Carbon Ion Radiotherapy: Clinical Concepts and Experience

Jürgen Debus
## Clinical Use Of Carbon Ions

*after pionierung work of Berkeley*

<table>
<thead>
<tr>
<th>Institution</th>
<th>Country</th>
<th>Start of treatment</th>
<th>Patients treated</th>
<th>Date of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIRS-HIMAC, Chiba</td>
<td>Japan</td>
<td>1994</td>
<td>7331</td>
<td>01/2013</td>
</tr>
<tr>
<td>HIBMC, Hyogo</td>
<td>Japan</td>
<td>2002</td>
<td>788</td>
<td>12/2011</td>
</tr>
<tr>
<td>GHMC, Gunma</td>
<td>Japan</td>
<td>2010</td>
<td>537</td>
<td>12/2012</td>
</tr>
<tr>
<td>GSI, Darmstadt HIT, Heidelberg</td>
<td>Germany</td>
<td>1997 / 2009</td>
<td>1560</td>
<td>06/2013</td>
</tr>
<tr>
<td>CNAO, Pavia</td>
<td>Italy</td>
<td>2012</td>
<td>22</td>
<td>03/2013</td>
</tr>
<tr>
<td>IMP-CAS/Lanzhou</td>
<td>China</td>
<td>2006</td>
<td>194</td>
<td>12/2012</td>
</tr>
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</table>

**centers to go clinical**: Shang-hai, Marburg, Vienna
**HIMAC (Heavy Ion Medical Accelerator in Chiba)**

**Room for Biological Experiments**

**Ion Source**

**Linear Accelerators**

**Main Accelerator (Synchrotron)**

**Beam Lines for Physics Research**

**Treatment Rooms**

**Specification of HIMAC**

- **Ion**: He ~ Ar
- **Max energy**: ~800 Mev/n
- **Treatment room**: (3) fixed vertical : A, fixed horizontal : C, V & H : C
- **The accelerated energy**
  - Vertical beam (290 MeV/u, 350 MeV/u)
  - Horizontal beam (290 MeV/u, 400 MeV/u)
- **The range of C-ion beam in water**
  - 290-MeV/u : 15 cm
  - 350-MeV/u : 20 cm
  - 400-MeV/u : 25 cm
- **Maximum field size**: 15 cm by 15 cm

New Compact Accelerator for C-ion RT at Gunma U.

Realized 1/3 cost and size of HIMAC
To produce uniform irradiation fields, a passive beam delivery system was employed. We use a pair of wobbler magnets and a scatterer. The range shifter is used for adjusting the residual range of carbon ions in the patient. The ridge filter is used to spread out the Bragg peak in the depth-dose distribution of carbon ions.

Kanai et al. IJROBP1999, 44:201-210
Technique at HIMAC

- Immobilization
- Beam delivery
- Targeting
- Treatment planning
- Gating, patch, and spacer

- Fixed beam line
- Passive beam and raster scanning
  - Hitting a moving target
- SOBP; Dose description
Start Of Carbon Ion Radiotherapy in Heidelberg: Pilot Project At GSI – Medicine in A Physics Lab
HIT Accelerator System

- Ion sources
- Injector
- Synchrotron
- HEBT+Gantry
- Medical Areas

Ions:
- clinical: H, C-12
- Exp: He, O-16

1. Ion gantry

patient treatment since 2009
Design for HIT

isocentric barrel-type

world-wide first ion gantry

2D beam scanning upstream to final bending, almost parallel due to edge focussing

± 180° rotation
3° / second

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

MT Mechatronics
MT Aerospace
Optimized Beam Scanning:

Typically 30-50 energy slices, in total 20000-50000 raster points

treatment console: online monitor
Rationale For „Bragg-peak“ Radiotherapy

„Bragg“-peak

Depth dose profiles

- photons 21 MeV
- $^{12}$C 270 MeV/u
- protons 148 MeV/u

plateau

Lateral Scattering

- Proton
- Helium
- Carbon

initial FWHM = 4 mm
Charged Particle Radiotherapy: Influence of Scattering in Tissue

Protons: 220 MeV

20 cm

50 mm
Rasterscanning:
Influence of Scattering in Tissue

Carbon Ion
380 MeV/u
Beam Scanning - IMPT

2D-example for fluence (intensity) modulation

original photograph  fluence map  irradiated radiographic film rasterscan @ HIT

Courtesy Jakob Naumann (HIT), Martin Bräuer (SIEMENS)
Carbon Radiotherapy In A Pregnant Patient: low scattered dose to the fetus

<table>
<thead>
<tr>
<th></th>
<th>photon dose (µSv/fraction)</th>
<th>neutron dose (µSv/fraction)</th>
<th>Number of fractions</th>
<th>Total dose (µSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal field</td>
<td>3.0 *</td>
<td>1.4</td>
<td>15</td>
<td>66</td>
</tr>
<tr>
<td>Boost field</td>
<td>2.2 **</td>
<td>1.0</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Total treatment</td>
<td></td>
<td></td>
<td>20</td>
<td>82</td>
</tr>
</tbody>
</table>

IMRT with 6 MeV photons: $4 \times 10^4$ µSv !

