Proton beam therapy for liver tumors

University of Tsukuba, Japan

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introduction
Neoplasms in the liver
Classification of Liver Cancer
Liver Cancer Study Group of Japan

- Primary liver cancer
  - Hepatocellular Carcinoma (HCC)
  - Intrahepatic Cholangiocarcinoma (CCC)
  - Combined HCC & CCC
  - Cystadenocarcinoma
  - Hepatoblastoma

- Metastatic Liver cancer
  - Colon, Rectum, Breast etc.
Regional variations in the mortality rates of HCC

Age-adjusted mortality / 100,000

El-Serag HB, Gastroenterology 2007
Treatment options for HCC

• Surgical resection
  – The mainstay Tx but majority are not eligible

• Liver transplantation
  – Solitary, < 5cm or < 3 nodules, < 3cm

• Percutaneous ablation: RFA, PEI
  – < 3 nodules, < 3 cm

• Transcatheter Arterial Chemoembolization
  – Suitable for multiple, unresectable HCC

• Radiotherapy: particles, SBRT, Y90-IRT
Characteristics of HCC & requirements for the treatment

- Hepatitis virus related (cirrhosis)
  - 90% of pts. with HCC have hepatitis C virus infection  
    → save functional liver volume

- Multicentric progression
  → repeatable for new lesion

- Vascular invasion (portal v. & IVC)
  → RT rather than operation
Before treatment

Tumor shrinkage (just like surgery)

4 years later

normal liver enlargement (functional recovery)
National Laboratory for High Energy Physics (KEK)

Particle Radiation Medical Science Center (PARMS) 1983 – 1992
Proton Medical Research Center (PMRC) 1993 -
Mt. Tsukuba

University Hospital of Tsukuba

Proton Medical Research Center

(450 cases/year)
Patients in PMRC, Tsukuba
(1983 – 2014.3.)

HCC 32.9%
Prostate 11.8%
Lung 11.4%
Mets 10.2%
Esophagus 6.1%
H & N 5.8%
Pediatrics 5.1%
Brain 3.9%
Bladder 2.8%

Total 3,816

Number of patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Practice</th>
<th>Trial</th>
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<td>450</td>
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<tr>
<td>2011</td>
<td>300</td>
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<td>2010</td>
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<td>250</td>
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<td>2009</td>
<td>150</td>
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<tr>
<td>2008</td>
<td>100</td>
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</table>
system
Synchrotron

LINEAC

Hydrogen
A fiducial marker is used to adjust the daily positioning.

In-situ fiducial marker

Deep seated Moving target

digital radiography for tumor localization

Platinum fiducial markers
Respiratory gated irradiation

- **Lase Gauge**
- **Patient**
- **Couch**
- **Strain Gauge**

**Trigger and pre-trigger**

**Respiratory wave**

**Beam signal**
(Proton beams were released during the expiratory phases)
Protocols & results
Dose, Fractionations for HCC @ PMRC Tsukuba

1) 66 GyE / 10 fraction (EQD$_2$ = 91.3GyE) peripheral tumor

2) 72.6GyE / 22 fractions (EQD$_2$ = 80.5GyE) central tumor close to porta hepatis (< 2cm)

3) 74.0 GyE / 37 fractions (EQD$_2$ = 74GyE) close to GI < 2cm

RBE (relative biological effectiveness) = 1.1, 1 GyE = 1.1 Gy
Dose distribution for a peripheral type HCC
(HCC 72 y.o., LC (C), Pugh sc. 5, 7.5cm)

66 GyE/ 10 fr/ 15 day

white: GTV
red: 100% dose
blue: 10% dose
CT findings after proton therapy for HCC

before  66GyE/ 10fr/ 15day

2 mo

4 mo

28 mo
Central type HCC 81 yr., LC (C), Pugh score: 6, Vp4

72.6GyE/22 fr.
Central type HCC  72.6 GyE/ 22fr.

pre PBT

6 Mo. after
HCC close to the GI tract

74GyE / 37 fr. (77 GyE/ 35 fr)

Local control rates

- Protocol A: 1yr: 98%, 3yr: 87%, 5yr: 81%
- Protocol B
- Protocol C

Overall survival rates

- 1yr: 87%
- 3yr: 61%
- 5yr: 48%

Grade 3 GI complication: 3 cases in protocol C
HCC larger than 10cm

Median target volume
567 cc (335-1398cc)

72.6 GyE / 22 fractions
(47.3-89.1 GyE / 10-35 fractions)

Local control
87%

(Sugahara S et al., Int J Radiat Oncol Biol Phys 76: 460-466, 2010)
PBT as an initial Tx for HCC
Survival after PBT in HCC (fresh case)

