Protons for Advanced HCC

Theodore S. Hong, MD
Director, Gastrointestinal Radiation Oncology
Massachusetts General Hospital
Co-Leader, Gastrointestinal Malignancies Research Program
Dana-Farber/Harvard Cancer Center
Associate Professor of Radiation Oncology
Harvard Medical School
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  – Taiho
  – Astra-Zeneca
  – Bristol Myers Squibb
  – Clinical Genomics
Outline

• Protons for small HCC
  – Proton therapy: Why consider it?
  – Rationale and data for protons and small HCC

• Protons for advanced HCC
  – Selection of patients
  – Data for large HCC
  – Data for Central HCC
  – High Risk patients
SBRT: Bujold et al, JCO 2013

• Pooled analysis of a Phase I/II trial of 50 pts and a Phase II trial of 52 patients.
  – Eligibility: Child A pts with HCC who were not current candidates for surgery, RFA, TACE, or EtOH ablation and at least 700ml of uninvolved liver (800ml for Trial 1).
  – GTV = arterially enhancing lesion w/ washout on delayed venous phase. Optional CTV was 5mm in Trial 2 (8mm in Trial 2). PTV = CTV + ≥5mm to account for breathing.
  – Dose: 30 to 54 Gy (24 to 54 Gy in trial 1) delivered to PTV in six fractions delivered every other day.
    • Dose determined by Veff (maximum Veff was 600 ml in Trial 2).
• Endpoints: Toxicity and local control at one year
Bujold et al, continued.

- **Patients:**
  - 38% HBV, 38% HCV.
  - 55% had tumor vein thrombosis.
  - 62% CLIP ≥ 2
  - 52% had progressed through prior treatment.

- **Lesions:**
  - Median size was 7.2 cm (PTV volume 283.5 ml).
  - 61% had multiple lesions. Median sum of largest diameters of the lesions was 10.2 cm.

- **SBRT Delivery**
  - Median minimum dose to PTV was 30 Gy.
  - Median Veff was 44%.
  - Median mean dose to the liver was 15.9 Gy.
Bujold et al: LC and OS

- Median f/u 31.4 months
- LC at 1 yr: 87% (95%CI 78-93%)
  - CR: 11 patients (11%)
  - PR: 44 patients (43%)
  - Stable disease: 45 pts (44%)
- Median OS: 17 mos (95%CI 10.4-21.3 mos)
  - Trial 2 enrollment and lack of TVT significant for OS on MVA.
- Median TTP: 6 mos (95% CI 3.4 to 6.4 mos)
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3 No.</th>
<th>Grade 3 %</th>
<th>Grade 4 No.</th>
<th>Grade 4 %</th>
<th>Grade 5 No.</th>
<th>Grade 5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>27</td>
<td>26.5</td>
<td>3</td>
<td>2.9</td>
<td>7</td>
<td>6.9</td>
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<tr>
<td>Fatigue</td>
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<td>1.0</td>
<td>0</td>
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</tr>
<tr>
<td>Biochemical†</td>
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<td>Albumin</td>
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<td>AST/ALT</td>
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<td>10.9</td>
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<tr>
<td>Bilirubin</td>
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<td>Creatinine</td>
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<td>INR</td>
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<td>Hematologic†</td>
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<td>Hemoglobin</td>
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<td>Leukocytes</td>
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<td>0.0</td>
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<td>0.0</td>
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<td>Platelets</td>
<td>9</td>
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<td>0</td>
<td>0.0</td>
<td>0</td>
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<tr>
<td>GI</td>
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<td>Cholangitis</td>
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<td>1.0</td>
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<td>Gastritis/GI bleed</td>
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<td>Liver failure</td>
<td>1</td>
<td>1.0</td>
<td>1</td>
<td>1.0</td>
<td>5</td>
<td>4.9</td>
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<tr>
<td>Nausea/vomiting</td>
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<td>1.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
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<tr>
<td>Pain (RUQ/chest wall)</td>
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<td>1.0</td>
<td>0</td>
<td>0.0</td>
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Proportion of patients with CTP deterioration, without progressive disease, %

<table>
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<tr>
<th></th>
<th>3 months</th>
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<th>12 months</th>
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<tr>
<td>Score</td>
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<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class</td>
<td>29</td>
<td>6</td>
<td></td>
<td></td>
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## HCC Proton Prospective Data

