Introduction of Carbon ion beam therapy in Europe and clinical trials

Jürgen Debus

PTCOG 2019, Manchester UK
## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
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</table>
1980-1997 biolog. treatment planning
1993: first prototype of rasterscanner
1994: medical treatment room
1997: First patient treated with C-12 at GSI

440 Patients, 1998-2008

- Chordoma
- Chondrosarcoma
- Adenoidcystic Ca.
- Others, incl. Prostate
- Re-irradiation
Patient Positioning In The Early Clinical Studies (1997-2008)

Stereotactic Setup

Daily IGRT

Online in-beam PET
Early Clinical Response: Adenoidzystic Carcinoma:

Before RT  
6 Weeks after RT
Acceptable Skin Reaktion

Biol. Wirkung:
Local Effect Model: LEM
Radiotherapy of Skull Base Chordomas
Motivation: Dose Response Relationship

Motivation: Dose Response Relationship

- FSRT
- Protons
- C-Ions
- FSRT
- conventional RT

D. Schulz-Ernter, IJROBP 2007
1998: Project proposal for „HIT“
2000: Feasibility study: HIT is feasible
2001: Scientific board agrees, planning started
2004: Foundation stone ceremony
2009: first patient at HIT
Heidelberg Ion Therapy Center

**HIT** is the world’s first heavy ion treatment facility with a **360° rotating beam delivery** system (gantry).

**HIT** is Europe’s first combined treatment facility using **protons and heavy ions** for radiation therapy.
### Indications currently treated at HIT and MIT

<table>
<thead>
<tr>
<th>Indications</th>
<th>Within phase II clinical trials</th>
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</thead>
<tbody>
<tr>
<td><strong>Tumors in children and young adults</strong></td>
<td><strong>Adenoid cystic carcinoma (ACC)</strong></td>
</tr>
<tr>
<td>Ependymoma, Retinoblastoma, Medulloblastoma, Glioma, Lymphoma, Sarcoma,</td>
<td><strong>Glioma Grad II/III in adults, glioblastoma</strong></td>
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<tr>
<td>Neuroblastoma, Teratoma, Craniopharyngeoma</td>
<td><strong>Paraspinal sarcoma and carcinoma</strong>, non-operative osteo- and chondrosarcoma of axis skeleton</td>
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<tr>
<td><strong>Chordoma and Chondrosarcoma of the skull base</strong></td>
<td><strong>Meningeoma of skull base</strong> – (&gt; 15 ccm) and atypical forms, incompletely resected or sinus</td>
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<tr>
<td></td>
<td>cavernosus involvement</td>
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<tr>
<td><strong>Cerebral Arterioveneuous Malformations (AVM)</strong></td>
<td><strong>Advanced head and neck tumors</strong> without distant metastases</td>
</tr>
<tr>
<td><strong>Mediastinal Lymphoma (protons)</strong></td>
<td><strong>Hepatocellular carcinoma</strong></td>
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<td><strong>Thoracic tumors:</strong></td>
<td><strong>Thoracic tumors:</strong></td>
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<tr>
<td>Lung carcinoma (NSCLC, inoperable stage I–III), and pleural mesothelioma</td>
<td>Lung carcinoma (NSCLC, inoperable stage I–III), and pleural mesothelioma stage I–III, if pleuropneumonectomy is not possible</td>
</tr>
<tr>
<td>stage I–III, if pleuropneumonectomy is not possible</td>
<td>Locally advanced <strong>gynecological malignoma</strong>, previously treated with RT or not suitable for BRACHYTERAPIE</td>
</tr>
<tr>
<td>Locally advanced</td>
<td><strong>Esophageal carcinoma not resectable</strong></td>
</tr>
<tr>
<td>gynealogical malignoma, previously treated with RT or not suitable for</td>
<td></td>
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<tr>
<td>Brachytherapy.</td>
<td><strong>Soft tissue sarcoma/chordoma am Körperstamm</strong> (neo)–adjuvant and primary if inoperable and</td>
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<tr>
<td></td>
<td>extremities after extremity conserving surgery</td>
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<tr>
<td>Locally advanced</td>
<td><strong>Pancreatic carcinoma</strong> TxNxM0 with (neo-)adjuvant particle therapy or inoperability</td>
</tr>
<tr>
<td>pancreatic carcinoma **TxNxM0 with (neo-)adjuvant particle therapy or</td>
<td><strong>Pituitary gland adenoma</strong> (inoperable, not suitable for radiosurgery /SRS)</td>
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<tr>
<td>inoperability**</td>
<td><strong>Craniopharyngeoma</strong></td>
</tr>
<tr>
<td><strong>Pituitary gland adenoma</strong> (inoperable, not suitable for radiosurgery /SRS</td>
<td><strong>Akusticus neurinoma</strong> (inoperable, not suitable for radiosurgery /SRS)</td>
</tr>
</tbody>
</table>
Evaluation Of Plan Robustness In Particle RT: Quantitate Dose Uncertainty Incl. RBE
In Room Imaging
For Particle RT