Muenter MW, Fertil Steril 2010
Carbon Ion Radiotherapy for Pediatric Patients and Young Adults Treated for Tumors of the Skull Base (n=17)

- Local control 94% (1 in-field recurrence chordoma, 60 months after C-12)
  exzellent cosmetic outcome
  1 pt with hypopituitarism

Combs SE et al., Cancer, 2009
Phase I/II Study Of Carbon Ion Therapy In Inoperable Osteosarcoma

Neoadjuvant Chemotherapy (e.g. EURAMOS1) week 1 to 10

Proton / Carbon Ion-radiotherapy (HIT) (54 GyE +18 GyE), week 11 bis 17

Adjuvant Chemotherapy (e.g. EURAMOS1, HR1 (MAP)) week 17 bis 34

FDG-PET, optional

Inclusion at least 3 weeks before HIT

Required Diagnostics HIT:

- FDG-PET
- CT/MRT
- Tc99 - scintigramm

Week 7-10

Required Diagnostics after HIT:

- FDG-PET Week 17
- CT/MRI and Tc99 bone scintigramm Week 19

Follow-up Diagnostics
6, 12, 24, 36, 48 and 60 months after HIT
High tumor dose, normal tissue sparing
Effective for radioresistant tumors
Effective against hypoxic tumor cells
Increased lethality in the target because cells in radioresistant (S) phase are sensitized
Fractionation spares normal tissue more than tumor
Reduced angiogenesis and metastatization

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<th>Potential advantages of high LET RT</th>
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<td>Reduced angiogenesis and metastatization</td>
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Increased RBE For High LET Beams:

\[ X-ray \]
\[ \alpha = 0.178 \text{ Gy}^{-1} \]
\[ \beta = 0.040 \text{ Gy}^{-2} \]
\[ \alpha / \beta = 4.45 \text{ Gy} \]

Carbon
\[ \alpha = 1.89 \text{ Gy}^{-1} \]
\[ \text{RBE}_{10} = 4.66 \]

Combs, Int J Rad Oncol Bio Phys, 2009
Which tumors might be better treated by ions?

Tumors, which are refractory to low LET irradiation

Radioresistance

Genetic alterations
- upregulated oncogenes
- mutated tumor suppressor genes
- deregulated apoptosis

Intratumoral micromilieu
- Deprivation of oxygen
- Up-regulated defense system
- High angiogenic potential

Proliferation status
- High content of quiescent cell clones
- Slow proliferation activity
Carbon Ion Radiotherapy At GSI

N=440, 1998-2008

- Chordoma
- Chondrosarcoma
- Adenoidcystic Ca.
- Others, incl. Prostate
- Re-irradiation
Patient Distribution Enrolled in Carbon Ion Therapy at NIRS
(Treatment: June 1994～July 2011)

Total
6,619
Clinical Practice: 3,509

Prostate
1382 (20.9%)
CP: 1057

Bone & Soft tissue
901 (13.6%)
CP: 666

Head & Neck
763 (11.5%)
CP: 440

Lung
695 (10.5%)
CP: 118

Liver
443 (6.7%)
CP: 213

P/O rectum
341 (5.2%)
CP: 274

Scanning
8 (0.1%)
CP: 16

Lacrimal
23 (0.3%)
CP: 52

Esophagus
6 (1.0%)
CP: 62

PA L/N
69 (1.0%)
CP: 62

Skull Base
81 (1.2%)
CP: 52

CNS
105 (1.6%)

Eye
114 (1.7%)
CP: 72

GYN
170 (2.6%)
CP: 1

Pancreas
175 (2.6%)
CP: 1

Miscellaneous
1208 (18.3%)
CP: 538

Re-irradiation
75 (1.1%)
CP: 16

Miscellaneous
1208 (18.3%)
CP: 538

Total
6,619
Clinical Practice: 3,509
before RT
dose 60 GyE

Follow-up
3 months

chordoma
Chordoma: response after carbon ion RT

Prior to C12: rt. hemianopsia 60 GyE

Good partial remission 6 months
Carbon ion RT in skull base chordomas

- 5y-OS 88.5%
- 5y-LC 70%
- LC 75 Gy E vs >75 Gy E

Schulz-Ertner et al. IJROBP 2007
Local Recurrence – Free Survival
Non-Chondroid Chordoma By Sex

