Clinical Experience of Carbon-Ion Radiotherapy at NIRS

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Research Center for Charged Particle Therapy
National Institute of Radiological Sciences (NIRS)
Nuclei of the atoms that are accelerated to near the light speed is called charged particle beams.

Mass

<table>
<thead>
<tr>
<th>20Ne</th>
<th>12C</th>
<th>1n</th>
<th>1p</th>
<th>π</th>
<th>e⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>1/7</td>
<td>1/1800</td>
</tr>
</tbody>
</table>

Carbon ion
Carbon nucleus (6+)

Hydrogen
Proton (1+)
Comparison of dose distributions

Carbon-ions

X-rays

Tumor

Relative Dose vs. Depth (cm)
Comparison of dose distributions

Skull base tumour

C-ions (3 fields)

- Red: 96%
- Green: 50%
- Blue: 30%
- Purple: 10% irradiation

X-rays (IMRT: 9 fields)

- 50%
DNA damage caused by different type of radiations

(Courtesy of NIRS: Nature 508, 133–138 (03 April 2014))
Carbon ion (6+)

LET & RBE Values of Carbon Ions
(Carbon ion, 290MeV, SOBP=60mm)

Ionization density increases with depth so that the biological effectiveness increases as beams travel deeper in the body.

Equivalent to fast neutron
# Peak-to-Plateau Ratio of RBE for Jejunal Crypt Cell

<table>
<thead>
<tr>
<th>Ion</th>
<th>$RBE_{sd}$ Peak/Plateau</th>
<th>$RBE_{sd}$ Ratio</th>
<th>$RBE_2$ Peak/Plateau</th>
<th>$RBE_2$ Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton</td>
<td>1.2/1.1</td>
<td>1.1</td>
<td>1.3/1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Helium</td>
<td>1.2/1.1</td>
<td>1.1</td>
<td>1.5/1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Carbon</td>
<td>1.4~1.5/1.3</td>
<td>1.1~1.2</td>
<td>1.6~2.2/1.3</td>
<td>1.2~1.7</td>
</tr>
<tr>
<td>Neon</td>
<td>1.5~1.6/1.4</td>
<td>1.1</td>
<td>2.6~3.0/2.1</td>
<td>1.2~1.4</td>
</tr>
<tr>
<td>Argon</td>
<td>1.8~2.0/2.1</td>
<td>0.9</td>
<td>3.6~3.8/4.3</td>
<td>0.8~0.9</td>
</tr>
</tbody>
</table>

$RBE_{sd}$: single dose, $RBE_2$: fractionated

Progress of C-ion RT at NIRS

• Since 1994, clinical application of carbon ions has been conducted using HIMAC (Heavy Ion Medical Accelerators in Chiba) at NIRS, Japan.

• The HIMAC has been used for cancer therapy during the day time and for fundamental physics/biological research at night.

• So far, around 9,000 patients have been treated based on more than 60 phase I and II protocol studies, focusing on development of therapeutic techniques and dose-fractionations.
Step by step procedures in C-ion Therapy

1. CT scanning
2. Calculation of dose distributions
3. Simulation
4. Treatment room
Annual Patient Accrual for Carbon Ion Therapy at NIRS (Treatment : June 1994 ~ March 2014)

Total Number: 8931

Treatment Period:
April 〜 July
September 〜 February

Clinical study
Clinical Practice (n=5396)

Clinical practice:
NPP accident

Annual Patient Accrual for Carbon Ion Therapy at NIRS (Treatment : June 1994 ~ March 2014)
Patient Distribution Enrolled in Carbon Therapy at NIRS (Treatment: June 1994 ~ March 2014)

Total:
- 8,931 patients
- CP: 5,396

Prostate: 2,009 (22.5%)
- CP: 1,677

Sarcomas: 1,109 (12.4%)
- CP: 845

Head/Neck: 928 (10.4%)
- CP: 603

Lung: 875 (9.8%)
- CP: 286

Liver: 521 (5.8%)
- CP: 283

P/O Rectum: 447 (5.0%)
- CP: 376

Pancreas: 439 (4.9%)
- CP: 196

GYN: 239 (2.7%)
- CP: 19

Miscellaneous: 1,793 (20.1%)
- CP: 843

Esophagus: 78 (0.9%)
- CP: 105

Eye: 147 (1.6%)
- CP: 105

Skull Base: 88 (1.0%)
- CP: 99

PA Lymph: 106 (1.2%)
- CP: 99

CNS: 106 (1.2%)
- CP: 99

Scanning: 11 (0.1%)
- CP: 99

Lacrimal: 28 (0.3%)
- CP: 5

Kidney: 3 (0.03%)
- CP: 2
Tumor Types and Clinical Situations Where Carbon Ion Radiotherapy Offers a Therapeutic Advantage

◆ Effective to photon-resistant tumors
  Sarcoma, Malignant Melanoma, Adenoca, Adenoid cystic ca, etc.