Carbon Ion Nozzle with Airo -CT

week 1

week 2
Dose Tracking In Prostate Cancer
## Clinical trials

<table>
<thead>
<tr>
<th>Category</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chordoma &amp; Sarkoma</strong></td>
<td>Chordoma of the scull base: H1 vs. C12 recruiting</td>
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<tr>
<td></td>
<td>ISAC (C12/H1 for sacral chordoma) recruiting</td>
</tr>
<tr>
<td></td>
<td>SB chondrosarcomas: H1 vs. C12 recruiting</td>
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<tr>
<td></td>
<td>OSCAR (H1 + C12 boost; inoperable osteosarkoma) recruiting</td>
</tr>
<tr>
<td><strong>Head &amp; Neck</strong></td>
<td>COSMIC (C12 boost RT; salivary glands ACC) published</td>
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<tr>
<td></td>
<td>ACCO (C12 only; salivary glands ACC) approved</td>
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<td>ACCEPT (C12 boost RT + Erbitux for ACC) recruiting</td>
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<td>TPF-C HIT (C12 boost RT; head&amp;neck) closed</td>
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<td>IMRT HIT-SNT (C12 boost RT; sinu-nasal cancer) recruiting</td>
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<tr>
<td><strong>Brain</strong></td>
<td>CLEOPATRA (H1 vs. C12 boost RT; prim. glioblastoma) f/u phase</td>
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<tr>
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<td>CINDERELLA (C12 recurrent glioblastoma) f/u phase</td>
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<td>MARCIE (C12 boost RT, meningeomas grade 2) recruiting</td>
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<tr>
<td><strong>Prostate</strong></td>
<td>IPI (C12/H1 for prostate cancer) f/u phase</td>
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<tr>
<td></td>
<td>PROLOG (hypofract. H1 for prostate cancer recurrence) f/u phase</td>
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<tr>
<td></td>
<td>PAROS (hypofract H1 vs IMRT prostate-CA adjuvant/salvage)</td>
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<tr>
<td></td>
<td>KOLOG (hypofract. C12 for Prostate cancer recurrence) f/u phase</td>
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<tr>
<td><strong>GI</strong></td>
<td>PROMETHEUS (C12 for HCC) recruiting</td>
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<tr>
<td></td>
<td>PANDORA (C12 for recurrent rectal carcinoma) recruiting</td>
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<tr>
<td><strong>Lung</strong></td>
<td>INKA (neoadj. C12 for inop. sulcus superior tumors NSCLC) recruiting</td>
</tr>
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</table>
Skull Base Chondrosarcoma
local control

- C-12 treatment 1997-2007 (GSI)
- act. 10 yrs LC 88 %
- act. 10 yrs LC (< 45 J): 98%

Uhl et al. Cancer, 2014
Chondrosarcoma

Symptoms at Diagnosis: Double vision

2005  2007  2011  2015

Before C-12 RT  Follow-up
Petroclival Chondrosarcoma

Reduction of neurological symptoms

18 year old patient

before RT

6 weeks after RT

12 / 27 patients show reduced symptoms
Skull Base Chordomas treated at GSI

*Uhl M et al., Cancer 2014; 120(10): 1579–1585.*

**Local control**

- 3-, 5-, 10-year: 82%, 72%, 54%
- PaR: (123) (80) (34) (17)