<table>
<thead>
<tr>
<th>Site</th>
<th>Yr</th>
<th>N</th>
<th>CP</th>
<th>Tumor size</th>
<th>Dose, fraction</th>
<th>OS</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsukuba Prospective</td>
<td>2009</td>
<td>51</td>
<td>80% A 20% B</td>
<td>45pts&lt; 5cm</td>
<td>66GyE, 10 fx</td>
<td>38.7% at 5 yrs</td>
<td>87.8% at 5 yrs</td>
</tr>
<tr>
<td>Loma Linda</td>
<td>2011</td>
<td>76</td>
<td>24% C</td>
<td>Mean size 5.5cm</td>
<td>63 GyE, 15 fx</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>MGH/MDA CC/UPenn</td>
<td>2016</td>
<td>44</td>
<td>73% A 21% B</td>
<td>Mean size 5 cm</td>
<td>67.5 GyE, 15 fx</td>
<td>60% at 2 yrs</td>
<td>95% at 2 yrs</td>
</tr>
</tbody>
</table>
MGH/MDACC/UPENN Phase II: Protons for HCC/ICC

• Multicenter, single arm ph II study (MGH/MDACC/UPenn)
• Sample size calculated to demonstrate >80% LC at 2 yrs
• Eligibility
  – No cirrhosis or Child’s A/B
  – ECOG PS 0-2
  – No extrahepatic disease
  – No Prior RT
  – Max tumor size 12 cm

Treatment

- 15 Fractions
- Peripheral - 67.5 Gy
- Central (within 2 cm porta hepatis) – 58 Gy
## Patient Characteristics

### Table 1. Patient and Treatment Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>All Patients N=83</th>
<th>HCC N=44</th>
<th>ICC N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP</td>
<td>A</td>
<td>79.5% (66)</td>
<td>72.7% (32)</td>
<td>87.2% (34)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>15.7% (13)</td>
<td>20.5% (9)</td>
<td>10.3% (4)</td>
</tr>
<tr>
<td></td>
<td>No Cirrhosis</td>
<td>4.8% (4)</td>
<td>6.8% (3)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>BCLC Stage</td>
<td>A/B</td>
<td>50.0% (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>47.7% (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Missing]</td>
<td>2.3% (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clip Score</td>
<td>0-1</td>
<td>68.2% (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>31.8% (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Missing]</td>
<td>0.0% (0)</td>
<td></td>
<td></td>
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<tr>
<td>Tumor Vascular Thrombosis</td>
<td>Yes</td>
<td>28.9% (24)</td>
<td>29.5% (13)</td>
<td>28.2% (11)</td>
</tr>
<tr>
<td>Disease Status</td>
<td>Locally Recurrent</td>
<td>6.0% (5)</td>
<td>9.1% (4)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td></td>
<td>Newly Diagnosed</td>
<td>94.0% (78)</td>
<td>90.9% (40)</td>
<td>97.4% (38)</td>
</tr>
<tr>
<td>Number of Nodular Tumors</td>
<td>1</td>
<td>79.5% (66)</td>
<td>72.7% (32)</td>
<td>87.2% (34)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>15.7% (13)</td>
<td>22.7% (10)</td>
<td>7.7% (3)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4.8% (4)</td>
<td>4.5% (2)</td>
<td>5.1% (2)</td>
</tr>
<tr>
<td>Longest Tumor Dimension, cm</td>
<td></td>
<td>5.7 (1.9 - 12.0)</td>
<td>5.0 (1.9 - 12.0)</td>
<td>6.0 (2.2 - 10.9)</td>
</tr>
<tr>
<td>Sum of Longest Tumor Diameters, cm</td>
<td></td>
<td>5.8 (1.9 - 12.0)</td>
<td>5.7 (1.9 - 12.0)</td>
<td>6.0 (2.4 - 10.9)</td>
</tr>
<tr>
<td><strong>Biochemical Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Bilirubin, mg/dL</td>
<td></td>
<td>0.7 (0.2 - 3.2)</td>
<td>0.8 (0.2 - 3.2)</td>
<td>0.6 (0.2 - 3.2)</td>
</tr>
<tr>
<td>Platelets, k/UL</td>
<td></td>
<td>151.0 (55.0 - 463.0)</td>
<td>132.5 (55.0 - 336.0)</td>
<td>183.0 (59.0 - 463.0)</td>
</tr>
<tr>
<td>AFP, ng/mL*</td>
<td></td>
<td>7.0 (1.3 - 66081)</td>
<td>18.6 (1.3 - 66081)</td>
<td>4.6 (1.3 - 461.9)</td>
</tr>
<tr>
<td>CA-19.9 (u/mL)*</td>
<td></td>
<td>38.1 (0.0 - 10549)</td>
<td>31.0 (0.0 - 398.0)</td>
<td>72.0 (0.0 - 10549)</td>
</tr>
<tr>
<td><strong>Previous Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Surgical Resection</td>
<td>Yes</td>
<td>4.8% (4)</td>
<td>6.8% (3)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Any Transarterial Chemoembolization</td>
<td>Yes</td>
<td>6.0% (5)</td>
<td>11.4% (5)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Any Radiofrequency Ablation</td>
<td>Yes</td>
<td>2.4% (2)</td>
<td>2.3% (1)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Any Chemotherapy</td>
<td>Yes</td>
<td>32.5% (27)</td>
<td>6.8% (3)</td>
<td>61.5% (24)</td>
</tr>
<tr>
<td>Any Other</td>
<td>Yes</td>
<td>15.7% (13)</td>
<td>9.1% (4)</td>
<td>23.1% (9)</td>
</tr>
<tr>
<td>None</td>
<td>Yes</td>
<td>54.2% (45)</td>
<td>68.2% (30)</td>
<td>38.5% (15)</td>
</tr>
</tbody>
</table>

