Welcome

The CLDF would like to thank our supporter, Bristol Myers Squibb, for providing an educational grant for this initiative.
• Over 50% of HCC patients are intermediate or advanced stage
  – Should every intermediate stage patient get TACE?
  – Should every advanced stage patient get sorafenib?

• There may be room for a more individualized treatment strategy
Overview of Therapies
Transarterial Chemoembolization
Conventional TACE

- Chemotherapy (doxorubicin or cisplatin) emulsified with ethiodized oil is administered into tumor-bearing artery
  - Selective killing of tumor, which is supplied only by the hepatic artery
  - Normal liver survives, due to dual blood supply with portal vein
- Proven by RCTs to improve survival in intermediate HCC
  - Patient selection: ECOG 0-2, Child A or B, no extrahepatic spread
  - Repeated treatments often necessary
- Post-embolization syndrome
  - Pain, nausea, low-grade fever, fatigue
  - 1-2 day hospitalization

3-year survival:
26-29% with TACE
3-17% with supportive care

Meta-analysis:
2-year mortality significantly reduced with TACE (OR 0.54)

Transarterial Chemoembolization

Drug-eluting Bead TACE

- Similar to conventional TACE, but beads rather than ethiodized oil carry the chemotherapy
  - Simultaneous chemotherapy and embolization
  - Small beads = more effective tumor kill (?)
  - Slower elution = fewer systemic side effects (?)

Complete Response
Objective Response
DC Bead cTACE
Disease Control

<table>
<thead>
<tr>
<th></th>
<th>% Patients</th>
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<tbody>
<tr>
<td>DC Bead</td>
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<tr>
<td>Complete Response</td>
<td>59 (63%)</td>
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<tr>
<td>Objective Response</td>
<td>48 (52%)</td>
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<tr>
<td>Disease Control</td>
<td>25 (27%)</td>
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<tr>
<td>cTACE</td>
<td></td>
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<tr>
<td>Complete Response</td>
<td>56 (52%)</td>
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<tr>
<td>Objective Response</td>
<td>47 (44%)</td>
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<tr>
<td>Disease Control</td>
<td>24 (22%)</td>
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Transarterial administration of radioactive microspheres (Yttrium-90)

- Very high local radiation dose (100-1000 Gy or more)
- 40x higher dose to tumor than external beam radiation
- Not dependent on flow occlusion

Two-step procedure

- Initial mapping angiogram
  - Check for arteries in treatment area going to stomach or bowel
  - Test dose of Tc-MAA to measure shunt fraction to lungs
- 1-2 weeks later, Y90 delivery performed

Mild side effect profile

- Less post-embolization syndrome
- Can treat entire lobe at one time (large lesions, multiple lesions)
- Fully outpatient procedure

Transarterial Radioembolization Radiation Segmentectomy

- Superselective Y90 delivery into one hepatic segment
- Radioembolization was traditionally performed in lobar fashion
  - Large tumors
  - Multifocal disease
- Radiation segmentectomy can be employed in treatment of localized tumors
  - Deliver entire lobar dose into one segment (ablative dose)
  - Radiation damage is limited to the segment treated
- High complete response rates with low toxicity
The Latest Data
Conventional TACE
The Latest Data

- 101 articles including over 10,000 patients
- Objective response rate 52.5%
- Overall survival 70% at 1 year, 32% at 5 years
- Median OS was 19 months
- Mortality rate 0.6%

Fig. 2. OS rates after lipiodol TACE for HCC. Data based on a systematic review of 101 clinical studies including 10,108 subjects. Bars show 95% CIs.
Conventional TACE Predictors of 5-year survival

TACE outcomes are poor in 3 groups

- Very large tumors
- Widely multifocal disease
- Portal vein invasion

Largest tumor size
- Up to 2 cm = 39%
- 2.1-3 cm = 28%
- 3.1-5 cm = 23%
- >5 cm = 16%

Number of lesions
- 1 = 33%
- 2-3 = 24%
- 4 or more = 16%

PV invasion
- None = 28%
- Branch = 12%
- Main = 0%

Drug-eluting Bead TACE
The Latest Data

Randomised controlled trial of
doxorubicin-eluting beads vs conventional
chemoembolisation for hepatocellular
carcinoma

- 177 patients randomized to DEB-TACE or cTACE
- No difference in objective response rates
- No difference in median survival
  - 28 months for cTACE
  - 29 months for DEB-TACE
- Significant adverse events rare in both groups (<7%)
  - Abdominal pain more frequent with cTACE
- Conventional TACE and DEB TACE are equivalent

\[ P = 0.949 \]
Transarterial Radioembolization
The Latest Data

- 459 patients in 25 French centers
  - 237 treated with single SIR-Spheres treatment
  - 222 treated with sorafenib 400 mg BID
- Objective response rate better for Y90 (19% vs 12%)
- Overall survival not significantly different (8 vs 9.9 months)
- SAE more common with sorafenib (63% vs 41%)
- Y90 produces better response rate, better QoL and fewer SAE than sorafenib
Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial

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Limitations…

45% of patients had previous failed TACE

33% of patients had main portal vein invasion

Centers were not skilled or experienced with Y90
Transarterial Radioembolization
The Latest Data

Institutional Decision to Adopt Y90 as Primary Treatment for Hepatocellular Carcinoma Informed by a 1,000-Patient 15-Year Experience

Riad Salem,1,2 Ahmed Gabr,2,3 Absum Riaz,1 Ronald Moro,4 Reham Ali,1 Michael Abecassis,2 Ryan Hickey,1 Laura Kilik,1 Daniel Ganger,1 Steven Flamum,1 Rohit Atassi,3 Bassel Atassi,1 Kent Stan,1 Al B. Benson,2 Mary F. Muktab,2 Nadine Abochaleh,4 Ali Al Asadi,1 Kush Desai,1 Bartley Thornburg,2 Michael Vovitch,1 Ali Habib,1 Jean Caicedo,5 Frank H. Miller,1 Vahid Yaghmai,1 Joseph R. Kallin,1 Sandeep Monik,1 and Robert J. Lewandowski1,5

- Largest cohort of HCC patients treated with Y90
- 152 patients were BCLC B (intermediate HCC)
  - Median survival 25 months if Child class A
  - Median survival 15 months if Child class B
- 541 patients were BCLC C (advanced HCC)
  - Median survival 15 months if Child class A
  - Median survival 8 months if Child class B
Transarterial Radioembolization
The Latest Data

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Y90 median survival 15-25 months
Compare to 19 months for TACE

Y90 median survival 8-15 months
Compare to 8-10 months for sorafenib
185 patients with HCC and PVT treated with Y90
  - 42% main PVT, 23% segmental, 35% branch

Median survival 13.9 months for CP-A, 6.9 months for CP-B7

Some patients had long-term survival

Low toxicity

Lobar vs. branch PVT similar

Y90 is effective for CP-A patients with HCC and PVT
- 185 patients with HCC and PVT treated with Y90
  - 42% main PVT, 23% segmental, 35% branch
- Median survival 13.9 months for CP-A, 6.9 months for CP-B7
- Some patients had long-term survival
- Low toxicity
- Lobar vs. branch PVT similar
- My take: Y90 gives hope in HCC with PVT. 10% long-term survival is better than 0.
Radiation Segmentectomy
The Latest Data

- 102 patients with HCC up to 5 cm not amenable to RFA
- Treated with radiation segmentectomy
  - Complete response in 47%
  - Partial response in 39%
- Median overall survival 34 months (!)
- 33 patients had OLT
  - All had >90% tumor necrosis on path
- No major complications

Table 3. Pathological Outcome by Radiation Dose

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>PN</th>
<th>CPN</th>
<th>Total</th>
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<tbody>
<tr>
<td>&lt;190 Gy</td>
<td>9</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>&gt;190 Gy</td>
<td>7</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>17</td>
<td>33</td>
</tr>
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$P = 0.03$ (Fisher’s exact test).
Comparisons Between Therapies
Comparisons Between Therapies
Conventional TACE vs Drug-eluting Bead TACE

- DEB-TACE expected to improve response rates and reduce side effects
- 2016 meta-analysis
  - Four RCTs, 8 observational studies
    - DEB-TACE with doxorubicin vs. conventional TACE with varied chemotherapy
  - 1449 patients
    - Liver function and tumor stage comparable between the groups
  - No significant difference in 1-year, 2-year and 3-year survival
  - No difference in objective response rates
  - No difference in adverse events
- No significant difference between DEB-TACE and conventional TACE

Comparisons Between Therapies
TACE vs Radioembolization (Y90)

- 245 comparable patients with unresectable intermediate-stage HCC and no PVT
- 123 underwent TheraSphere Y-90 vs. 122 had TACE
  - Response rate 49% vs. 36% (p=0.104)
  - Time to progression 13 vs. 8 months (p=0.046)
  - Overall median survival 20 vs. 17 months (ns)
  - Less abdominal pain and LFT increase with Y90

Comparisons Between Therapies
Radiation Segmentectomy vs. TACE

- Retrospective study of segmental TACE vs segmental Y90 for localized HCC
  - TACE patients (n=77) had worse performance status and worse Child class
  - Y90 patients (n=101) had larger tumors, more infiltrative tumors, more PVI
- Complete response rate better for Y90 (92% vs 74%)
- Index tumor progression rate better for Y90 (15% vs 42%)
- Segmental Y90 (radiation segmentectomy) yields better local response rate than segmental TACE
Comparisons Between Therapies
Radiation Segmentectomy vs. TACE+ablation

- 121 matched patients with solitary HCC < 3 cm
  - 41 had radiation segmentectomy
  - 80 had TACE followed by MWA

- No difference in CR rate, 83% (RS) vs 82% (TACE/MWA)

- No difference in TTP (11 vs 12 months)

- No difference in overall survival

- 90-day mortality rate 0% in both groups

- Radiation segmentectomy can effectively cure small HCC