**Overall survival**

- 3-, 5-, 10-year: 95%, 85%, 75%
- PaR: (140) (95) (45) (22)
HIT Trial for Skull Base Chondrosarcomas

SB Chondrosarcoma
n = 154

63 Gy(RBE) C12 (21 Fx)
70 Gy(RBE) Protons (35 Fx)

Start: 2010
Recruitment 6/18: 77
High Control Rates of Proton- and Carbon-Ion-Beam Treatment With Intensity-Modulated Active Raster Scanning in 101 Patients With Skull Base Chondrosarcoma at the Heidelberg Ion Beam Therapy Center

An age < 46 years was associated with a trend for a better outcome

Carbon ion group: Sub group analysis of age

An age < 46 years was associated with a trend for a better outcome

Carbon ion group: Sub group analysis of CTV

$P = .149$

$P = .601$

Figure 3. Subgroup analysis of age in the carbon-ion group.

Figure 4. Subgroup analysis of the clinical target volume in the carbon-ion group.
Skull Base Chordomas treated at GSI

Uhl M et al., Cancer 2014; 120(10): 1579–1585.

Prognostic factors

- Boost Volume
  - <= 75 ml: p=0.002

- age
  - <= 48 y: p=0.033
  - <= 30 y: p=0.009
HIT Trial for Skull Base Chordomas
prospective, randomized phase III trial

Hypothesis: 10% increase in LPFS by using carbon ions

Start: 2010
Recruitment 6/18: 105

SB Chordoma
n = 344

60-66 GyE C12 (20-22 Fx)

72-76 GyE Protons (36-38 Fx)

Nikoghosyan et al. BMC Cancer 2010. 10, 607
ISAC- Trial
Ion irradiation of SACrococcygeal Chordoma
Hypofractionated Protons- vs. C-12-RT

Pilot trial
Prospective randomized phase II trial
2-armed
100 Patients (50 per Arm)
Stratification CTV <1000ml>

Primary endpoint: Feasibility/Toxicity (Incidence >=Grad 3-5)
secondary endpoint: OS, LPFS, QoL

randomization

Arm A (proton therapy):
• Total dose to the PTV: 64 GyE a 4 GyE SD.
  • BED: 96Gy

Arm B (carbon ion therapy):
• Total dose to the PTV: 64 GyE a 4 GyE SD.
  BED: 96Gy

16 x 4 GyE =
64 GyE C12
≈96GyE (BED)
COSMIC Trial

Combined therapy of malignant salivary gland tumors with IMRT and carbon ions

- Phase II feasibility study
- 53 Patients
- median follow-up 42 months;

Patient characteristics
- microscopically incomplete resections (R1, n = 20),
- gross residual disease (R2, n = 17),
- inoperable disease (n = 16)
- 89% ACC,
- 57% had T4 tumors.

Most common primary sites
- paranasal sinus (34%),
- submandibular gland, palate
Carbon ion (C-12) Boost and IMRT is highly effective in Salivary gland tumors

- No dose limiting acute toxicity
- Late Toxicity > CTC grade 2 : < 5%

Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44
ACC Initial treatment response and acute toxicity

Initial

Complete remission after 6 Months

25 x 2 Gy IMRT + 8x 3 GyE C-12

Acute toxicity remains low (< grade 4) in IMRT with carbon ion boost; also in R1-resected patients and patients undergoing re-irradiation. R2-resected patients showed high rates of treatment response.
COSMIC- trial : long term results

Better local tumor control by C-12 irradiation leads to better long-term survival of locally advanced adenoid cystic carcinoma

(p=0.033)

Jensen et al. 2015, Cancer

Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

Alexandra D. Jensen MD, MSc, Anna V. Nikoghosyan MD, Melanie Poulakis DDS, Angelika Höss MSc, Thomas Haberer PhD, Oliver Jäkel PhD, Marc W Münter MD, Daniela Schulz-Ertner MD, Peter E. Huber MD, PhD, Jürgen Debus MD, PhD

