Rationale for Liver-Directed Therapies in Metastatic Colorectal Cancer

- ~150,000 cases of colorectal cancer per year in the United States
- ~70,000 cases with liver metastases
- Median survival of patients with metastatic colorectal cancer has improved from approx. ~12 months to ~24 months
- Aggressive treatment may improved survival for patients with limited volume metastatic disease
Criteria for Patient Selection of Surgical Therapy

- Goal is to resect all metastases with negative (R0) histologic margins
- Two adjacent liver segments can be spared
- Adequate vascular inflow and outflow and biliary drainage can be preserved
- Volume of liver remaining after resection will be adequate (at least 20% of total estimated liver volume)


Perioperative Mortality with Hepatic Resection


Radiofrequency Ablation


Local Control with RFA


TABLE 1. RFA studies with CRC patients in which the rate of local tumor growth at the RFA site is identified

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>CRC patients</th>
<th>Procedures</th>
<th>Tumor diameter (cm)</th>
<th>Median follow-up (m)</th>
<th>RFA failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seiffert</td>
<td>1997</td>
<td>22</td>
<td>Peritoneal</td>
<td>10.3</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Cox et al.</td>
<td>1999</td>
<td>81</td>
<td>Peritoneal/open</td>
<td>15</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2000</td>
<td>37</td>
<td>Peritoneal/open</td>
<td>3.0</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Maue et al.</td>
<td>2001</td>
<td>25</td>
<td>Peritoneal</td>
<td>20.5</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>Seiffert</td>
<td>2001</td>
<td>117</td>
<td>Peritoneal</td>
<td>2.4</td>
<td>39.1</td>
<td></td>
</tr>
<tr>
<td>Cho et al.</td>
<td>2002</td>
<td>9</td>
<td>Peritoneal/open</td>
<td>2.5</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Pawlik</td>
<td>2003</td>
<td>124</td>
<td>RFA plus liver resection</td>
<td>21.3</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>De Bree et al.</td>
<td>2003</td>
<td>133</td>
<td>Peritoneal</td>
<td>2.3</td>
<td>18</td>
<td>5.6</td>
</tr>
<tr>
<td>Dickson et al.</td>
<td>2005</td>
<td>16</td>
<td>Open</td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Linsley et al.</td>
<td>2005</td>
<td>35</td>
<td>Peritoneal</td>
<td>2.1</td>
<td>28</td>
<td>40</td>
</tr>
</tbody>
</table>

RFA, radiofrequency ablation; CRC, colorectal cancer.
LR with RFA according to size

<table>
<thead>
<tr>
<th>Percutaneous (%)</th>
<th>Laparoscopy/Laparotomy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 cm</td>
<td>16.0</td>
</tr>
<tr>
<td>3–5 cm</td>
<td>25.9</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>60.0</td>
</tr>
</tbody>
</table>

Tumors >6 cm not considered suitable for RFA


Stereotactic Ablative Body Radiation (SABR)

- Highly conformal with steep dose distribution
- High dose per treatment
- Image guidance – stereotactic
- Motion management
- Convenient - 5 treatments or less
- Biologic rationale
  - Ablative technique
  - Induce vascular damage
  - Increase antigen release → immune response, abscopal effect

Overview of Liver SABR Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of irradiation</th>
<th>Number of lesions</th>
<th>Median Dose (Gy)</th>
<th>Median Follow-up (months)</th>
<th>Local Control</th>
<th>Overall Survival</th>
<th>Toxic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz et al. (2007)</td>
<td>Retrospective</td>
<td>20</td>
<td>174</td>
<td>30–55</td>
<td>76%</td>
<td>46%</td>
<td>0</td>
</tr>
<tr>
<td>Van der Pool et al. (2010)</td>
<td>Retrospective</td>
<td>20</td>
<td>15–17 GY × 3</td>
<td>26</td>
<td>74%</td>
<td>83%</td>
<td>2</td>
</tr>
<tr>
<td>Ambrosino et al. (2009)</td>
<td>Prospective</td>
<td>140</td>
<td>1–3</td>
<td>25–60</td>
<td>74%</td>
<td>24%</td>
<td>9 patients</td>
</tr>
<tr>
<td>Herfarth et al. (2001)</td>
<td>Prospective (phase I–II)</td>
<td>21</td>
<td>56</td>
<td>14–26</td>
<td>75%</td>
<td>72%</td>
<td>0</td>
</tr>
<tr>
<td>Méndez-Romero et al. (2006)</td>
<td>Prospective (phase I–II)</td>
<td>117</td>
<td>34</td>
<td>12.5 GY × 3</td>
<td>100%</td>
<td>85%</td>
<td>0</td>
</tr>
<tr>
<td>Ruuthoven et al. (2009)</td>
<td>Prospective (phase I–II)</td>
<td>15</td>
<td>63</td>
<td>12–20 GY × 3</td>
<td>95%</td>
<td>30%</td>
<td>0</td>
</tr>
<tr>
<td>Lee et al. (2009)</td>
<td>Prospective (phase I)</td>
<td>16</td>
<td>70</td>
<td>27.7–60</td>
<td>71%</td>
<td>47%</td>
<td>10%</td>
</tr>
<tr>
<td>Rule et al. (2011)</td>
<td>Prospective (phase I)</td>
<td>17</td>
<td>37</td>
<td>10 GY × 3–5</td>
<td>56%</td>
<td>89%</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: LC, local control; OS, overall survival; PF, progression-free survival; PTV, planning target volume; RILD, radiation-induced liver disease.

