Niches for Stereotactactic Radiation Therapy in HCC

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Therapeutic Radiology
Radiation Therapy for Liver Tumors

• Historically, liver-directed RT was limited to the palliative setting due to the risk of radiation-induced liver disease (RILD)

• Because liver parenchyma has parallel architecture, high-dose RT can be delivered to small volumes of the liver

• With modern RT techniques including intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and image guidance, liver-directed RT is now a safe and effective treatment option

• Ablative doses can be delivered to the tumor without compromising liver function
Stereotactic Body Radiation Therapy (SBRT)

- SBRT uses multiple conformal beams or arcs to deliver high doses of RT with rapid dose fall-off beyond the target volume
- Typically 1–5 fractions
- The high radiation doses result in an ablative effect on the tumor through vascular injury, in addition to the DNA damage and cell death seen in conventionally fractionated RT
Stereotactic Body Radiation Therapy (SBRT)

- SBRT depends on accurate target identification, precise and reproducible patient immobilization, and assessment of target motion
- Patients are immobilized in a full body mold (vacloc)
- Abdominal compression is applied to reduce organ and target motion with respiration
- A four-dimensional (4D) planning CT is obtained to evaluate respiratory motion
- A CT is obtained on the linac for alignment prior to each fraction
- Fiducial markers can be placed in the tumor to assist with alignment
- Respiratory gating can be used to deliver RT only during certain phases of the respiratory cycle
SBRT Program at Yale

- Approximately 250 cases per year
  - Lung
  - Liver
  - Pancreas
  - Prostate
  - Oligometastastic disease
SBRT for HCC

1. Localized HCC in Nonsurgical Candidates
2. Locally Advanced Unresectable HCC
3. Advanced Disease with Portal Vein Thrombosis
4. Bridge Therapy
SBRT for HCC

- Largest prospective trial: Phase I/II trial at Princess Margaret Hospital
  - 102 patients with primary HCC treated with six-fraction SBRT
  - All had CTP class A liver disease
  - 61% had multiple liver lesions
  - 55% had tumor vascular thrombosis
  - Median tumor size of 7.2 cm
  - One-year local control: 87%
  - Median OS 17 months
  - A decline in CTP class was seen in 29% of patients at 3 months, resolving in all but 6% at 12 months
  - Patients who experienced liver toxicity had higher mean liver doses, underscoring the importance of sparing a sufficient volume of normal liver

Bujold et al, JCO 2013
SBRT in Patients with More Advanced Cirrhosis

- SBRT is challenging because most patients have significant underlying liver disease
- Several studies, including a Phase I/II trial at Indiana University included CTP-B patients
  - Kaplan-Meier 2-year LC
    - 91% for CTP-A; 82% for CTP-B
- Grade 3 or greater liver toxicity was increased in patients with CTP-B disease
  - 11% of CTP-A patients and 38% of CTP-B
- Liver toxicity was associated with the volume of liver receiving low doses
- Appropriate patients for SBRT:
  - CTP-A and select CTP-B patients
  - Tumor distribution or size that allows for normal liver sparing
    - Mean liver dose <15 Gy; At least 500 cc <7 Gy for 3 fraction SBRT