Data from JLCAG

<table>
<thead>
<tr>
<th>treatment</th>
<th>1Y</th>
<th>2Y</th>
<th>3Y</th>
<th>4Y</th>
<th>5Y</th>
<th>6Y</th>
<th>7Y</th>
<th>8Y</th>
<th>9Y</th>
<th>10Y</th>
<th>11Y</th>
<th>12Y</th>
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<tr>
<td>all</td>
<td>77.5</td>
<td>64</td>
<td>52.5</td>
<td>43.1</td>
<td>25.4</td>
<td>29.6</td>
<td>24.6</td>
<td>20.5</td>
<td>17.3</td>
<td>14.7</td>
<td>(%)</td>
<td></td>
<td>96,404</td>
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<tr>
<td>surgery</td>
<td>87.8</td>
<td>78.3</td>
<td>69.2</td>
<td>61.1</td>
<td>53.4</td>
<td>47.5</td>
<td>41.1</td>
<td>35.9</td>
<td>31.2</td>
<td>27.7</td>
<td></td>
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<td>27,062</td>
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<td>RFA, PEI</td>
<td>92.3</td>
<td>79.7</td>
<td>66</td>
<td>53.2</td>
<td>42</td>
<td>33.3</td>
<td>26.3</td>
<td>20.8</td>
<td>16.7</td>
<td>13.2</td>
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<td>Proton</td>
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<td>86.6</td>
<td>75.9</td>
<td>59.7</td>
<td>48.5</td>
<td>41.9</td>
<td>38.9</td>
<td>32.5</td>
<td>24</td>
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</table>

JLCAG: Japan Liver Cancer Study Group, RFA: radiofrequency ablation, PEI: percutaneous Ethanol injection

Med. F/U Period: 37.3 Mon.  (2.3-155.3)
Alive: 61, Dead 53
Overall survival (n=114)
OS according to liver function (Child-Pugh)

Overall survival

<table>
<thead>
<tr>
<th>Child-Pugh</th>
<th>1Y</th>
<th>2Y</th>
<th>3Y</th>
<th>4Y</th>
<th>5Y</th>
<th>6Y</th>
<th>7Y</th>
<th>8Y</th>
<th>9Y</th>
<th>10Y</th>
<th>24 (%)</th>
<th>N</th>
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<tbody>
<tr>
<td>all</td>
<td>94.4</td>
<td>86.6</td>
<td>75.9</td>
<td>59.7</td>
<td>48.5</td>
<td>41.9</td>
<td>38.9</td>
<td>32.5</td>
<td>24</td>
<td>24</td>
<td>24 (%)</td>
<td>114</td>
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<tr>
<td>C-PA</td>
<td>98.6</td>
<td>93.1</td>
<td>82.7</td>
<td>74.9</td>
<td>64</td>
<td>57.7</td>
<td>53.6</td>
<td>44.7</td>
<td>33.1</td>
<td>33.1</td>
<td>82</td>
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<tr>
<td>C-PB</td>
<td>91.7</td>
<td>86.8</td>
<td>70.8</td>
<td>27</td>
<td>13.5</td>
<td>6.7</td>
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<td></td>
</tr>
<tr>
<td>C-PC</td>
<td>62.5</td>
<td>25</td>
<td>25</td>
<td>12.5</td>
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* * p<0.001
Toxicity

• Acute
  – No patient discontinued treatment due to acute reactions.
  – Gr. 3 hematologic toxicity: 4 (3.2%, PLT < 50000)

• Late
  – GI Gr.3: 3 2.6%
  – Biliary stenosis, biloma: 3 2.6%
  – Rib fracture: 3 2.6%
Liver function as most important risk factor

Child-Pugh score & OS (n = 250)

- Child A group (n=197); median 64 months; 3y 70%, 5y 58%
- Child B/C group (n=53); median 20 months; 3y 32%, 5y 18%
Liver function as most important risk factor

ICG R15 & OS for only Child-Pugh A cases (n = 197)

ICG R15: >40 (n=18)
3y 38%, 5y 30%

ICG R15: 30-39

ICG R15: 20-29

ICG R15: 10-19

ICG R15: 0-9

Survival rate

Time (months)
PVTT
(Vp3-4)

Strahlenther Onkol 2009;185:782-788
Cancer 2005;104:794-801
Portal vein tumor thrombosis (PVTT)

Case of 7 years survival with no evidence of disease progression
63 y.o. male 77.0GyE/35 fr Vp4

pretreatment

18 months after PBT

Complete response
Re-canalization
HCC with PVTT (1991-2005)
Main trunk or major branches of PV
n = 35

