Radioembolisation in colorectal liver metastasis

Bernhard Gebauer
Klinik für Strahlenheilkunde
Charité
Berlin, DE
Disclosure

Speaker name: Bernhard Gebauer

I have the following potential conflicts of interest to report:

☐ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☒ Other(s): Parexel, C.R. Bard, Sirtex Medical, St. Jude Medical, Cook Medical, AngioDynamics, PharmaCept, Roche, Merck, 3M, Beacon Bioscience/ICON, Ipsen, Bayer, Pfizer
☐ I do not have any potential conflict of interest
Radioembolization (RE, SIRT)

- Yttrium-90: pure β-emission
- mean penetration: 3.9 mm
- max. range: 11 mm
- max. energy: 2.27 MeV
- half-life: 64 h (< 3% after 14 d)

Kennedy-AS, Int J Rad Oncol Phys 2004
No embolizing effect of radioembolization before SIR-Spheres after SIR-Spheres
Liver metastasis in colorectal cancer

- Liver metastasis are responsible for 2/3 of cancer related deaths in colorectal cancer.

- Resectable: 10-20%
  - Adjuvant chemotherapy?
  - Hepatic recurrence in 65-72%
  - 5-years OS 30-40%

- Non-resectable: 80-90%
  - (Conversion) chemotherapy
  - Resectable: med. OS 37.5 months
  - Non-resectable: med. OS 28.4 months

- 5-years OS 1-2%

References:
- Van den Eynde-M, Reviews on Recent Clinical Trials 2009
- Shimada-H, Langenbecks Arch Surg 2009
- Nordlinger-Lancet 2008
- Brasso-M, Medicine (Baltimore) 2016
Scenarios for Radioembolisation in CRC

• **1st Line-Situation**
  – primary treatment of inresectable hepatic metastasis

• **Salvage-Situation**
  – inresecable hepatic metastasis with progress under standard chemotherapy (oxaliplatin, irinotecan) or with severe adverse events (SAE) under standard chemotherapy
1st line: Survival

- patients without previous chemotherapy
- 5-FU/LV (n=10) vs. 5-FU/LV (n=11) + RE
- SIRT at 3rd or 4th day of 2nd chemotherapy cycle

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Med. OS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/LV</td>
<td>12.8 mo</td>
<td>0.02</td>
</tr>
<tr>
<td>5-FU/LV + RE</td>
<td>29.4 mo</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Fig. 1. Survival by treatment.

van Hazel-G, J Sur Oncol 2004
mCRC: SIRFLOX

Eligible Patients:
- Unresectable liver-only or liver-predominant colorectal cancer metastases
- No prior chemotherapy for advanced disease
- Fit for combination therapy and selective internal radiation therapy (SIRT)

Schema:
- Stratify
  - Presence of extra-hepatic metastases
  - Degree of liver involvement
  - Institution
  - Use of bevacizumab
- Randomise 1:1 n >500
- SiR-Spheres® Y-90 resin microspheres
- FOLFOX6m± bevacizumab

Indication:
- unresectable liver-only or liver predominant colorectal cancer metastasis
- no prior chemotherapy for advanced disease
- fit for combination therapy and selective internal radiation therapy (SIRT)

End point:
- progression-free survival (PFS), analysis of overall PFS and hepatic PFS

Ricky A. Sharma ASCO 2017, Abstract #: 3507, Clinical Trial Registry Number: 83867919, Citation: J Clin Oncol 35, 2017 (suppl; abstr 3507); http://meetinglibrary.asco.org/record/147171/abstract
3 prospective, randomized studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Geographic region</th>
<th>Recruitment completed</th>
<th>Patients recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRFLOX</td>
<td>ANZ, EME, USA</td>
<td>2013</td>
<td>530</td>
</tr>
<tr>
<td>FOXFIRE</td>
<td>UK</td>
<td>2014</td>
<td>364</td>
</tr>
<tr>
<td>FOXFIRE global</td>
<td>ANZ, AP, EME, USA</td>
<td>2014</td>
<td>209</td>
</tr>
</tbody>
</table>

Vrdee-PS, JMIR Res Protocol 28, 2017

Ricky A. Sharma ASCO 2017, Abstract #: 3507, Clinical Trial Registry Number: 83867919, Citation: J Clin Oncol 35, 2017 (suppl; abstr 3507); http://meetinglibrary.asco.org/record/147171/abstract
Key eligibility criteria