First published: 4 June 2015

DOI: 10.1002/cncr.29443

Cited by: 0 articles

numbers at risk:

<table>
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<th>C12:</th>
<th>photons:</th>
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</table>
COSMIC- trial: long term results

Better local tumor control by C-12 irradiation leads to better long-term survival of locally advanced adenoid cystic carcinoma

(p=0.015)

Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

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First published: 4 June 2015  Full publication history
DOI: 10.1002/cncr.29443  View/save citation
Cited by: 0 articles  Check for new citations

Jensen et al. 2015, Cancer
Late toxicity after carbon ion RT: dose response for contrast enhancement in the temporal lobes

\(n = 59, \text{2002-2003, Follow-up 2,5 years}\)

\[TD5 (D_{\text{max}}, V-1\text{cm}^3) = 68.8 \pm 3.3 \text{ GyE}\]

\(2/59\) clinical symptoms

# ACC Study Comparison

## Locoregional Control

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>3 yrs</th>
<th>4 yrs</th>
<th>5 yrs</th>
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<tr>
<td>IMRT</td>
<td>Jensen, 2015</td>
<td>56 %</td>
<td>43 %</td>
<td>40 %</td>
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<tr>
<td>IMRT + C12</td>
<td>Jensen, 2015</td>
<td>84 %</td>
<td>70 %</td>
<td>60 %</td>
</tr>
<tr>
<td>C12</td>
<td>Ikawa, 2017</td>
<td>89 %</td>
<td>82 %</td>
<td>69 %</td>
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<tr>
<td>C12</td>
<td>Mizoe, 2004</td>
<td>75 %</td>
<td>65 %</td>
<td>60 %</td>
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</table>
**ACC trial**

**Adenoid Cystic carcinoma Carbon Only**

- Prospective, randomized two armed Phase II trial
- 175 patients in 4 years
- ACC inoperable and/or R1/R2 resected and/or (Pn+) and/or pT3/pT4

### Experimental arm: Carbon only

<table>
<thead>
<tr>
<th>CTV_GP</th>
<th>CTV_BP</th>
<th>CTV_GP</th>
<th>CTV_BP</th>
</tr>
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<tbody>
<tr>
<td>3 Gy(RBE)</td>
<td>3 Gy(RBE)</td>
<td>2 Gy</td>
<td>3 Gy(RBE)</td>
</tr>
<tr>
<td>51 Gy(RBE)</td>
<td>15 Gy(RBE)</td>
<td>50 Gy</td>
<td>24 Gy (RBE)</td>
</tr>
<tr>
<td>61 Gy</td>
<td>18 Gy</td>
<td>50 Gy</td>
<td>29 Gy</td>
</tr>
</tbody>
</table>

- **BED2Gy**
  - 61 Gy
  - 18 Gy

- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

- **Einzeldosis**
  - 3 Gy(RBE)
  - 3 Gy(RBE)

- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

- **Einzeldosis**
  - 3 Gy(RBE)
  - 3 Gy(RBE)

- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

- **BED2Gy**
  - 61 Gy
  - 18 Gy

- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

### Control arm: bimodal RT (IMRT + Carbon)

<table>
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</thead>
<tbody>
<tr>
<td>2 Gy</td>
<td>3 Gy(RBE)</td>
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<td>50 Gy</td>
<td>24 Gy (RBE)</td>
</tr>
<tr>
<td>50 Gy</td>
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</table>

- **Gesamtdosis**
  - 51 Gy(RBE)
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- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

### Dosage

- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

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  - 51 Gy(RBE)
  - 15 Gy(RBE)

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  - 51 Gy(RBE)
  - 15 Gy(RBE)

- **Gesamtdosis**
  - 51 Gy(RBE)
  - 15 Gy(RBE)

### Dosing Schedule

- **22 FX in 4 weeks**
  - 5-6 FX per week

- **33 FX in ca. 6 weeks**
ACCO trial

Adenoid Cystic carcinoma Carbon Only

- Prospective, randomised phase II trial
- 175 Patienten in 4 years
- ACC inoperabel and/or R1/R2 resected and/or (Pn+) and/or
  - pT3/pT4