Lasley et al, Pract Radiat Oncol 2015
### Prospective Trials of SBRT for HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>BCLC stage</th>
<th>Prior liver therapy</th>
<th>No. of tumors</th>
<th>Dose</th>
<th>1-year LC</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andolino (2011)</td>
<td>60</td>
<td>NR, 38% OLT recipients</td>
<td>NR</td>
<td>85% single lesion</td>
<td>CPA median 44 Gy/3 fx CPB median 40 Gy/5 fx</td>
<td>2-year 90%</td>
<td>35% grade 3+ hematologic or hepatic dysfunction</td>
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<tr>
<td>Lasley (2015)</td>
<td>59</td>
<td>NR, 80% T1N0</td>
<td>15%</td>
<td>81% single lesion</td>
<td>CPA 48 Gy/3 fx CPB 40 Gy/5 fx</td>
<td>CPA 91%</td>
<td>CPA: 11% grade 3+ CPB: 38% grade 3+</td>
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<tr>
<td>Scorsetti (2015)</td>
<td>43</td>
<td>A: 10, 44% B: 15, 36% C: 9, 20%</td>
<td>44%</td>
<td>57% single lesion</td>
<td>&lt; 3 cm: 48–75 Gy/3 fx 3–6 cm: 36–60 Gy/6 fx</td>
<td>86%</td>
<td>16% grade 3+</td>
</tr>
<tr>
<td>Feng (2018)</td>
<td>90 (69)</td>
<td>NR, 78% with prior TACE</td>
<td>Median 2 treatments</td>
<td>80% single lesion</td>
<td>Median 49 Gy/5 fx</td>
<td>99%</td>
<td>14% CTP 1 point increase 7% CTP 2 point increase 1% grade 3+ GI ulcer</td>
</tr>
<tr>
<td>Kang (2012)</td>
<td>47</td>
<td>A: 8, 17% B: 31, 66% C: 8, 17%</td>
<td>100%</td>
<td>83% single lesion</td>
<td>42–60 Gy/3 fx</td>
<td>2-year 95%</td>
<td>11% grade 3+ GI toxicity 15% grade 3+ hematologic toxicity</td>
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<tr>
<td>Tse (2008)</td>
<td>41 (31)</td>
<td>A: 3, 10% B: 10, 32% C: 18, 58%</td>
<td>61%</td>
<td>NR</td>
<td>Median 36 Gy/6 fx</td>
<td>65%</td>
<td>26% grade 3+ hepatic dysfunction 13% grade 3+ nausea/fatigue 3% grade 3+ hematologic toxicity</td>
</tr>
<tr>
<td>Bujold (2013)</td>
<td>102</td>
<td>A/B: 35, 34% C: 67, 66%</td>
<td>52%</td>
<td>61% multiple lesions</td>
<td>Median 36 Gy/6 fx</td>
<td>87%</td>
<td>30% grade 3+</td>
</tr>
<tr>
<td>Culleton (2014)</td>
<td>29</td>
<td>B: 2, 7% C/D: 27, 93%</td>
<td>14%</td>
<td>Median 2 lesions</td>
<td>Median 30.9 Gy/6 fx</td>
<td>100%</td>
<td>31% grade 3+ hepatic dysfunction 17% grade 3+ hematologic toxicity</td>
</tr>
</tbody>
</table>

Xu et al, Semin Liver Dis 2019
# SBRT vs RFA: University of Michigan Study

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RFA</th>
<th>SBRT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>161</td>
<td>63</td>
<td>—</td>
</tr>
<tr>
<td>No. of lesions</td>
<td>249</td>
<td>83</td>
<td>—</td>
</tr>
<tr>
<td>No. of lesions treated per patient</td>
<td></td>
<td></td>
<td>.13</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-6</td>
<td>1-4</td>
<td></td>
</tr>
<tr>
<td>No. of lesions treated per patient</td>
<td></td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>1</td>
<td>109</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>&gt; 2</td>
<td>19</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>238 (95.6)</td>
<td>65 (78.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No. of prior liver-directed therapies</td>
<td></td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-7</td>
<td>0-7</td>
<td></td>
</tr>
<tr>
<td>Tumor diameter, maximum, cm</td>
<td></td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Median</td>
<td>1.8</td>
<td>2.2</td>
<td></td>
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<tr>
<td>Range</td>
<td>0.6-7.0</td>
<td>0-10.0</td>
<td></td>
</tr>
</tbody>
</table>

Wahl et al, JCO 2015
SBRT vs RFA: University of Michigan Study

- LC at 1 yr: 97% w/SBRT vs 84% w/RFA
- LC curves meet at 2 yrs (84 vs 80%)
- Lesions >2 cm had improved LC w/SBRT
- Grade ≥3 toxicity: 11% w/RFA vs 5% w/SBRT

Wahl et al, JCO 2015
Localized HCC in Nonsurgical Candidates

- While there have been no prospective randomized trials of SBRT published to date, multiple retrospective and prospective Phase I/II studies have demonstrated the safety and efficacy of SBRT for HCC.