- Adenocarcinoma of the colon or rectum
- Liver metastasis not surgically resectable or ablatable
- Eligible for systemic chemotherapy as first-line treatment for metastatic CRC
- WHO performance status 0-1
- Limited extra-hepatic metastasis
- Permitted to have primary tumor in situ
- No evidence of ascites cirrhosis or portal hypertension
Patients characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemo (n = 549)</th>
<th>Chemo+SIRT (n = 554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>63 (23 – 89)</td>
<td>63 (28 – 90)</td>
</tr>
<tr>
<td>Male</td>
<td>65.8%</td>
<td>65.5%</td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>63.2%</td>
<td>63.9%</td>
</tr>
<tr>
<td>1</td>
<td>36.4%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Extra-hepatic metastases</td>
<td>34.8%</td>
<td>35.9%</td>
</tr>
<tr>
<td>&gt;25% liver involvement</td>
<td>30.6%</td>
<td>32.3%</td>
</tr>
<tr>
<td>Intent to treat with biologicals</td>
<td>54.5%</td>
<td>53.8%</td>
</tr>
<tr>
<td>Synchronous presentation with liver mets</td>
<td>86.5%</td>
<td>87.2%</td>
</tr>
<tr>
<td>Primary tumor in situ</td>
<td>55.0%</td>
<td>50.2%</td>
</tr>
</tbody>
</table>

Ricky A. Sharma ASCO 2017, Abstract #: 3507, Clinical Trial Registry Number: 83867919, Citation: J Clin Oncol 35, 2017 (suppl; abstr 3507); http://meetinglibrary.asco.org/record/147171/abstract
## Treatment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemo (n = 549)</th>
<th>Chemo+SIRT (n = 554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not receive SIRT: Total</td>
<td>-</td>
<td>8.5%</td>
</tr>
<tr>
<td>Reasons in FOXFIRE:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clinical deterioration</td>
<td>-</td>
<td>(33.3%)</td>
</tr>
<tr>
<td>• Aberrant vascular anatomy/lung shunting</td>
<td>-</td>
<td>(40.0%)</td>
</tr>
<tr>
<td>• Withdrew consent to SIRT</td>
<td>-</td>
<td>(20.0%)</td>
</tr>
<tr>
<td>Cycles of oxaliplatin received at full protocol dose</td>
<td>49.1%</td>
<td>43.8%</td>
</tr>
<tr>
<td>Median (IQR) number of cycles of FOLFOX chemotherapy</td>
<td>12 (7-13)</td>
<td>12 (7-15)</td>
</tr>
<tr>
<td>Patients receiving bevacizumab</td>
<td>46.6%</td>
<td>35.6%</td>
</tr>
<tr>
<td>Patients receiving cetuximab</td>
<td>1.6%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Ricky A. Sharma ASCO 2017, Abstract #: 3507, Clinical Trial Registry Number: 83867919, Citation: J Clin Oncol 35, 2017 (suppl; abstr 3507); http://meetinglibrary.asco.org/record/147171/abstract
Overall survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Events</th>
<th>Median (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>549</td>
<td>411</td>
<td>23.3</td>
</tr>
<tr>
<td>Chemo + SIRT</td>
<td>554</td>
<td>433</td>
<td>22.6</td>
</tr>
</tbody>
</table>

HR: 1.04 (p=0.609)