<table>
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<tr>
<th></th>
<th>carbon ions only</th>
<th>photons + carbon ions</th>
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<td>CTV_GP</td>
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<td>single dose</td>
<td>3 Gy(RBE)</td>
<td>3 Gy(RBE)</td>
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<tr>
<td>total dose</td>
<td>51 Gy(RBE)</td>
<td>15 Gy(RBE)</td>
</tr>
<tr>
<td>BED2Gy*</td>
<td>61 Gy</td>
<td>18 Gy</td>
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<tr>
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<th>CTV_GP</th>
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<td>single dose</td>
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<td>50 Gy</td>
<td>29 Gy</td>
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</tbody>
</table>

- Primary endpoint: loco-regional control (5 years)
Accelerated Hypofractionated Active Raster-Scanned Carbon Ion Radiotherapy (CIRT) for Laryngeal Malignancies: Feasibility and Safety

Sati Akbaba¹,²,³, Kristin Lang¹,²,³, Thomas Held¹,²,³, Olcay Cem Bulut⁴, Matthias Mattke¹,²,³, Matthias Uhl¹,²,³, Alexandra Jensen⁵, Peter Plinkert⁴, Stefan Rieken¹,²,³, Klaus Herfarth¹,²,³, Juergen Debus¹,²,³ and Sebastian Aebig¹,²,³,⁎
ACC, T4, definitive carbon ion RT 2016
ACC, T4, definitive carbon ion RT 2016
Chondrosarcoma (G1) of the larynx: organ preserving radiotherapy with 60 GyE C-12
Individualized radiation dose prescription in HNSCC based on F-MISO-PET Hypoxia-Imaging

**INDIRA-MISO Trial**

**Stage III or IV HNSCC**
- **Radio-chemotherapy feasible?**
  - **Observational arm**
    - **non HPV driven**
    - **HPV driven**
  - **Planning-CT:**
  - **Baseline F-MISO**
  - **treatment start with 10 fractions RCTx**
  - **F-MISO scan: residual hypoxia?**
    - yes
    - no

- **yes / no**
  - **dose escalation feasible**
    - yes
    - no

- **RCTx to 77 Gy**
- **RCTx to 70 Gy**
- **Carbon Ion Boost**
- **RCTx to 77 Gy**

**Secondary Aims of the Trial:**
- LC, OS and tox of dose-escalation compared to standard therapy
- QoL during and after treatment
- evaluate FMISO uptake kinetics before treatment and after ten fractions of treatment in comparison to outcome
- investigate the association of pre-therapeutic FMISO-uptake and FMISO-uptake during radiochemotherapy to site of subsequent failure
- compare the uptake characteristics of primary tumors and recurrent tumors.
- assess of different radiation qualities (photons, protons, carbon) in the treatment of hypoxic tumors.
Neo-Adjuvant Trials

PROMETHEUS Trial

Inoperable Liver Cancer

- Monocentric
- Dose escalation trial
- 4 x 10-14 Gy (RBE(NIRS)) C12
- 4 x 7.1-10.5 Gy (RBI(GSI)) C12
- Safety & Response
- Start 5/11

Combs et al., BMC Cancer 2011
Mapping of RBE-Weighted Doses Between HIMAC— and LEM—Based Treatment Planning Systems for Carbon Ion Therapy

Olaf Steinsträter, Ph.D.,* Rebecca Grün, M.Sc.,*†‡ Uwe Scholz, M.Sc.,*§ Thomas Friedrich, Ph.D.,* Marco Durante, Ph.D.,*§ and Michael Scholz, Ph.D.*

Table 1 Comparison of median and EUD calculated for LEM estimated RBE-weighted dose distributions in dependence of prescribed HIMAC RBE-weighted doses, $d_{\text{HIMAC}}$, for 60-mm SOBPs (depth according to Fig. 1b) and both RBE tables (LEM I/LEM IV)

<table>
<thead>
<tr>
<th>Prescribed RBE-weighted dose HIMAC, Gy (RBE)</th>
<th>RBE-weighted dose LEM, Gy (RBE)</th>
<th>LEM IV</th>
<th>LEM I</th>
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<tr>
<td></td>
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</table>

