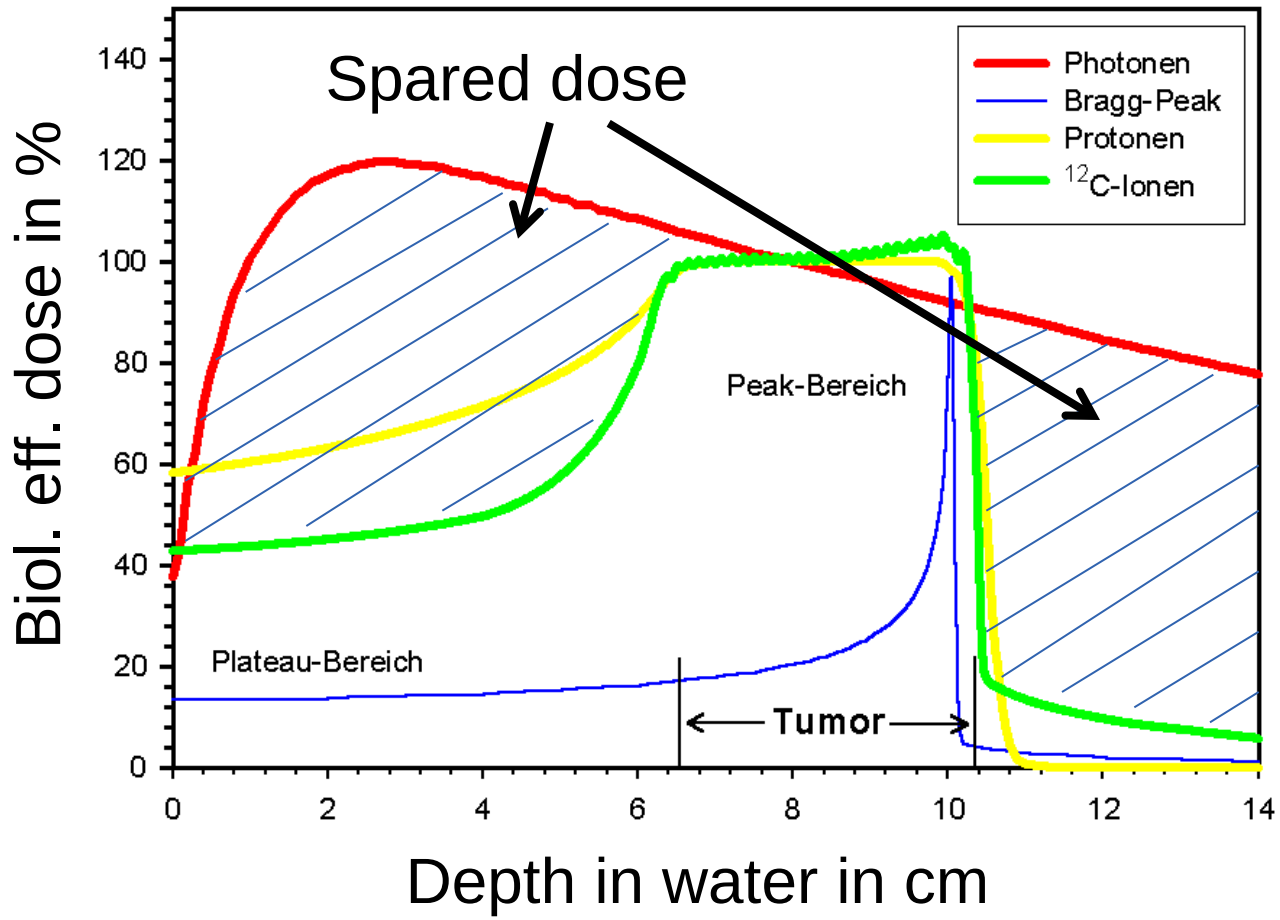
1939 Nobel Prize in physics

Why use protons and ions for radiotherapy?

1946 Robert Wilson suggests the use of ion beams for RT.

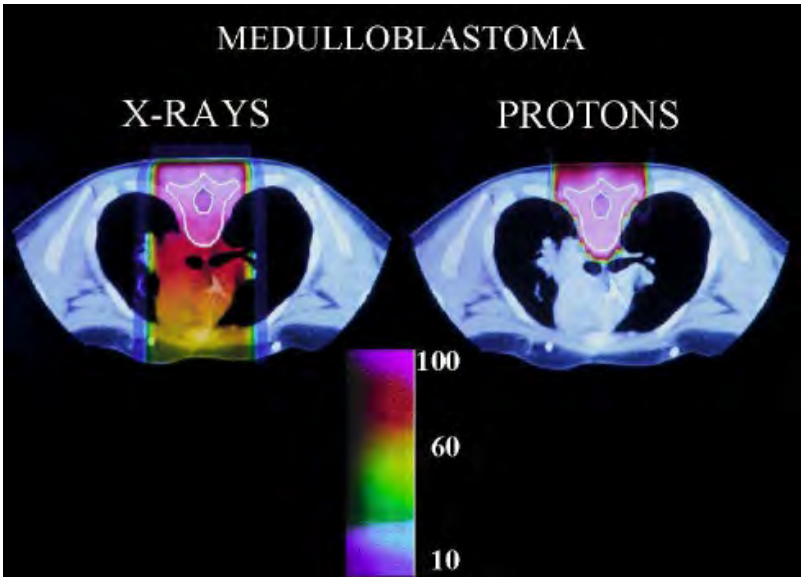
R. Wilson "Radiological use of fast protons," Radiology 47, 487 (1946).

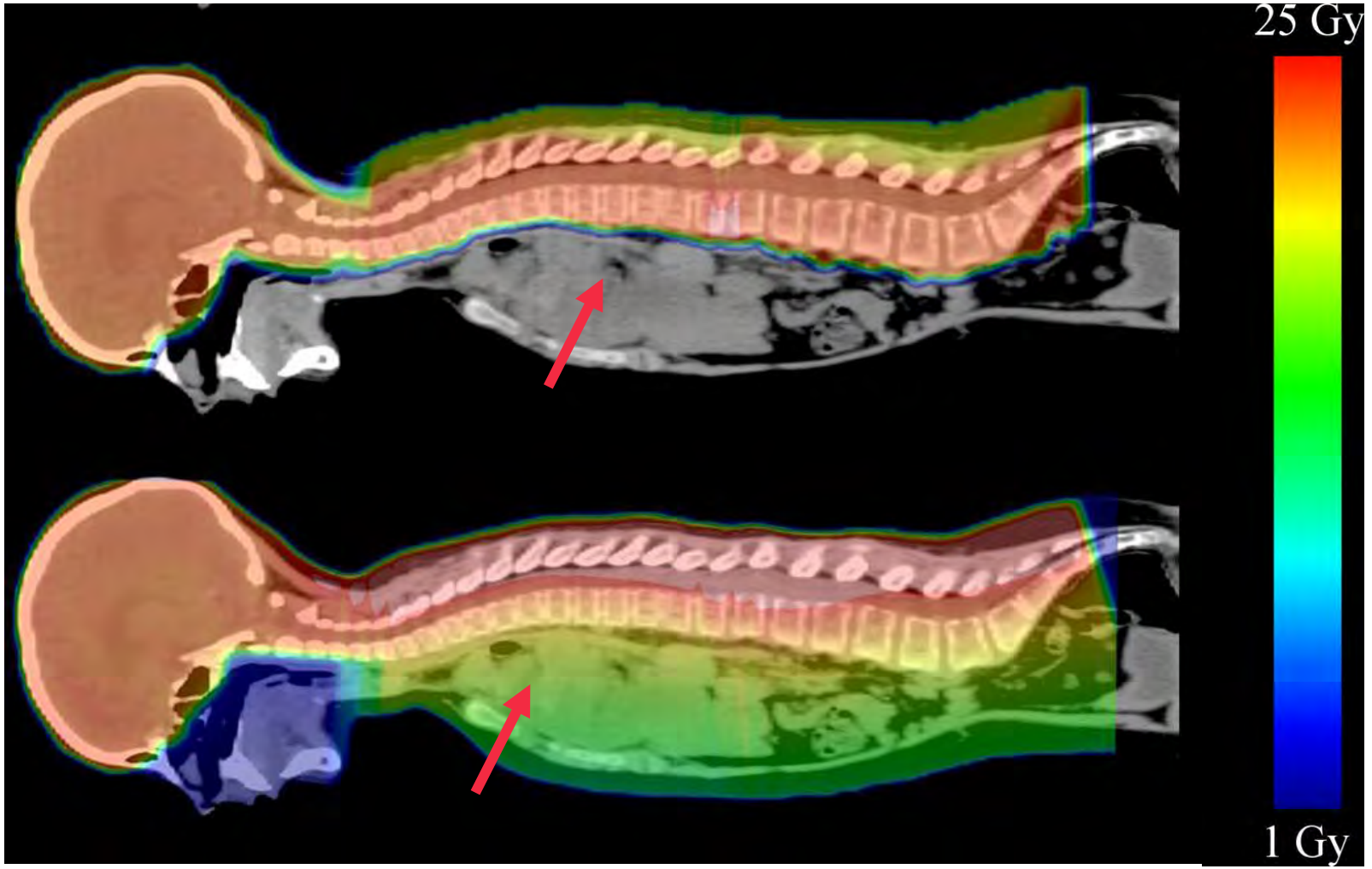




Significant reduction of dose in normal tissue

Protonentherapy for medulloblastoma patients





Stokkevåg et al. *Acta Oncol* **2014**

No dose in the heart, lung, mediastinum, bowels, …

The first proton-RT machine in Berkeley: 1946-1992

The 184 inch, 125MeV cyclotron


Ernest and John Lawrence


1946: Ernest Lawrence, Glenn Seaborg, Robert Oppenheimer at the control panel

1938: 1. patient treated w. neutrons
1954: " w. protons
1956: " w. Helium ions (> 2000 patients)
1977: " w. Ne, N, O, C, Si, Ar (total 433 pat.)

Helium treatments at LNBL

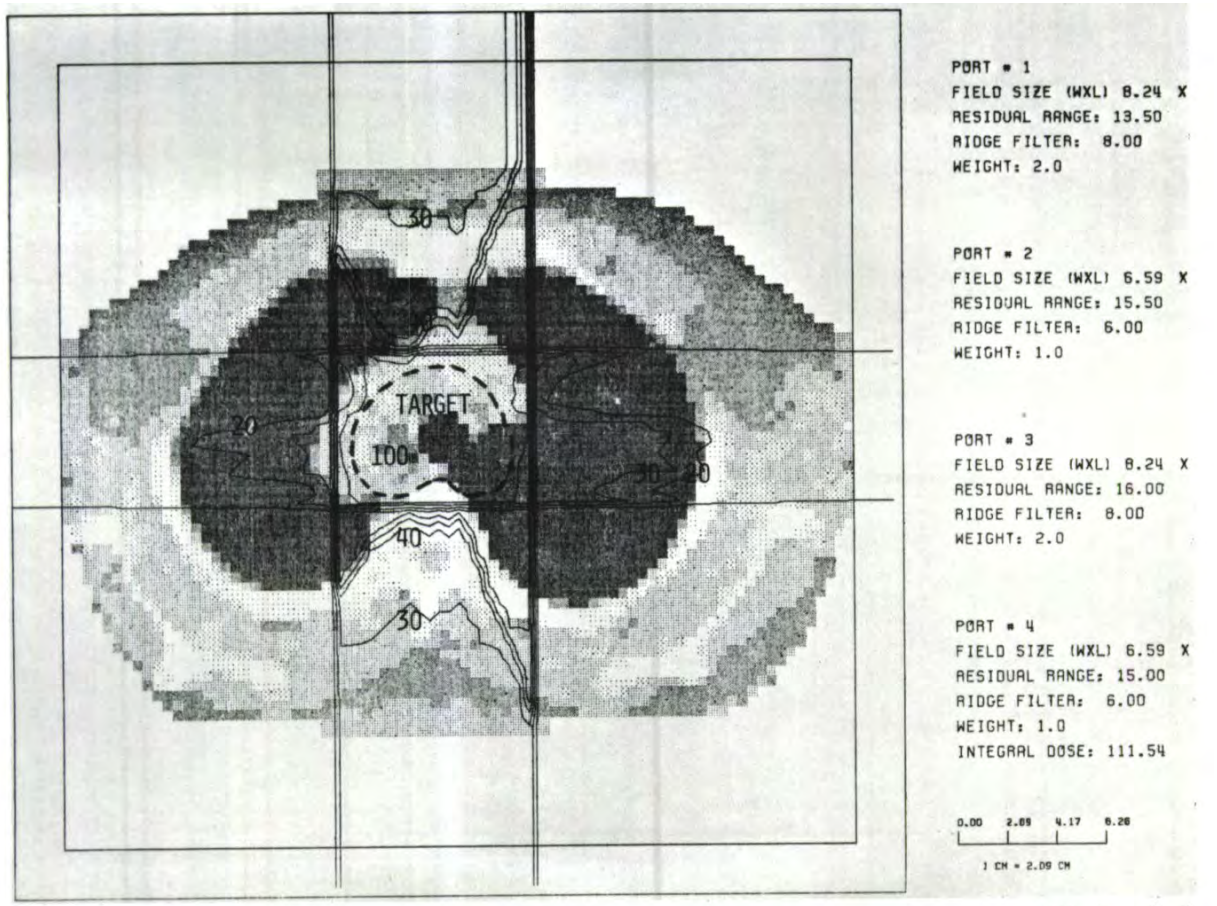


FIGURE 5. Sample biologically corrected isodose plot for helium charged particle therapy of squamous carcinoma of the esophagus. RBE values utilized for helium ranged from 1.2 to 1.4 across the spread Bragg peak.

