HCC Stereotactic Body Radiotherapy: A Multifaceted Approach

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Disclosures

• Licensing agreement from Raysearch, paid to institution

• Advisory board: Merck ongoing
• Advisory board: SIRTEX 2016

• Research funding from Merck, paid to institution
Stereotactic Body Radiotherapy, SBRT

- Very conformal dose distribution
- Highly potent doses
- High dose per fraction
- Motion management
- Image guidance (‘stereotactic’)
- Few number of fractions (~1-6)

- Convenient, efficient, non-invasive
- Widely available
- SBRT techniques may be used for any fractionation
Typical HCC SBRT Plan

- Tumor dose often limited by:
  - Liver
  - Duodenum, bowel

- Strong need for advanced RT techniques
  - Individualized doses
  - Breathing motion management
  - Multi-phasic + multi-modality imaging
  - IGRT

Unpublished data provided by L. Dawson
Biologic Rationale for SBRT/Hypofractionation

• High dose/fraction specific effects
  – Preclinical data
  – Threshold ~ 5-8 Gy/fraction

• Postulated mechanisms of RT injury
  • Ablative direct cell kill
  • Endothelial target (Fuks)
  • Immune
    – RT increases tumor Ag-specific immune response ^*
  • Abscopol effect
    – Local therapy causes systemic response
    – Elusive in practice

RT has a potential important role to play in the treatment of HCC across all stages.
Early stage HCC, unsuitable for standard curative therapies

- 78 year old lady with single HCC, Hep C
- Laparotomy
  - Resection aborted due to cirrhosis
  - Decompensation post-op
- 8 weeks post op
  - Improving, but not at baseline
  - PS 2, Child Pugh B8
  - Growing HCC (4.8 cm)
SBRT 45 Gy in 5 #: no progression at month 24

Barry, Wei, Knox, Dawson, JCO Grand Rounds, Jan 2016
HCC is a RT sensitive tumor

- No dose response for HCC (33-54 Gy in 3-5 fractions)
- 3 year local control 86%

AAPM Consensus TCP project, Ohir, Dawson, Tome

- Pooled analysis from 5 trials
- n = 431
SBRT: Korean Registry

- N=93 HCC patients (26% CP B)
  - All refractory or unsuitable for TACE
- Dose: 30 - 40 Gy in 3- 4#
  - 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 in 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#
  - 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%
French Study: HCC SBRT

- N=77 (median size 2.4 cm)
- SBRT: 45 in 3 fractions
- Local control: 1 and 2 years 99%
- Survival: 1 and 2 years: 82% and 56%
  - CP B worse survival
- 8% with liver toxicity < 6 months

Huertas A et al. Radiother Oncol. 2015;115(2):211–6
Indiana Phase II HCC Study

- 60 pts with HCC, 87% T1N0 (unsuitable for transplant)
  - Median volume 32cc (range 2–107)
- Dose: 48 Gy in 3# (CP A) or 40 Gy in 5# (CP B)
- Factors associated with survival:
  - CP class, HCC volume, liver toxicity and transplant (after downstaged) significant factors

<table>
<thead>
<tr>
<th></th>
<th>Child Pugh A</th>
<th>Child Pugh B</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=60</td>
<td>N=39</td>
<td>N=21</td>
</tr>
<tr>
<td>6 month local control</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Med survival</td>
<td>51 mo</td>
<td>22 mo</td>
</tr>
<tr>
<td>3 year survival</td>
<td>62%</td>
<td>24%</td>
</tr>
<tr>
<td>Med PFS</td>
<td>33 mo</td>
<td>17 mo</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>28%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Abstract #257 presented at: ASTRO, San Antonio, 18–21 October 2015
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)
    - 76% portal vein tumor thrombosis
    - 69% Child Pugh B7
    - 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)

Culleton S,… Dawson, Radiat Oncol 2014
Meta-analysis (5204 patients)

1 Year Survival

Particle RT 5 year survival: 37%

SBRT 5 year survival 31%
## Meta-analysis (5204 patients)