- **Consider SBRT as a non-invasive alternative to RFA in patients who are:**
  - Nonsurgical candidates due to comorbidities or performance status
  - Have Child-Pugh Class A or B liver function
  - An adequate volume of normal liver can be spared
  - And RFA is limited due to tumor location (close to large blood vessels or central biliary structures) or size (>3cm)
1. Localized HCC in Nonsurgical Candidates
2. **Locally Advanced Unresectable HCC**
3. Advanced Disease with Portal Vein Thrombosis
4. Bridge Therapy
SBRT vs. TACE

- University Hospital Freiburg
- SBRT patients:
  - higher Child Pugh scores
  - more prior treatment
  - more advanced disease (BCLC C and multifocal)
- Propensity score matching:
  - LC comparable with TACE and SBRT (82.9% vs. 84.8%)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TACE</th>
<th>SBRT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>n = 367</td>
<td>n = 35</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>314 (85.6)</td>
<td>29 (83)</td>
<td>0.802</td>
</tr>
<tr>
<td>Female</td>
<td>53 (14.4)</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>66.8 ± 9.2</td>
<td>69.0 ± 8.1</td>
<td>0.305</td>
</tr>
<tr>
<td>Child Score</td>
<td>5.9 ± 1.3</td>
<td>6.4 ± 1.3</td>
<td>0.006</td>
</tr>
<tr>
<td>Child A</td>
<td>269 (73.3)</td>
<td>19 (4.3)</td>
<td>0.020</td>
</tr>
<tr>
<td>Child B</td>
<td>95 (25.9)</td>
<td>16 (45.7)</td>
<td>0.017</td>
</tr>
<tr>
<td>Child C</td>
<td>3 (0.8)</td>
<td>0</td>
<td>0.999</td>
</tr>
<tr>
<td>Previous treatmenta</td>
<td>5 (1.3)</td>
<td>29 (83.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>362 (98.6)</td>
<td>6 (17.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgery</td>
<td>2 (0.5)</td>
<td>8 (22.9)</td>
<td>0.899</td>
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<tr>
<td>Sorafenib</td>
<td>2 (0.5)</td>
<td>12 (9)</td>
<td>0.324</td>
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<tr>
<td>TACE</td>
<td>1 (0.3)</td>
<td>28 (80.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intrahepatic tumor expansion</td>
<td></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>Oligonodular</td>
<td>144 (39.2)</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>223 (60.8)</td>
<td>29 (83)</td>
<td></td>
</tr>
<tr>
<td>BCLC²</td>
<td></td>
<td></td>
<td>0.046</td>
</tr>
<tr>
<td>B</td>
<td>299 (81.5)</td>
<td>24 (68.6)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>68 (18.5)</td>
<td>11 (31.4)</td>
<td></td>
</tr>
<tr>
<td>Largest tumor diameter [cm]</td>
<td>6.1 ± 3.4</td>
<td>8.4 ± 7.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Bettinger et al, BMC Cancer 2018
SBRT vs. TACE

- University of Michigan
- 209 patients with 1 to 2 tumors
- TACE (n=84) to 114 tumors
- SBRT (n=125) to 173 tumors
- Propensity score analysis used to compare outcomes
- Underlying liver dx and function similar
- SBRT patients were older, had more prior liver-directed tx
- 1 yr LC: 97% w/SBRT vs 47% w/TACE
- 2 yr LC: 91% vs 23%
TACE + SBRT: Residual Disease after TACE

- Phase II trial, 50 patients
- Mostly CTP-A disease
- Mostly BCLC stage B, up to 10cm
- TACE 1-5x before salvage SBRT
- 42 – 60 Gy in 3 fractions
- 2-year LC: 94.6%,
- 2-year OS: 68.7%
- 6.4% grade 3 GI toxicity
- 4.3% grade 4 gastric ulcer
- SBRT after incomplete TACE for inoperable HCC achieves promising rates of response and local control