< Treatment for esophagus ca. with He-RT, 30-35 Fx of 2Gy (RBE=1.3), 4 beams

Castro et al. Am. J. Clin. Oncol. '83

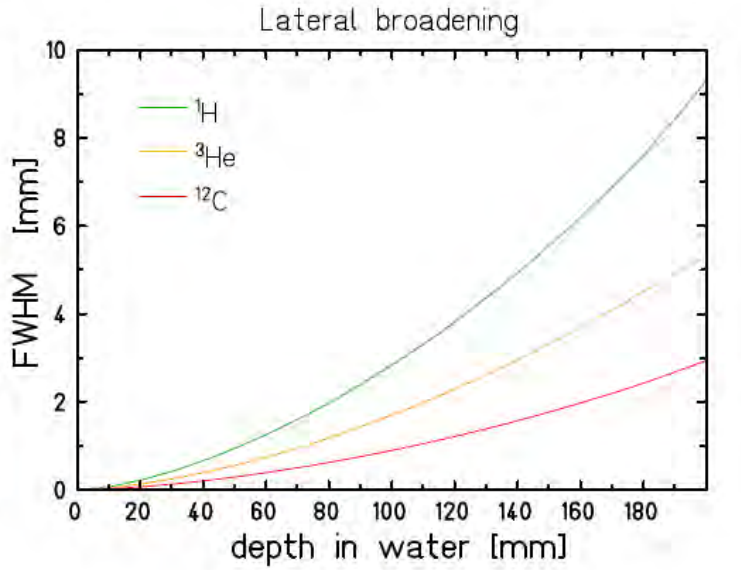
Treatments started already at the old cyclotron in 1956

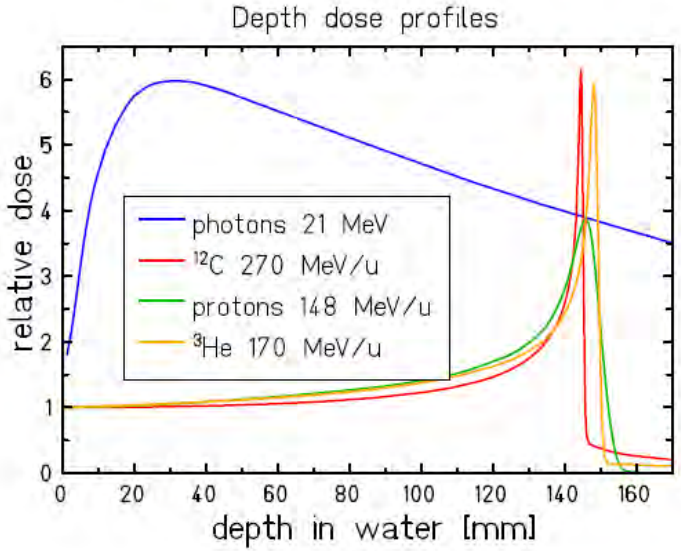
Continuation at the Bevalac from 1977-1992

Delivery partially based on a treatment chair

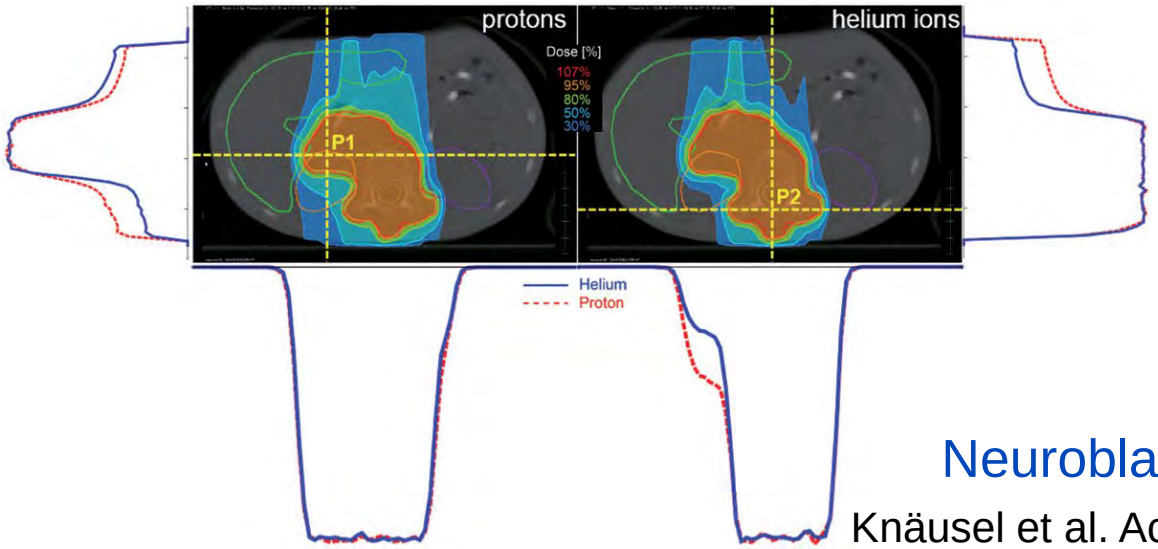
"… helium beam has not shown increased biological potential over low LET photon therapy. In this respect helium seems to be similar to proton therapy."

Rationale for Helium: dose conformation





Krämer et al. Med. Phys. 2016



Neuroblastoma TP

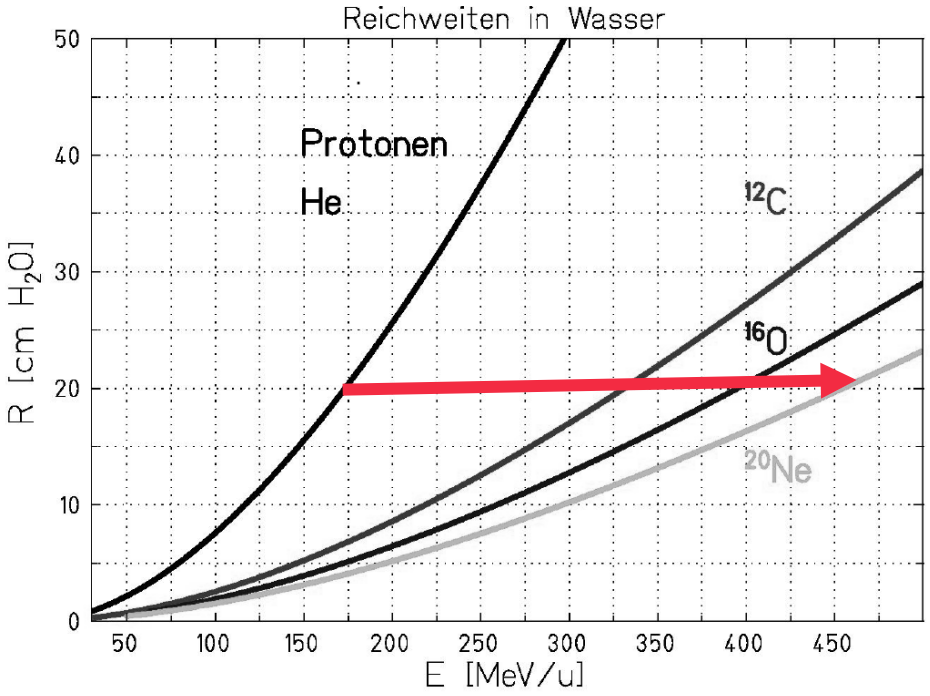
Knäusel et al. Acta Oncol. 2016

- Sharper lateral penumbra
- Steeper distal dose fall-off
- Lower entrance dose

} vs. p

- No tail dose, less neutrons (vs. C)
- Little advantage due to RBE

Energy loss and range of Protons, Helium, Carbon , Oxygen



$

[courtesy D. Schardt, GSI]

Heavier ions → higher energies (higher LET) → larger machines

A He-machine may still be quite small and affordable…

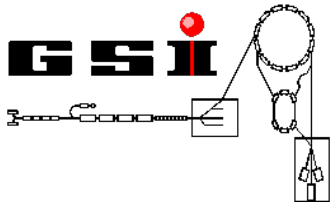
Carbon Ion Therapy: Pilot Project at GSI 1997-2008

Cooperation between GSI, Heidelberg University Hospital, DKFZ, HZ Rossendorf

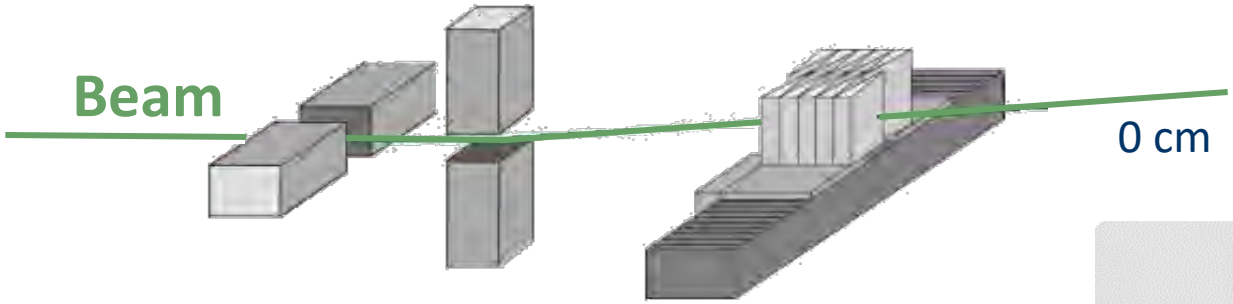
1. Patient treated on Friday Dec. 13th 1997

