PTCOG 46
Educational Workshop
Session IV
CLINICAL
Head & Neck
J. Mizoe (NIRS, Japan)
Radiation

Photon
  - X-Ray
  - γ-Ray

Electron
  - Fast Neutron
    - Proton
    - Helium
    - Carbon
    - Neon
    - Argon
    - π- Meson
  - Charged

Heavy Particle
  - Non-Charged
Physical Characteristics of Radiation

- SOBP
- Proton
- Carbon
- Electron
- Fast Neutron
- High energy X-ray

Relative Dose vs. Depth (cm)
SOBP by Ridge Filter

Bragg Peak (mono)

Ridge Filter

Z

Depth in Water

SOBP

Bolus

Collimator

Range Shifter

Target

Target Thickness

Target Thickness

Biological Dose

Physical Dose

Depth in Water

Depth in Water

Target Thickness
Physical characteristics of heavy ions

Distal distribution (290 MeV/n)

Lateral distribution
Carbon ion beam in the water

Distance in the water (cm)
Biological characteristics of heavy ions

High LET (linear energy transfer) radiation

a) No dependency for cell cycle
b) No or little repair from damage
c) High efficacy for low OER cells
Bird 1972
V79 cells

Survival (%)

Hours After Mitotic Selection

M-G1  S  G2-M

250 rad carbon ions

950 rad X rays
Repair

\( \gamma \text{-ray} \)

Left:
- Single fraction
- 5 Fractions

Right:
- Single fraction
- 5 Fractions

Carbon
74 keV/\mu m

TUMOR CONTROL (%) vs DOSE (Gy)
TUMOR CONTROL (%) vs DOSE (GyE)
OER (oxygen enhancement ratio)
Carbon Ion Radiotherapy for Head & Neck Cancer
Patients enrolled into Carbon Ion Radiotherapy
(June 1994 ~ February 2007)

- Skull Base: 46 (1.4%)
- Lacrimal Gl.: 12 (0.4%)
- Miscellaneous: 665 (20.9%)
- Prostate: 515 (16.2%)
- Lung: 472 (14.9%)
- Head & Neck: 408 (12.8%)
- Digestive: 47 (1.5%)
- Liver: 212 (6.7%)
- Bone & Soft Tissue: 349 (11.0%)
- Eye: 72 (2.3%)
- Pancreas: 84 (2.6%)
- Rectum: 88 (2.8%)
- CNS: 93 (2.9%)
- Gynecological: 115 (3.6%)
- TOTAL: 3,178
C$^{11}$–Methionine PET
Fusion with MR
Fusion with PET
MMM (NASAL)

CT-MR Fusion

CT-PET Fusion

PINNACLE3D
ADENOCARCINOMA (PARANASAL)

CT-MR Fusion

CT-PET Fusion
DVH Analysis of Optic Nerve
CLINICAL INVESTIGATION

OUTCOMES OF VISUAL ACUITY IN CARBON ION RADIOTHERAPY:
ANALYSIS OF DOSE-VOLUME HISTOGRAMS AND PROGNOSTIC FACTORS

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AND HIROHIKO TSUJII, M.D., PH.D.*

*Hospital, Charged Particle Research Center, National Institute of Radiological Sciences, Chiba, Japan; †Department of
Ophthalmology, Juntendo University Urayasu Hospital, Chiba, Japan

Purpose: To analyze the tolerance dose for retention of visual acuity in patients with head-and-neck tumors
 treated with carbon ion radiotherapy.

Methods and Materials: From June 1994 to March 2000, 163 patients with tumors in the head and neck or skull
base region were treated with carbon ion radiotherapy. Analysis was performed on 54 optic nerves (ONs)
 corresponding to 30 patients whose ONs had been included in the irradiated volume. These patients showed no
evidence of visual impairment due to other factors and had a follow-up period of >4 years. All patients had been
informed of the possibility of visual impairment before treatment. We evaluated the dose-complication probability
and the prognostic factors for the retention of visual acuity in carbon ion radiotherapy, using dose-volume
histograms and multivariate analysis.