Abbreviations: EUD = equivalent uniform dose; HIMAC = Heavy-Ion Medical Accelerator facility, National Institute of Radiological Science, Japan; LEM = Local Effect Model (versions I and IV); RBE = Relative Biological Effectiveness; SOBP = spread-out Bragg peak.
Neo-Adjuvant Trials

**PROMETHEUS Trial**

Preliminary Results

- **21 Patients**
  - **Recurrences**
    - 1/3 liver progression
    - 2 patients with distant metastases
  - **Toxicity**
    - Few low grade toxicity
    - NW (fatigue, diarrhea)

*median f/u = 16 months*  
*after 44 months*
Neo-Adjuvant Trials: INKA trial

- Sulcus superior tumor
- trimodal treatment
- RT: 13 x 3 GyE C12
- Biolog. dose using GTV $\alpha/\beta=10$Gy

\[ C = \text{Cisplatin } 80 \text{ mg/m}^2 \text{ KOF} \]
\[ V = \text{Vinorelbine } 25 \text{ mg/m}^2 \text{ KOF} \]
\[ Vr = \text{Vinorelbine (reduziert) } 15 \text{ mg/m}^2 \text{ KOF} \]
Neo-Adjuvant Trials

- Sulcus superior tumor
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INKA trial

C = Cisplatin 80 mg/m2 KOF
V = Vinorelbine 25 mg/m2 KOF
Vr = Vinorelbine (reduziert) 15 mg/m2 KOF

forward calculation all GTV $\alpha/\beta=2$Gy
Clinical trial: OSCAR

OSTeosarcoma – CArbon Ion Radiotherapy: Phase I/II therapy trial

Safety and efficacy of heavy ion radiotherapy in patients with inoperable osteosarcoma

Endpoints: LC, DFS, PFS, OS and the role of FDG-PET in response monitoring

<table>
<thead>
<tr>
<th>Neoadjuvant Chemotherapy according to standard protocols (e.g. EURAMOS1)</th>
<th>Proton / Carbon Ion-radiotherapy (HIT) (54 GyE + 18 GyE C-12),</th>
<th>Adjuvant Chemotherapy (e.g. EURAMOS1, HR1 (MAP))</th>
</tr>
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<tbody>
<tr>
<td>Week 1 to 10</td>
<td>Week 11 to 17</td>
<td>Week 18 to 36</td>
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</table>

FDG-PET, optional

Inclusion of patients at least 3 weeks before HIT

FDG-PET, CT/MRT, Tc99 bone scintigram, Blood tests
Week 7-10

Required Diagnostics before HIT:

Required Diagnostics after HIT:

✓ FDG-PET Week 17 and 36
✓ CT/MRI and Tc99 bone scintigram Week 23 and 36
✓ Blood tests week 17, 23, 36

Follow-up Diagnostics 6, 12, 24, 36, 48 and 60 months after HIT
Clinical trial: OSCAR

OSteosarcoma – CArbon Ion Radiotherapy: Phase I/II therapy trial
Safety and efficacy of heavy ion radiotherapy in patients with inoperable osteosarcoma
Endpoints: LC, DFS, PFS, OS and the role of FDG-PET in response monitoring

Male patient, 28 years

FDG PET prior to RT

Basic proton plan

Follow up

FDG PET, 8 months after radiotherapy complete remission

MRI prior to RT

carbon ion boost plan

MRI 7 years after radiotherapy (2019)
HIT operates 24/7

08:00 - 22:00 h Patient treatment
22:00 – 08:00 h Research and QA

Staff
A team of more than 70 experts comprising:
• Medical doctors
• Nurses,
• Medical radiology assistants
• Physicists
• Engineers
• Technicians
High tumor dose, normal tissue sparing

Effective for radio-resistant tumors

Effective against hypoxic tumor cells

Increased lethality in the target because cells in radio-resistant (S) phase are sensitized

Fractionation spares normal tissue more than tumor

Reduced angiogenesis and metastasis
Carbon irradiation overcomes glioma radioresistance by eradicating stem cells and forming an antiangiogenic and immunopermissive niche