* AFP: N=82  
CA-19.9: N=76
Table 2. Treatment characteristics overall and by disease type

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients N=83</th>
<th>HCC N=44</th>
<th>ICC N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV Volume, cm³*</td>
<td>127.2 (3.7 - 2045.0)</td>
<td>106.4 (4.4 - 2045.0)</td>
<td>133.7 (3.7 - 599.7)</td>
</tr>
<tr>
<td>Whole Liver Volume, cm³</td>
<td>1600.1 (612.9 - 3369.3)</td>
<td>1744.0 (895.0 - 3369.3)</td>
<td>1487.0 (612.9 - 2522.4)</td>
</tr>
<tr>
<td>Mean Liver Dose, GyRBE</td>
<td>19.2 (3.2 - 29.5)</td>
<td>18.4 (6.2 - 29.3)</td>
<td>21.4 (3.2 - 29.5)</td>
</tr>
<tr>
<td>Dose Delivered, GyRBE</td>
<td>58.0 (15.1 - 67.5)</td>
<td>58.0 (40.5 - 67.5)</td>
<td>58.0 (15.1 - 67.5)</td>
</tr>
<tr>
<td>Dose Completed</td>
<td>94.0% (78)</td>
<td>95.5% (42)</td>
<td>92.3% (36)</td>
</tr>
</tbody>
</table>

* GTV: N=82
Gr 3 Radiation-Related Toxicity
3 pts (4%)

- Hyperbilirubinemia – 1 pt
- Stomach ulcer – 1 pt
- Liver failure – 1 pt
- Ascites – 1 pt