Results: The median age of 30 patients (14 men, 16 women) was 57.2 years. Median prescribed total dose was 56.0
gray equivalents (GyE) at 3.0–4.0 GyE per fraction per day (range, 48–64 GyE; 16–18 fractions; 4–6 weeks).
Of 54 ONs that were analyzed, 35 had been irradiated with <57 GyE (maximum dose $D_{\text{max}}$) resulting in no
visual loss. Conversely, 11 of the 19 ONs (58%) irradiated with >57 GyE ($D_{\ldots}$) suffered a decrease of visual
Images of gadolinium-enhanced T1-weighted magnetic resonance imaging, isodose distribution, and dose–volume histograms of the optic nerve. Isodose level: red 96%; orange 90%; green 50%; cyan 30%; purple 10%. Contours: yellow clinical target volume; blue optic nerve. LON left optic nerve; RON right optic nerve.
## Cox proportional hazards model for optic neuropathy

### Univariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>$p$</th>
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<tbody>
<tr>
<td>Gender (male vs. female)</td>
<td>0.0034</td>
</tr>
<tr>
<td>Chemotherapy (yes vs. no)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Anemia (yes vs. no)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs. no)</td>
<td>0.0013</td>
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<tr>
<td>Prescribed tumor dose (GyE)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Maximum dose to ON (GyE)</td>
<td>0.0000</td>
</tr>
<tr>
<td>D10 (GyE)*</td>
<td>0.0000</td>
</tr>
<tr>
<td>D20 (GyE)*</td>
<td>0.0000</td>
</tr>
<tr>
<td>D30 (GyE)*</td>
<td>0.0000</td>
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<tr>
<td>D40 (GyE)*</td>
<td>0.0000</td>
</tr>
<tr>
<td>D50 (GyE)*</td>
<td>0.0001</td>
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### Multivariate Analysis

<table>
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<tr>
<th></th>
<th>$p$</th>
<th>HR</th>
<th>(95% CI)</th>
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<tbody>
<tr>
<td>D20 (GyE)*</td>
<td>0.0000</td>
<td>1.3250</td>
<td>(1.1358–1.5457)</td>
</tr>
</tbody>
</table>

**Abbreviation:** CI  confidence interval; ON  optic nerve.

* Dose to each volume of optic nerve.
Dose–complication probability curve.
The broken line in the middle indicates the 50% dose–complication probability.

*Dose to each volume percentage of the optic nerve.
Daily Verification System
Orthogonal X-TV Verification System
Result of Phase I/II Trial
Clinical Trials in Head and Neck Cancer

Phase II (9602) 16 f/4 w

- Phase I/II (0006)
  Bone & Soft Tissue
  16 f/4 w

- Phase II (0007)
  Malignant Melanoma
  16 f/4 w + DAV x 5

- Phase I/II (9301)
  18 f/6 w
Results of Phase I/II Clinical Trial for Head & Neck Cancer

   17 patients
   48.6, 54.0, 59.4, 64.8, 70.2 GyE

   19 patients
   52.8, 57.6, 64.0 GyE
Local Control of Phase I/II Studies

TIME in MONTHS

PROBABILITY

16 f./4 wks (19)
18 f./6 wks (15)

P = 0.8601
Survival of Phase I/II Studies

TIME in MONTHS

PROBABILITY

16 f./4 wks (19)

18 f./6 wks (17)

P = 0.5293
DOSE ESCALATION STUDY OF CARBON ION RADIOTHERAPY FOR
LOCALLY ADVANCED HEAD-AND-NECK CANCER

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Yoshisuke Matsuoka, M.D.,† Hiroshi Tsuji, M.D. Yasuhiro Osaka, M.D.,†
Azusa Hasegawa, D.Ds., Nobuhiro Yamamoto, D.Ds.,* Satoshi Ebihara, M.D.,§
Akiyoshi Konno, M.D.,‖ FOR ORGANIZING COMMITTEE FOR THE WORKING GROUP FOR
HEAD-AND-NECK CANCER

