Clinical Session 3
Liver Cancer

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Proton Medical Research Center
University of Tsukuba
Liver Cancer: Topics for today

- Anatomy
- Epidemiology
- Risk factors of liver cancer
- Clinical presentation
- Diagnostic work-up
- Pathology
- Treatment options
- Particle therapy
Liver Cancer: Topics for today

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Anatomy

- The largest organ in the body (1200 – 1500g)
- Lies in the right upper quadrant
- Pyramid like shape
- Has a double blood supply: portal vein and hepatic artery
The structure of normal human liver

Hepatic lobule

From: Sheila Sherlock, Diseases of the Liver and Biliary System
Function of the liver

- Metabolism
  - anabolism of protein, cholesterol, etc.
  - catabolism of protein, fat, etc.
- Nutrient storage and supply
- Detoxification
- Bile production and excretion
- Regulation of circulating blood volume
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• Particle therapy
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.
Primary liver cancer is the fifth most common cancer worldwide and the third most common cause of cancer mortality.

Hepatocellular carcinoma (HCC) accounts for between 85% and 90% of primary liver cancers.

Today’s talk will be focused on HCC
Epidemiology of HCC

• Variations among geographic regions, racial and ethnic groups
• Male : Female = 2 : 1 – 4 : 1
• Environmental potentially preventable risk factors
Regional variations in the mortality rates of HCC

Age-adjusted mortality / 100,000

El-Serag HB, Gastroenterology 2007
Average yearly age-adjusted incidence rates for HCC men and women in the US

Whites include approx. 25% Hispanics

El-Serag HB, Gastroenterology 2007
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• Particle therapy
Risk factors of HCC

• Hepatitis virus infection  HBV, HCV
• Alcohol
• Toxic exposure
  – Afratoxin, Vinyl chloride
• Nonalcoholic fatty liver disease (NASH)
• Obesity
• Diabetes Mellitus
Proportion of patients with HCC related to HCV viral hepatitis

Hassan MM, J Clin Gastroenterol 2002
Liver Cancer: Topics for today

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• Pathology
• Treatment options
• Particle therapy
Clinical presentation

- Asymptomatic in early stage to sometimes advanced stage
- Screening for cohort at risk by elevation of AFP or ultrasonography
- Symptoms: Hepatic insufficiency
  - General fatigue, jaundice, ascites, leg edema
- Symptoms: Portal hypertension
  - Vascular spider, GI bleeding
- Symptoms: Tumore-related
  - Palpable mass, pain, abdominal fullness
  - Symptom induced by metastasis
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Diagnostic Work-Up

• Clinical history of
  – Hepatitis, jaundice, blood transfusion
  – Drugs, Aflatoxin

• Blood test
  – Serology for HBV, HCV, AFP, PIVKA-II
  – Liver function

• Imaging
  – Ultrasound, CT, MRI

• Biopsy
  – who plan to have a nonsurgical Tx
Two types of human hepatocarcinogenesis

• Upper: de novo hepatocarcinogenesis
• Lower: stepwise development from high-grade DN, high-grade DN with well-differentiated HCC foci, and overt HCC

Modified from Matsui O, Radiology 1991
Hypervascular malignant foci in borderline lesions of HCC

Transverse CTAP shows a spotty hypoattenuating area within an slightly hypoattenuating nodule. Transverse CTHA shows a spotty hyperattenuating area within the isoattenuating nodule. Transverse on the arterial dominant phase of dynamic CT shows a hypervascular focus within a slightly hypoattenuating nodule.

Shinmura R, Eur Radiol 2008
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Liver cirrhosis

Normal liver

The small finely nodular liver of *micronodular cirrhosis*

The glossly distorted coarsely nodular liver of *macronodular cirrhosis*
Histology of cirrhotic liver

Normal liver tissue: HE stain

Cirrhotic liver tissue: HE stain

Collagens are stained in blue

http://www.kanazawa-med.ac.jp

Cirrhotic liver tissue: Azan stain
Macroscopic types of HCC

- Single nodular type
- Multiple nodular type
- Massive type
- Diffuse type

Classification of Primary Liver Cancer: Liver Cancer Study Group of Janan
Histology of HCC

Well differentiated

Moderately differentiated

Poorly differentiated

Undifferentiated

Classification of Primary Liver Cancer: Liver Cancer Study Group of Jnan
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Requirements for the treatment of HCC