Male
Female

Log-Rank p = 0.0001

0 2 4 6 8 10
Years

Skull Base

Courtesy John Munzenrider, 1996
Carbon Ion RT: follow-up in low grade chondrosarcoma: slow response

RT in 2005  2007  2013
81 patients treated with carbon ion
Median follow-up was 91 months (range, 3-153 months)
8 relapses (still alive)
9 pts. died in the fu-period (cause of dead: „other“)

91.5% (5y) 88.8% (10y)

5-year-OS: 96.1% neue Daten

Unpublished data, in preparation
Assessment of early toxicity and response in patients treated with proton and carbon ion therapy at the Heidelberg Ion Therapy Center (HIT) using the rasterscanning technique

Stefan Rieken MD¹, Daniel Habermehl MD¹, Anna Nikoghosyan MD¹, Alexandra Jensen MD¹, Thomas Haberer Ph D², Oliver Jäkel Ph D²,³, Marc W. Münter MD¹, Thomas Welzel MD¹, Jürgen Debus MD PhD¹ and Stephanie E. Combs MDF¹

Conclusions

Side effects related to particle treatment were rare and overall tolerability of the treatment could be shown. Initial response is promising. The data confirms safe delivery of carbon ions and protons at the newly opened Heidelberg facility.

Int J Rad Oncol Bio Phys (2011) 81:693

Clinical trials: HIT1,2, CLEOPATRA, MARCIE, MIRANDA, CINDERELLA, PROMETHEUS, …
Hypothesis: Dose Response Relationship Radiotherapy of Skull Base Chordomas

2 Phase III Randomized Studies @ HIT:

Skull Base Chordoma (HIT1-study):
comparison of proton and carbon ion radiotherapy:
21 x 3 GyE carbon vs 36 x 2 GyE proton

Skull Base Chondrocarcoma (HIT2-study):
comparison of proton and carbon ion radiotherapy
20 x 3 GyE carbon vs 35 x 2 GyE proton

Nikoghosian et al, BMC Cancer 2010, 10:606

[Schulz-Ertner, IJROBP 2007]
Chordoma of the sacrum

Case 1
6 years

Case 2
5 years

Case 3
6 years

Kamada, Estro teaching course 2011
Sacral Chordomas

ISAC trial

16 x 4 GyE C12 vs. 16 x 4 GyE H1
Sacral Chordoma

16 x 4 GyE C12
COSMIC Study: Response

Treatment planning

FU @ 6 weeks after C12
FSRT / IMRT vs. FSRT / IMRT + C12
locally advanced adenoidcystic carcinoma

2 Phase II Studies @ HIT:

To increase local control:
Increase of Boost dose to 24 Gy E – COSMIC-Study
Jensen et al., BMC Cancer 2010

To tackle local control & distant metastases:
Combination with Cetuximab: ACCEPT Study

- no dose limiting acute toxicity
- late toxicity > CTC grade 2 < 5%

Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44
Phase II (9602) for Malignant Head-and-Neck Tumors
Local Control of ACC (n=129) according to Carbon ion Dose

Kamada, Estro teaching course 2011
Combined Chemotherapy and C-ion RT for MMM

**Local Control**
- C-ions + DAV (n=85) 5-year; 81%
- C-ions alone (n=102) 5-year; 76%

**Overall Survival**
- C-ions + DAV (n=85) 3-year; 67%, 5-year; 62%
- C-ions alone (n=102) 3-year; 53%, 5-year; 37%

Local Control and Overall Survival of Mucosal Malignant Melanomas

Kamada, Estro teaching course 2011
Results of carbon ion radiotherapy for skin carcinomas in 45 patients


*Department of Heavy Ion Radiation Medicine, Institute of Modern Physics, Chinese Academy of Sciences, Lanzhou 730000, China

Fig 2. Actuarial local control in 45 skin carcinoma patients with 16 squamous cell carcinoma (A), 12 basal cell carcinoma (B), seven malignant melanoma (C) and 10 Bowen and Paget diseases (D), treated with carbon ion radiotherapy (Kaplan–Meier curve).
Late toxicity after carbon ion RT:
dose response for contrast enhancement in the temporal lobes