*Hospital, Research Center of Charged Particle, National Institute of Radiological Sciences, Chiba, Japan; †Department of Radiology, Iwate Prefecture Central Hospital, Morioka, Japan; ‡Department of Radiology, Hokkaido University Hospital, Sapporo, Japan; §Department of Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan; ‖Center of Allergic Head and Neck Disease, Southern Tohoku Research Institute for Neuroscience, Koriyama, Japan

Purpose: To evaluate the toxicity and efficacy of carbon ion radiotherapy for head-and-neck cancer in a Phase I/II dose escalation clinical trial.
Methods and Materials: Between June 1994 and January 1997, 36 patients with locally advanced, histologically proven, and new or recurrent cancer of the head and neck were treated with carbon ions. A dose escalation study was conducted, delivering 18 fractions through 6 weeks for 17 patients (Group A) and 16 fractions through 4 weeks for
Preliminary Result of Phase II Trial
Clinical Trials in Head and Neck Cancer

- **Phase II (9602) 16 f/4 w**
  - **Phase II (0006)**
    - Bone & Soft Tissue 16 f/4 w
  - **Phase II (0007)**
    - Malignant Melanoma 16 f/4 w + DAV x 5

Timeline:
- **94.06 ~ 96.04**
- **97.04 ~**
- **01.04 ~**

Timeline details:
- **P I/II (9301) 18 f/6 w**
- **P I/II (9504) 16 f/4 w**
Phase II Clinical Trial for Head and Neck Cancer

239 cases treated between Apr. 1997 to Feb. 2006
Guide Line for Carbon Ion RT

- Histologically proven, measurable head and neck malignancy.
- N0M0 in principle.
- No co-existent malignant active tumor.
- No distant metastasis to other parts.
- Age between 15 and 80 years old.
- Prospective survival prognosis of at least 6 months or longer.
- Karnofsky Index (K.I.) is 60% or more.
- Absence of prior radiotherapy for the carbon treatment area.
- No chemotherapy within 4 weeks
- Absence of intractable inflammatory lesion.
- Written informed consent.
Patients Characteristics

Age: from 16 to 80, averaging 56.4 years
Sex: with 126 male and 113 female
K.I.: from 60% to 100%, median 90%.

Treatment Characteristics

57.6GyE/16 fraction/4 weeks: 218
64.0GyE 21
The sites of disease (239 sites)

- Paranasal sinus: 60 cases
- Nasal cavity: 55 cases
- Salivary gland: 30 cases
- Oral cavity: 25 cases
- Orbita: 20 cases
- Pharynx: 15 cases
- Thyroid gland: 10 cases
- Auricula: 5 cases
- Other sites: 10 cases

Number of Cases
Histology (239 sites)

Number of Cases

- Malignant melanoma
- Adenoid cystic carcinoma
- Adenocarcinoma
- Papillary adenocarcinoma
- Squamous cell carcinoma
- Mucoepidermoid carcinoma
- Epitelial myoepithelial carcinoma
- Rhabdomyosarcoma
- Osteosarcoma
- Others

Malignant melanoma has the highest number of cases, followed by adenoid cystic carcinoma and adenocarcinoma.
Clinical Stage (239 sites)

- Post carbon ion
- Post ope. and chemo.
- Post chemotherapy
- Post operative
- T 4
- T 3
- T 2
- T 1

Number of Cases
### Acute reaction

<table>
<thead>
<tr>
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<th>G0</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
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<tr>
<td>Skin</td>
<td>7</td>
<td>45</td>
<td>41</td>
<td>8</td>
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<tr>
<td>Mucosa</td>
<td>12</td>
<td>40</td>
<td>37</td>
<td>11</td>
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### Late reaction

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<th>G0</th>
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<th>G2</th>
<th>G3</th>
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<tbody>
<tr>
<td>Skin</td>
<td>45</td>
<td>50</td>
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<tr>
<td>Mucosa</td>
<td>76</td>
<td>21</td>
<td>3</td>
<td>0</td>
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</table>
Malignant Melanoma
57.6GyE/16fr/ 4 wks

Pre RT

53 months
Malignant Melanoma of the left Nasal Cavity

57.6 GyE/16 fr./4 wks

Pre RT

After 7 Months
ACC  57.6GyE/16fr/ 4 wks

Pre RT

24 Months
9602-43, Adenoid Cystic Carcinoma

Pre RT

32 m
9602–20

ACC of the rt maxilla
57.6 GyE/16 f.