– Because of underlying liver dysfunction and multicentric occurrence

• High local control rate
• To save functioning liver volume as much as possible
• Repeatable for newly developing lesions
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
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250 MeV protons degraded from 500MeV horizontal & vertical, fixed beam
New proton therapy facility in the University Campus

Dedicated to medical use
Treatment parameter

- **Energy**
  - 70 - 250 MeV (155, 200, 250 MeV)

- **Dose rate**
  - 1 - 3 Gy / min

- **Maximum field size**
  - Circle (200 mm)
  - 160 mm square

- **SOBP**
  - 10 - 120 mm
    (10 mm interval)

- **Bolus**
- **MLC (5 mm thickness)**
Technical innovations for treating liver tumors

- Real-time tumor localization using fluoroscope (beam’s eye view) 1988
- Fiducial marker implanted under ultrasonographic guidance 1990
- Respiratory gated irradiation (ReGIS) 1991

Standard treatment procedure was established in late 1991
In-situ fiducial marker

Iridium
A fiducial marker is used to adjust the daily positioning under the respiratory gating.
Respiratory gated irradiation

Proton beams were released during the expiratory phases.

Respiratory wave
Trigger and pre-trigger
Beam signal (Proton beams were released during the expiratory phases)
Treatment Plan for solitary HCC
radiation-induced hepatic injury demonstrated along the beam path
66 M  Nodular HCC with cirrhosis (Child B)

80 Gy/ 20fx/ 43D, ant. & rt. lateral portals

3.5 Mo. after completion of PRT
Clinical results of particle therapy for HCC

<table>
<thead>
<tr>
<th>Series</th>
<th>Particle</th>
<th>Patient No.</th>
<th>Dose (GyE)/Fx</th>
<th>ED in 2Gy/Fx</th>
<th>Prior therapy</th>
<th>Local control @2yr</th>
<th>Overall survival @2yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawashima 2005</td>
<td>P</td>
<td>30</td>
<td>76/ 20</td>
<td>87.4</td>
<td>none</td>
<td>96%</td>
<td>66%</td>
</tr>
<tr>
<td>Bush 2004</td>
<td>P</td>
<td>34</td>
<td>63/ 15</td>
<td>74.6</td>
<td>none</td>
<td>75%</td>
<td>55%</td>
</tr>
<tr>
<td>Fukumitsu 2009</td>
<td>P</td>
<td>51</td>
<td>66/ 10</td>
<td>91.3</td>
<td>65%</td>
<td>94.5%</td>
<td>49.2%</td>
</tr>
<tr>
<td>Mizumoto 2008</td>
<td>P</td>
<td>53</td>
<td>72.6/ 22</td>
<td>80.5</td>
<td>72%</td>
<td>86%</td>
<td>45.1%</td>
</tr>
<tr>
<td>Nakayama 2009</td>
<td>P</td>
<td>318</td>
<td>78.3-91.3</td>
<td>47%</td>
<td>N.A.</td>
<td>64.7%</td>
<td></td>
</tr>
<tr>
<td>Kato 2004</td>
<td>C</td>
<td>24</td>
<td>49.5-79.5/ 15</td>
<td>none</td>
<td>81%</td>
<td></td>
<td>50%</td>
</tr>
</tbody>
</table>

ED: equivalent dose, Fx: fraction, N.A. not assessed
RBE: 1.1 for proton, 3.0 for carbon
Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients.


Department of Gastroenterology, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan.

### Characteristics of 162 patients treated from 1985 to 1998 (HCC)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 (41-84)</td>
</tr>
<tr>
<td>Men / Women</td>
<td>124 / 38</td>
</tr>
<tr>
<td>PS 0-1 / 2-3</td>
<td>140 / 22</td>
</tr>
<tr>
<td>Liver damage I/ II/ III</td>
<td>58 / 82 / 22</td>
</tr>
<tr>
<td>Number of Tumors</td>
<td></td>
</tr>
<tr>
<td>1 / multiple</td>
<td>80 / 82</td>
</tr>
<tr>
<td>No prior Tx/ Prior Tx</td>
<td>45 / 117</td>
</tr>
</tbody>
</table>
### Classification of liver damage

*Liver Cancer Study Group of Japan*

<table>
<thead>
<tr>
<th>Items</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Responsive</td>
<td>Unresponsive</td>
</tr>
<tr>
<td>Bil (mg/dl)</td>
<td>&lt;2.0</td>
<td>2.0-3.0</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>&gt;3.5</td>
<td>3.0-3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>ICGR(_{15}) (%)</td>
<td>&lt;15</td>
<td>15-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>PT (%)</td>
<td>&gt;80</td>
<td>50-80</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