NCT Biological Dose Prescription (BioDose) P

Chiblak et al. JCI Insight. 2019

Beneficial effect of CIR in syngeneic, orthotopic murine GL261 glioma model

PDX GliomaStemCell model NCH644
Highlight project: Carbon irradiation overcomes glioma radioresistance by eradicating stem cells and forming an antiangiogenic and immunopermissive niche

NCT Biological Dose Prescription (BioDose)

S. Chiblak et al. JCI Insight. 2019
Carbon irradiation (CIR) is superior to photon irradiation (PIR) in patients with *recurrent* high-grade glioma

**In DKT-K-KOG multicenter cohort** *(n=565)* rHGG patients (grade III: 63, IV: 479) underwent RiP between 1997-2016 with a median dose of 36 Gy in 14 fractions

Dashed line: loglogistic parameteric survival regression fit. Solid lines: Kaplan-Meier curves.

**197 patients** with rHGG (grade III: 71, IV: 126) received RiCi between Nov 2009 and Feb 2018 at HIT with a median dose of 42GyRBE in 14 fractions

Median follow up: **34.2 months** for RiCi

**7.1 months** for RiP (DKTK)
Integrating Physical Dose and RBE - Uncertainty by Modelling Spatial- and Time-Resolved Quantitative Imaging Data

- Enables comparative analysis of different models for estimation of physical and biological effective dose in 3D within minutes and in excellent agreement with Monte Carlo simulation.
Next step: clinical helium-beams at HIT

3rd Ion source was optimized for $^4$Helium
Rationale for 4He-beam therapy: scattering

---

Precision and penetration depth

Beam

Protons
175 MeV

Helium ions
175 MeV/u

Carbon ions
330 MeV/u
Pregnant patient at HIT: Proton RT scanning beam
Measured doses (belly)

- Patient was irradiated from 4 directions
- Doses accumulated to total dose show significant differences
- Dose optimization can only be done on a highly individual basis
Risk of subsequent primary cancers after carbon ion radiotherapy, photon radiotherapy, or surgery for localised prostate cancer: a propensity score-weighted, retrospective, cohort study

Osama Mohamed, Takahiro Tabuchi, Yuki Nitta, Akihiro Nemoto, Akira Sato, Goro Kasuya, Hirokazu Makishima, Hak Choy, Shigeru Yamada, Toshitaka Morishima, Hiroshi Tsuji, Isao Miyashiro*, Tadashi Kamada*

Mohamed et al. Lancet Oncol. 2019

Carbon ion radiotherapy vs photon radiotherapy: HR 0.71 (95% CI 0.58–0.88); p=0.0019
Photon radiotherapy vs surgery: HR 1.18 (95% CI 1.02–1.37); p=0.024
Carbon ion radiotherapy vs surgery: HR 0.86 (95% CI 0.72–1.04); p=0.11

Cumulative incidence (%)
Conclusion

• Phase II data with C-12 warrant further investigations
• Since 2009 over 18 clinical studies on ion therapy started
• Challenge: state of the art IGRT and ART compared to photons
• Clinical application of He ions in the near future
• Research platforms are now available, providing p, He, C, and O ions in experimental beam lines
• The mechanism of high LET is beyond cell kill the modulation of the microenvironment
• Various research projects ranging from physics to biology: open to researchers from different fields
The ENLIGHT network was established in 2002 to coordinate European efforts in hadrontherapy, and today has more than 700 participants from 25 European countries. A major achievement of ENLIGHT has been the blending of traditionally separate communities so that clinicians, physicists, biologists and engineers with experience and interest in particle therapy are working together.
Particle Therapy Co-Operative Group
An organisation for those interested in proton, light ion and heavy charged particle radiotherapy

58TH ANNUAL CONFERENCE OF THE PARTICLE THERAPY CO-OPERATIVE GROUP

The premier scientific meeting in the field of particle therapy showcasing cutting edge science, NHS oncology and clinical practice in action.

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Thank You !!!
HIRO
Heidelberg Institute for Radiation Oncology

National Center for Radiation Research in Oncology Heidelberg

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Heidelberg Ion-Beam Therapy Center (HIT)
Medical Faculty Heidelberg