Selection of Patients With Metastatic Colorectal Cancer For SIRT

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Walter and Eliza Hall Institute
Advantages Of First Line Therapy

- Patient will receive SIRT

- Proven impact on overall survival with 5-FU, but standard of care = Combination CT + Biologic

- Promising data with FOLFOX
  - High response rates, durable responses, resections….

  **BUT** no randomised data to support this **YET**
Disadvantages Of First Line Therapy

- Adverse events of concern
  1. Gastric ulceration – may have prolonged symptoms / perforation
  2. Liver failure – 1 in 200?
Selection Criteria For SIRT vs Combination Chemotherapy + Biologic – First Line

1. Patient factors = Fit for standard treatment
   – Age
   – Co-morbidity
Treatment Of Metastatic Colorectal Cancer In Routine Clinical Practice (n=1450)
## Two Randomised Studies Combining SIRT With Fluoropyrimidine

<table>
<thead>
<tr>
<th>Study Arms</th>
<th>N = 70 patients</th>
<th>Time To Liver Progression (p=0.001)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IH FUDR vs</td>
<td>34 FUDR alone</td>
<td>9.7 months</td>
<td>1 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2yr 68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3yr 29%</td>
</tr>
<tr>
<td>SIRT + IH FUDR</td>
<td>36 SIRT + FUDR</td>
<td>15.9 months</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17%</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study</th>
<th>Response</th>
<th>Time To Progression (P &lt; 0.005)</th>
<th>Survival (P = 0.02)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/LV vs</td>
<td>0 / 10</td>
<td>3.6 months</td>
<td>12.8 months</td>
</tr>
<tr>
<td>SIRT + 5-FU/LV</td>
<td>8 / 11 = 73%</td>
<td>18.6 months</td>
<td>29.4 months</td>
</tr>
</tbody>
</table>

#1 – frail /elderly patient
85 y.o. male
Isolated liver metastasis
CLL, prostate cancer
Impaired renal function, & bone marrow reserve

Selective treatment + 5FU
Died at 12 months without PD
57 y.o. male, renal transplant with renal impairment, immunosuppression and steroids - diagnosed October 2009

December 2010
Selection Criteria For SIRT vs Combination Chemotherapy + Biologic – First Line

For a young and fit patient...........

Extent of metastatic disease is the major factor

- Bulk of liver metastases
  - Potentially resectable with a great response
  - OR
  - Close to catastrophe
**SIR-Spheres microspheres as consolidation of 1st-line Chemotherapy for Colorectal Cancer Liver Metastases**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>n</th>
<th>Treatment</th>
<th>ORR</th>
<th>PFS</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sangro</td>
<td>23</td>
<td>SIR-Spheres†</td>
<td>nr</td>
<td>6.2 mo&lt;sup&gt;cens.&lt;/sup&gt;</td>
<td>16.6 mo&lt;sup&gt;cens.&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.0 mo&lt;sup&gt;cens.&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*In patients still unresectable after >3 months of triple-combination chemotherapy (FOLFOXIRI; FOLFOX + bevacizumab; FOLFOX + cetuximab; etc)*

- Patients remained unresectable (91% with PR or SD following chemotherapy)
- 3 patients (13%) down-sized to resection/ablation, but are censored from the Kaplan-Meier analysis

† SIR-Spheres microspheres; ‡ retrospective data; nr: not reported; cens. censored from the KM analysis of PFS and survival

*Sangro et al. ASCO GI Symp 2010; Abs 250.*
SIR-Spheres microspheres as consolidation of 1<sup>st</sup>-line Chemotherapy for Colorectal Cancer Liver Metastases

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<tbody>
<tr>
<td>Sangro</td>
<td>23</td>
<td>SIR-Spheres†‡</td>
<td>nr</td>
<td>6.2 mo&lt;sub&gt;cens.&lt;/sub&gt; 16.6 mo&lt;sub&gt;cens.&lt;/sub&gt;</td>
<td>11.0 mo&lt;sub&gt;cens.&lt;/sub&gt; 23.3 mo&lt;sub&gt;cens.&lt;/sub&gt;</td>
</tr>
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- Patients remained unresectable (91% with PR or SD following chemotherapy)
- 3 patients (13%) down-sized to resection/ablation, but are censored from the Kaplan-Meier analysis