PT: prothrombin time; Bil: serum bilirubin; Alb: serum albumin
## Dose fractionation

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median dose</td>
<td>79.2 GyE/16 fractions</td>
</tr>
<tr>
<td>Range</td>
<td>35.8 GyE - 96.3 GyE</td>
</tr>
<tr>
<td></td>
<td>10 - 30 fractions</td>
</tr>
<tr>
<td>LQ model</td>
<td></td>
</tr>
<tr>
<td>$\alpha/\beta=10$</td>
<td>98.7 GyE with 2 Gy/fraction</td>
</tr>
<tr>
<td>$\alpha/\beta=3$</td>
<td>125.9 GyE with 2 Gy/fraction</td>
</tr>
<tr>
<td>RBE</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Irradiation technique

CTV
  GTV + 5-10 mm margin

PTV
  CTV + 5 mm margin

Internal margin
  5 mm for respiratory movements

Respiratory gated irradiation (ReGIS)
Overall survival

Proportion surviving

Time after Tx (month)

N=162

23.5%

Overall survival

Proportion surviving

Time after Tx (month)

N=162

23.5%
### Prognostic factors: multi-variates analysis

<table>
<thead>
<tr>
<th>P values</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>0.10</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td>0.11</td>
</tr>
<tr>
<td>Number of tumors</td>
<td>0.02</td>
</tr>
<tr>
<td>PVTT</td>
<td>0.75</td>
</tr>
<tr>
<td>Impairment of liver function</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AFP value</td>
<td>0.07</td>
</tr>
<tr>
<td>Total dose (&lt;72, &gt;=72)</td>
<td>0.95</td>
</tr>
<tr>
<td>Fraction dose</td>
<td>0.82</td>
</tr>
<tr>
<td>Prior Tx</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Local control rate

Proportion surviving

Time after Tx (month)

86.9%
New lesions in the liver

- Proportion having new lesions:
  - 84.8% at Time after Tx (month)
Survival by degree of liver damage (J-classif.)

Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>44.3%</td>
<td>58</td>
</tr>
<tr>
<td>II</td>
<td>16.9%</td>
<td>82</td>
</tr>
<tr>
<td>III</td>
<td>4.5%</td>
<td>22</td>
</tr>
</tbody>
</table>

Time after Tx (month)
Case: a 47 year old woman with chronic hepatitis (B) and aplastic anemia


Proton beam therapy can be repeatable.
Survival of a favorable subgroup
(Liver damage Gr. I, no prior Tx, solitary, 2< Tumor diameter< 5cm )

Proportion surviving

Time after Tx (month)

N=24
61.5%
**Clinical results of various modalities for HCC (liver damage of Gr. I, 2cm<Diameter<5cm, solitary lesion)**

<table>
<thead>
<tr>
<th>Tx</th>
<th>Survival at 5 years</th>
<th># of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton</td>
<td>61.5%</td>
<td>24</td>
</tr>
<tr>
<td>Surgery</td>
<td>58.3</td>
<td>2722</td>
</tr>
<tr>
<td>PEI</td>
<td>38.6</td>
<td>587</td>
</tr>
</tbody>
</table>

PEI: percutaneous ethanol injection
76 F, HCC: 10 X 7cm, Tx with PRT alone, 81Gy/27fx/48days
76 F, HCC: 10 X 7cm, 81Gy/ 27fx/ 48days

Proton beam therapy works well even if the tumor is this big!
# Treatment sequelae in 185 courses

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute – subacute</strong></td>
<td></td>
</tr>
<tr>
<td>Elevation of bilirubin</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Elevation of transaminase level</td>
<td>18 (9.7)</td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td></td>
</tr>
<tr>
<td>Infectious biloma</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Common bile duct stenosis</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Gastrointestinal tract bleeding</td>
<td>2 (1.1)</td>
</tr>
</tbody>
</table>
## Dose, Fractionations for HCC @ PMRC Tsukuba