2-year local control rate: 91%
Median survival: 22mo
2-year overall survival: 48%

RTOG with very mild side effects

(Sugahara S et al., Strahlenther Onkol 185: 782-8, 2009)
## Radiation therapy for HCC with PVTT

<table>
<thead>
<tr>
<th>Author</th>
<th>No. Case</th>
<th>PVTT</th>
<th>treatment method</th>
<th>RR*</th>
<th>MST (Mo.)</th>
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<tr>
<td>Tazawa J</td>
<td>24</td>
<td>Vp3,4</td>
<td>TACE+RT50Gy</td>
<td>50</td>
<td>CR,PR;9.7, NC,PD;3.8</td>
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<td>Yamada K</td>
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<td>Vp3</td>
<td>TACE+RT60Gy+TACE</td>
<td>38</td>
<td>5.7(+2)</td>
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<tr>
<td>Ishikura S</td>
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<td>Vp3</td>
<td>TACE+RT</td>
<td>50</td>
<td>5.3</td>
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<tr>
<td>Nakagawa K</td>
<td>52</td>
<td>Vp2,3,4</td>
<td>3DCRT57Gy (39-60)</td>
<td>50</td>
<td>(25.3%;2YSR)</td>
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<tr>
<td>Kim DY</td>
<td>59</td>
<td>Vp3,4</td>
<td>3DCRT30-54Gy</td>
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<td>Lin CS</td>
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<td>Vp3,4</td>
<td>RT45Gy/15fr:22</td>
<td>75</td>
<td>6.0</td>
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<td>3DCRT45Gy/25fr:21</td>
<td>83</td>
<td>6.7</td>
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<td>Tsukuba</td>
<td>35</td>
<td>Vp3,4</td>
<td>PBT 72.6GyE (55-77)</td>
<td>91</td>
<td>22</td>
</tr>
</tbody>
</table>

*RR: response rate
HCC with PVTT (2009-2013, recent data)

Radical treatment: all GTV can be irradiated with intentional dose

\[
p < 0.0001
\]

\[
\text{MST: 6.33} \quad \text{MST: 26.9}
\]
Proton beam therapy for Cholangiocellular carcinoma (CCC)

Concurrent use of TS-1
Chemoproton therapy

1-year later

CCC

3-year later
CCC 73 yo female, cT3N0M0, 14x9 cm

74GyE/ 37fr/ 58 days, combined TS-1
Overall survival rate vs. time (month)

Curative group (n=12)
- Local control 9/12 (curative group)
- MST > 2 years (curative group)

Incurative group (n=8)
- MST by no surgery < 1 year
- MST by surgery = 2 years

p=0.048

OS in Proton for CCC (-2010, Tsukuba)
Mets & others
Metastatic and/or recurrent tumors

60yo woman liver metastasis from colon cancer

Obstruction of portal vein & bile duct
Chemoresistant & inoperable

Improvement of CT
High control rate for micrometastasis

Importantly to treat gross tumor with PBT

- 5 y NED
- Normal liver function

Salvage RT for metastatic and/or recurrent tumors
- PBT for central region
- Surgery for lateral lobe
PBT for liver metastasis

Dose: median 72.6 GyE (44-77 GyE)
Concurrent Chemo.: 28 cases

1Y: 68%
3Y: 43%
5Y: 31%

3-y survivor = 17 solitary : 7 multiple
2 y.o.- girl, hepatoblastoma. Stage IVA

Initial

Before PBT

61.6GyE/16fr 3fr/wks

Change of AFP

16 years after

(Oshiro Y. et al., Acta Oncol ISSN 0284-186X print/ISSN 1651-226X online © 2013)
summary
PBT for HCC

- 90% control with very less side effects

Multimodality therapy

RFA  surgery  TACE

X-SRT  PBT

Inoperable  Large volume  PVTT  elder medical problem

IVCTT
HCC with cirrhosis, multicentric fashion
Multimodality therapies based on tumor condition

- potentially proposed RCTs

PBT vs X-SRT vs RFA for 3cm HCC
PBT vs surgery for more than 3cm HCC

RCT?
A trial in Japan

Non randomized controlled study comparing proton beam therapy and hepatectomy for resectable hepatocellular carcinoma

Newly diagnosed solitary & nodular HCC
- 3 cm, 12 cm >, age 20 – 80 y.o.
- Child-Pugh 5 - 7, PS 0 - 1

The treatments (S or P) can be chosen by patient

- surgery
- Proton
  - 66Gy / 10 fr.
  - 72.6Gy / 22 fr.
Acknowledgment

Special thanks to all of the staffs who have been involved in PBT at University of Tsukuba