Stereotactic Body Radiation Therapy (SBRT) for Hepatocellular Carcinoma

Laura A. Dawson, M.D.
Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario

Disclosures

- Research funding from Bayer and Elekta, paid to institution.

Hypotheses

- Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation therapy (SABR), should improve outcomes in patients with HCC who are unsuitable for standard local therapies.
  - Quality of life
  - Local control
  - Survival

Stereotactic Body Radiotherapy, SBRT

- Very conformal dose distribution
- Highly potent doses
- High dose per fraction
- Motion management
- Image guidance (“stereotactic”)
- Few number of fractions (3 - 6)

HCC: 5 Fraction SBRT Plan

Avoidance of normal tissues a priority
Dose dependent on normal tissues
- Volume of spared liver
- Proximity to luminal GI organs

35 Gy, 5#

Image Guided Radiotherapy (IGRT)

And more: combined technologies, MR-linac, ... Dawson, Jaffray, JCO, 2007
Biologic Rationale for SBRT

- High dose / fraction specific effects
  - Threshold ~ 8Gy/fraction
- Postulated mechanisms of RT injury
  - Ablative direct cell kill
  - Endothelial target
    - Rapid injury enhances RT response (Fuks)
    - Injury over days lead to secondary tumor cell death
  - Immune
    - RT increases tumor antigen-specific immune response
  - Abscopal effect
    - Local therapy causes systemic response

**Postulated mechanisms of RT injury**

- Ablative direct cell kill
- Endothelial target
  - Rapid injury enhances RT response (Fuks)
  - Injury over days lead to secondary tumor cell death (Fuks)
- Immune
  - RT increases tumor antigen-specific immune response
- Abscopal effect
  - Local therapy causes systemic response

**HCC BCLC: No RT**

HCC BCLC: Where RT fits

**Selected Early HCC SBRT Series**

<table>
<thead>
<tr>
<th>No. pts</th>
<th>Dose/Fraction</th>
<th>Tumor size</th>
<th>Med FU (mo)</th>
<th>Response Rate</th>
<th>Local control</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>Blomgren, 98</td>
<td>9</td>
<td>5-15 Gy/1-3#</td>
<td>NR</td>
<td>NR</td>
<td>70%</td>
<td>NR</td>
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<tr>
<td>Choi, 06</td>
<td>20</td>
<td>50 Gy / 5-10#</td>
<td>3.8 cm (3-4.0cm)</td>
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<td>LC 1 yr: 82%</td>
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<td>Tae, 08</td>
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<td>56 Gy / 6# (8-54 Gy)</td>
<td>173 cc (15 - 177cc)</td>
<td>18</td>
<td>LC 1 yr: 63%</td>
<td>1 yr: 48%</td>
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<td>Louis, 10</td>
<td>25</td>
<td>CP A + B</td>
<td>45 Gy / 3#</td>
<td>150 cc</td>
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<td>CP A 90%</td>
<td>30 – 33 Gy / 2-3#</td>
<td>15 - 32 cc</td>
<td>29</td>
<td>86%</td>
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<tr>
<td>Facciuto, 11</td>
<td>37</td>
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<td>2.0 cm +/- 0.8 cm</td>
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Korean Registry-HCC SBRT

- N=93 HCC patients (26% CP B)
  - All refractory or unsuitable for TACE
  - Dose: 30 - 40 Gy in 3-4 fractions
    - Size: median 2 cm (1-6 cm)
    - Improved local control for smaller tumors (100% < 2cm, 93% 2-3cm, 76% 3-6)
  - Toxicity: Decline in CP score ~9.7% (gr 5, n=1 CP B pt)

3 yr local control 92% 3 yr survival 54%

Yoon, PLOS 2013

Japanese Retrospective Series-HCC SBRT

- N=221 (~84% T1) HCC patients (CP A:B=178:27)
  - 56-61% received TACE < 3 months prior to SBRT
  - Dose: 40 Gy in 5 fractions
    - 35 Gy: for CP B, and so < 20% liver ≥20Gy, n=48
    - Size: median 2.7 cm (35 Gy), 2.4 cm (40 Gy), max 5.0 cm
    - No sign. differences in outcomes for 35 vs 40 Gy
  - Toxicity: Decline in CP score ~10% (gr 5, n=2 CP B pts)