<table>
<thead>
<tr>
<th></th>
<th>D(GyE)</th>
<th>D(GyE)</th>
<th>Fx.</th>
<th>Gy10</th>
<th>Gy3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex-standard</td>
<td>79.2</td>
<td>4.95</td>
<td>16</td>
<td>118.4</td>
<td>209.9</td>
</tr>
<tr>
<td>Low risk</td>
<td>66.0</td>
<td>6.6</td>
<td>10</td>
<td>109.6</td>
<td>211.2</td>
</tr>
<tr>
<td>Porta hepatis</td>
<td>72.6</td>
<td>3.3</td>
<td>22</td>
<td>96.6</td>
<td>152.5</td>
</tr>
<tr>
<td>GI interference</td>
<td>74.0</td>
<td>2.0</td>
<td>37</td>
<td>88.8</td>
<td>123.3</td>
</tr>
<tr>
<td>PVTT</td>
<td>60.0</td>
<td>4.0</td>
<td>15</td>
<td>84.0</td>
<td>140.0</td>
</tr>
</tbody>
</table>

RBE: 1.1
Proton Beam Therapy for HCC with Portal Vein Tumor Thrombus (Vp3-4)
64 M  HCC with tumor thrombus in PV and IVC

PVTT

IVC tumor thrombs
Proton beam therapy can preserve uninvolved liver tissue and function effectively!

50Gy/ 10fx/ 18D through right lateral portal

19 months after completion of PRT
# Radiation Therapy for PVTT

<table>
<thead>
<tr>
<th>Name</th>
<th>Case</th>
<th>Vp</th>
<th>Treatment Method</th>
<th>RR</th>
<th>MST (Mo.)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tazawa J</td>
<td>24</td>
<td>Vp3,4</td>
<td>TACE+RT 50Gy</td>
<td>50</td>
<td>CR, PR: 9.7</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NC, PD: 3.8</td>
<td></td>
</tr>
<tr>
<td>Yamada K</td>
<td>8</td>
<td>Vp3</td>
<td>TACE+RT 60Gy + TACE</td>
<td>38</td>
<td>5.7 (+2)</td>
<td>2001</td>
</tr>
<tr>
<td>Ishikura S</td>
<td>20</td>
<td>Vp3</td>
<td>TACE+RT</td>
<td>50</td>
<td>5.3</td>
<td>2002</td>
</tr>
<tr>
<td>Nakagawa K</td>
<td>52</td>
<td>Vp2,3,4</td>
<td>3DCRT 57Gy (39-60)</td>
<td>50</td>
<td>(25.3%; 2YSR)</td>
<td>2005</td>
</tr>
<tr>
<td>Kim DY</td>
<td>59</td>
<td>Vp3,4</td>
<td>3DCRT 30-54Gy</td>
<td>45.8</td>
<td>CR, PR: 10.7</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NC, PD: 5.3</td>
<td></td>
</tr>
<tr>
<td>Lin CS</td>
<td>43</td>
<td>Vp3,4</td>
<td>RT 45Gy/15fr: 22</td>
<td>75</td>
<td>6.0</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3DCRT 45Gy/25fr: 21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Tsukuba</td>
<td>35</td>
<td>Vp3,4</td>
<td>PBT 72.6GyE (55-77)</td>
<td>91</td>
<td>22</td>
<td>2010</td>
</tr>
</tbody>
</table>

*RR: response rate
Conclusions

• Proton beam therapy is effective and safe for the treatment of patients with HCC.
• Local control is expected even for the case of big tumor size or with vascular invasion.
• Proton beam therapy is repeatable, if remnant liver function is good enough.
Special thanks to

@ KEK: Shigeki SUWA, Toshio KITAGAWA, Sadayoshi FUKUMOTO, Tetsuo INADA, Hirohiko TSUJI, Masayoshi AKISADA, Yuji ITAI, Akira MARUHASHI, Yoshihisa TAKADA, Yoshinori HAYAKAWA, Junichiro TADA, Kiyoshi OHARA, Yutaka HIROKAWA, Takuro ARIMOTO, Shigeyuki MURAYAMA, Hiroshi TSUJI, Toshiya CHIBA, Kenji HASEZAWA

@ Univ.Camp.: Yasuyuki AKINE, Koji TSUBOI, Hideyuki SAKURAI, Takeji SAKAE, Koichi TOKUUYE, Kiyoshi YASUOKA, Shinji SUGAHARA, Toshiyuki TERUNUMA, Yoshiyuki SHIOYAMA, Kenji KAGEI, Hiroshi IGAKI, Masaharu HATA, Nobuyoshi FUKUMITSU, Hidetsugu NAKAYAMA, Takayuki HASHIMOTO, Masashi MIZUMOTO, Yoshiko OSHIRO