Kang et al, Cancer 2012
TACE + SBRT

- Phase II study including 90 patients not amenable to surgery or RFA
- CTP-A or B, solitary tumor up to 4cm
- TACE SBRT (35-40 Gy in 5 fx)
- TACE omitted in 32 patients (not amenable, or patient refused)
- Median follow-up 42 months
- 3-year LC: 96.3%
- 3-year liver-related CSS: 72.5%
- 3-year OS: 66.7%
- Grade 3 lab abnormalities (elevated transaminases, thrombocytopenia) in 6 patients
- No grade 4-5 liver toxicities
- 8 patients had Child-Pugh scores that declined by 2 points

Takeda et al, Cancer 2016
Long-term Outcomes: TACE + SBRT

- 65 patients (CTP-A or B) with 74 tumors; <3 lesions; <5cm
- TACE, then 1-3 mths later SBRT (48 Gy in 4 fractions)
- Median follow up = 41 mths; 62 mths for surviving patients
- 3 and 5 year LC = 100%
- 5 yr PFS = 10.6%
- 5 yr OS = 41%
- **Liver toxicities ≥ grade 3 in 15 (23.1%) patients**
  - Elevated total bilirubin, elevated AST/ALT, ascites, thrombocytopenia
  - Did not increase after 1 year

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>0–6 months</th>
<th>6–12 months</th>
<th>After 1 year</th>
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<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Elevated total bilirubin</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Elevated AST/ALT</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ascites</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>0</td>
<td>9</td>
<td>9</td>
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<td></td>
<td></td>
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</tbody>
</table>

Kubo et al, Hepatol Res 2018
Transcatheter Arterial Chemoembolization Plus Radiotherapy Compared With Chemoembolization Alone for Hepatocellular Carcinoma
A Systematic Review and Meta-analysis

- 25 trials involving 2577 patients
- Response rates and survival were improved with combination therapy
- The survival benefit of TACE plus RT over TACE alone progressively increased with each year up to 5 years
- TACE plus RT had significantly better partial and complete response rates, and less progressive disease and non-responders compared with TACE alone
- TACE + SBRT can be considered for patients with locally advanced disease

<table>
<thead>
<tr>
<th>Year</th>
<th>OR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>1</td>
<td>1.36 (1.20-1.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>1.55 (1.30-1.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3</td>
<td>1.91 (1.55-2.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4</td>
<td>3.01 (1.38-6.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5</td>
<td>3.98 (1.86-8.51)</td>
<td>&lt;.001</td>
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<table>
<thead>
<tr>
<th>Response</th>
<th>OR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Progressive disease</td>
<td>0.43 (0.31-0.60)</td>
<td>&lt;.001</td>
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<tr>
<td>No response</td>
<td>0.56 (0.44-0.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Partial response</td>
<td>1.47 (1.23-1.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Complete response</td>
<td>2.73 (1.95-3.82)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Huo et al, JAMA Onc 2015
SBRT for HCC

1. Localized HCC in Nonsurgical Candidates
2. Locally Advanced Unresectable HCC
3. *Advanced Disease with Portal Vein Thrombosis*
4. Bridge Therapy
SBRT for HCC

- Phase I/II trial at Princess Margaret Hospital
  - 102 patients with primary HCC treated with six-fraction SBRT
  - All had CTP class A liver disease
  - 61% had multiple liver lesions
  - **55% had tumor vascular thrombosis**
    - Median tumor size of 7.2 cm
    - One-year local control: 87%
    - **Median OS 17 months**
    - Toxicity ≥ grade 3 in 30% of patients, mostly fatigue
    - In patients without progressive disease, a decline in CTP class was seen in 29% at 3 months and in 6% at 12 months

Bujold et al, JCO 2013
Patients with PVT

Systematic review

Comparison of radiation therapy modalities for hepatocellular carcinoma with portal vein thrombosis: A meta-analysis and systematic review

Chai Hong Rim\(^a\), Chul Yong Kim\(^b\), Dae Sik Yang\(^c\), Won Sup Yoon\(^a,\ast\)

\(^a\) Department of Radiation Oncology, Ansan Hospital, Korea University Medical College, Ansan; \(^b\) Department of Radiation Oncology, Anam Hospital, Korea University Medical College; and \(^c\) Department of Radiation Oncology, Guro Hospital, Korea University Medical College, Seoul, Republic of Korea