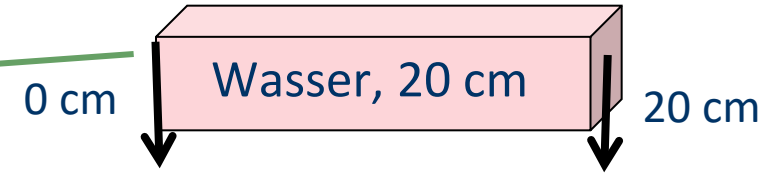
Gerhardt Kraft
Dep. Biophysics

Treatment of 435 patients using a **scanned carbon ion beam**

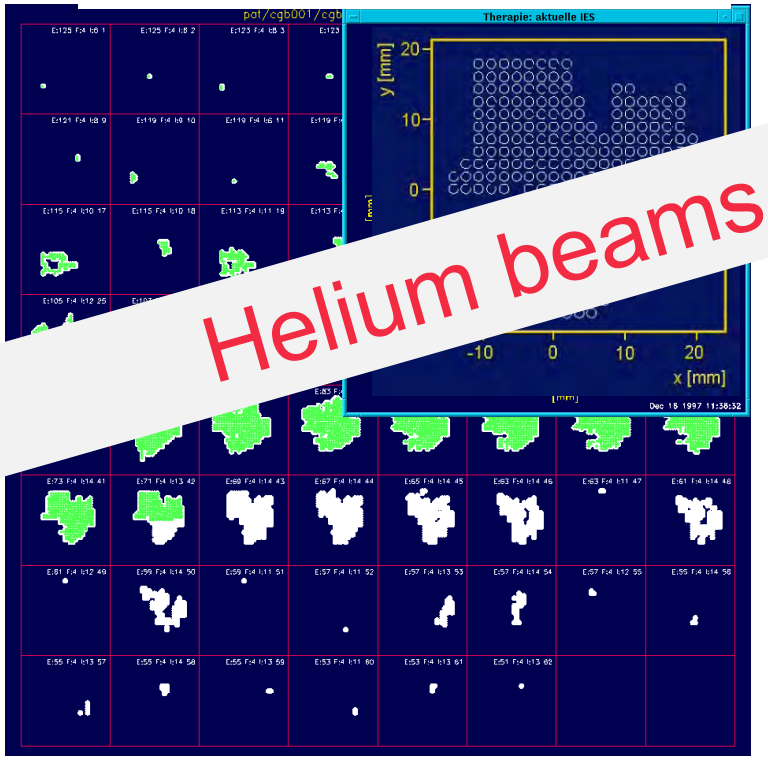


Beam delivery with beam scanning

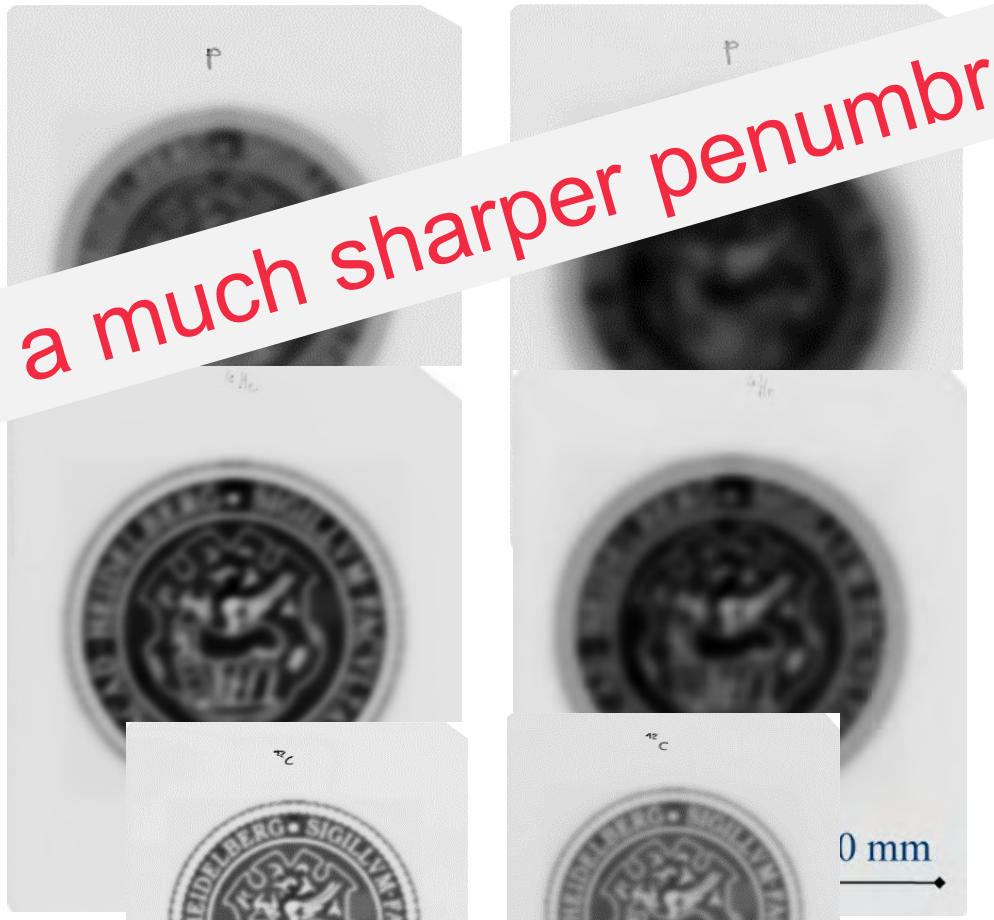




High precision delivery



Helium beams offer a much sharper penumbra

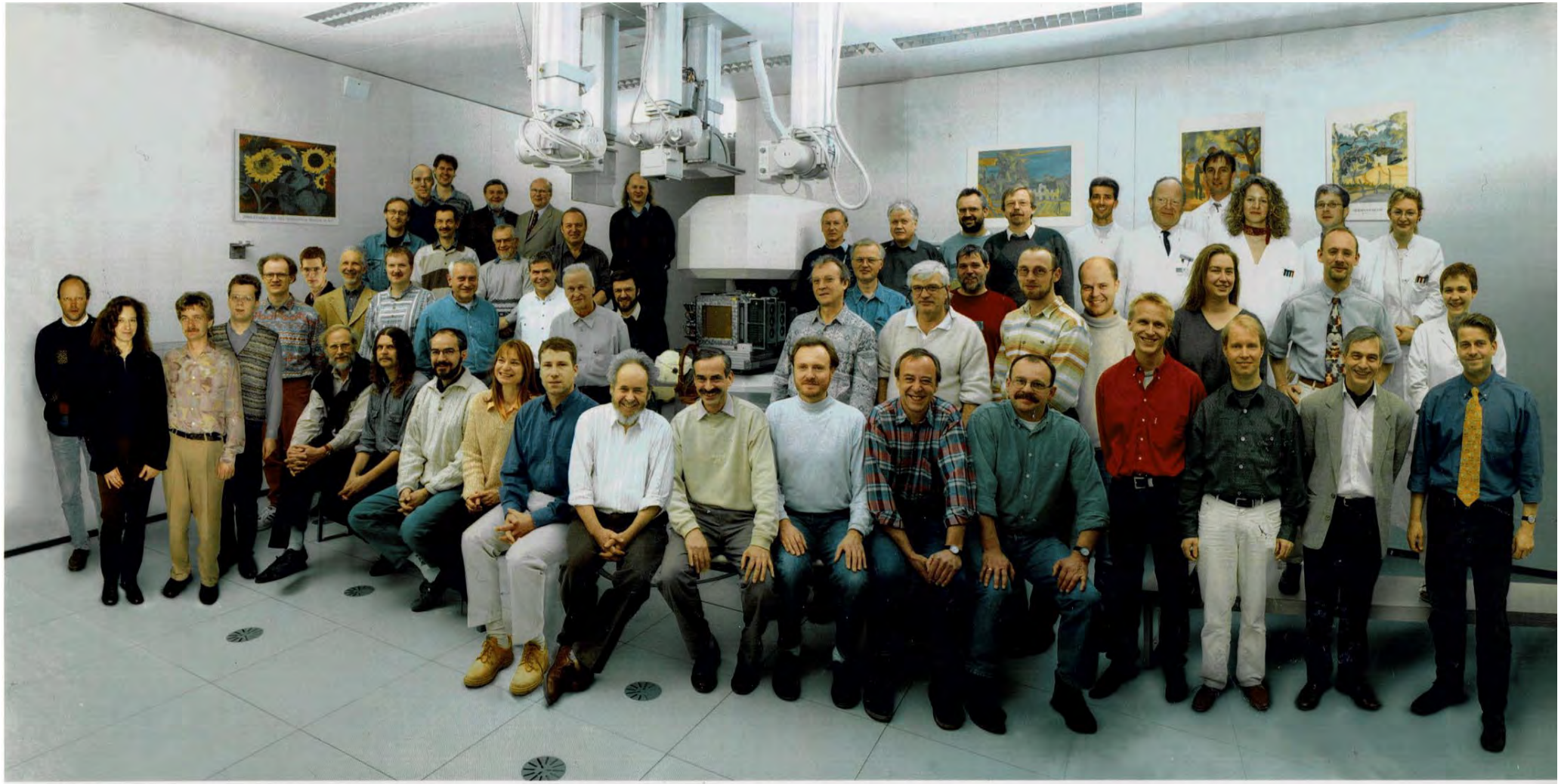


Protons
175 MeV

Helium ions
175 MeV/u

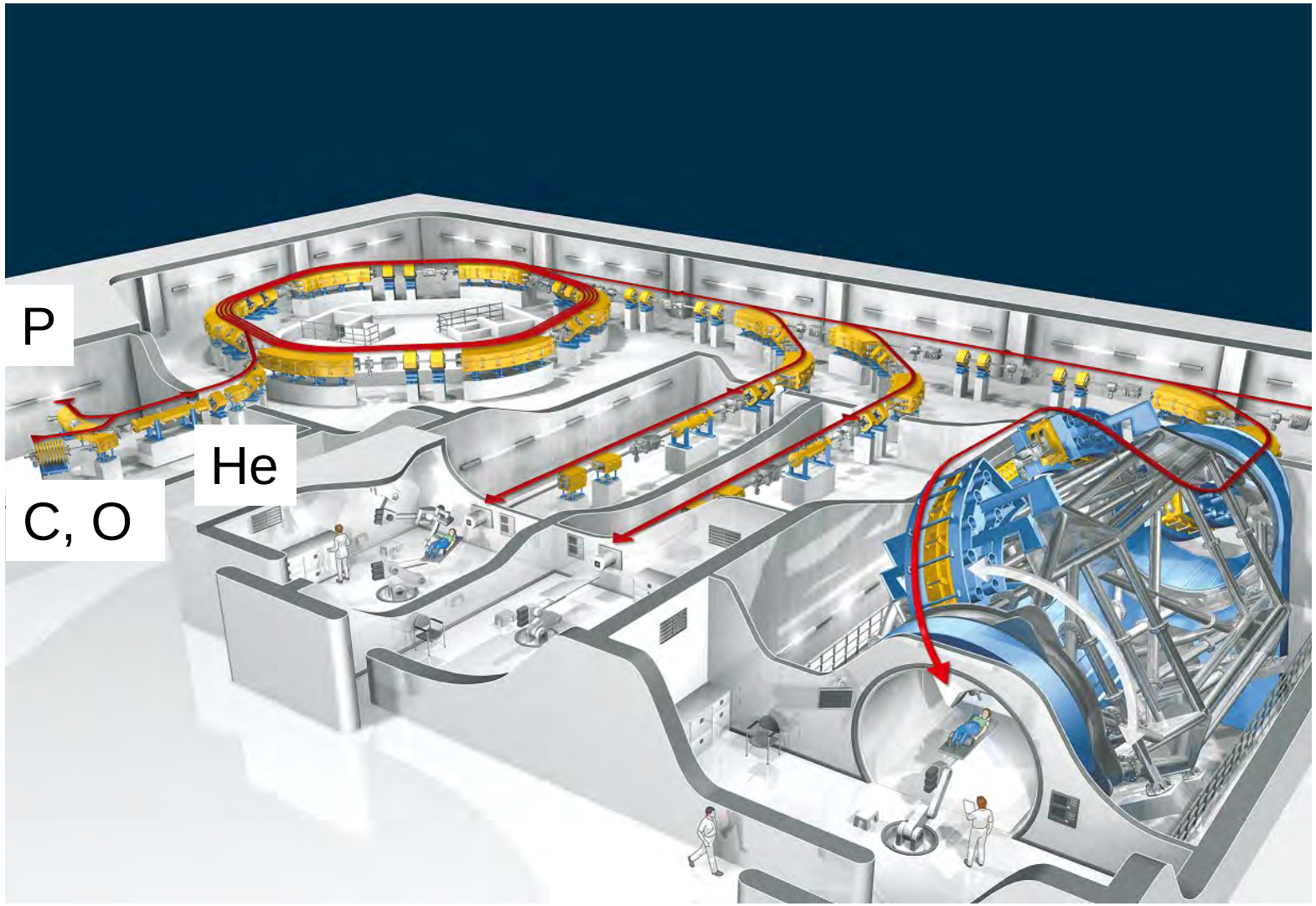
Carbon ions
330 MeV/u

The *beam team* at GSI in 1997



Heavy-Ion Therapy at GSI Dec. 1997
Collaboration: FZ Rossendorf - GSI Darmstadt - Radiol. Klinik Heidelberg - DKFZ Heidelberg

Heidelberg Ion Beam Therapy Center



11/2009: 1. patient RT

10/2012: 1. Gantry pat.

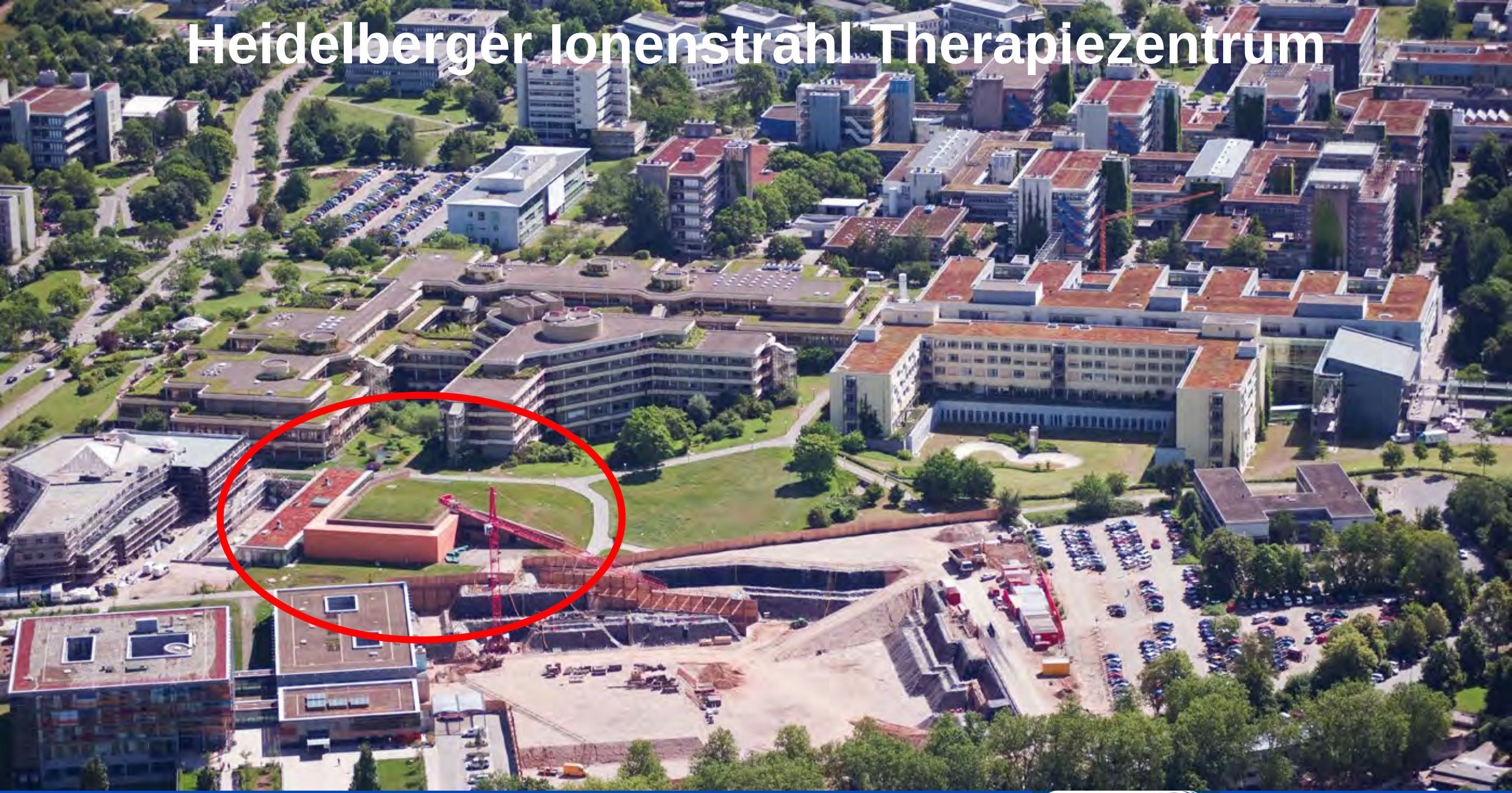
Today: 10‘000 patients !