Pre RT

32 mon.
Adeno Carcinoma

Pre RT

After 6 Months
9602-44

Adeno ca. of the ethmoid sinus
57.6 GyE/16 f.

Pre RT

19 mon.
9602-47

Adeno Ca. of the rt-Epipharynx
57.6 GyE/16 f.

Pre RT

20 mon.
9602 H&N CANCER (1997.02 ~ 2006.02)

LOCAL CONTROL (239)

70.2%

SURVIVAL (236)

41.1%

TIME IN MONTH

PROBABILITY
9602 H&N CANCER (1997.02 ~ 2006.02)

PROBABILITY OF LOCAL CONTROL

TIME IN MONTH

5y LC
- Orbita(20) 90.0%
- Salivary(31) 80.4%
- Thyroid(11) 76.2%
- Nasal(56) 75.7%
- Pharynx(19) 72.0%
- Pasanasal(61) 63.3%
- Oral(26) 61.6%
9602 H&N CANCER (1997.02 ~ 2006.02)

Time in Month

Probability of Survival

Orbita (20) 62.8%
Salivary (31) 64.1%
Nasal (56) 25.8%
Thyroid (11) 21.8%
Pharynx (18) 49.6%
Pasanasal (61) 44.6%
Oral (26) 46.9%

5yOS
9602 H&N CANCER (1997.02 ~ 2006.02)

TIME IN MONTH

PROBABILITY OF LOCAL CONTROL

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
<th>Probability</th>
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<tr>
<td>ACC</td>
<td>70</td>
<td>74.0%</td>
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<tr>
<td>Adeno</td>
<td>27</td>
<td>76.0%</td>
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<tr>
<td>MMM</td>
<td>85</td>
<td>74.7%</td>
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<tr>
<td>Papillary</td>
<td>13</td>
<td>80.8%</td>
</tr>
<tr>
<td>SCC</td>
<td>12</td>
<td>60.2%</td>
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</table>

5yLC

Papillary (13) 80.8%
MMM (85) 74.7%
Adeno (27) 76.0%
ACC (70) 74.0%
SCC (12) 60.2%
9602 H&N CANCER (1997.02 ~ 2006.02)

5yOS
ACC (69) 69.7%
Adeno (27) 46.6%
MMM (85) 31.3%
Papillary (13) 26.3%
SCC (12) 19.4%
## Salivary gland carcinoma

*Cancer* 2005 Jun 15;103(12):2544-50

<table>
<thead>
<tr>
<th>UF</th>
<th>Numb.</th>
<th>Treatment</th>
<th>5y-LC</th>
<th>5y-OS</th>
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<td>RT</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>160</td>
<td></td>
<td>SURG + RT</td>
<td>90</td>
<td>66</td>
</tr>
<tr>
<td>NIRS</td>
<td>31</td>
<td>Carbon ion</td>
<td>80</td>
<td>64</td>
</tr>
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</table>

## Adenoid cystic carcinoma of the head and neck

*Head Neck* 2004 Feb;26(2):154-62

<table>
<thead>
<tr>
<th>UF</th>
<th>Numb.</th>
<th>Treatment</th>
<th>5y-LC</th>
<th>5y-OS</th>
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<tr>
<td>101</td>
<td></td>
<td>RT</td>
<td>56</td>
<td>57</td>
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<tr>
<td></td>
<td></td>
<td>SURG + RT</td>
<td>94</td>
<td>77</td>
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<tr>
<td>NIRS</td>
<td>69</td>
<td>Carbon ion</td>
<td>74</td>
<td>70</td>
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Clinical Trials in Head and Neck Cancer

- Phase I/II (9301) 18 f/6 w
- Phase II (9602) 16 f/4 w
- Phase I/II (0006) Bone & Soft Tissue 16 f/4 w
- Phase II (0007) Malignant Melanoma 16 f/4 w + DAV x 5
Treatment characteristics