Ricky A. Sharma ASCO 2017, Abstract #: 3507, Clinical Trial Registry Number: 83867919, Citation: J Clin Oncol 35, 2017 (suppl; abstr 3507); http://meetinglibrary.asco.org/record/147171/abstract
### Overall survival: subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver-only</td>
<td>713</td>
<td>525</td>
<td>1.00 (0.85 - 1.19)</td>
</tr>
<tr>
<td>Liver-dominant</td>
<td>390</td>
<td>319</td>
<td>1.07 (0.85 - 1.33)</td>
</tr>
<tr>
<td>Liver involvement ≤ 25%</td>
<td>754</td>
<td>545</td>
<td>1.00 (0.84 - 1.18)</td>
</tr>
<tr>
<td>Liver involvement &gt; 25%</td>
<td>347</td>
<td>297</td>
<td>1.12 (0.89 - 1.41)</td>
</tr>
<tr>
<td>Age &lt; 65 years</td>
<td>623</td>
<td>470</td>
<td>0.97 (0.81 - 1.16)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>479</td>
<td>374</td>
<td>1.14 (0.93 - 1.41)</td>
</tr>
<tr>
<td>Male</td>
<td>724</td>
<td>556</td>
<td>1.11 (0.94 - 1.31)</td>
</tr>
<tr>
<td>Female</td>
<td>378</td>
<td>288</td>
<td>0.88 (0.70 - 1.12)</td>
</tr>
<tr>
<td>No primary tumor in situ</td>
<td>521</td>
<td>390</td>
<td>0.98 (0.80 - 1.19)</td>
</tr>
<tr>
<td>Primary tumor in situ</td>
<td>580</td>
<td>453</td>
<td>1.10 (0.92 - 1.33)</td>
</tr>
<tr>
<td>WHO performance status 0</td>
<td>701</td>
<td>514</td>
<td>1.03 (0.86 - 1.22)</td>
</tr>
<tr>
<td>WHO performance status 1</td>
<td>398</td>
<td>328</td>
<td>1.07 (0.86 - 1.32)</td>
</tr>
<tr>
<td>Primary tumor location - left</td>
<td>540</td>
<td>389</td>
<td>1.14 (0.93 - 1.39)</td>
</tr>
<tr>
<td>Primary tumor location - right</td>
<td>179</td>
<td>147</td>
<td>0.67 (0.48 - 0.92)</td>
</tr>
<tr>
<td>Bevacizumab received</td>
<td>465</td>
<td>336</td>
<td>0.97 (0.78 - 1.20)</td>
</tr>
<tr>
<td>Bevacizumab not received</td>
<td>638</td>
<td>508</td>
<td>1.04 (0.87 - 1.24)</td>
</tr>
<tr>
<td>Synchronous disease</td>
<td>958</td>
<td>739</td>
<td>1.02 (0.89 - 1.18)</td>
</tr>
<tr>
<td>Metachronous disease</td>
<td>139</td>
<td>101</td>
<td>0.99 (0.66 - 1.48)</td>
</tr>
</tbody>
</table>
Salvage-Situation: Survival

- Chemotherapy-refractory liver mets
- 224 patients with CRC, 242 RE treatments
- comparison with 29 patients standard treatment

**Bester-L, JVIR 2012**

- **med. OS CRC-mets**
  - control: 6.6 mo
  - RE: 11.9 mo

**Complications (n=339 patients)**

- Ulcus: 3%
- REILD: 2.9%
- Cholecystitis: 1.8%
Salvage-Situation: Survival

- Chemotherapy-refractory CRC liver mets
- 29 RE treatments vs. 29 patients “best supportive care” (Matched-Pair Comparison)

Seidensticker-R, CVIR 2012

```
<table>
<thead>
<tr>
<th></th>
<th>OS CRC-mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.5 mo</td>
</tr>
<tr>
<td>RE</td>
<td>8.3 mo</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
```

```
<table>
<thead>
<tr>
<th>Complications</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcus</td>
<td>10.3 %</td>
</tr>
<tr>
<td>REILD</td>
<td>10.3 %</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>1.8%</td>
</tr>
</tbody>
</table>
```
Salvage-Situation: Survival

- PD after oxaliplatin and irinotecan chemotherapy
- RE in 50 patients (46 with RECIST evaluable)
- CR 2%; PR 22%; SD 24%; PD 44%

<table>
<thead>
<tr>
<th></th>
<th>Pat.</th>
<th>Med. OS</th>
<th>1-y-surv.</th>
<th>2-y-surv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>50</td>
<td>12.6 mo</td>
<td>50.4%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Responder (CR+PR+SD)</td>
<td>28</td>
<td>16.0 mo</td>
<td>79.2%</td>
<td>40.3%</td>
</tr>
<tr>
<td>Non-Responder (PD)</td>
<td>22</td>
<td>8.0 mo</td>
<td>20.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>P = 0.0006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cosimelli-M, Br J Cancer 2010
Summary

• Radioembolisation in unresectable hepatic CRC metastasis
  – no benefit if added to a 1st line chemotherapy
  – survival benefit if used in salvage situation after failure or standard chemotherapy
Radioembolisation in colorectal liver metastasis

Bernhard Gebauer
Klinik für Strahlenheilkunde
Charité
Berlin, DE