Experimental area

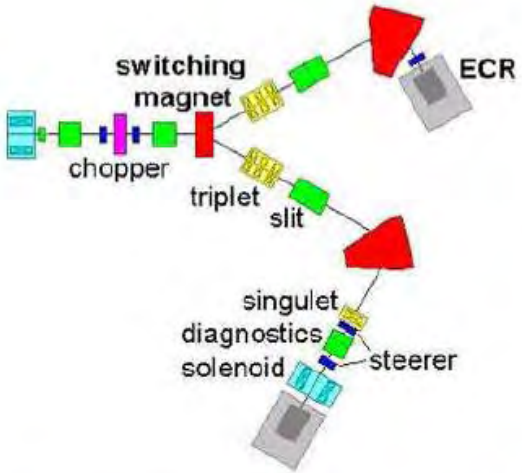
Research Labs

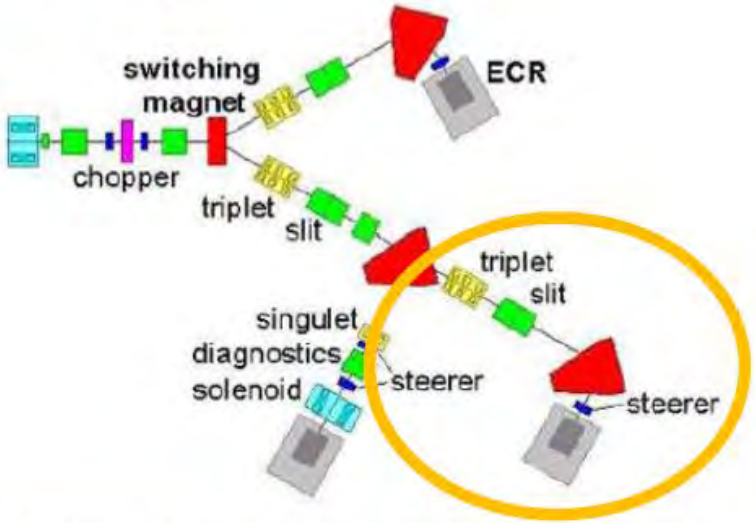
HIT is routinely operating with **p,** He, **C** and O beams for **RT** and research

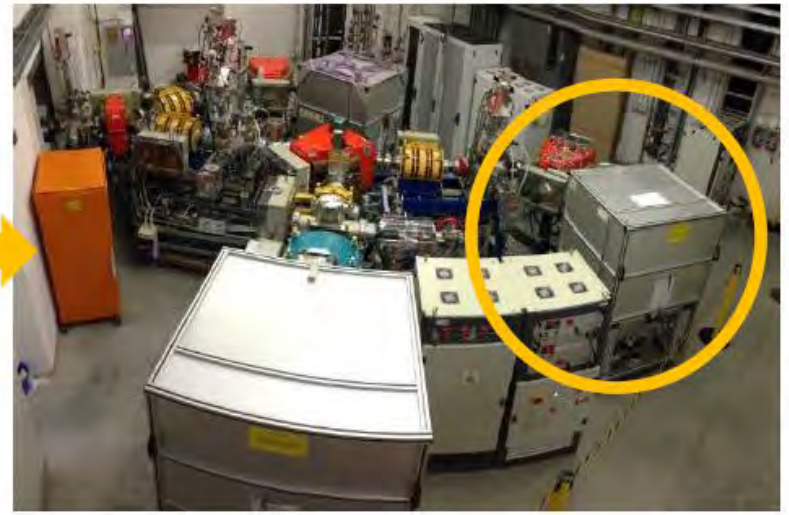
Heidelberger Ionenstrahl Therapiezentrum



Integration of the Helium source at HIT







Ion sources can be switched within seconds

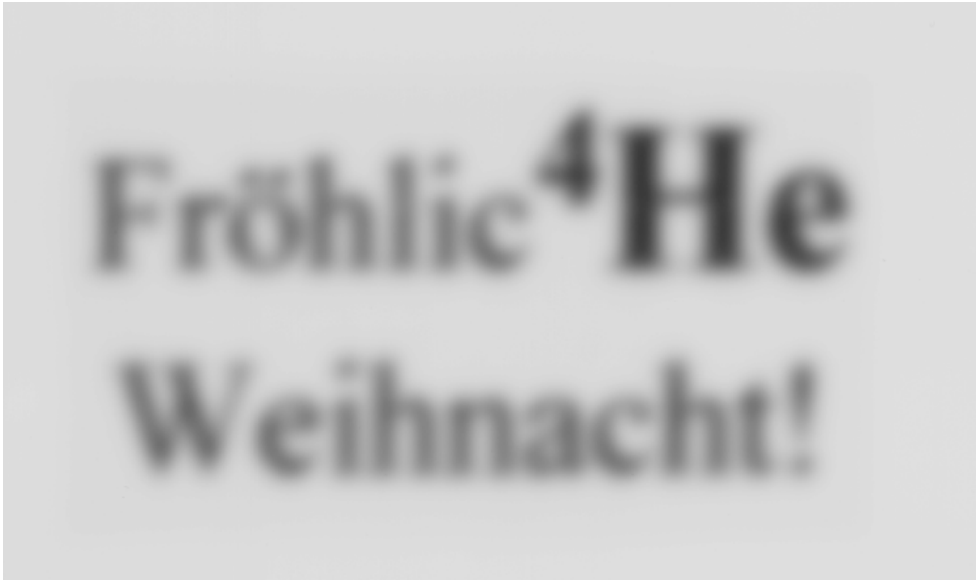
Helium beam line tuning

- He source installation in late 2012
- Tuning of LEBT, LINAC, MEBT

- 23.11.2013: 1st extraction from synchrotron
- 13.12.2013: 1st scanned beam QA room

S. Scheloske and A. Gaffron

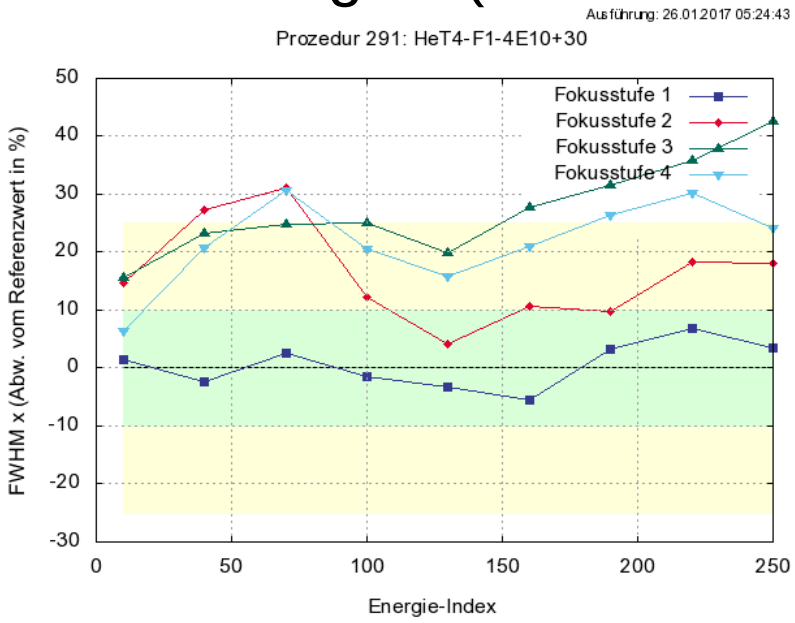
Scanning on radiographic film

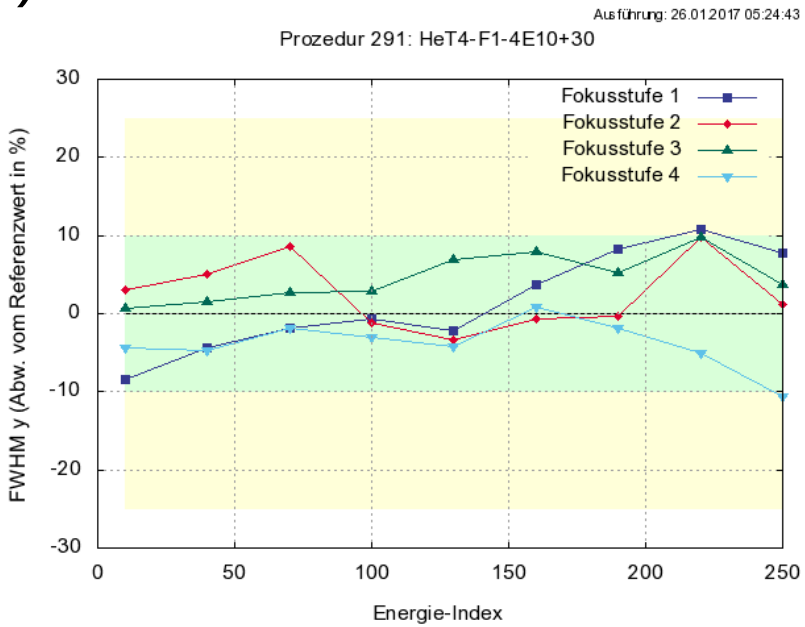


Scanned He beams are being used routiney for research since 2014

Helium HEBT tuning in 2016

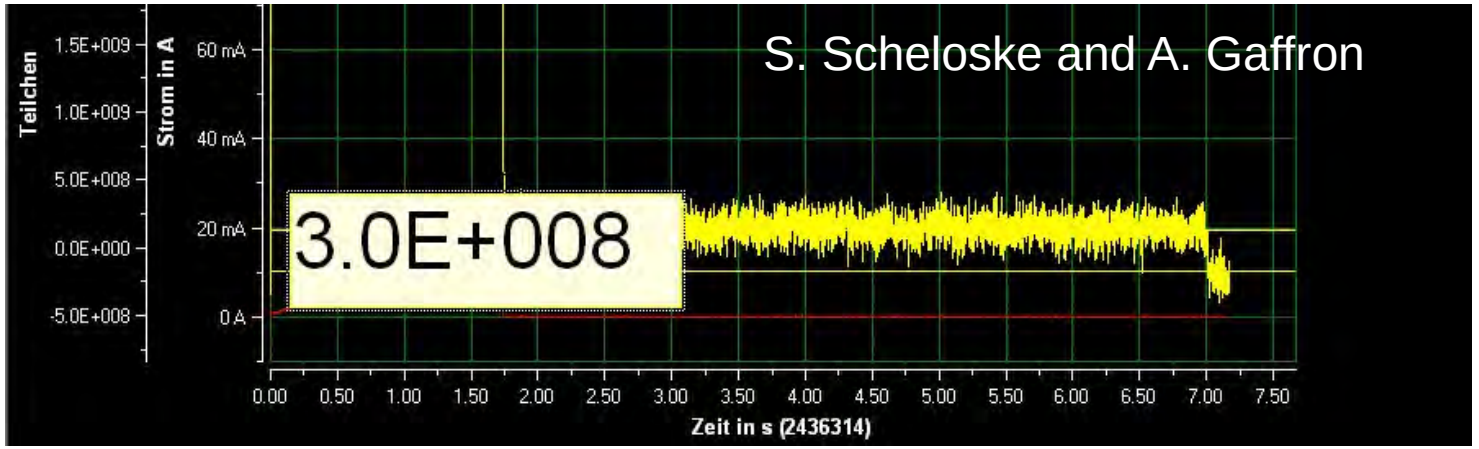
- Set-up of 4 focus levels at 255 energies (50-320MeV/u)
- Tuning of focus levels





- Optimization of direct intensity control (DIC)
- 10 intensity levels

  (max. 9*10^8/s)



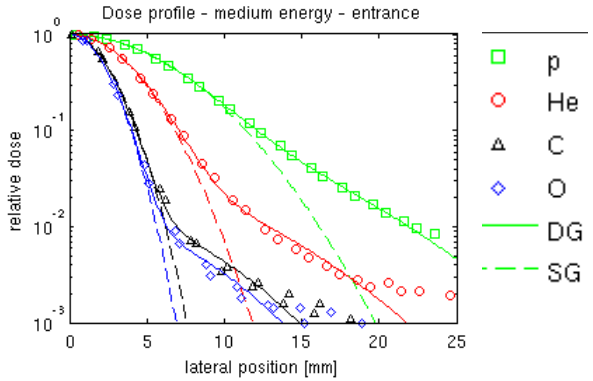
Clinical implementation of Helium RT

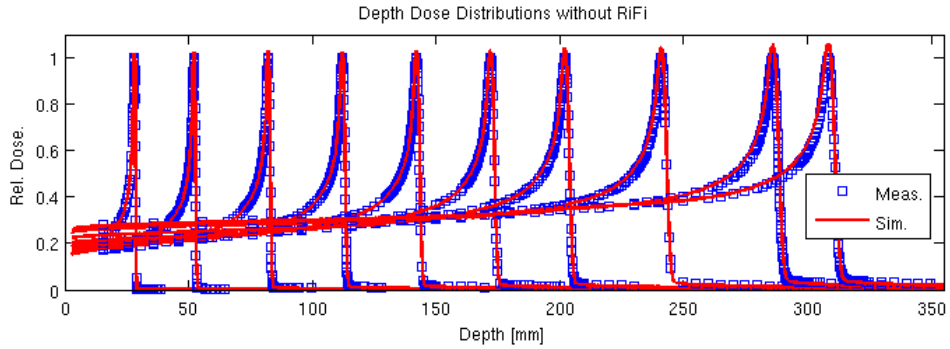
- Commissioning of TPS
- Commissioning of interface to Treatment control system
- Optimize fragmentation model
- Commissioning of He-beams
- Establish QM-program
- RBE model validation in-vitro
- RBE exp. in vivo
- Planning studies

RaySearch Laboratories — PRODUCTS SERVICES CAREER MEDIA INVESTORS

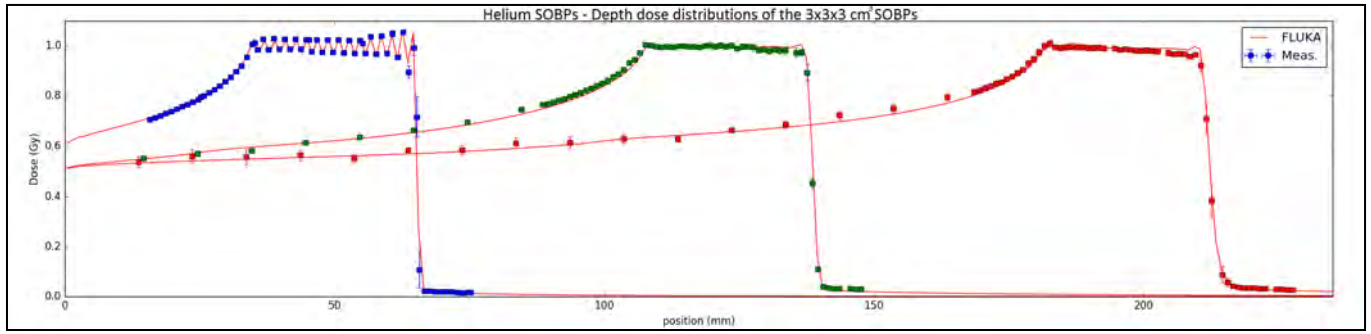
June 15, 2020

Germany's Heidelberg University Hospital will become the world's first cancer center to use RayStation for helium ion therapy planning





