Five Years Comprehensive Experience in Proton Radiotherapy in PMRC Tsukuba

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Where is Tsukuba?
Mt. Tsukuba and Tsukuba Science City
Layout of the proton therapy facility
Cases treated at PMRC during the last 5 years (2003.1 – 2007.12)

194  224  212  209  185*
Cases treated at PMRC during the last 5 years (2003.1 – 2007.12)

1024
Hepatocellular carcinoma (HCC)

1) 66 GyE / 10 fractions
   Solitary tumor
   10 cm or less in diameter
   2 cm away from the port hepatis or the GI tract
   Child-Pugh A or B
   → 51 cases

2) 72.6 GyE / 22 fractions
   Within 2 cm from the port hepatis
   → 53 cases

3) 70.0 GyE / 35 fractions
   within 2 cm from the GI tract
26 y.o. man 66 GyE/10 fractions

Pre-treatment

38 months later

Planning
Local Control Rate of Patients Treated by 66 GyE/10 fractions

n = 51
3 years: 93.8 %
5 years: 83.3 %
Overall Survival of Patients Treated by 66 GyE/10 fractions

- **n = 51**
- **MST: 35.0 months**
- **3 years: 48.0 %**
- **5 years: 35.2 %**
Hepatocellular carcinoma (HCC)

1) 66 GyE / 10 fractions
   Solitary tumor
   10 cm or less in diameter
   2 cm away from the port hepatis or the GI tract
   Child-Pugh A or B
   \(\rightarrow\) 51 cases

2) 72.6GyE / 22 fractions
   Within 2 cm from the port hepatis
   \(\rightarrow\) 53 cases

3) 70.0 GyE / 35 fractions
   within 2 cm from the GI tract
Survival of cases with 72.6GyE/22 fractions

- Local Control
  - 3 year: 86%
  - MST: 34 months

- Overall Survival
  - 3 year: 45.1%
  - MST: 14.4 months

- Progression-Free Survival
  - 3 year: 25.1%
  - MST: 14.4 months

n = 53
Overall survival of cases with 72.6GyE/22 fractions

- Child-Pugh class A, single tumor, and AFP $\leq 100$
  - $n = 14$
  - 3 year: 83.9%

- Child-Pugh class B or C, multiple tumors, or AFP $\geq 100$
  - $n = 39$
  - 3 year: 32.9%
A current clinical trials in HCC

1) Phase I-IIa trial of combination of proton radiotherapy and novel immunological adjuvant therapy

2) Phase II clinical trial of proton radiotherapy for HCC with portal vein tumor thrombus.
   - Tumor thrombus at the main portal vein and its first branches
   - 72.6GyE / 22 fractions
## Non-small cell lung cancers

### Stage I: 37 cases  Phase II trial

*Peripheral*: Tumors in the zone outside of the proximal bronchial tree:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>24 cases</td>
<td></td>
</tr>
<tr>
<td>CTV = GTV + 5 -10 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTV = CTV + 5 -10 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66GyE/ 10 fractions</td>
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</tbody>
</table>

*Proximal*: Tumors in the zone of the proximal bronchial tree defined in RTOG 0618

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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>13 cases</td>
<td></td>
</tr>
<tr>
<td>CTV = GTV + 5 -10 mm</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>72.6 GyE/22 fractions</td>
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</table>

### Stage II-III: 34 cases  Retrospective analysis

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>CTV1 = GTV1 (primary) + 5 -10 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTV2 = GTV2 (LN) + 5 -10 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTV= CTV1 + CTV2 + 5 -10 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Local control of stage I peripheral type

CR: 79.1% (19/24)
PR: 16.7% (4/24)
SD: 4.0% (1/24)
PD: 0% (0/24)
Progression free survival of stage I peripheral type

<table>
<thead>
<tr>
<th>Months</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>94.7%</td>
</tr>
<tr>
<td>2 years</td>
<td>82.1%</td>
</tr>
<tr>
<td>3 years</td>
<td>73.0%</td>
</tr>
<tr>
<td>4 years</td>
<td>48.7%</td>
</tr>
</tbody>
</table>
Overall survival of stage I peripheral type

Median observation time: 22.9 months

Alive 23
Dead 1

83.3 y.o. woman  cT1NOMO
Died of NSCLC at 39.9 months
Non-small cell lung cancers