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

TD5 (Dmax,V-1cm3)  68.8 ± 3.3 GyE
2/59 clinical symptoms

Schlampp et al., Int J Radiat Oncol Biol Phys, (2011) 80: 815ff
Therapeutic Window In Soft Tissue Sarcoma

- Local Control
- Major Complication

Kamada et al., ESTRO teaching course 2011
Carbon ion Radiation Therapy – Recurrent Glioblastoma
Randomised Phase I/II Study to Evaluate Carbon Ion Radiotherapy versus Fractionated Stereotactic Radiotherapy in Patients with Recurrent or Progressive Gliomas: The CINDERELLA Trial

- unifocal recurrent glioma post 1 or 2 treatments
- no other re-irradiation performed
- largest diameter of contrast enhancement: 4cm

Arm A: Experimental Arm
- C12
- „Best-Dose“ of Phase I
- 10 x 3Gy E to 16 x 3 Gy E Single Dose

Arm B: Standard Arm
- FSRT
- Combs SE, JCO 2005
- 36 Gy / 2 Gy single dose

Study Coordinator: Combs SE
in cooperation with:
Prof. Dr. Wolfgang Wick, Neuroonkology
Prof. Dr. Andreas Unterberg, Neurosurgery
Dr. L. Edler, Dr. I. Burkholder, dkfz-Biostatistics
Combs SE et al., BMC Cancer 2010
Randomized Phase II study Evaluating a **Carbon Ion Boost applied after Combined Radiochemotherapy with Temozolomide** versus a **Proton Boost after Radiochemotherapy with Temozolomide** in Patients with Primary Glioblastoma

**The CLEOPATRA Trial**

- Glioblastoma at primary Diagnosis
- Makroscopic tumor after biopsy or partial resection
- Indication for radiochemotherapy with temozolomide

**Arm A: Experimental Arm**

- 6 FX C 12 to the macroscopic tumor
- T1-contrast enhancement, FET-PET

**Arm B: Standard Arm**

- 5 FX low-LET up to standard dose of 60 Gy

**Study Coordinator Combs SE**

in Cooperation with

Prof. Dr. Wolfgang Wick, Neurooncology
Prof. Dr. Andreas Unterberg, Neurosurgery
Prof. Dr. Meinhard Kieser, Biostatistics

DFG / Klinische Forschergruppe Schwerionentherapie

Combs SE et al., BMC Cancer 2010
Simulated OS curves for GBM (A) and AA (B): The SIM-Curves represents a hypothetical population treated with C12 and TMZ. The difference to RCHT with TMZ indicates a potential benefit.
Phase I study evaluating the treatment of patients with hepatocellular carcinoma (HCC) with carbon ion radiotherapy: The PROMETHEUS-01 trial

Stephanie E Combs¹, Daniel Habermehl¹, Tom Ganten², Jan Schmidt³, Lutz Edler⁴, Iris Burkholder⁵, Oliver Jäkel⁶, Thomas Haberer⁶, Jürgen Debus¹
Phase I Study evaluating the treatment of patients with advanced hepatocellular carcinoma (HCC) with Carbon Ion Radiotherapy: 
*The Prometheus-01 Trial*

- histologically confirmed or imaging-confirmed HCC
- makroscopic tumor, localized, no metastases
- also potential candidates for liver transplantation (bridging therapy)

**Arm A: Experimental Arm**
- Carbon Ion Radiotherapy
- Dose Escalation
  - 4 x 10 Gy E 40 Gy E
  - Increasing fraction size
  - 4 x 14 Gy E 56 Gy E

**Arm B: Historical Controls**
- TACE, Sorafenib-Systemtherapie, HeiLIVCA

Study Coordinator Combs SE in cooperation with
Prof. Dr. Jan Schmidt, Surgery
Dr. Tom Ganten, Gastroentereology
Dr. L. Edler, Dr. I. Burkholder, dkfz-Biostatistics
DFG Klinische Forschergruppe Schwerionentherapie

Combs SE et al., BMC Cancer 2010
HCC after Carbon Ion RT: Quick Response
Histological Investigation Of Radiation Effects:
- optimization of targeting
- better understanding of biological effects

transplantation 63 days after carbon RT
Quantification Of Radiation Effects:
   Computerized Analysis Of Fibrosis

\[
\text{area of fibrosis:} \quad \frac{38,7994}{(25,5049 + 38,7994)} \times 100 \\
= 60.34\%
\]
Single Fraction Carbon ion therapy for Stage I non small cell lung cancer

Local control rate (5 y) : 79%
Cause-spec. survival rate (5y) : 75%
Overall survival rate (5y) : 64%

Single dose of 36-46 Gy (n=121)