- 57.6 GyE/16 fr./4 wks (3.6 GyE): 218
- 64.0 GyE/16 fr./4 wks (4.0 GyE): 21

- Sarcomas: 11
  - Osteo sarcoma: 5
  - Rhabdomyo sarcoma: 2
  - Lipo sarcoma: 2
  - Fibro sarcoma: 1
  - Chondro sarcoma: 1

- Malignant melanoma: 4
- ACC: 3
- SCC: 2
Phase I/II clinical trial
for bone & soft tissue tumors
( Apr. 2001 ~ )

Dose escalation study
Starting dose : 70.4 GyE/16 f./4 wks ( 4.4 GyE)
Reduction of skin dose by multi portal irradiation
Clinical Trials in Head and Neck Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial Details</th>
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<tr>
<td>94.06~</td>
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<td>96.04~</td>
<td>P I/II (9504) 16 f/4 w</td>
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<tr>
<td>97.04~</td>
<td>Phase II (9602) 16 f/4 w</td>
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<tr>
<td>01.04~</td>
<td>Phase I/II (0006) Bone &amp; Soft Tissue 16 f/4 w</td>
</tr>
<tr>
<td>01.04~</td>
<td>Phase II (0007) Malignant Melanoma 16 f/4 w + DAV x 5</td>
</tr>
</tbody>
</table>
Chemo-Radiation for MMM

1. 2001.04 ~ 2002.03 (9 Cases)

2. 2002.04 ~ 2006.02 (52 Cases, 53 sites)
   CARBON
### Clinical characteristics of reported cases of malignant mucosal melanoma in the head and neck region

*(Pathology Oncology Research Vol 9, No 1, 7–12, 2003)*

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases</th>
<th>Tumor location</th>
<th>Treatment modalities</th>
<th>5-year overall survival (%)</th>
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<td>Gilligan</td>
<td>28</td>
<td>Sinonasal</td>
<td>Radiotherapy</td>
<td>18</td>
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<td>Shibuya</td>
<td>28</td>
<td>Upper jaw</td>
<td>Radiotherapy +/- surgery</td>
<td>25</td>
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<tr>
<td>Shah</td>
<td>74</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy</td>
<td>22</td>
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<tr>
<td>Chaudhry</td>
<td>41</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy</td>
<td>17</td>
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<tr>
<td>Lund</td>
<td>58</td>
<td>Sinonasal</td>
<td>Surgery +/- postoperative radiotherapy +/- chemotherapy (BCG, melphalan)</td>
<td>28</td>
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<tr>
<td>Pandey</td>
<td>60</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy</td>
<td>28</td>
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<tr>
<td>Chang</td>
<td>163</td>
<td>Head and neck</td>
<td>Surgery +/- radiotherapy +/- chemotherapy</td>
<td>32</td>
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<td>Patel</td>
<td>59</td>
<td>Sinonasal and oral</td>
<td>Surgery +/- postoperative radiotherapy +/- chemotherapy</td>
<td>35</td>
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<td>Stern</td>
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<td>Sinonasal and oral</td>
<td>Surgery +/- radiotherapy +/- chemotherapy +/- immunotherapy</td>
<td>40</td>
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<td>Guzzo</td>
<td>48</td>
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<td>Surgery +/- radiotherapy +/- chemotherapy +/- immunotherapy</td>
<td>21</td>
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<td>NIRS-1(9602)</td>
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<td>Head and neck</td>
<td>Carbon ion radiotherapy</td>
<td>30</td>
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<td>NIRS-2(0007)</td>
<td>53</td>
<td>Head and neck</td>
<td>Carbon ion radiotherapy +/- chemotherapy</td>
<td>57</td>
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<tr>
<td>NIRS-2 &lt; 60cc (GTV)</td>
<td>38</td>
<td></td>
<td></td>
<td>66</td>
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(*: 4 year overall survival)
Summary of Carbon Ion Radiotherapy

- High local control of H&N malignancies.
- Better local control by higher dose for B&S sarcomas.
- Good overall survival by concomitant chemo-carbon ion therapy for malignant melanoma.