**Stage I:** 37 cases  
Phase II clinical study  
*Peripheral:* Tumors in the zone outside of the proximal bronchial tree:  
  24 cases  
  $CTV = GTV + 5 - 10 \text{ mm}$  
  $PTV = CTV + 5 - 10 \text{ mm}$  
  $66\text{ GyE/10 fractions}$

*Proximal:* Tumors in the zone of the proximal bronchial tree defined in RTOG 0618  
  13 cases  
  $CTV = GTV + 5 - 10 \text{ mm}$  
  $PTV = CTV + 5 - 10 \text{ mm}$  
  $72.6 \text{ GyE/22 fractions}$

**Stage II-III:** 34 cases  
Retrospective analysis  

$CTV1 = GTV1 \text{ (primary)} + 5 - 10 \text{ mm}$  
$CTV2 = GTV2 \text{ (LN)} + 5 - 10 \text{ mm}$  
$PTV = CTV1 + CTV2 + 5 - 10 \text{ mm}$
Local control rate of stage I proximal type

CR: 69.2% (9/13)
PR: 15.4% (2/13)
SD: 7.6% (1/13)
PD: 7.6% (1/13)
Progression free survival of stage I proximal type

<table>
<thead>
<tr>
<th>Months</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>87.5</td>
</tr>
<tr>
<td>2 years</td>
<td>58.3</td>
</tr>
<tr>
<td>3 years</td>
<td>58.3</td>
</tr>
</tbody>
</table>
Overall survival of stage I proximal type

Median observation time: 15.2 months

Alive: 13 cases
Dead: none
Non-small cell lung cancers

**Stage I: 37 cases**

**Peripheral:** Tumors in the zone outside of the proximal bronchial tree:

- **24 cases**
  - CTV = GTV + 5-10 mm
  - PTV = CTV + 5-10 mm
  - 66 GyE/10 fractions

**Proximal:** Tumors in the zone of the proximal bronchial tree defined in RTOG 0618

- **13 cases**
  - CTV = GTV + 5-10 mm
  - PTV = CTV + 5-10 mm
  - 72.6 GyE/22 fractions

**Stage II-III: 34 cases**

These patients did not undergo surgery and chemotherapy for some reasons.

- CTV1 = GTV1 (primary) + 5-10 mm
- CTV2 = GTV2 (LN) + 5-10 mm
- PTV = CTV1 + CTV2 + 5-10 mm
### Prescribed doses to stage II-III

*(Retrospective analysis)*

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 GyE/10 frac</td>
<td>3</td>
</tr>
<tr>
<td>((\alpha/\beta=3,\ 108\ GyE))</td>
<td></td>
</tr>
<tr>
<td>72.6 GyE/22 frac</td>
<td>9</td>
</tr>
<tr>
<td>((\alpha/\beta=3,\ 83.2\ GyE))</td>
<td></td>
</tr>
<tr>
<td>77 GyE/35 frac</td>
<td>14</td>
</tr>
<tr>
<td>((\alpha/\beta=3,\ 80.1\ GyE))</td>
<td></td>
</tr>
<tr>
<td>83.6 GyE/38 frac</td>
<td>8</td>
</tr>
<tr>
<td>((\alpha/\beta=3,\ 86.9\ GyE))</td>
<td></td>
</tr>
</tbody>
</table>
Local control rate of stage II-III

CR: 14.7% (5/34)
PR: 52.9% (18/34)
SD: 17.6% (6/34)
PD: 29.4% (5/34)
Progression free survival of stage II-III

MST: 16.4 months

1 year: 56.0%
2 years: 34.0%
3 years: 34.0%
4 years: 27.2%
5 years: 27.2%

No chemotherapy
No surgery
A current clinical trials in NSCLC

Phase I/II clinical trial of proton radiotherapy with concurrent chemotherapy for stage II, IIIA and IIlb NCSLC

• Dose escalation form 74GyE/37 frac to 78GyE/39 frac
• Concurrent administration of cisplatin and vinorelbine
Intracranial lesions

- Malignant gliomas
- Meningiomas
- Neurinomas
Proton therapy for AVM in PMRC (1990-1999)

• 33 cases, M/F = 23/10, Age: 35.6 y.o.
  – Treatment
    • SRS: 28 cases
    • SRT: 5 cases (2 frac: 2, 3 frac:2, 15 frac:1)
    • Dose: 17Gy-25Gy (Av. 22.5Gy)
    • 3 – 6 ports
  – Results
    • Complete cure 21 / 25 (75%)
    • Decrease in size 3 / 25 (11%)
    • No change 2 / 25 (7%)
    • Enlargement 2 / 25 (7%)
    • Hemorrhage 1 / 25 (4%)
    • Necrosis 2 / 25 (7%)
### 18 cases with AVM ≥3 cm at Tsukuba