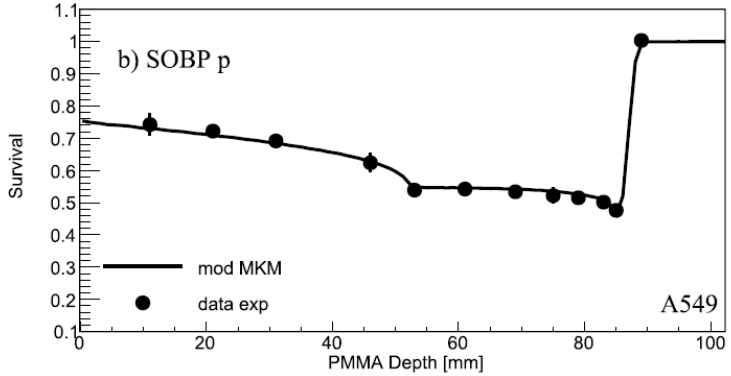
Tessonier et al. Phys. Med. Biol. 2017

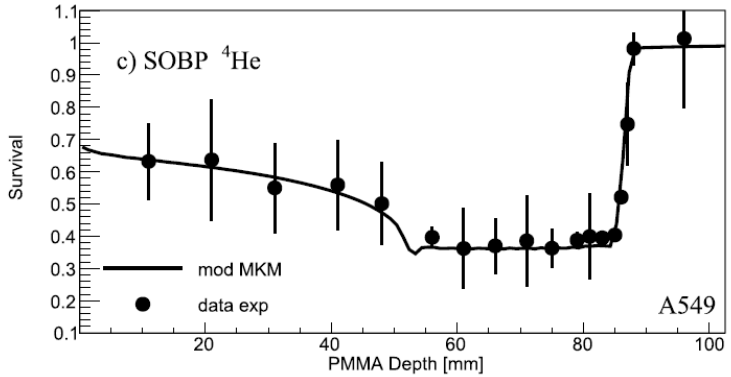


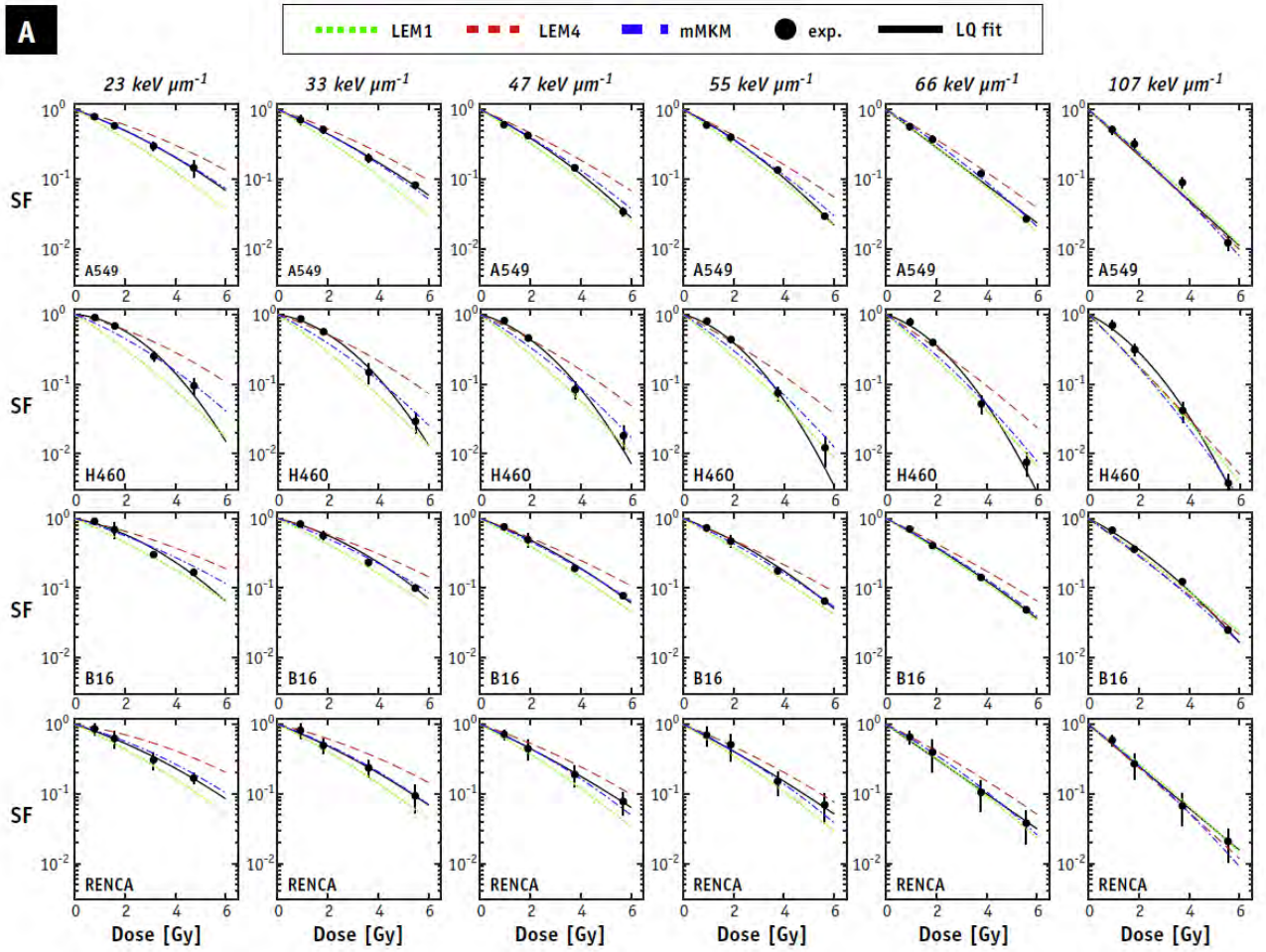
RBE modelling: optimization of mMKM

Optimizing the modified microdosimetric kinetic model input parameters for proton and ^{4}He ion beam therapy application

A Mairani[1,2], G Magro[1], T Tessonnier[3,4], T T Böhlen[5], S Molinelli[1], A Ferrari[6], K Parodi[2,3,4], J Debus[2,3] and T Haberer[2]



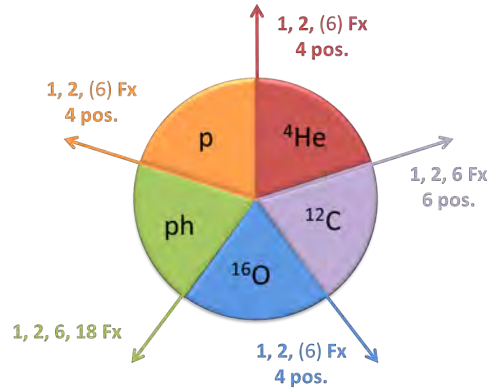




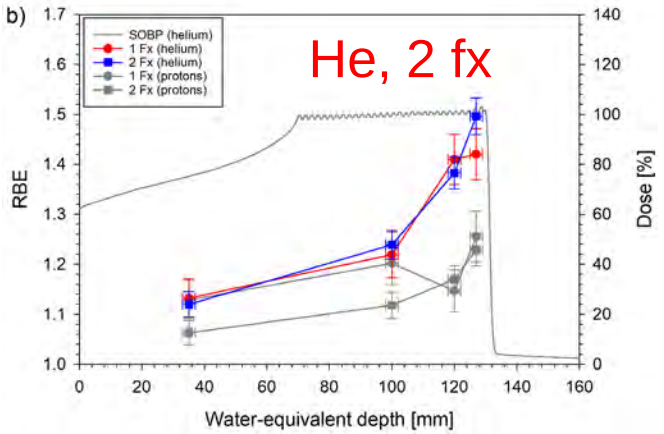
Optimizing the mMKM parameters yields a consistent description of $RBE_{p,He}$ (LET, D, cell line)

Benchmarking against in-vivo data

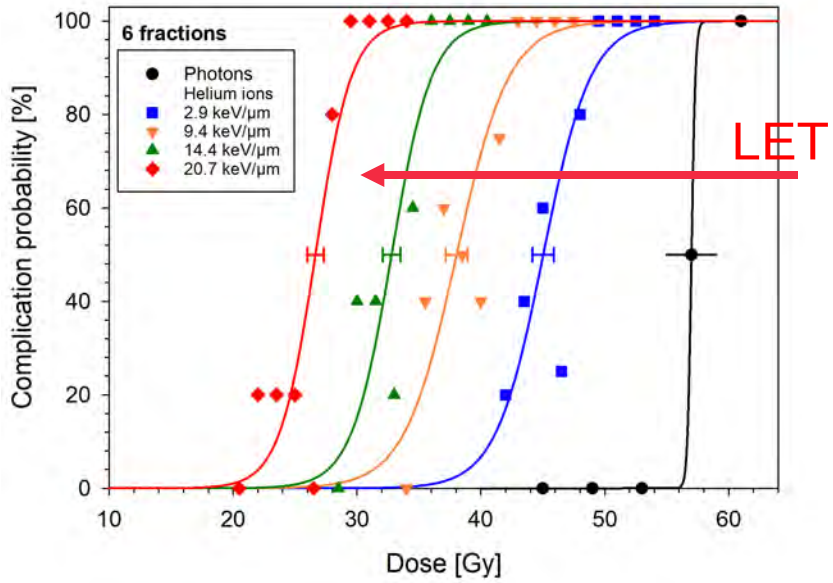
RBE of rat spinal chord for various fraction doses and LET

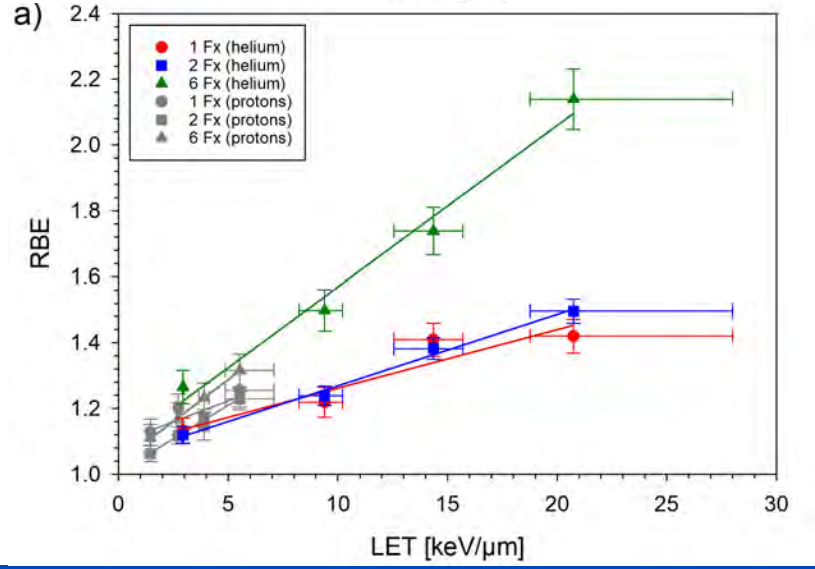


- Hintz et al Radiother. Oncol (2022): He 1 + 2 Fx
- Saager et al. Radioter Oncol 2015, 2018, C 1- 6 Fx
- Karger et al (in preparation): He ions 6Fx
- Mein et al. IJROBP 2020: RBE modelling comparison



He, 6 fx





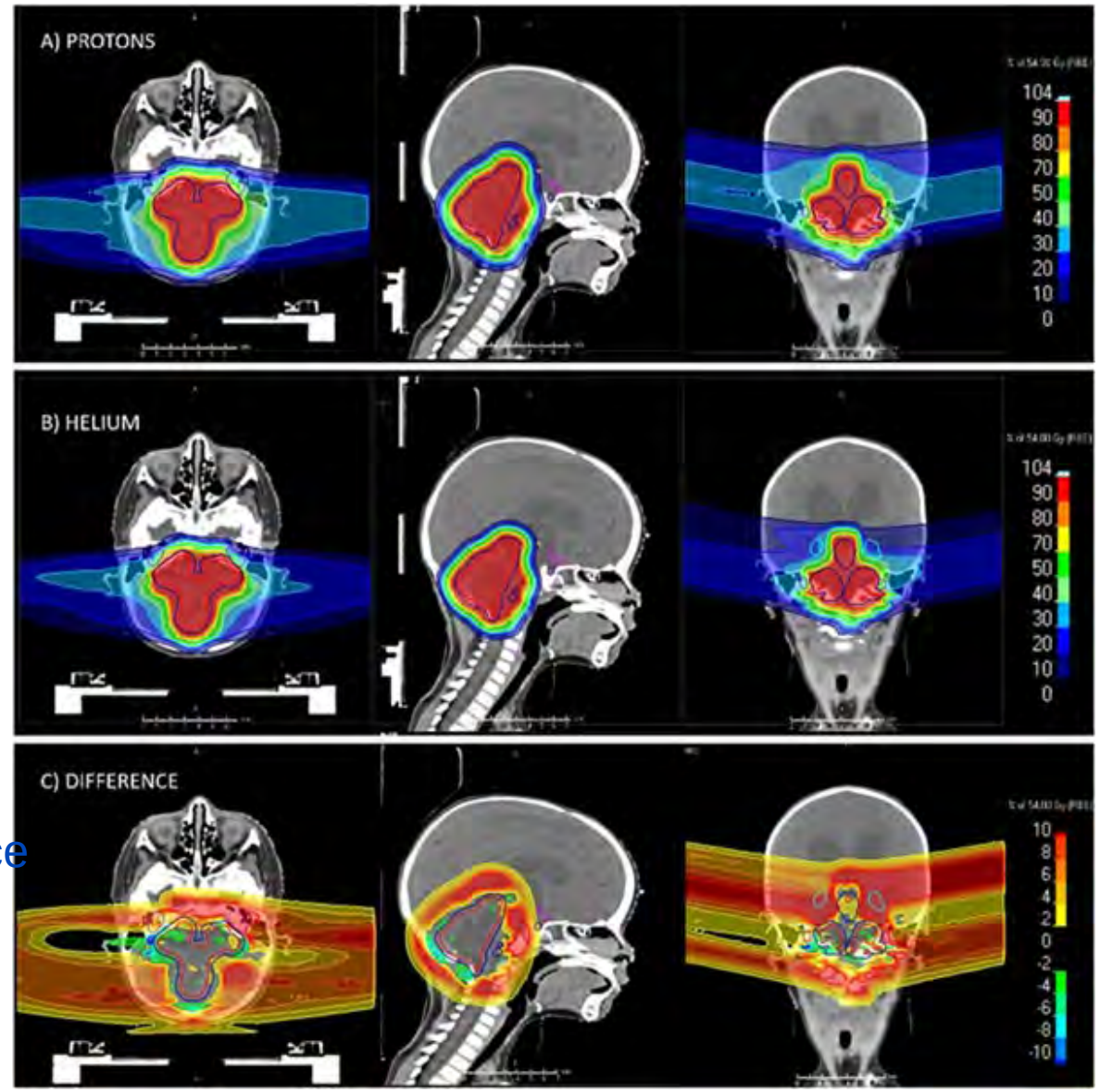
Consistent benchmark of RBE models for p, C, He an O in vivo.