◆ Effective to tumors difficult to operate
  Skull base, Head & neck, Pelvis, etc

◆ Hypofractionated RT is feasible
  Treatment period can be reduced to half or shorter when compared to other RT
  Average: 12.0 fr / 3 wks
  Stage I Lung → single session
  Hepatpma → 2 sessions
  Prostate and many others → 12 sessions
Maxillary Cancer (Adenoid Cystic Cancer)
Target volume=189 ml

Pre-treatment

Post 76 months

57.6 GyE/16 frs.
Malignant Melanoma in the Left Maxillary Sinus (Target volume = 151.9 ml)

64 GyE/16 fx
(4Gy x 16 fx) +
DAV
Osteosarcoma

32 y.o. female
OS of the lt. mandible

Before treatment  CIRT: 70.4 GyE/16Fr.  6 years later
Experiments with carbon ions and fast neutrons demonstrated that increasing their fraction dose tended to lower the RBE for both the tumor and normal tissues, but the RBE for the tumor did not decrease as rapidly as the RBE for the normal tissues.

These results substantiate that the therapeutic ratio increases rather than decreases even though the fraction dose is increased in such tumors as NSCLC and prostate ca, etc..

RBE vs Fraction Size in Carbon Ion Irradiation

LET and RBE of Carbon(Ion) Beams

Dose per Fraction (Gy)

Skin

Tumor

Relative Dose

Depth in Water (cm)

LET: 2.0 4.0 6.0 8.0
RBE: 2.0 2.3 2.5 3.0

Clinical Study on Carbon Beam Therapy for Stage I NSCLC (Peripheral Type)

- **Phase I/III (1994)**: 18 fr / 6 wks, 47 pts
  - Dose-escalation: 59.4 GyE, 68.4 GyE, 72.0, 75.6, 79.2, 86.4, 90.0, 95.4
  - Dose recommended: 90 GyE, 72 GyE

- **Phase I/II (1997)**: 9 fr / 3 wks, 34 pts

- **9802**: Phase II (4/99 - 11/00)
  - 9 fr / 3 wks, 50 pts
  - Total 129 pts

- **0001**: Phase I/II (12/00 - 11/03)
  - 4 fr / 1 wk, 79 pts
  - 72 GyE for stage IA
  - 52.8 GyE for stage IB

- **0201**: Phase I/II (12/03 ~)
  - Single fraction, 218 pts

- **Dose**
  - 28 GyE: 6
  - 30: 27
  - 34: 34
  - 36: 18
  - 38: 14
  - 40: 20
  - 42: 15
  - 44: 44
  - 46: 20
  - 48: 10
  - 50: 10

- **9 fr / 3 wks**: 34 pts

- **4 fr / 1 wk**: 79 pts

- **Single fraction**: 218 pts
Metallic Markers and Respiratory-gated RT

Tumor magnified

Respiration Curve
- Inspiratory
- Expiratory

Pulse beam
Gate Signal
Beam On

Metallic Markers and Respiratory-gated RT
Single Fraction C-ion RT for Stage I NSCLC

71 yr female, cT2N0M0 Squamous cell ca.
40.0GyE/single fraction

18 mo after CIRT

Skin reaction Grade 1
Local control and total dose (n=218) in $\leq 34.0$GyE or $\geq 36.0$GyE

- 5-y Local control rate
  - $\geq 36.0$GyE (n=151): 79.2%
  - $\leq 34.0$GyE (n=67): 54.4%

P=0.0003
Log-rank test
Local Control and Survival in Stage I NCSLC Single fraction C-ion RT with 48-50GyE (n=35)

3-y LC 90.3%

3-y OS 95.0%

Median FU 24.2mo. (7.2~40.5)
67 y/o, M
S4, 70mm
72.0GyE/15frs
5 yr

73 y/o, M
S1, 48mm
66.0GyE/12frs
2.5 yr

72 y/o, M
S1, 46mm
52.8GyE/4frs
1 yr

71 y/o, M
S7, 11.2cm
48.0GyE/2frs
2 yr
Prospective Studies on Hypofractionated C-ion RT In Prostate Cancer at NIRS

20fr. / 5wks

Dose-escalation study
>>> Recommended dose; 63.0GyE (3.15x20)

