Evidence Based Integration of SIRT into HCC Management

Dr Thomas W.T. Leung, MBBS MD
Associate Director
Comprehensive Oncology Centre
Hong Kong Sanatorium and Hospital

Second Asia Pacific Symposium on Liver Directed Y-90 Microspheres Therapy
1 November 2014
HCC Management - The BCLC Staging Classification

**Stage 0**
- Normal
  - Single or 3 nodules < 3cm, PS 0
  - PST 0, Child-Pugh A

**Stage A - C**
- Intermediate stage (B)
  - Multinodular, PS 0
  - Associated diseases
  - Portal pressure/bilirubin
    - Increased
    - Associated diseases
    - No
    - Yes
  - 3 nodules ≤3cm

**Stage D**
- Advanced stage (C)
  - Portal invasion, N1,M1, PS 1-2
  - Portal invasion, N1,M1
    - No
    - Yes

**Stage 0**
- Resection
- Liver Transplantation
- RFA
- Chemoembolisation
- Sorafenib

**Curative Treatments**
- 50% - 75% at 5 years

**Randomised controlled trials**
- 40% - 50% at 3 y vs 10% at 3 y

**Symptomatic treatment**

Lancet, 2003
Selective Internal Radiation Therapy (SIRT)

- Intra-arterial unsealed isotope (Y-90) treatment

**Indications:**
- Inoperable localized HCC
- No/minimal extra-hepatic disease
- Acceptable liver function
- BCLC intermediate stage B and some advanced stage C (Mo)

(y-90 microspheres in suspension. x300)
HCC Management - The BCLC Staging Classification

Stage 0
PST 0, Child-Pugh A

Very early stage (0)
Single < 2cm.
Carcinoma in situ

Early stage (A)
Single or 3 nodules < 3cm, PS 0

Intermediate stage (B)
Multinodular, PS 0

Advanced stage (C)
Portal invasion, N1,M1

Stage D
Okuda 3, PST >2, Child-Pugh C

Terminal stage (D)

Stage A - C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Resection
Liver Transplantation
RFA
Chemoembolisation
Sorafenib

Curative Treatments
50% - 75% at 5 years

Randomised controlled trials
40% - 50% at 3 yr vs 10% at 3yr

Symptomatic treatment

Increased
Associated diseases

No
Yes

Portal pressure/bilirubin

Normal

Lancet, 2003
TACE and RE in Clinical Practice
Patient Profiles (BCLC Stages)

TACE
- Meyer
- Jung
- Burrell

RE
- Hilgard
- Salem
- Sangro


## Treatment Outcome: SIRT for HCC

<table>
<thead>
<tr>
<th>Author Year</th>
<th>No. of patients</th>
<th>ORR (%)</th>
<th>Median OS (months)</th>
<th>1-year (%)</th>
<th>2-years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau, 1994</td>
<td>18</td>
<td>44.4</td>
<td>7.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lau, 1998</td>
<td>71</td>
<td>26.7</td>
<td>9.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dancey, 2000</td>
<td>20</td>
<td>20</td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carr, 2004</td>
<td>65</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salem, 2005</td>
<td>43</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sangro, 2006</td>
<td>24</td>
<td>23.8</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kulik, 2006</td>
<td>35</td>
<td>50</td>
<td>26.6</td>
<td>84</td>
<td>54</td>
</tr>
<tr>
<td>Kulik, 2008</td>
<td>108</td>
<td>42.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaba, 2009</td>
<td>17</td>
<td>64</td>
<td>36.6</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>D’Avola, 2009</td>
<td>35</td>
<td></td>
<td>16</td>
<td>65</td>
<td>36</td>
</tr>
<tr>
<td>iñarrairaegui, 2010</td>
<td>72</td>
<td>12</td>
<td>13</td>
<td>52</td>
<td>24</td>
</tr>
</tbody>
</table>

### Time to Progression (Intermediate Stage)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SIRT (1)</th>
<th>SIRT (2)</th>
<th>TACE (3)</th>
<th>DEB-TACE (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>65</td>
<td>17</td>
<td>31</td>
<td>153</td>
</tr>
<tr>
<td>Response rate</td>
<td>71%</td>
<td>53%</td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td>Median TTP (mo)</td>
<td>13.3</td>
<td>13</td>
<td>4.9</td>
<td>5.5</td>
</tr>
</tbody>
</table>