Treatment planning study: He vs. Protons

Protons

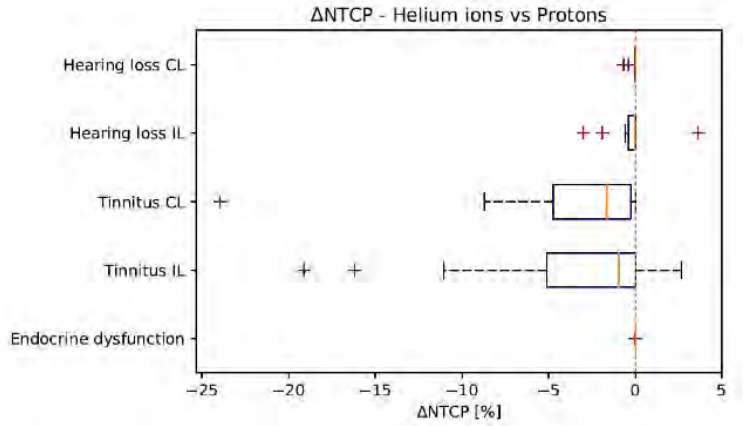
Helium

Difference



15 Ependymoma patients, Wickert, Cancers 2022

Doses reduce by up to 10% (5,4Gy RBE)
Reduced NTCP for endocrine & neurocognitive outcome

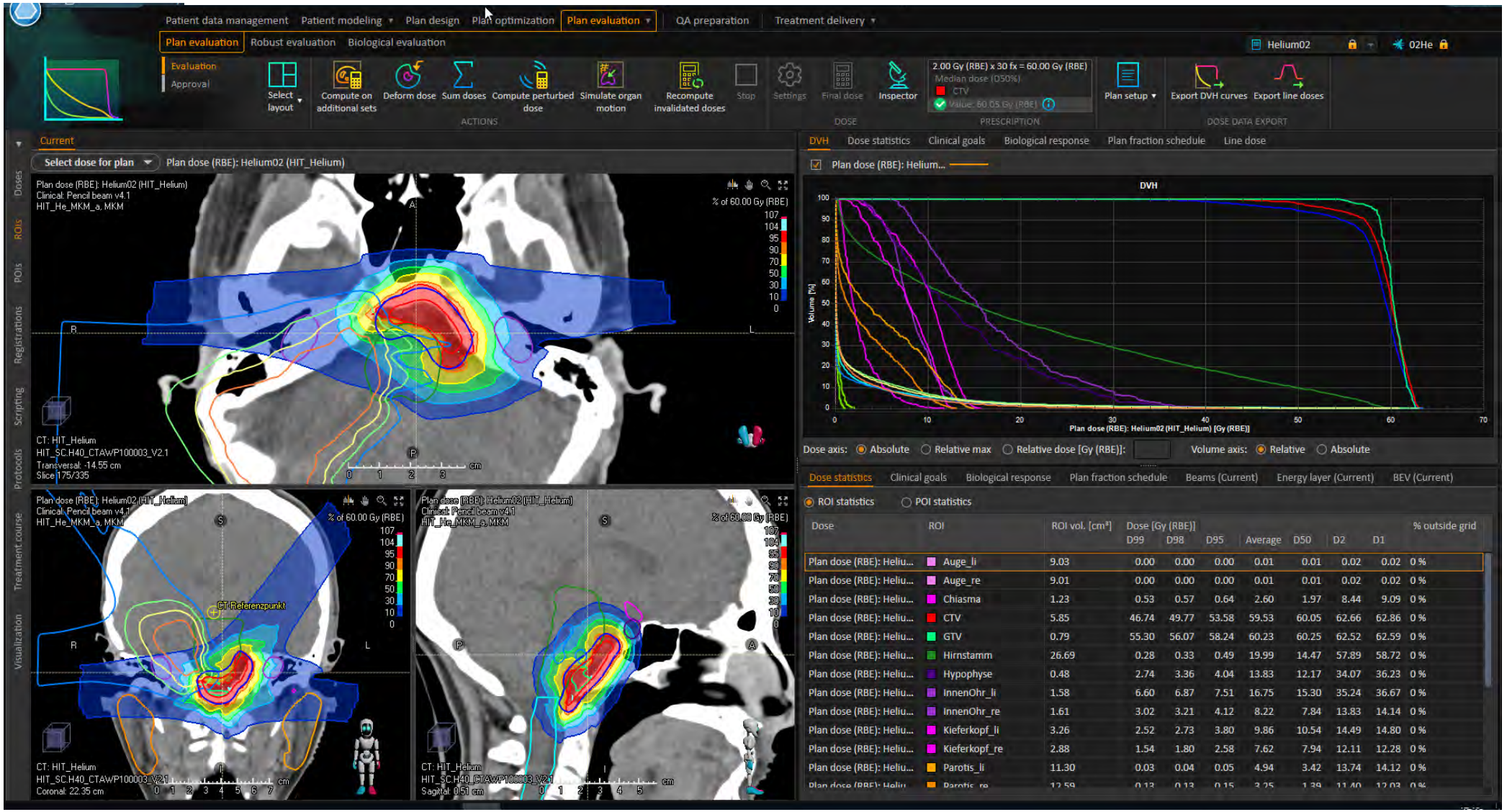


Better sparing of brain stem, cochleae, pituitary gland, hippocampi

Mairani et al. P*hys. Med. Biol.* **67** 2022

1st Helium RT with a scanned beam

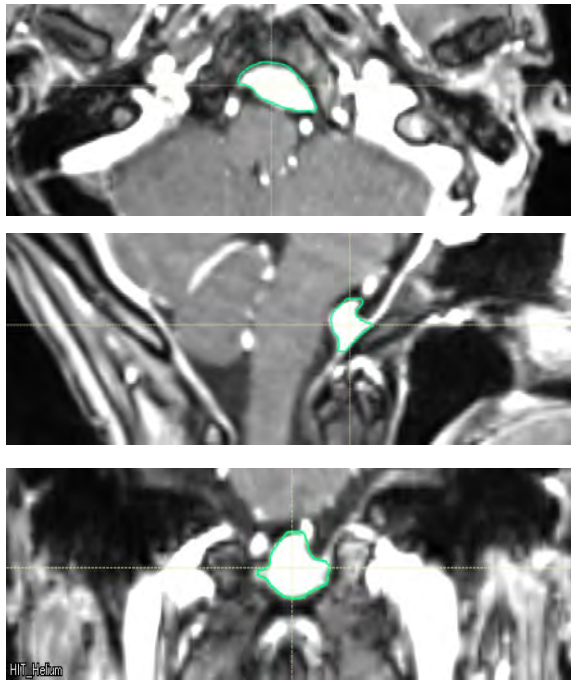
at HIT (July 20th 2021)



- 30y old patient
- **Recurrent** solitary fibrous tumour of the dura
- 20 x 2Gy (RBE)
- RBE: 1.4-2.1
- p-RT 2015: 30 x 2Gy (RBE)
- **stable tumor remission > 2yr**

Follow-up of first Hel-RT patient at HIT

Baseline Planning MRT

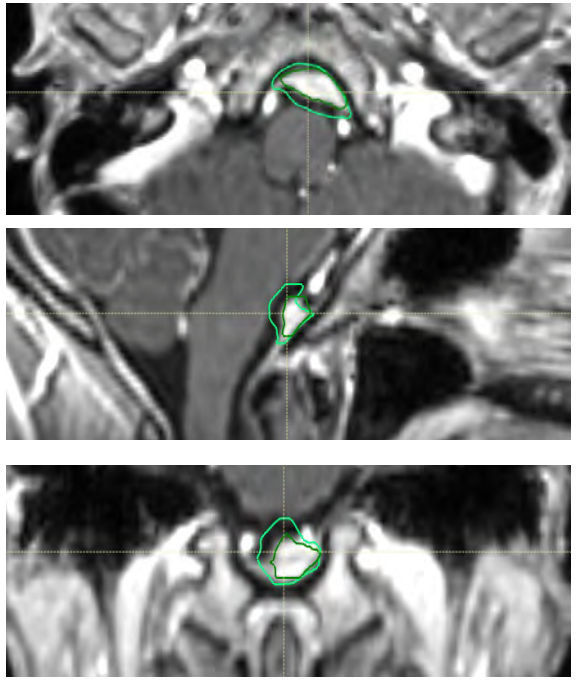


GTV pre RT

0,8 ml

Helium RT

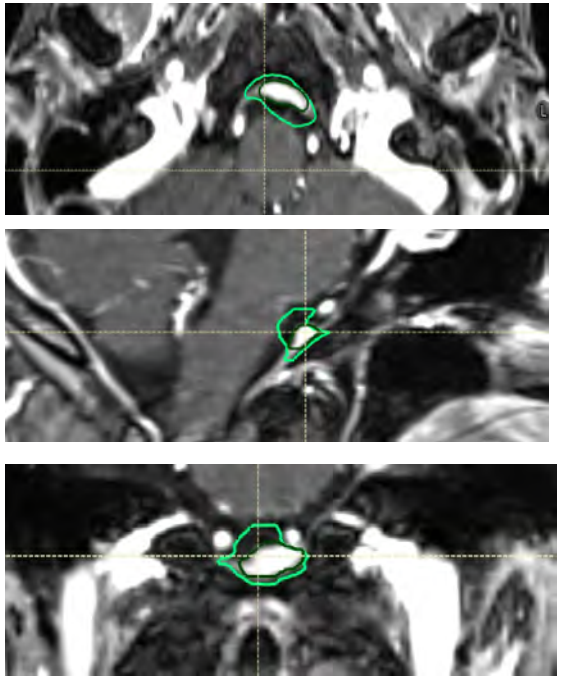
1. controlle at 6 weeks



GTV post RT

0,3 ml

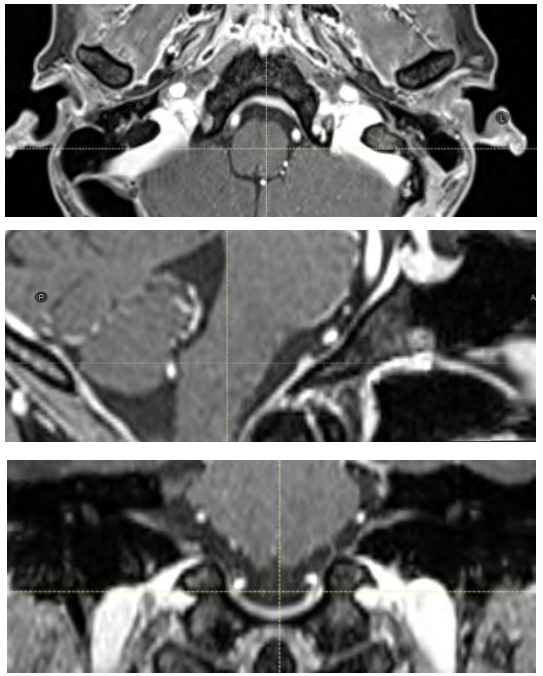
2. Control at 5 months



GTV post RT

0,2 ml

4. Control at 1 year

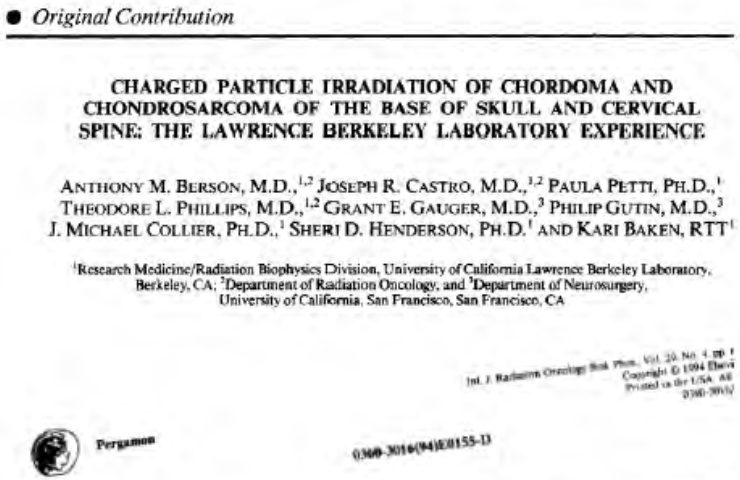


komplette Remission

Stable remission until > 2 years

Significant experience with He-RT at LNBL

including several phase I/II trials for skull base and cervical chordoma/chondrosarcoma, paraspinal tumors, uveal melanoma, pituitary gland, pancreas, esophagus, …