Worsening CP score at 3 mo 3%
Local Control

A

Cumulative Incidence Function

- Red: Death without local recurrence
- Blue: Local recurrence

Months from Radiation Start Date

B

Probability of Local Recurrence

- Red: LCC
- Blue: ICC

Months from Radiation Start Date

C

Probability of Local Recurrence

- Red: 60+ GyE
- Blue: <60 GyE

Months from Radiation Start Date
Survival
### Patterns of Failure

#### Table 4. Patterns of failure

<table>
<thead>
<tr>
<th>PFS Status</th>
<th>All Patients N=83</th>
<th>HCC N=44</th>
<th>ICC N=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive, No Progression</td>
<td>31.3% (26)</td>
<td>40.9% (18)</td>
<td>20.5% (8)</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>45.8% (38)</td>
<td>38.6% (17)</td>
<td>53.8% (21)</td>
</tr>
<tr>
<td>Local Failure and Distant Metastases</td>
<td>3.6% (3)</td>
<td>4.5% (2)</td>
<td>2.6% (1)</td>
</tr>
<tr>
<td>Isolated Local Failure</td>
<td>6.0% (5)</td>
<td>0.0% (0)</td>
<td>12.8% (5)</td>
</tr>
<tr>
<td>Dead of Disease, No Progression</td>
<td>2.4% (2)</td>
<td>0.0% (0)</td>
<td>5.1% (2)</td>
</tr>
<tr>
<td>Dead of Other Causes, No Progression</td>
<td>10.8% (9)</td>
<td>15.9% (7)</td>
<td>5.1% (2)</td>
</tr>
</tbody>
</table>
Conclusions

• High dose, hypofractionated protons is associated with high rates of local control in HCC
• Low risk of worsening hepatic function at 3 mo, though it can happen later
Large HCCs: Tsukuba University

- 22 patients
- Median tumor size 11 cm (range 10-14 cm)
- CP-A 50%; CP-B 50%
- 90% central tumors
- 72.6 GyE in 22 fx

Sugahara et al. IJROBP 2010
Large HCCs- Results

- OS-2 36%
- PFS-2 24%
- LC-2 87%
- Liver related deaths- 14%
Protons and Portal Vein Tumor Thrombus (Tsukuba)

- 35 pts
- HCC with PVTT
- 72.6 GyE in 22 fx

Sugahara et al. Strahlenther Onkol 2009
PVTT Results

- LC-2- 91%
- Complete response- 54%
- Recanalization of PV- 43%
Advanced Cirrhosis (CP B/C)

- Rates of CP worsening
  - Loma Linda- 76 pts- (CP-B 47%, CP-C 24%)
    - 0%
  - Tsukuba-259 pts- (CP-B 22%)
    - CP-A 16%
    - CP-B 11%
  - MGH/MDACC/UPenn- 44 pts- (CP-B 21%)
    - 3.6%

- COMPARE TO SBRT (Bujold) (29%)
HCC CP-C (Tsukuba)

- 19 pts
- CP 10-14
- 72 GyE in 16 fx
- Death from liver failure – 42%
- No CP score progression
- CP score improvement- 74%

Hata et al. Strahlenther Oncol 2006
Selecting patients for protons

Gandhi et al. Pract Radiat Oncol 2015
Protons in Advanced HCC

- Selection
  - Large tumors
  - Deep anatomic location
  - Poor Hepatic Function
NRG GI-003
Protons v Photons for HCC

- Planned Number of fractions, 5 or 15 (Determined by treating physician)
- Tumor vascular thrombus

Radiation Therapy (Protons)
Individualized Dosing

Radiation Therapy (Photons)
Individualized Dosing

Primary Endpoint- Overall Survival
Endpoints

• Primary
  – Overall Survival

• Secondary
  – PFS
  – LC
  – Toxicity
    • Liver function as measured by CP, AIBi
    • PROs (FACT-Hep v.4)
Eligibility

- Patients must have biopsy proven unresectable or locally recurrent hepatocellular cancer. Patients may have single or multinodular tumors (up to 3). Diagnosis by pathologic confirmation OR radiographic criteria will be allowed. Patients with a single lesion must be 15 cm or less in greatest dimension. For patients with two lesions, no lesion may be greater than 10 cm in greatest dimension. For patients with three lesions, no lesion may be greater than 6 cm in greatest dimension. There must be no evidence of extrahepatic tumor. Portal vein involvement or thrombosis is allowed.
- The combined tumor diameter must be ≥ 4 cm.
- Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan.
- Patients may have had prior chemotherapy, targeted biological therapy (e.g. sorafenib), surgery, transarterial chemoembolization (TACE), radiofrequency ablation, or percutaneous ablation (radiofrequency, microwave, irreversible electroporation, ethanol injection, cryotherapy) for their disease.
- Patients must be 18 years of age or older.
- Life expectancy of greater than three months.
- Child’s A or B7 cirrhosis, or no cirrhosis
HGF- Impact on CTP increase
HGF- Impact on survival
Conclusions

• Protons may be best utilized for large tumors, challenging locations, poor hepatic function

• Randomized trial has been initiated