3 yr local control 91% 3 yr survival 70%

Sanuki, Acta Oncol 2013

HCC Bridge to Transplant RT Series

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>RT Dose</th>
<th>%OLT</th>
<th>TACE?</th>
<th>Time to OLT</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>O’Connor, 2012</td>
<td>10</td>
<td>33-54/3</td>
<td>100%</td>
<td>40%</td>
<td>4 mo</td>
<td>5yr OS 100%</td>
</tr>
<tr>
<td>Katz, 2012</td>
<td>18</td>
<td>50-55/10</td>
<td>61%</td>
<td>11.1%</td>
<td>6.3 mo</td>
<td>2yr OS 100%</td>
</tr>
<tr>
<td>Bush, 2011</td>
<td>76</td>
<td>33/15</td>
<td>24%</td>
<td>0</td>
<td>13 mo</td>
<td>3yr OS 70%</td>
</tr>
<tr>
<td>Andolina, 2011</td>
<td>60</td>
<td>CPA-30-48/3</td>
<td>38%</td>
<td>NA</td>
<td>7 mo</td>
<td>2yr PFS 69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPB-24-48/5</td>
<td></td>
<td></td>
<td></td>
<td>5yr OS 96%</td>
</tr>
<tr>
<td>Sandroussi, 2009</td>
<td>10</td>
<td>33-54/1-6</td>
<td>80%</td>
<td>30%</td>
<td>5 mo</td>
<td>2yr RFS 70%</td>
</tr>
<tr>
<td>Al-Hamad, 2009</td>
<td>1</td>
<td>50/5</td>
<td>100%</td>
<td>0</td>
<td>NA</td>
<td>1yr OS 100%</td>
</tr>
</tbody>
</table>

* No local progression or morbidity at time of transplant
Explant: 50-100% necrosis

Klein, Dawson, UROBP, 2013

HCC BCLC: Where RT fits

Dawson, SRO, 2011
RT & TACE vs TACE - HCC: Korea

- 73/105 HCC incomplete response to TACE
  - 35 TACE repeated
  - 38 received radiotherapy
- Multivariate analysis sign. factors (survival)
  - Tumour size
  - Treatment

<table>
<thead>
<tr>
<th>2 yr survival</th>
<th>RT</th>
<th>no RT</th>
<th>All *</th>
<th>5-7 cm</th>
<th>63%</th>
<th>42%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All *</td>
<td>37%</td>
<td>14%</td>
<td>37%</td>
<td>63%</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

(Shim et al., 2005)

Can RT control HCC with portal vein thrombosis (PVT)?

- HCC portal vein thrombosis (PVT) invasion is a strong prognostic factor
- RT for HCC with PVT: High variability in series
  - Some studies combine RT with TACE
  - Prognostic factors: Child score, HCC burden, main PVTT, complete occlusion, extrahepatic disease
- Recanalization of portal vein thrombosis occurs in ~50% of patients post RT
- Median time to maximal response ~6 months
- Median survival 4–13 months

Clinical Case: Resolution of PVTT w RT

Jan 2009
AFP 10,000

Sept 2009
AFP 24

RT for HCC with Portal Vein Thrombus

<table>
<thead>
<tr>
<th>Author, y</th>
<th>Patients</th>
<th>Design</th>
<th>CP (%)</th>
<th>CP (%)</th>
<th>RT only (Gy)</th>
<th>RT + TACE (Gy)</th>
<th>Fractionation</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim, 2012</td>
<td>45</td>
<td>Rot</td>
<td>38</td>
<td>0</td>
<td>7%</td>
<td>30</td>
<td>3 Gy ×6</td>
<td>11.2</td>
</tr>
<tr>
<td>Tsai, 2012</td>
<td>412</td>
<td>Ret</td>
<td>26</td>
<td>0</td>
<td>29%</td>
<td>30</td>
<td>1.5 Gy ×9</td>
<td>10.6</td>
</tr>
<tr>
<td>Charns, 2011</td>
<td>20</td>
<td>Ret</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>30-48</td>
<td>3.4 Gy ×9</td>
<td>12</td>
</tr>
<tr>
<td>Katunem, 2009</td>
<td>16</td>
<td>Ret</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>30-45</td>
<td>3 Gy ×9</td>
<td>7.5</td>
</tr>
<tr>
<td>Zhang, 2009</td>
<td>16</td>
<td>Ret</td>
<td>19</td>
<td>6</td>
<td>0</td>
<td>30-60</td>
<td>2 Gy ×9</td>
<td>7</td>
</tr>
<tr>
<td>Huang, 2009</td>
<td>326</td>
<td>Ret NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>2-3 Gy ×9</td>
<td>4</td>
</tr>
<tr>
<td>Han, 2008</td>
<td>40</td>
<td>Prot</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>45</td>
<td>25 Gy ×10</td>
<td>13.1</td>
</tr>
<tr>
<td>Yip, 2007</td>
<td>38</td>
<td>Rot</td>
<td>24</td>
<td>0</td>
<td>0%</td>
<td>17.5-50.4</td>
<td>3 Gy ×7</td>
<td>9.6</td>
</tr>
<tr>
<td>Liu, 2006</td>
<td>22 SRT</td>
<td>Prot</td>
<td>30</td>
<td>18</td>
<td>0%</td>
<td>45</td>
<td>3 Gy ×3</td>
<td>6</td>
</tr>
<tr>
<td>21 CRT</td>
<td>33</td>
<td>CRT</td>
<td>45</td>
<td>0</td>
<td>45</td>
<td>1.8 Gy ×9</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Kim, 2005</td>
<td>59</td>
<td>Rot</td>
<td>12</td>
<td>0</td>
<td>100%</td>
<td>30-54</td>
<td>2.5 Gy ×6</td>
<td>7.8</td>
</tr>
<tr>
<td>Zeng, 2005</td>
<td>44</td>
<td>Rot NA</td>
<td>23</td>
<td>0</td>
<td>33-60</td>
<td>2 Gy ×9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Nomura, 2003</td>
<td>19</td>
<td>Prot</td>
<td>32</td>
<td>5</td>
<td>0</td>
<td>60</td>
<td>2 Gy ×9</td>
<td>7</td>
</tr>
<tr>
<td>Ishikawa, 2002</td>
<td>12</td>
<td>Prot</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>25 Gy ×2</td>
<td>5.3</td>
</tr>
<tr>
<td>Tazawa, 2001</td>
<td>24</td>
<td>Rot</td>
<td>33-17</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>25 Gy ×3</td>
<td>CP-A: 12.7</td>
</tr>
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Klein, Dawson, IJROBP, 2013