● *Original Contribution*

CHARGED PARTICLE IRRADIATION OF CHORDOMA AND CHONDROSARCOMA OF THE BASE OF SKULL AND CERVICAL SPINE: THE LAWRENCE BERKELEY LABORATORY EXPERIENCE

ANTHONY M. BERSON, M.D.,[1,2] JOSEPH R. CASTRO, M.D.,[1,2] PAULA PETTI, PH.D.,[1] THEODORE L. PHILLIPS, M.D.,[1,2] GRANT E. GAUGER, M.D.,[3] PHILIP GUTIN, M.D.,[3] J. MICHAEL COLLIER, PH.D.,[1] SHERI D. HENDERSON, PH.D.[1] AND KARI BAKEN, RTT[1]

[1]Research Medicine/Radiation Biophysics Division, University of California Lawrence Berkeley Laboratory, Berkeley, CA; [2]Department of Radiation Oncology, and [3]Department of Neurosurgery, University of California, San Francisco, San Francisco, CA

Int. J. Radiation Oncology Biol. Phys., Vol. 29, No. 4, pp. 1
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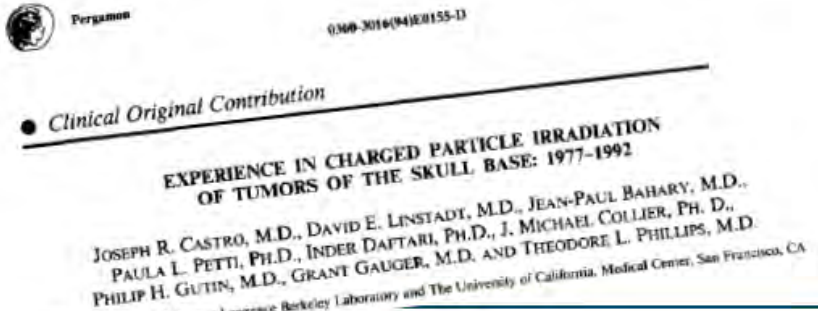
Pergamon

0360-3016(94)E0155-D

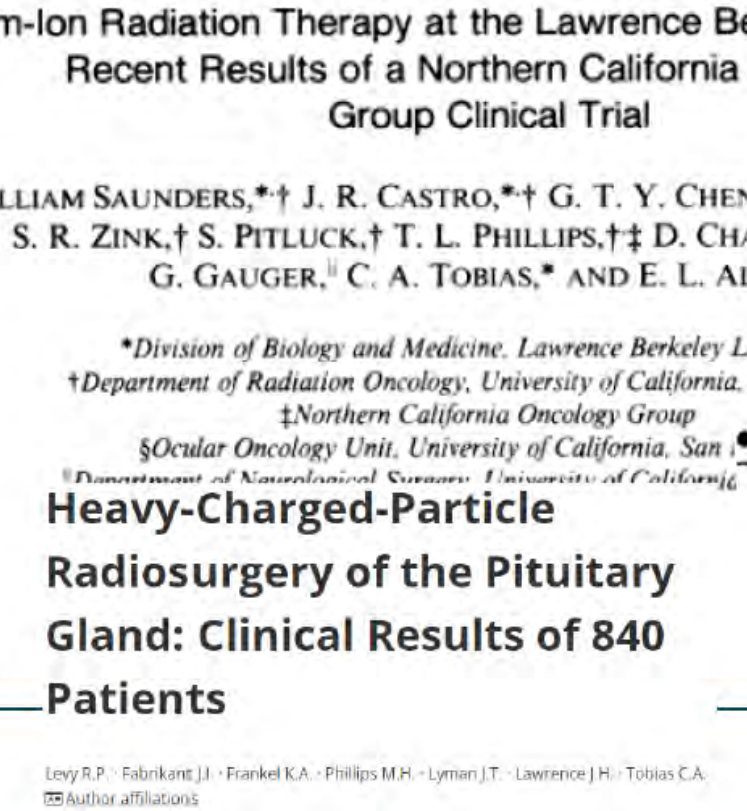


● *Clinical Original Contribution*

EXPERIENCE IN CHARGED PARTICLE IRRADIATION OF TUMORS OF THE SKULL BASE: 1977–1992

JOSEPH R. CASTRO, M.D., DAVID E. LINSTADT, M.D., JEAN-PAUL BAHARY, M.D., PAULA L. PETTI, PH.D., INDER DAFTARI, PH.D., J. MICHAEL COLLIER, PH. D., PHILIP H. GUTIN, M.D., GRANT GAUGER, M.D. AND THEODORE L. PHILLIPS, M.D.

The University of California Lawrence Berkeley Laboratory and The University of California, Medical Center, San Francisco, CA



Helium-Ion Radiation Therapy at the Lawrence Berkeley Laboratory: Recent Results of a Northern California Oncology Group Clinical Trial

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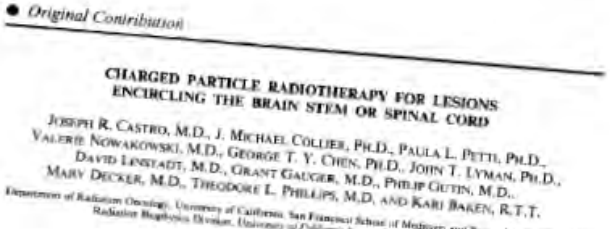
Heavy-Charged-Particle Radiosurgery of the Pituitary Gland: Clinical Results of 840 Patients

Levy R.P. · Fabrikant J.I. · Frankel K.A. · Phillips M.H. · Lyman J.T. · Lawrence J.H. · Tobias C.A.
Author affiliations



● *Original Contribution*

CHARGED PARTICLE RADIOTHERAPY FOR LESIONS ENCIRCLING THE BRAIN STEM OR SPINAL CORD

JOSEPH R. CASTRO, M.D., J. MICHAEL COLLIER, PH.D., PAULA L. PETTI, PH.D., VALERIE NOWAKOWSKI, M.D., GEORGE T. Y. CHEN, PH.D., JOHN T. LYMAN, PH.D., DAVID LINSTADT, M.D., GRANT GAUGER, M.D., PHILIP GUTIN, M.D., MARY DECKER, M.D., THEODORE L. PHILLIPS, M.D. AND KARI BAKEN, R.T.T.

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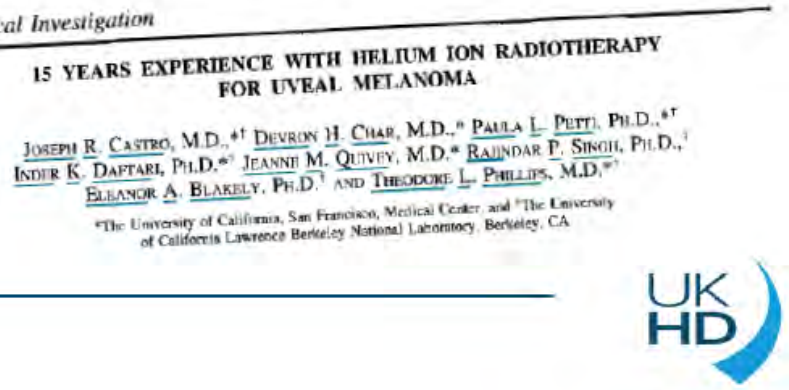


● *Clinical Investigation*

15 YEARS EXPERIENCE WITH HELIUM ION RADIOTHERAPY FOR UVEAL MELANOMA

JOSEPH R. CASTRO, M.D.,*† DEVRON H. CHAR, M.D.,* PAULA L. PETTI, PH.D.,*† INDER K. DAFTARI, PH.D.,*† JEANNE M. QUIVEY, M.D.,* RAJINDAR P. SINGH, PH.D.,† ELEANOR A. BLAKELY, PH.D.† AND THEODORE L. PHILLIPS, M.D.*†

*The University of California, San Francisco, Medical Center, and †The University of California Lawrence Berkeley National Laboratory, Berkeley, CA

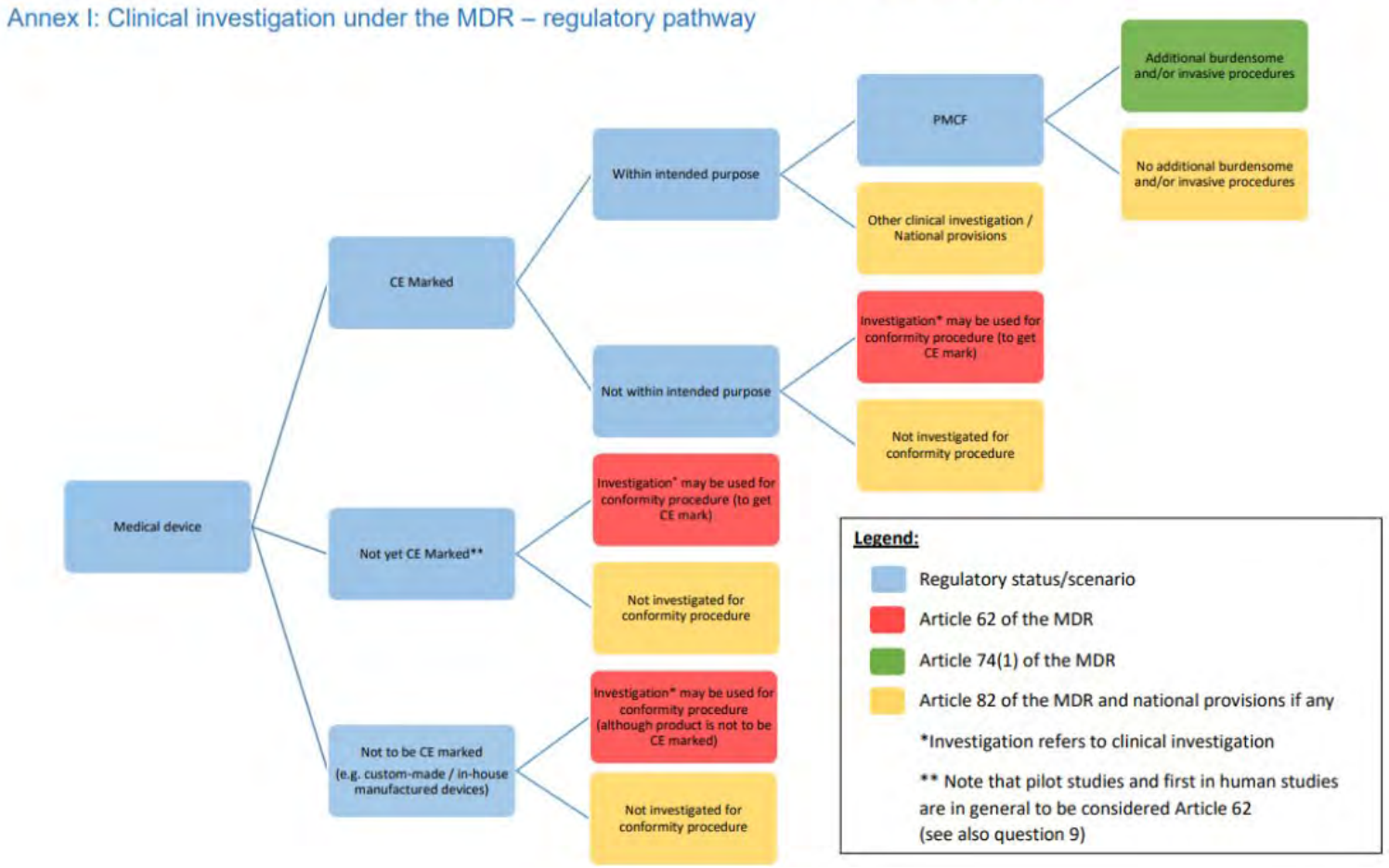
UK HD

Unfortunately all with passive beam delivery

HIT Heidelberger Ionenstrahl-Therapiezentrum

dkfz.

Navigating the Medical Device Regulation



Requirements regarding other clinical investigations

1. Clinical investigations, not performed pursuant to any of the purposes listed in Article 62(1), shall comply with the provisions of Article 62 (2) and (3), points (b), (c), (d), (f), (h), and (l) of Article 62(4) and Article 62(6).

2. In order to protect the rights, safety, dignity and well-being of subjects and the scientific and ethical integrity of clinical investigations not performed for any of the purposes listed in Article 62(1), each Member State shall define any additional requirements for such investigations, as appropriate for each Member State concerned.