16fr. / 4wks

Fixed dose; 57.6GyE (3.6x16)
>>> Comparable Tumor Control with Lower Toxicity

12fr. / 3wks

New Phase I/II Trial started in July 2010
Fixed dose; 51.6GyE (4.3x12)

More Hypofractionation

## Late radiation toxicity in prostate cancer

<table>
<thead>
<tr>
<th>Institutes</th>
<th>Treatment</th>
<th>Dose /Fractions</th>
<th>No. Pts</th>
<th>Late $\geq$G2 Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rectal</td>
</tr>
<tr>
<td>Christie H.</td>
<td>IMRT</td>
<td>60Gy/20fr</td>
<td>60</td>
<td>9.5%</td>
</tr>
<tr>
<td>Princess Margaret H.</td>
<td>IMRT</td>
<td>60Gy/20fr</td>
<td>92</td>
<td>6.3%</td>
</tr>
<tr>
<td>Cleveland CF.</td>
<td>IMRT</td>
<td>70Gy/28fr</td>
<td>770</td>
<td>4.4%</td>
</tr>
<tr>
<td>Stanford U.</td>
<td>SRT</td>
<td>36.25Gy/5fr</td>
<td>41</td>
<td>15.0%</td>
</tr>
<tr>
<td>RTOG 9406</td>
<td>3DCRT</td>
<td>68.4-79.2Gy/38-41fr</td>
<td>275</td>
<td>7-16%</td>
</tr>
<tr>
<td></td>
<td>3DCRT</td>
<td>78.0Gy/39fr</td>
<td>118</td>
<td>25-26%</td>
</tr>
<tr>
<td>Loma Linda U.</td>
<td>Proton</td>
<td>75.0GyE/39fr</td>
<td>901</td>
<td>3.5%</td>
</tr>
<tr>
<td>NIRS 7,8</td>
<td>Carbon</td>
<td>57.6GyE/16fr</td>
<td>539</td>
<td>0.6%</td>
</tr>
<tr>
<td>Gunma U.</td>
<td>Carbon</td>
<td>57.6GyE/16fr</td>
<td>459</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

## Comparison of Overall Survival Rate between C-ion RT and RTOG meta analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (Gy/f)</th>
<th>OS* in each Risk Group**</th>
<th>RTOG Meta analysis#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>RT alone</td>
<td>65-70/35</td>
<td>443</td>
<td>338</td>
</tr>
<tr>
<td>RT+ Short Hormone</td>
<td></td>
<td>70</td>
<td>88</td>
</tr>
<tr>
<td>RT+ Long Hormone</td>
<td></td>
<td>114</td>
<td>138</td>
</tr>
<tr>
<td>RTOG Meta analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon (66-63/20, 57.6/16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT+ Short Hormone</td>
<td>121</td>
<td>99%</td>
<td>-</td>
</tr>
<tr>
<td>RT+ Long Hormone</td>
<td>381</td>
<td>100%</td>
<td>321</td>
</tr>
</tbody>
</table>

*Overall Survival Rate**

**Risk Group:**
- Group 2: GS2-6, T3 or GS7, T1-2
- Group 3: GS7, T3 or GS8-10, T1-2
- Group 4: GS8-10, T3

#RTOG: Radiation Therapy Oncology Group

Neutrons are high-LET radiations similar to carbon ions and have a high RBE for slow-growing tumors such as salivary gland tumor, prostate ca, and bone and soft tissue tumors.
• In sacral chordoma that is generally radioresistant, higher dose is needed than other pathological types.
Chordoma of the Sacrum

Case 1. 81 y.o. M.

Case 2. 57 y.o. F.

Case 3. 83 y.o. M.

3.5 years

4 years

4.5 years
The result for carbon ion radiotherapy in sacral chordoma

<table>
<thead>
<tr>
<th>Institutes</th>
<th>No of pts</th>
<th>Treatment</th>
<th>5y-LC (%)</th>
<th>5y-OS (%)</th>
<th>10y-OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH 1)</td>
<td>27</td>
<td>Surgery+proton</td>
<td>72</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td>LBL 2)</td>
<td>14</td>
<td>Surgery+He-ion</td>
<td>55</td>
<td>85</td>
<td>22</td>
</tr>
<tr>
<td>Mayo 3)</td>
<td>52</td>
<td>Surgery</td>
<td>56</td>
<td>74</td>
<td>52</td>
</tr>
<tr>
<td>NIRS 4)</td>
<td>183</td>
<td>C-ion alone</td>
<td>88</td>
<td>86</td>
<td>74</td>
</tr>
</tbody>
</table>

LC: local control, OS: overall survival

Before Aher C-ion R

After C-ion R
Recurrent Rectal Cancer in right pelvic bone

Before Treatment

12M after Treatment

Before Treatment

6M after Treatment

Methionine PET/CT
Spacer is put to separate the tumor from the bowels.