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

- 47 patients with 63 liver metastases
- 60 Gy in 3 fractions prescribed to 80-90% isodose line
- Major prognostic factor was tumor size

2 year LC 92%

Phase I Dose Escalation Study of Liver SABR

- 28 Patients
- Dose Regimens
  - 30 Gy in 3 fractions
  - 50 Gy in 5 fractions
  - 60 Gy in 5 fractions
- One grade 3 toxicity related to CBD obstruction from progression of disease
- No grade 4/5 toxicity

SABR vs. RFA for colorectal mets

- 30 pts with 35 CRC liver metastases
- Matched to pts treated with RFA by number and size of lesions
- 24-26 Gy in single fraction prescribed to 70% isodose line
- BED low (~54-59 Gy)

Hepatocellular Carcinoma (HCC)

- 5th leading cause of cancer worldwide (626,000 cases/yr)
- In US, ~20,000 cases/yr
- 5 year survival ~5%
- Leading cause of cancer-related death
Indications for SABR in Hepatocellular Carcinoma

- Unsuitable for resection, transplant, or RFA
- Bridge to transplant
- Unsuitable or refractory to TACE
- Main Portal Vein Invasion

### Hepatocellular Carcinoma

- Challenging - Underlying liver disease i.e. cirrhosis
- Radiosensitive

### SABR for HCC

- **PMH experience**
  - Pooled analysis of 102 patients treated with SBRT (55% tumor thrombus, 12% extrahepatic spread)
  - CR in 11%, PR in 43%
  - Local Control 87%
  - Median OS 17 months
  - 30% Gr ≥3 toxicity

- **Alternative option to ablation/embolization strategies (NCCN guidelines, category 2B)**
  - Majority of data in Child Pugh A patients

### Table

<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>
</thead>
<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>
</tr>
<tr>
<td>Choi, 06</td>
<td>20</td>
<td>50 Gy / 5-10#</td>
<td>3.8 cm</td>
<td>(2-6.5 cm)</td>
<td>23</td>
<td>80%</td>
</tr>
<tr>
<td>Mendez, 06</td>
<td>11</td>
<td>CP A + B</td>
<td>25 Gy / 5#</td>
<td>30 - 37.5 Gy / 3#</td>
<td>30 - 37.5 Gy / 3#</td>
<td>NR</td>
</tr>
<tr>
<td>T se, 08</td>
<td>31</td>
<td>36 Gy / 6#</td>
<td>173 cc (3 – 1913 cc)</td>
<td>18</td>
<td>65%</td>
<td>1 yr: 48%</td>
</tr>
<tr>
<td>Louis, 10</td>
<td>25</td>
<td>CP A + B</td>
<td>45 Gy / 3#</td>
<td>150 cc 13</td>
<td>86%</td>
<td>1 yr: 79%</td>
</tr>
<tr>
<td>Kwon, 10</td>
<td>42</td>
<td>CP A</td>
<td>90%</td>
<td>30 – 39 Gy/ #</td>
<td>29</td>
<td>86%</td>
</tr>
<tr>
<td>Facciuto, 11</td>
<td>27</td>
<td>24-36/ 2-4#</td>
<td>2.0 cm +/- 0.8 cm</td>
<td>22</td>
<td>37%</td>
<td>2 yr: 82%</td>
</tr>
<tr>
<td>Seo, '10</td>
<td>38</td>
<td>33-57Gy/ 3 &lt;10cm</td>
<td>79%</td>
<td>68%</td>
<td>59%</td>
<td>48%</td>
</tr>
</tbody>
</table>

<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>
</thead>
</table>
NCCN.org
**RT and TACE**

- Retrospective study
  - 73 patients with incomplete response to TACE
    - 35 TACE repeated
    - 38 of the patients received radiotherapy


**Phase II: TACE +/- SABR**

- RTOG 1112
  - Objective: To determine if SABR ↑ OS added to sorafenib
  - Eligibility: Child Pugh A, unresectable HCC, not eligible for transplant; extrahepatic metastases excluded

<table>
<thead>
<tr>
<th>REGISTRATION</th>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular involvement (IVC, main portal vein or left main branch portal vein vs. other vascular involvement vs. none)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B vs. C vs. other</td>
<td></td>
</tr>
<tr>
<td>North American site vs. Non-North American site</td>
<td></td>
</tr>
<tr>
<td>HCC volume/liver volume (&lt;10% vs. 10-40 vs. &gt;40%)</td>
<td></td>
</tr>
</tbody>
</table>

**Arm 1**
- Daily sorafenib

**Arm 2**
- SBRT alone (27.5 Gy – 50 Gy in 5 fractions)
  - Followed by Sorafenib alone daily

SABR at UCSF

RTOG 1112

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*Additional TACE can be performed if specific criteria meet on re-imaging (see section 3.3 for details)*
Dose Guidelines

• SBRT 3-6 fractions
  – 95% of PTV to receive prescription dose
  – Mean normal liver dose (liver – GTV)
    - <13 Gy for HCC in 3 fractions
    - <18 Gy for HCC in 6 fractions
    - <15 Gy for liver mets in 3 fractions
    - <20 Gy for liver mets in 6 fractions
    - <6 Gy for HCC in Childs-Pugh B patients (4-6 Gy/fraction)
  – Critical volume model
    - At least 700 cc normal liver receives ≤15 Gy in 3-5 fractions
  – Prox Duodenum
    - V33Gy <1cc
    - V20Gy <3cc