?Would more have ended up resectable with up-front SIRT (due to radio-sensitisation)

† SIR-Spheres microspheres; ‡ retrospective data; nr: not reported; cens. censored from the KM analysis of PFS and survival

Sangro *et al.* ASCO GI Symp 2010; Abs 250.
Selection Criteria For SIRT vs Combination Chemotherapy + Biologic – First Line

1. Patient factors

2. Extent of metastatic disease
   – Bulk of liver metastases
     • Potentially resectable with a great response
     OR
     • Close to catastrophe

3. Presence of extra-hepatic disease
Selection Criteria - Liver Only vs Liver + Extrahepatic Disease

Median PFS
- 9.3 months

Median PFS for 7 pts with liver only disease
- 14.2 months
Radioembolization in Combination with Systemic Chemotherapy as First-line Therapy for Liver Metastases from Colorectal Cancer

Suzanne Kosmider, MBBS, Thean T. Tan, MBBS, Desmond Yip, MBBS, Richard Dowling, MBBS, BMedSc, Meir Lichtenstein, MBBS, and Peter Gibbs, MD

**Figure 1.** PFS for all patients (N = 19) (a) and by presence (n = 5) or absence (n = 14) of EHD (b).

**Figure 2.** OS for all patients (N = 19) (a) and by presence (n = 5) or absence (n = 14) of EHD (b).
Liver-only or liver-predominant mCRC

1\textsuperscript{st} line chemotherapy
+ Radioembolization
+/- Biologic => +/- Maintenance

2\textsuperscript{nd} line chemotherapy
+ Radioembolization
+/- Biologic

Cetuximab (KRAS wt)

Regorafenib

Clinical trial (multiple)

Radioembolization

Surgical resection

is tumour resectable?

10–20%

<20%

Adapted from Kennedy AS et al. ICACT 2008.
Arguments Against Keeping SIRT Till Later

• Patients may not get to later lines of therapy
  – Treatment can only be effective when it is delivered.

• Less effective?
We studied 4,877 consecutive mCRC patients (pts) who started chemotherapy (Jan. 2004 – Mar. 2011) in U.S. academic, private or community hospital-based practices that employed a chemotherapy (CT) computerized order entry (COE) system to capture pt and physician characteristics, disease information and treatment data.

<table>
<thead>
<tr>
<th>CT line</th>
<th>No. pts/line</th>
<th>% pts/line</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>4877</td>
<td>100%</td>
</tr>
<tr>
<td>2nd line</td>
<td>2575</td>
<td>53%</td>
</tr>
<tr>
<td>3rd line</td>
<td>1373</td>
<td>23%</td>
</tr>
<tr>
<td>4th line</td>
<td>640</td>
<td>13%</td>
</tr>
</tbody>
</table>
A prospective evaluation of treatment with Selective Internal Radiation Therapy (SIR-spheres) in patients with unresectable liver metastases from colorectal cancer previously treated with 5-FU based chemotherapy

L Lim\textsuperscript{1}, P Gibbs\textsuperscript{1}, D Yip\textsuperscript{3}, JD Shapiro\textsuperscript{2}, R Dowling\textsuperscript{1}, D Smith\textsuperscript{3}, A Little\textsuperscript{2}, W Bailey\textsuperscript{2} and M Liechtenstein\textsuperscript{1}
Summary - Early lines of therapy

- Specific clinical scenarios where SIRT is a reasonable option
  - Patient not fit for combination chemotherapy
  - Patient not down-staged to resection after initial therapy?
  - Catastrophic disease??

=> Results of SIRFLOX are eagerly awaited

- What result(s) are required to impact practice
  - PFS
  - Response rate
  - Resection rate (and safety of resection)
  - (Overall survival)
Summary - Later lines of therapy

Proven benefit in the “chemorefractory” setting

• Modest difference in PFS only
  – ?No survival difference due to x-over
     ⇒ No impact on Australian practice, ?biases

• ?How best to integrate SIRT as the goal posts keep moving due to the addition of new lines of therapy
  – Regorafenib
  – TAS102

• ?Negative impact of previous bevacizumab

• ?? SIRT + EGFRI, regorafenib, TAS102, etc.,