59y/o F

Intestine → Tumor

70.4GyE/16fr

10.0
30.0
50.0
60.0
90.0
95.0

Spacer

12 mo. after
## Post-operative pelvic recurrence of rectal cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. Pats</th>
<th>Treatment</th>
<th>Overall Survival</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wanebo HJ</td>
<td>1999</td>
<td>53</td>
<td>Surgery</td>
<td>62% 31%</td>
<td>-</td>
</tr>
<tr>
<td>Saito N</td>
<td>2003</td>
<td>43</td>
<td>Surgery</td>
<td>78% 39%</td>
<td>-</td>
</tr>
<tr>
<td>Moriya Y</td>
<td>2004</td>
<td>48</td>
<td>Surgery</td>
<td>76% 36%</td>
<td>-</td>
</tr>
<tr>
<td>O’ Connel MJ</td>
<td>1982</td>
<td>17</td>
<td>Photon 50Gy</td>
<td>45% 0%</td>
<td>24% (2y)</td>
</tr>
<tr>
<td>Wong CS</td>
<td>1991</td>
<td>22</td>
<td>Photon 50Gy</td>
<td>27% 16%</td>
<td>9% (5y)</td>
</tr>
<tr>
<td>Lybeert MLM</td>
<td>1992</td>
<td>76</td>
<td>Photon 6-66Gy</td>
<td>61% (1y)</td>
<td>28% (3y)</td>
</tr>
<tr>
<td>NIRS</td>
<td>2013</td>
<td>161</td>
<td>Carbon</td>
<td>90% 51%</td>
<td>93% (5y)</td>
</tr>
</tbody>
</table>

Radiation Field for Pancreatic head cancer

- Cystic artery
- Portal vein
- Hepatic artery
- Aorta
- Celiac artery
- Celiac plexus
- Splenic artery
- Pancreatic duct
- Superior mesenteric artery
- Superior mesenteric vein
- Duodenum
- Tumor

Distance: 2 cm
GEM+CIRT for locally advanced pancreas cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Treatment</th>
<th>Dose</th>
<th>MST (mo)</th>
<th>Survival 1yr</th>
<th>Survival 2yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG (E4201)</td>
<td>2008</td>
<td>34</td>
<td>GEM+RT</td>
<td>50.4Gy</td>
<td>11.4</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37</td>
<td>GEM</td>
<td>-</td>
<td>9.2</td>
<td>32%</td>
</tr>
<tr>
<td>Ishii</td>
<td>2010</td>
<td>50</td>
<td>GEM</td>
<td>-</td>
<td>15.0</td>
<td>64%</td>
</tr>
<tr>
<td>Sudo</td>
<td>2011</td>
<td>34</td>
<td>S-1+RT</td>
<td>50.4Gy</td>
<td>16.8</td>
<td>71%</td>
</tr>
<tr>
<td>Small</td>
<td>2011</td>
<td>28</td>
<td>GEM+BZ* +RT</td>
<td>36Gy/15fr.</td>
<td>11.8</td>
<td>45%</td>
</tr>
<tr>
<td>Schellenberg</td>
<td>2011</td>
<td>20</td>
<td>GEM+SBRT</td>
<td>25Gy/1fr.</td>
<td>11.8</td>
<td>50%</td>
</tr>
<tr>
<td>NIRS</td>
<td></td>
<td>47</td>
<td>GEM+CIRT</td>
<td>45.6-55.2 GyE</td>
<td><strong>22.5</strong></td>
<td><strong>73%</strong></td>
</tr>
</tbody>
</table>

*Bevacizumab
Possible Advantages of C-ion RT

• Dose distribution is better than protons in both broad beam and scanning beam irradiation.
  → Less toxicity
• Radiobiological benefit has been confirmed to improve LC of photon-resistant tumors including:
  • Locally advanced large tumors
  • Non-squamous cell type of epithelial tumors
  • Sarcomas
  → More intensive
• Wider range of clinical indications has been demonstrated.
  → in Sarcomas, Rectal ca, Pancreas ca
• Hypofractionated RT has been feasible in almost all tumors.
  → Economically more advantageous
  → More convenient to the patients
Development of Charged Particle Therapy Facility at NIRS