RE for HCC
Patient outcomes according to tumor stage

Intermediate stage patients

- TACE (Salem, Gastro. 2011) - Intermediate HCC n = 73
- TACE (Wang, Eur J Cancer. 2008) - Intermediate HCC n = 741
- TACE (Chen, Eur J Cancer. 2009) - Intermediate HCC n = nr
- RE (Hilgard, Hepatology. 2010) - Intermediate HCC n = 51
- RE (Salem, Gastro. 2010) - Intermediate HCC n = 83
- RE (Sangro, Hepatology. 2011) - Intermediate HCC n = 87

Median overall survival (months)
# TACE vs SIRT for HCC
*(Non-randomized Single Institution Series)*

<table>
<thead>
<tr>
<th>Series</th>
<th>Salem, 2011</th>
<th>Moreno-Luna, 2013</th>
<th>Kooby, 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>TACE</td>
<td>SIRT</td>
<td>TACE</td>
</tr>
<tr>
<td>No. of patients</td>
<td>122</td>
<td>123</td>
<td>66</td>
</tr>
<tr>
<td>Bilobar</td>
<td>34</td>
<td>36</td>
<td>Nr</td>
</tr>
<tr>
<td>Child A</td>
<td>55</td>
<td>54</td>
<td>80</td>
</tr>
<tr>
<td>BCLC stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (A)</td>
<td>39</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>Intermediate (B)</td>
<td>20</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Advanced (C)</td>
<td>9</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>Survival (mo)</td>
<td>17.4</td>
<td>20.5</td>
<td>14.4</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.23</td>
<td></td>
<td>0.47</td>
</tr>
</tbody>
</table>
**TACE vs SIRT for HCC (non-randomized)**

<table>
<thead>
<tr>
<th>BCLC stage</th>
<th>SIRT</th>
<th>TACE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>23.9</td>
<td>18.6</td>
<td>0.4</td>
</tr>
<tr>
<td>B</td>
<td>16.8</td>
<td>13</td>
<td>0.16</td>
</tr>
<tr>
<td>C</td>
<td>8.4</td>
<td>10.1</td>
<td>0.47</td>
</tr>
<tr>
<td>All stages</td>
<td>15</td>
<td>14.4</td>
<td>0.47</td>
</tr>
</tbody>
</table>

(Moreno-Luna LE, et al. CVIR 2013; 36:714)
SIRTACE: A RANDOMISED MULTICENTRE PILOT TRIAL OF SELECTIVE INTERNAL RADIOEMBOLISATION (SIRT) WITH YTTRIUM-90 MICROSPHERES VERSUS TRANSARTERIAL CHEMO-EMBOLISATION (TACE) IN PATIENTS WITH UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)

- Pilot, open-label, randomized, prospective, cohort comparison conducted at 2 European centres:
  - University of Munich
  - Clinica Universidad de Navarra, Spain

(Kolligs F, et al. EASL 2013, Abs 113)
SIRTACE Trial Results

- No observed differences between SIRT (13 patients) and TACE (15 patients) in:
  - Health-related quality of life
  - Severity of adverse events
  - Tumour response or disease control rate
  - Progression-free survival
  - Overall survival

- Patients received mean number of treatment
  - 3.4 TACE interventions (range 1 – 11)
  - 1 SIRT procedure
Intermediate Stage HCC

- Similar survival between SIRT and TACE
- Similar quality of life after SIRT or TACE
- Less session of treatment for SIRT
Intermediate Stage HCC with Relative Contraindication for TACE

- Large solitary HCC > 10 cm
- Extensive bilobar disease
- Portal vein thrombosis
RE for HCC
Patient outcomes according to suitability for TACE

Advanced Stage HCC (BCLC stage C)

- Standard of care is oral sorafenib
- Worse prognosis for patient with PVT (8.1 months sor versus 4.9 months placebo)
Survival Reported Across Studies for Patients with PVT

- SHARP
- Mazzaferro
- Iñarraíraegui

**SORAFENIB**

**RADIOEMBOLIZATION**

Median Overall Survival (months)

- SHARP: 8 months
- Mazzaferro: 12 months
- Iñarraíraegui: 10 months

References:

RE for Advanced Stage Patients with PVT

Tumor response by EASL criteria
PVT patients (dotted bars):
Objective response: 37%
Disease control: 74%

Advanced HCC (BCLC C, PVT present)

Responders: 25%
Non-responders: 4.4%

Responders: 17 mo (95% CI 12-21)
Non-responders: 7 mo (95% CI 5-11)

Downstaging Unresectable HCC using SIRT

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Salvage procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau 2004</td>
<td>71</td>
<td>Liver resection 4 (5.6%)</td>
</tr>
<tr>
<td>Salem 2010</td>
<td>291</td>
<td>LT 34 (11%) LT resection 2 (0.7%)</td>
</tr>
<tr>
<td>Kulik 2006</td>
<td>35</td>
<td>LT 8 (23%) LT resection 1 (3%)</td>
</tr>
</tbody>
</table>
Pre-treatment CT
Tumour thrombus in main PV
Tumour in left liver (not shown)

24 months after once treatment

Yttrium-90 Microspheres Treatment
Downstaging of unresectable HCC with SIRT

- Series of 49 patients
- 4 treated with SIR-Spheres alone
- All 4 patients down staged for resection
- 5 treated with SIR-Spheres and Chemo (sequential therapy)
- Survival all patients: 3 year 64%  5 year 57%

Lau W, Ho S, Yu S, Lai E, Liew C and Leung T:

Salvage Surgery Following Downstaging of Unresectable HCC

## Results of Liver Transplantation after Tumour Downstaging with SIRT

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Liver Transplant</th>
<th>Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulik, 2006</td>
<td>34</td>
<td>8 (23.5%)</td>
<td>1, 2, 3 yr OS 84%, 54%, 27%</td>
</tr>
<tr>
<td>Lewandowski, 2009*</td>
<td>43</td>
<td>9 (20.9%)</td>
<td>1 yr RFS 89%</td>
</tr>
<tr>
<td>Ibrahim, 2011</td>
<td>8 involved caudate</td>
<td>3 (37.5%)</td>
<td>1, 2, 3 yr OS 75%, 75%, 24%</td>
</tr>
</tbody>
</table>

*SIRT gave higher rate of downsizing from UNOS T3 to T2 stage compared to TACE (58% vs 31%, p<0.023)
Also higher rate of RFA ablation after SIRT than TACE (42% vs 23%)
# Ongoing Clinical Trials of Radioembolization in Intermediate and Advanced Stage HCC

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>YES-P</th>
<th>SIRveNIB</th>
<th>SARAH</th>
<th>SORAMIC</th>
<th>STOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>SOR</td>
<td>SOR</td>
<td>SOR</td>
<td>SOR</td>
<td>SOR</td>
</tr>
<tr>
<td>Exp Arm</td>
<td>SIRT</td>
<td>SIRT</td>
<td>SIRT</td>
<td>SIRT + SOR</td>
<td>SIRT + SOR</td>
</tr>
<tr>
<td>End point</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>Region</td>
<td>US – Italy</td>
<td>Asia – Pacific</td>
<td>France</td>
<td>EU</td>
<td>Global</td>
</tr>
</tbody>
</table>
Conclusion

- SIRT has compelling evidence to be a better option for intermediate stage HCC and some patients with advanced stage HCC especially those with portal vein thrombosis

- Suggested indications of SIRT for HCC
  - Intermediate stage HCC: single, 2-3 nodules, CPA, multifocal tumour with reasonable LFTs
  - Advanced stage HCC: branch or main portal vein invasion with no extra-hepatic disease and normal liver function
  - Downstage to resectable or transplantable stage
Treatment Strategy based on BCLC HCC Staging System

HCC

Very early stage (0) → Single HCC → Portal pressure/bilirubin → Increased/Associated diseases → Resection

Early stage (A) → 3 nodules ≤3cm → No/Yes → Liver transplantation/RFA

Intermediate stage (B) → No → CEAP (Curative treatments)

Advanced stage (C) → Yes → Extrahepatic disease → No → CEAP (Randomized controlled trials)

Terminal stage (D) → Yes → CEAP (Symptomatic treatment)

Sorafenib

Adapted from Llovet JM, et al, Lancet 2003;362:1907–17