### ≥ Grade 3 Toxicity

<table>
<thead>
<tr>
<th>Acute toxicity</th>
<th>Included study</th>
<th>Events</th>
<th>Total</th>
<th>Events rate (95%CI)</th>
<th>$I^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT</td>
<td>14</td>
<td>21</td>
<td>830</td>
<td>3.1% (1.3–7.6%)</td>
<td>73.8</td>
<td>–</td>
</tr>
<tr>
<td>SBRT</td>
<td>19</td>
<td>59</td>
<td>1164</td>
<td>4.9% (3.0–8.1%)</td>
<td>66.8</td>
<td>0.19</td>
</tr>
<tr>
<td>CRT</td>
<td>10</td>
<td>111</td>
<td>995</td>
<td>9.9% (6.0–16%)</td>
<td>75.1</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Bone marrow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT</td>
<td>14</td>
<td>40</td>
<td>805</td>
<td>5.1% (1.9–12.7%)</td>
<td>84.3</td>
<td>–</td>
</tr>
<tr>
<td>SBRT</td>
<td>11</td>
<td>23</td>
<td>644</td>
<td>4.9% (3.4–7.2%)</td>
<td>0</td>
<td>0.47</td>
</tr>
<tr>
<td>CRT</td>
<td>12</td>
<td>26</td>
<td>1015</td>
<td>6.1% (4.3–8.8%)</td>
<td>63.5</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT</td>
<td>16</td>
<td>68</td>
<td>1172</td>
<td>6.1% (2.8–12.6%)</td>
<td>83.8</td>
<td>–</td>
</tr>
<tr>
<td>SBRT</td>
<td>21</td>
<td>137</td>
<td>1221</td>
<td>9.6% (6.0–15.1%)</td>
<td>81.3</td>
<td>0.16</td>
</tr>
<tr>
<td>CRT</td>
<td>13</td>
<td>172</td>
<td>1023</td>
<td>20% (13.2–29.2%)</td>
<td>82.8</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Late toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT</td>
<td>7</td>
<td>6</td>
<td>342</td>
<td>2.5% (1.3–4.9%)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>SBRT</td>
<td>6</td>
<td>17</td>
<td>387</td>
<td>6.4% (4.0–10.1%)</td>
<td>50.6</td>
<td>0.011</td>
</tr>
<tr>
<td>CRT</td>
<td>5</td>
<td>11</td>
<td>293</td>
<td>6.9% (3.9–1.2%)</td>
<td>75.4</td>
<td>0.011</td>
</tr>
</tbody>
</table>
HCC: SBRT vs RFA

- 2004–2012: 224 patients with unresectable HCC treated with RFA or SBRT
  - 161 treated with RFA to 249 tumors
  - 63 treated with SBRT to 83 tumors

- Similar patients and outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RFA</th>
<th>SBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from local progression (FFLP) 1 yr</td>
<td>84%</td>
<td>97%</td>
</tr>
<tr>
<td>FFLP 2 yr</td>
<td>80%</td>
<td>84%</td>
</tr>
<tr>
<td>Overall survival 1 yr</td>
<td>70%</td>
<td>74%</td>
</tr>
<tr>
<td>Gr 3+ toxicity</td>
<td>11%</td>
<td>5%</td>
</tr>
</tbody>
</table>

• Larger tumors less likely to be controlled by RFA

• No size dependency for SBRT
HCC BCLC: Where RT fits

Dawson LA et al. Semin Radiat Oncol. 2011;21:241
Phase III Trial of SBRT vs DEB as Bridging to Transplant

• 60 HCC patients, within Milan criteria, listed for transplant planned to be randomized to BED or SBRT (40 - 50Gy in 5#)
  • 16 - DEB (x 2)
  • 13 - SBRT

• Similar efficacy (path CR seen with both)

• Benefits of SBRT:
  • Less re-treatment
  • Fewer inpatient days
  • Lower toxicity
  • Improved QOL

Nugent et al, ASCO GI Symposium, JCO 35 suppl 4S, abstract 223, 2017
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>O’Connor, 2012¹</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, 2012²</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, 2011³</td>
<td>76</td>
<td>63/15</td>
<td>24%</td>
<td>0</td>
<td>13 mo</td>
<td>3yr OS 70%</td>
</tr>
<tr>
<td>Andolino, 2011⁴</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>Sandroussi, 2009⁵</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, 2009⁶</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>

Add path CR data – from proton RCT, indians and torotnoto OLT

* No local progression, no increased operative morbidity, 50–100% necrosis,
SBRT vs TACE & RFA: Bridge to Transplant

- Over 2007 – 2014, 406 / 594 (68%) HCC transplant patients received bridging therapies
  - RFA 60%, 88% within Milan
  - TACE 24%, 24% within Milan
  - SBRT 9% (if unsuitable for RFA or TACE), 36% within Milan
    - 36 Gy in 6 fractions (quartile range 30 - 40Gy)

Recurrence

Actuarial survival

No increased toxicity at time of transplant

Sapisochin G., LA Dawson, D Grant, Hepatology. 2017
Radiologic & Pathologic Responses to SBRT

- N=23 HCC patients who received SBRT and liver transplant
- Initial HCC volume: 64.6 (range: 2.3 to 232.7) cc
- Volume before transplant: 34.9 (range: 0.4 to 204.2) cc
- Median time to transplant 6 months (2 – 15 months)
- Radiologic RECIST response: 32% PR, 60% SD, 8% PD
- Pathologic median % necrosis: 51% (0-100%)
  - 35% > 85% necrosis
  - 9% 100% necrosis
  - RECIST radiographic response not well correlated with path