<table>
<thead>
<tr>
<th>Modality</th>
<th>Proton</th>
<th>γ-knife</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Re-bleeding</td>
<td>1 (9.1%)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Cure after 3 years</td>
<td>7 (63.7%)</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Nidus remaining after 3 years</td>
<td>4 (36.4%)</td>
<td>6 (85.7%)</td>
</tr>
<tr>
<td>Radiation necrosis</td>
<td>1 (9.1%)</td>
<td>1 (14.3%)</td>
</tr>
</tbody>
</table>
Thus, we assumed that $\alpha/\beta$-value for AVM $\geq 3$ cm obliteration is 3.5.
### Reported series of fractionated radiotherapy for large AVM

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>method</th>
<th>cases</th>
<th>dose/frac</th>
<th>follow</th>
<th>cure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redekop/1993</td>
<td>LINAC</td>
<td>10</td>
<td>45-50/15-28</td>
<td>4-10.5</td>
<td>20</td>
</tr>
<tr>
<td>Kocher/2004</td>
<td>LINAC</td>
<td>40</td>
<td>50/25</td>
<td>&gt;2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>20/4</td>
<td>&gt;2</td>
<td>0</td>
</tr>
<tr>
<td>Venzendaroglu/2004</td>
<td>LINAC</td>
<td>7</td>
<td>42/6</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>30/6</td>
<td>3.5</td>
<td>22</td>
</tr>
<tr>
<td>Chang/2004</td>
<td>LINAC</td>
<td>33</td>
<td>25-35/4</td>
<td>4.3</td>
<td>66</td>
</tr>
<tr>
<td>Silander/2004</td>
<td>Proton</td>
<td>9</td>
<td>20-25/2</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>20-25/4</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
\[ \alpha/\beta = 3.5 \]

<table>
<thead>
<tr>
<th>Fx size</th>
<th>Fx (D)</th>
<th>BED (Gy)</th>
<th>Oblit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>4 (32)</td>
<td>104.0</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>6 (42)</td>
<td>126.0</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>4 (24)</td>
<td>65.1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4 (20)</td>
<td>48.6</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>6 (30)</td>
<td>72.9</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>25 (50)</td>
<td>78.6</td>
<td>20</td>
</tr>
</tbody>
</table>

\[ \rightarrow 6 \text{ GyE/fx, Total 36 GyE: BED} = 97.7 \text{ Gy}_{3.5} \]
\[ 3 \text{ GyE/fx, Total 45 GyE: BED} = 83.6 \text{ Gy}_{3.5} \]
Recent cases (2008.4.20)

<table>
<thead>
<tr>
<th></th>
<th>Age Gender</th>
<th>Size (mm)</th>
<th>S-M Grade</th>
<th>Pre-treatment</th>
<th>Proton</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/M</td>
<td>48×45×45</td>
<td>5</td>
<td>Emboli×3</td>
<td>6×6</td>
<td>44 months</td>
</tr>
<tr>
<td>2</td>
<td>28/M</td>
<td>40×42×38</td>
<td>5</td>
<td>Emboli×4</td>
<td>6×6</td>
<td>5 months</td>
</tr>
<tr>
<td>3</td>
<td>71/M</td>
<td>35×25×22</td>
<td>4</td>
<td>None</td>
<td>3×15</td>
<td>4 months</td>
</tr>
<tr>
<td>4</td>
<td>28/F</td>
<td>52×48×36</td>
<td>5</td>
<td>None</td>
<td>6×6</td>
<td>2 months</td>
</tr>
<tr>
<td>5</td>
<td>25/F</td>
<td>45×23×30</td>
<td>4</td>
<td>None</td>
<td>6×6</td>
<td>2 months</td>
</tr>
<tr>
<td>6</td>
<td>40/M</td>
<td>32×25×20</td>
<td>4</td>
<td>None</td>
<td>6×6</td>
<td>1 month</td>
</tr>
</tbody>
</table>
23 y.o. man Left occipital AVM with Spezler-Martin grade 5 (48×45×45 mm)

36 GyE / 6 fractions

36 months later
Acknowledgement

Dr. Koichi Tokuuye
Dr. Hidetsugu Nakayama
Dr. Shinji Sugawara

At the Campus of the University of Tsukuba, Apr. 2008
Thank you for your attention.