RT - HCC + portal vein thrombosis - Korea

- Phase II study of 40 patients
  - RT 45 Gy in 25#, conformal RT
  - Concurrent hepatic arterial 5FU wk 1 and 5
  - Post RT hepatic arterial 5FU + Cisplatin
  - Median survival 13.1 months

Han, Seong, et al, Cancer 103, Sept 2008
Toronto Phase I/II HCC Study
- N=102 HCC patients unsuitable for resection, transplant, TACE or RFA
- Hep B : Hep C : alcohol 39% : 39% : 25%
- Prior therapies 50%
- Portal vein thrombosis 55%
- Extrahepatic disease 12%
- Size: median 9.9 cm (2 – 43 cm)
- Median dose 36 Gy in 6# (24 – 54 Gy, 6 #)

Local control
- 1 year local control 87% (95% 78-93%)
- Dose response observed

Tumor marker response (AFP)

Overall survival, n=102
Median survival 17 months
Survival by thrombosis
Survival by trial
- Median survival
  - No thrombosis 20.5 mo (95% CI 12.9, 36.9)
  - Thrombosis 11.0 mo (95% CI 11.3, NA)
- Trial 1
  - Median 11.1 months (95% CI 7.4-19.0)
- Trial 2
  - Median 25.5 months (95% CI 11.3, NA)

The bad news....
- 7 of 102 patients had death possibly related to therapy 1.1 – 7.7 months post SBRT
  - No RECIST parenchymal PD, but 2 PVT PD
  - 5 liver
  - 1 biliary (with gross HCC invasion to bile duct)
  - 1 duodenum bleed (post re-RT to LN)
- ~30% of patients had a decline by 2 or more in Child Pugh score at 3 months

Changes in Child Score
Hepatocellular Cancer: RTOG1112

- Planned randomized phase III trial, n = 368
- Primary endpoint: overall survival (median survival 10.5 to 14.5 months)

RTOG1112 Key Eligibility

**Inclusion Criteria**
- Measureable HCC
- Unsuitable for or refractory to:
  - Surgery
  - TACE
  - Child Pugh A
  - BCLC B or C
  - Platelets > 70 000 bil/L
  - INR < 1.7
  - Albumin ≥ 28 g/L
  - AST, ALT < 6xULN

**Exclusion Criteria**
- Prior Sorafenib
- Prior abdominal RT or Y-90
- > 15 cm single HCC
- > 20 cm sum of max diameters
- > 5 discreet HCC
- Extrahepatic disease > 2 cm
- HCC extension to stomach
- HCC extension to CBD
- Thrombolytic therapy within 28 days of study entry
- Bleeding within 60 days requiring transfusion

Conclusions

- SBRT can treat HCC safely
  - Advanced RT techniques, individualized RT and HCC multi-disciplinary team needed
  - Toxicity lowest if CP A, < 10 cm, no PVT HCC
- SBRT should be considered for T1/2 HCC unsuitable for resection or RFA and as a bridge to transplant
  - Best outcomes if < 6 cm and < 3 lesions
- Randomized trials needed
  - RTOG1112 accruing – please support
  - Opportunity for education, peer review and quality improvement for RT centers

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Doug Moseley
Catherine Costens
Mike Sharpe
Teo Stanescu
Tim Craig
Tom Purdie
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Kwalapirin Singh
Gina Lockwood, Christine Massey
PMH HCC tumor board
All referring MDs
ASCO CDA, Canadian Cancer Society
CIHR

Can RT be used safely in Child-Pugh B/C pts?

- Toronto review 1/2004- 7/2012, n= 40
  - N=11 bridge to liver transplant pts excluded
  - N=29 treated with definitive SBRT
    - 14 on prospective study (< 10 cm, < CP B9)
    - 69% portal vein tumor thrombosis
    - Median AFP: 4491 (0-94,921)
    - Median HCC volume 133 cc
  - Median survival: 7.9 months (2.8 – 15.1 mo)
  - Prognostic factors on MVA
    - Child Pugh B7 vs other (med OS 8.4 vs. 2.8 mo)
    - AFP < 4491 (correlated with disease burden)

Can RT be used safely in Child-Pugh B/C pts?

- Toxicity lowest and survival best in Child Pugh B7 versus > B7
- Spare as much liver as possible
  - Mean liver (minus GTV)
    - ≤ 6 Gy in 5-10 fractions
  - Maximize the volume spared from RT
    - >800 cc < 10 Gy (in 3-6 fractions)
- Comparative trials needed