- Meta-analysis of 37 studies comparing radioembolization (TARE) with 3D-conformal RT and SBRT
- 1-year OS was equivalent
  - 44% for 3D-CRT vs 47% for TARE vs 49% for SBRT
- Pooled local control rates were significantly higher with SBRT (86.9%) and 3D-CRT (82.8%) compared with TARE (57.5%)

Rim et al, Radiother Oncol 2018
RT in Patients with PVT

- 90 patients with portal vein invasion
- **Randomized to Sorafenib vs. TACE + RT** (45 Gy in 2.5-3 Gy fx)
- Median tumor diameter = 9.7cm
- 78.9% had multiple lesions
- Significantly longer median time to progression in the TACE-RT group vs the sorafenib group
  - 31.0 vs 11.7 weeks; \( P < .001 \)
- Significantly longer overall survival
  - 55.0 vs 43.0 weeks; \( P = .04 \)
- Locoregional control may improve outcomes in these patients

Yoon et al, JAMA Onc 2018
1. Localized HCC in Nonsurgical Candidates
2. Locally Advanced Unresectable HCC
3. Advanced Disease withPortal Vein Thrombosis
4. Bridge Therapy
SBRT as Bridge Therapy

- Indiana University phase I/II prospective trial
- 60 patients treated with SBRT
- 68% proceeded to transplant
- Median time to transplant of 7 months
- 2 year LC: 90%
- 35% grade 3 or higher heme or hepatic toxicities

- Additional single institution studies:
  - LC prior to transplant: 86-100%
  - Gr 3+ toxicity significantly less
  - Path Response: 37-70%

Andolino et al, IJROBP 2011
SBRT vs TACE vs RFA as Bridge Therapy

July 2004–December 2014
594 patients with HCC listed for a LT at Toronto General Hospital

406/594 (68.4%) received bridging therapies

27/406 (6.7%) Others

36/406 (8.9%) SBRT GROUP
Drop-out 16.7%
30 patients LT

99/406 (24.4%) TACE GROUP
Drop-out 20.2%
79 patients LT

244/406 (60.1%) RFA GROUP
Drop-out 16.8%
203 patients LT

Sapisochin et al, J Hepatol 2017
SBRT vs TACE vs RFA as Bridge Therapy

- Median dose of 36 Gy in six fractions
- Complete tumor necrosis:
  - 13% of SBRT patients
  - 24% of TACE patients
  - 49% of RFA patients
- May be due to lower RT dose compared to other studies or time from treatment to transplant (tumor response after SBRT may be delayed)
- No differences in transplant or perioperative complications

Sapisochin et al, J Hepatol 2017
Potential Candidates for SBRT

1. Localized HCC in Nonsurgical Candidates
   - As an alternative to ablation or embolization techniques, particularly if:
     - Efficacy of ablation may be limited:
       - near major vessels, central biliary structures, diaphragm
       - or >2-3 cm
     - Child class A cirrhosis, select class B
     - Sufficient volume of normal hepatic parenchyma
     - Sufficient distance from stomach or bowel

2. Locally Advanced Unresectable HCC
   - Incomplete response to TACE or in combination with TACE

3. Advanced Disease with Portal Vein Thrombosis

4. As Bridge to Transplant
### Ongoing Studies

- Randomized trial comparing TACE and SBRT for patients ineligible for surgery or RFA (Erasmus Medical Center in Europe, NCT02470533)
- Randomized trial comparing TACE and SBRT as a bridge to transplant (Lahey Clinic, NCT02182687)
- RTOG 1112: Randomized Phase III Study of Sorafenib vs SBRT Followed by Sorafenib in HCC
  - For patients not eligible for surgery, RFA, or TACE
  - Patients with vascular involvement are included

<table>
<thead>
<tr>
<th>Registration</th>
<th>Randomize</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none)</td>
<td>Arm 1&lt;br&gt;Daily sorafenib</td>
</tr>
</tbody>
</table>
| Hepatitis B vs. C vs. other | Arm 2<br>SBRT alone (27.5 Gy – 50 Gy in 5 fractions)  
Followed by Sorafenib alone daily |
| North American site vs. Non-North American site |  |
| HCC volume/liver volume (<10% vs. 10-40 vs. >40%) |  |
Thank You!