Germany: §47 MPDG (Medizinproduktedurchführungsgesetz)

Navigating the German Medical Product Regulation

Requirements:

- Conduct a trial „**Other clinical investigation**“
- Preparation/submission of **49 documents** to federal bureau for drugs and medical products (BfARM)
- IRB vote (local ethics committee)
- Application for a trial involving radiation at federal bureau for radiation protection (BfS)
- Answer 25 questions, iterate, more questions …
- Preparation of docs in 2023, submission in 12/2023; approval in 10/2024
- 3months FU after RT and submission of report
- **No changes of the system during trial!!**

Other clinical investigation for He-RT

Aim: demonstrate the safety and performance of the product to obtain permission to conduct regular clinical trials with Helium ions to answer scientific questions

- Primary endpoint: tocicity ≥ CTC °3;
- Patient number: n=29 (brain, skull base, thoracic, prostate, …)
- **Weekly clinical exams during RT**
- 3months FU
- **Inclusion criteria**: Patients with tumor disease and indication for radiotherapy;

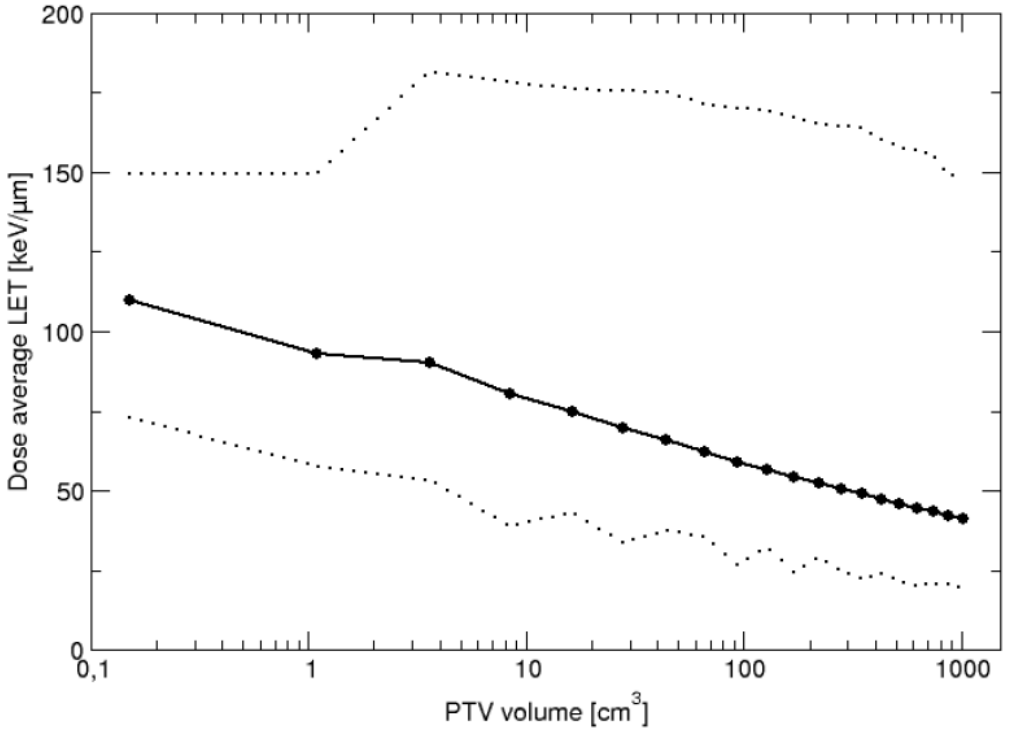
  KI >60% oder ECOG 0/1; Age > 18 yrs; ability to consent; written consent

- **RT from Oct 24 – Dec 24**
- End of FU in mid March 2025 (end of RT, 90days, 3months)
- Helium is now used regularly as standard of care since autumn 2025

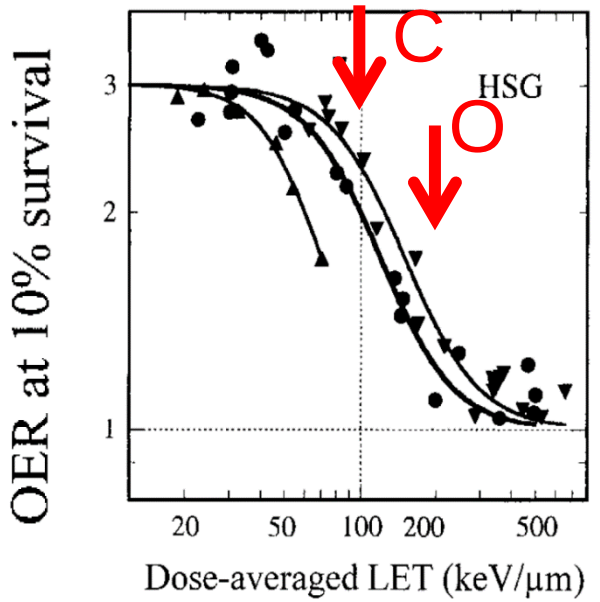
Technically no difference comapred to p-RT (or carbon) with curative intent, w.r.t. indications, treatment planning, prescrition dose, fractionation, image guidance, follwo-up

What's next at HIT?

Is Carbon really high LET radiation?



N. Bassler, O. Jäkel, et. al., Acta Oncologica 49 (2010), 1170

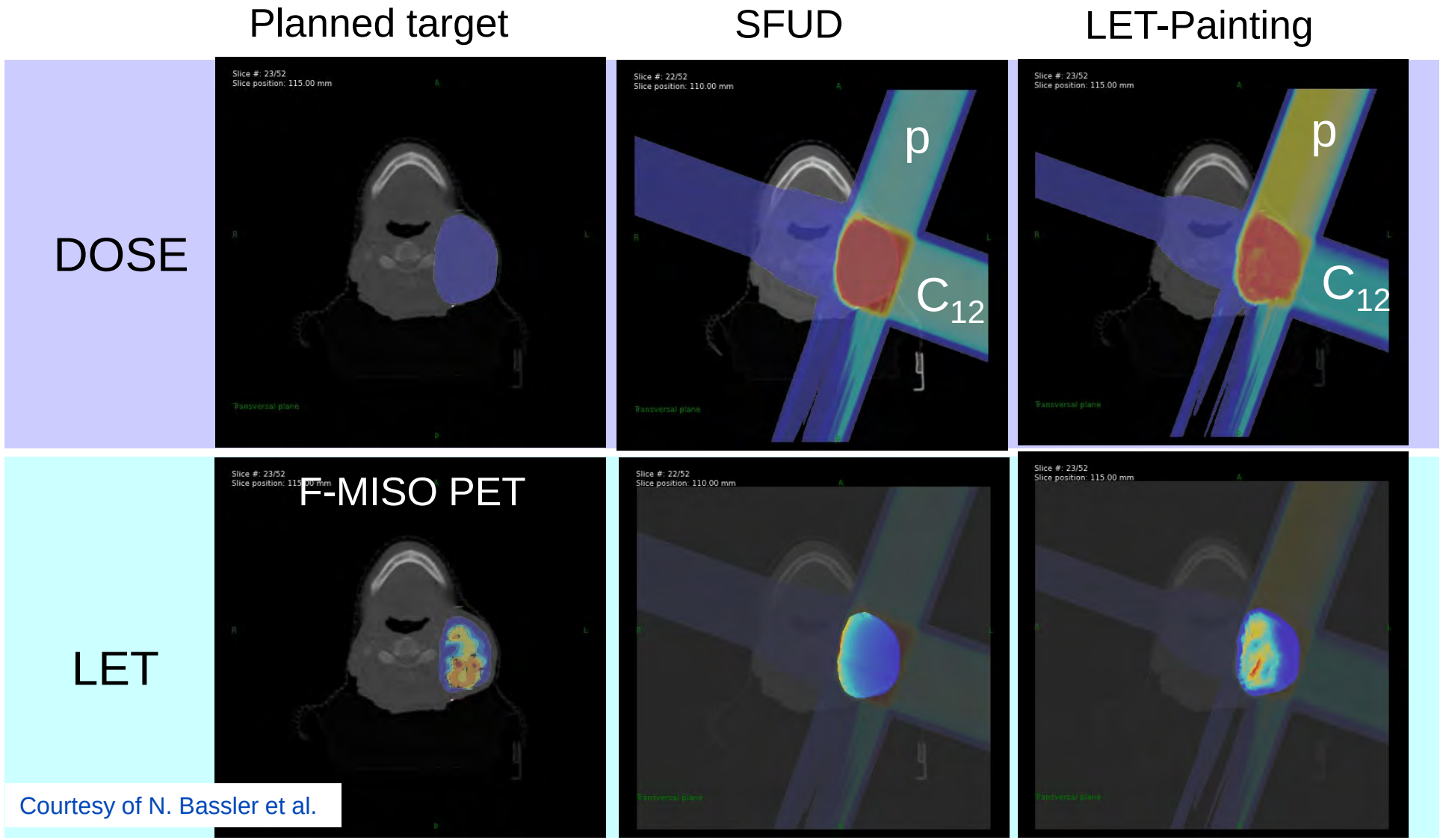


He: ▲,
^{12}C: ●,
^{20}Ne: ▼

Commissioned 2015

In larger volumes, LET is diluted and Oxygen may be a suitable solution
Implementation at HIT not foreseen before 2030!

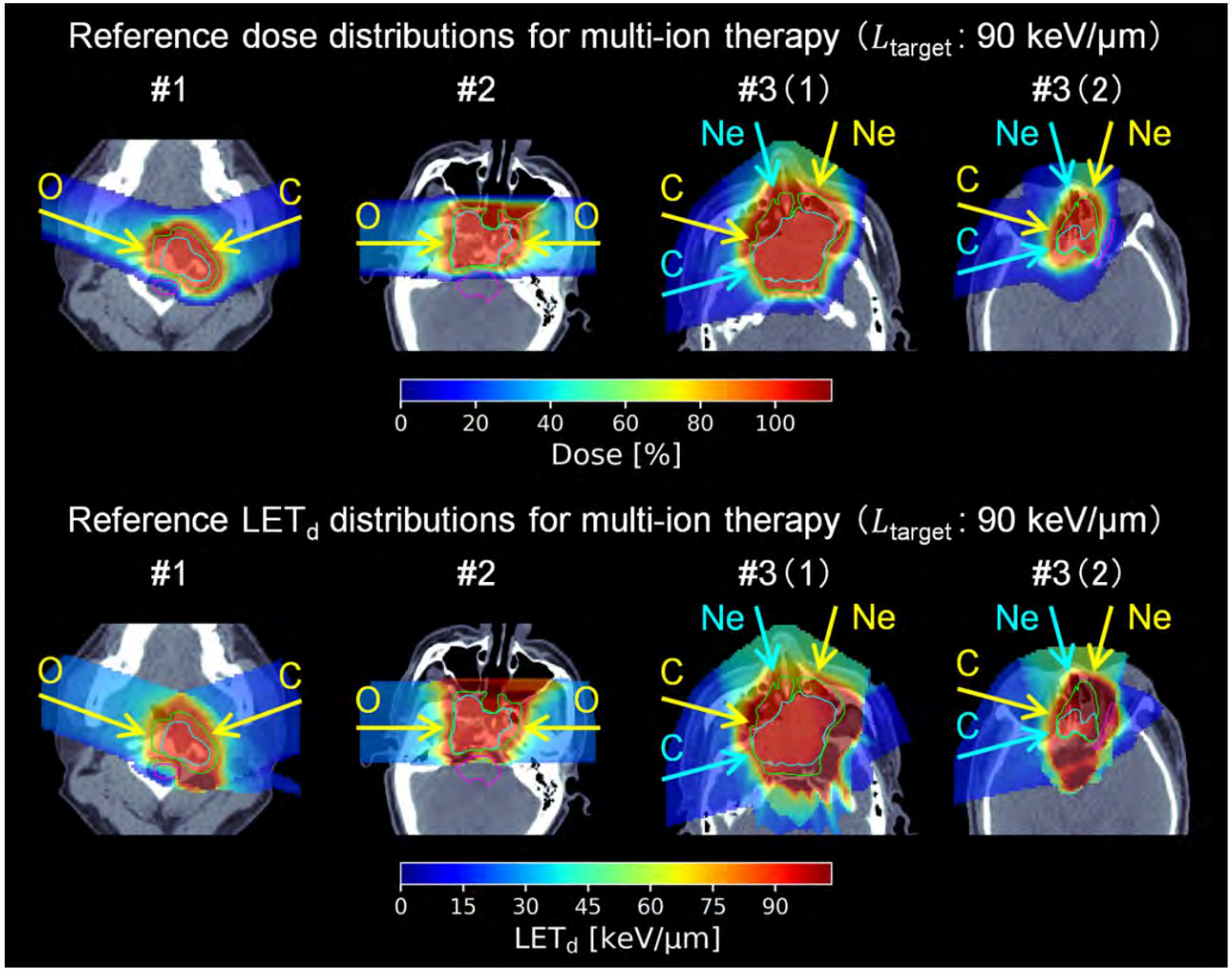
LET Painting for hypoxic tumors



Courtesy of N. Bassler et al.

Scanning/IMPT offers additional degrees of freedom for adapting high LET

QST (NIST) in Japan started Multi-Ion Therapy



Phys. Med. Biol. **71** (2026) 035016 https://doi.org/10.1088/1361-6560/ae387b

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

PAPER

Robustness of LET_d-optimized multi-ion therapy against range and setup uncertainties: evaluation and enhancement with carbon-, oxygen-, and neon-ion beams

Takamitsu Masuda[1,*], Hiroaki Ikawa[2], Makoto Shinoto[2], Masashi Koto[2,3], Koki Kasamatsu[1], Yusuke Nomura[1], Nobuyuki Kanematsu[1] and Taku Inaniwa[1]

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Home Archive Volume 15, Issue 10

Radiology and imaging
Protocol

Dose-averaged LET escalation with multi-ion therapy for head and neck cancers: a phase I study protocol for a prospective, open-label, single-arm, single-centre trial (MULTI-ION-HN-I)

Hiroaki Ikawa [1], Makoto Shinoto [1], Masashi Koto [2], Takamitsu Masuda [3], Taku Inaniwa [3], Hirotoshi Takiyama [1], Tetsuro Isozaki [1], Shigeru Yamada [1], Hitoshi Ishikawa [1]

International Journal of Radiation Oncology*Biology*Physics
Volume 108, Issue 3, Supplement, 1 November 2020, Pages S67-S68

Oral Scientific Session

Back to the Future: Helium Ion Therapy 2020

Conclusions

- Implementation and Commissioning finalized
- Regulatory issues solved
- Trial applications submitted
- ~120 patients have been treated (brain tumors)
- Indications:

  Difficult p-RT indications, recurrent tumors,

  trials for pediatric patients, pregnant patients (registry trial already initiated) radiosurgery..
- Facility will undergo an upgrade: HIT 2.0 until 2030

A big team effort:

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Jakob Naumann
Malte Ellerbrock
Abdallah Qubala
Harald Latzel
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Katharina Weusthof
Ricarda Wickert
Katharina Seidensaal
Ivana Dokic
Klaus Herfarth
Line Höltgen
Stewart Mein
Julia Bauer

Thank you for your attention!