T2N0M0 Sq.CC  71 F

NO Grade 3 Reactions in this series

Before
After

Kamada, Estro teaching course 2011
Technical approach to individualized respiratory-gated carbon-ion therapy for mobile organs

Mutsumi Tashiro · Takayoshi Ishii · Jun-ichi Koya · Ryosuke Okada · Yuji Kurosawa · Keisuke Arai · Satoshi Abe · Yoshiaki Ohashi · Hiroyuki Shimada · Ken Yusa · Tatsuaki Kanai · Satoru Yamada · Hidemasa Kawamura · Takeshi Ebara · Tatsuya Ohno · Takashi Nakano

Fig. 2  Relationship among respiratory motion of patient, monitored waveform, and gate signal. Reconstructed 4D CT phases are shown as numbers.
Long-Term Outcome of Proton Therapy and Carbon-Ion Therapy for Large (T2a–T2bN0M0) Non–Small-Cell Lung Cancer

Hiromitsu Iwata, MD, PhD,* †‡ Yusuke Demizu, MD, PhD, † Osamu Fujii, MD, PhD, †
Kazuki Terashima, MD, PhD, † Masayuki Mima, MD, † Yasue Niwa, MD, † Naoki Hashimoto, MD, PhD, †
Takashi Akagi, PhD, § Ryohei Sasaki, MD, PhD, ‖ Yoshio Hishikawa, MD, PhD, † Mitsuyuki Abe, MD, PhD, †
Yuta Shibamoto, MD, PhD, * Masao Murakami, MD, PhD, §† and Nobukazu Fuwa. MD, PhD†

(J Thorac Oncol. 2013;8: 726–735)

...... carbon (n=27)
●●●● proton (n=43)

Nagoya University, Hyogo Ion Beam Center
Hypo-fractionation

**Pros**
- Similar effectiveness
- Convenient for patient
- More economic
- More cytokine or bystander effect?
- Immunologic effect?

**Cons**
- Potentially More toxic
- Less experience
- Less re-oxygenation
- Less repair... etc
- Small therapeutic window
### Why Re-irradiation with Carbon?

- Regrowth of a radio-resistant clone often hypoxic
- “different approach”
- **Tumor bed effect:**
  - damage of tumor vasculatures and stromal elements (fibrosis and necrosis) - poor blood supply and impairment of local defense (immune? ) system
- **Low tolerance of surrounding normal tissue**
Local Control and Survival in Re-irradiation with Carbon Ion Therapy

Overall Survival (n=60)

Local control (n=68)

90%

70%

NIRS Re-irradiation after X-ray with C-ion beam

- 60 cases (68 lesions) treated Dec-'04. to Aug-'10.
- X-ray Dose: 20-72 Gy (median 50 Gy)
- X-ray to C-ion time: 4 - 275 months (median 31 mon.)

Kamada, Estro teaching course 2011
Clinical trials @ HIT

- SB chordomas: H1 vs. C12 recruiting
- SB chondrosarcomas: H1 vs. C12 recruiting
- CLEOPATRA (H1 vs. C12 boost RT; prim. glioblastoma) recruiting
- CINDERELLA (C12 recurrent glioblastoma) recruiting
- MARCIE (C12 boost RT, meningeomas grade 2) recruiting
- COSMIC (C12 boost RT; salivary glands) finished recruiting
- TPF-C HIT (C12 boost RT; head&neck) recruiting
- IMRT HIT-SNT (C12 boost RT; sinu-nasal cancer) recruiting
- ACCEPT (C12 boost RT + Erbitux for ACC) recruiting
- PROMETHEUS (C12 for HCC) recruiting
- OSCAR (H1 + C12 boost; inoperable osteosarkoma) recruiting
- PANDORA (C12 for recurrent rectal carcinoma) recruiting
- IPI (C12/H1 for Prostate cancer) recruiting
- ISAC (C12/H1 for sacral chordoma) recruiting
- PROLOG (hypofract. H1 for Prostate cancer recurrence) recruiting
More than 50 phase I and phase II protocols have been conducted at NIRS since 1994.
Conclusion

- Clinical data obtained in prospective phase I/II and phase II trials support the hypothesis that there is a role of carbon ions in oncology.
- Data of the centers in Europe and Asia are consistent.
- Randomized studies are underway.
- New indications demand for strong translational research.

Areas of research:
- Beam generation,
- Beam application,
- Medical physics,
- Radiation biology,
- Clinical research.

Principles Of Operation:
- Power and endurance,
- Balance and harmony.
Radiation Oncology

University of Heidelberg

research

teach

Treat