Unpublished, 2017
HCC BCLC: Where RT Fits

HCC

Stage 0
PST 0, Child-Pugh A
Very early stage (0)
Single<2cm.
Carcinoma in situ

Stage A-C
PST 0-2, Child-Pugh A-B
Early stage (A)
Single or 3 nodules <3cm, PS 0

Stage D
PST >2, Child-Pugh C
Advanced stage (C)
Portal invasion, N1,M1, PST 1-2

HCC

Intermediate stage (B)
Multinodular, PST 0

End stage (D)

Increased
Associated diseases

Normal
No
Yes

Symptomatic ttc (20%)
Survival<3mo

Curative Treatments (30%)
5-yr survival: 40-70%

Randomized controlled trials (50%)
Median survival 11-20mo

Unsuitable/refractory to TACE
Definitive RT

Unsuitable for resection, transplant or RF
Definitive RT

RT as bridge to transplant

Symptomatic
Low dose RT

Portal invasion
Definitive RT & sorafenib

Randomized trials needed to demonstrate benefit

Liver Transplantation (CLT / LDLT)
PEI/RF
TACE
Sorafenib

Dawson LA et al. Semin Radiat Oncol. 2011;21:241
SBRT post TACE (Korea)

Alabama, Retrospective comparison of TACE +/- SBRT, for HCC > 3cm

Patients (161)  Local recurrence  Median survival

- 124 TACE  26%  20 mo
- 37 TACE & RT  11%  33 mo

Jacob, HBP 2015
HCC BCLC: Where RT Fits

- **Stage 0**
  - PST 0, Child-Pugh A
  - Very early stage (0)
    - Single < 2cm
    - Carcinoma in situ

- **Stage A-C**
  - PST 0-2, Child-Pugh A-B
  - Early stage (A)
    - Single or 3 nodules < 3cm, PS 0
  - Intermediate stage (B)
    - Multinodular, PST 0
  - Advanced stage (C)
    - Portal invasion, N1,M1, PST 1-2

- **Stage D**
  - PST >2, Child-Pugh C
  - End stage (D)

- **Curative Treatments** (30%)
  - Resection
  - Liver Transplantation (CLT / LDLT)
  - PEI/RF
  - 5-yr survival: 40-70%

- **Randomized controlled trials** (50%)
  - TACE
  - Median survival 11-20mo

- **Symptomatic ttc (20%)**
  - Sorafenib
  - Survival < 3mo

- **Where RT fits**
  - Unsuitable for resection, transplant or RF
    - Definitive RT
  - RT as bridge to transplant
  - Unsuitable/refractory to TACE
    - Definitive RT
  - Symptomatic
    - Low dose RT
  - Portal invasion
    - Definitive RT & sorafenib
    - Randomized trials needed to demonstrate benefit

Dawson LA et al. Semin Radiat Oncol. 2011;21:241
Korean series of HCC PVTT, n=281

- Prognostic factors for overall survival on MVA:
  - ECOG performance status, CP
  - Degree of PVTT: main branch, complete occlusion
  - Tumor size, multiplicity, LN metastases
  - Response to RT

Yu, Park et al. JKMS 28 (8), 10167-1022, 2011
PMH Phase I/II HCC Study

- 102 HCC patients, unsuitable for transplant, resection, RFA or TACE
- Hep B: Hep C: alcohol 39%: 40%: 25%
- Prior therapies 50%
- Portal vein HCC thrombosis 55%
- Extrahepatic disease 12%
- Size: median 10 cm (2–43 cm)
- Median dose 36 Gy in 6# (7.5–54 Gy)
- 6 fractions, every other day

Survival

- 1 year local control 87% (95% CI 78–93%)
- Median survival 17 months

Median survival
- No thrombosis 20.5 mo (95% CI 12.9, 36.9)
- Thrombosis 11.0 mo (95% CI 11.3, NA)

Median survival
- Trial 1 11.1 months (95% CI 7.4-19.0)
- Trial 2 25.5 months (95% CI 11.3, NA)

Bujold, …Dawson, JCO April 2013
RTOG 1112 Phase III Study

Randomized phase III study
Sample size: 368
Primary endpoint: overall survival (10.5 → 14.5 mo)
Case

baseline
Case

3 months post SBRT
Case

Sustained normalization of AFP at ~12 months
Conclusions

• HCC is a radiosensitive tumor
• SBRT is ready for prime time in selected HCC patients
  – SBRT outcomes best in CP A, small (< 8 cm) HCC
  – HCC with vascular invasion, if not suitable for other treatments

• Rationale for trials of SBRT with regional or systemic therapies
• Need for improved evidence regarding SBRT for HCC
  – Randomized trials are ongoing
  – International collaborations, propensity matching and large databases are recommended in addition to phase III trials
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Andrea Marshall  

Jen Knox  

PMH HCC tumor boards  
All patients & referring MDs