HIMAC
- He〜Ar
- $E_{\text{max}}$ 800 MeV/n
- Wobbler method
- Respiratory gating
- Broad beam method

Compact Facility
- C
- $E_{\text{max}}$ 400 MeV/n
- Spiral wobbler
- Respiratory gating
- Stack layer irrad

New Treatment Research Facility
- C, O, ($^{11}$C, $^{15}$O)
- $E_{\text{max}}$ 430 MeV/n
- Respiratory gating
- 3D Scanning
- Rotating gantry
A New Treatment Facility

Building facade with green curtain

Waiting hall (B2F)

Entrance hall (1F)

Treatment Room E (B2F)
Beam Delivery System at NIRS

Wobbler method

- C\textsuperscript{6+} Beam
- Wobbler Magnets
- Scatter
- Multi Leaf Collimator
- Bolus
- Tumor tissue

Scanning method

- C\textsuperscript{6+} Beam
- Scanning Magnets
- Tumor tissue

Beam image
Scanning and Wobbler

Scanning

Wobbler (Broad beam)
These works were performed under research agreement with ELEKTA.
Comparative Treatment Planning; Carbon vs Proton/Prostate

"These works were performed under research agreement with ELEKTA"
PET image of auto-activation in C-ion RT of prostate ca.
Development of SC gantry at NIRS

Use of superconducting (SC) magnets

- Ion kind: $^{12}$C
- Irradiation method: 3D Scanning
- Max. beam energy: 430 MeV/n
- Max. range: 30 cm in water
-Scan size: 200 mm × 200 mm
- Beam orbit radius: 5.45 m
- Length: 13 m

Installation will be completed by the end of March 2015.
Carbon-Ion Radiotherapy

Available Formats:
- eBook (gross) price for Japan
  - ISBN 978-4-431-54457-9
  - digitally watermarked, no DRM
  - Included Format: PDF and EPUB
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About this book
Published	
in	
Jan,	
2014
Springer
http://www.springer.com/de/

This book serves as a practical guide for the use of carbon ions in cancer radiotherapy. On the basis of clinical experience with more than 7,000 patients with various types of tumors treated over a period of nearly 20 years at the National Institute of Radiological Sciences, step-by-step procedures and technological development of this modality are highlighted. The book is divided into two sections, the first covering the underlying principles of physics and biology, and the second section is a systematic review by tumor site, concentrating on the role of therapeutic techniques and the pitfalls in treatment planning.

Readers will learn of the superior outcomes obtained with carbon-ion therapy for various types of tumors in terms of local control and toxicities. It is essential to understand that the carbon-ion beam is like a two-edged sword: unless it is used properly, it can increase the risk of severe injury to critical organs. In early series of dose-escalation studies, some patients experienced serious adverse effects such as skin ulcers, pneumonitis, intestinal ulcers, and bone necrosis, for which salvage surgery or hospitalization was required. To preclude such detrimental results, the adequacy of therapeutic techniques and dose fractionations was carefully examined in each case. In this way, significant improvements in treatment results have been achieved and major toxicities are no longer observed. With that knowledge, experts in relevant fields expand upon techniques for treatment delivery at each anatomical site, covering indications and optimal treatment planning.

With its practical focus, this book will benefit radiation oncologists, medical physicists, medical dosimetrists, radiation therapists, and senior nurses whose work involves radiation therapy, as well as medical oncologists and others who are interested in radiation therapy.

Content Level » Professional/practitioner

Keywords » Cancer radiotherapy - HIMAC - Heavy ion - Ion beams - Protons - Relative biological effectiveness
HIMAC International Symposium 2015
20-Year Anniversary Event

Date 19-20 January 2015
Venue Akiba Hall, Tokyo, Japan
Capacity 150 People
Registration Free

This symposium will take place as a special international event to commemorate the 20-year anniversary of the initiation of heavy ion therapy at NIRS-HIMAC. Since 1994, HIMAC has carried out the clinical trial of cancer treatments using carbon beams. After accumulating clinical experiences in various types of malignant tumors, NIRS was successful in obtaining approval from the Ministry of Health, Welfare and Labor to carry out "Highly Advanced Medical Technology" in 2003. In the meanwhile, carbon ion therapy has achieved for itself a solid place in the general practice of cancer treatment. The total number of patients will reach 10,000 by the next year. In addition, treatment with scanned carbon beam was started in 2011 to provide more patient-friendly cancer therapy. In this event, the participants are to share the latest information and future prospects for the future development in this area. It is our pleasure to welcome you to the anniversary symposium.

Please register online at http://www.nirs.go.jp/information/event/ev-app-id-e_1140.php?1140

Thank You