An illustrated atlas...
In general terms, the main categories of treatment available for human cancers include...

1. Surgery
2. Chemotherapy
3. Radiotherapy
4. Biologic therapies (in more recent times)
But unfortunately for liver cancer patients not all of these treatments have been widely available...

- Surgery ✓
- Chemotherapy ✓
- Radiotherapy 

Because...
- Normal liver tissue is sensitive to radiation
- Organs near the liver are sensitive to radiation

Therefore...
- Liver cancer patients have missed out on a highly effective cancer treatment option
When liver tumours grow, they recruit their own blood supply from the hepatic artery…

This process in known as angiogenesis… literally “new blood vessels”
SIR-Spheres microspheres exploit the tumour’s own blood supply…

…to deliver radiation therapy to liver tumours “from the inside out” instead of “the outside in”
Two internationally recognised clinician experts…

Professor Valerie Vilgrain – Paris, France

Professor Peter Gibbs – Melbourne, Australia
Hepatocellular Carcinoma (HCC): An Emerging Role for Selective Internal Radiation Therapy (SIRT)?

Prof. Valérie Vigrain
Hôpital Beaujon, Paris, France

Melbourne, 25th February 2014
Sydney, 26th February 2014
Overview of today’s talk

1. Introduction

2. Hepatocellular carcinoma – what is it and how is it treated?

3. Overview of key SIRT data in HCC

4. The SARAH study – SIRT versus sorafenib (Nexavar®)
1. Introduction
Who am I (1)?

- Head of Radiology, Hôpital Beaujon, Paris
  - Radiology employs imaging equipment to diagnose disease

- Diagnostic radiologist
  - Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) etc.
Who am I (1)?

- Head of Radiology, Hôpital Beaujon, Paris
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Who am I (1)?

- Head of Radiology, Hôpital Beaujon, Paris
  - Radiology employs imaging equipment to diagnose disease
- Diagnostic radiologist
  - Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) etc.
Who am I (2)?

- Interventional radiologist (IR)
  - Use intra-arterial or percutaneous access for minimally invasive ("key hole") treatments

- Principal Investigator on French SARAH study
What do interventional radiologists do?

- Interventional radiology is a sub-specialty of radiology
  - We use imaging equipment to perform minimally invasive ("key hole") treatments

  - Commonly employed in lieu of "open" surgery

  - Smaller incision, reduced invasiveness, reduced toxicity & complications, faster wound healing, less time in hospital

- Interventional oncologist
  - Interventional radiologist with an interest in treating patients with cancer

  - "Fourth arm" of oncology with Medical, Surgical, Radiation Oncology
1. Introduction…

About Hôpital Beaujon, Paris

- Special focus on liver
  - Top 1 – 2 liver transplantation programs (J. Belghiti)
  - Top 1 viral hepatitis (P. Marcellin)
  - Top 1 – 3 hepatocellular carcinoma (D. Valla, L. Castera)

- > 15 research teams on liver

- Paris Sorbonne Cité Université
1. Introduction...

About Hôpital Beaujon, Paris (cont.)
2. Hepatocellular carcinoma – what is it and how is it treated?
2. Hepatocellular carcinoma – what is it and how is it treated?

**Hepatocellular carcinoma (HCC) = primary liver cancer**

- **Worldwide incidence (latest WHO statistics)**
  - 780,000 cases per year
  - 746,000 deaths per year

- **HCC is**
  - First cause of mortality from cirrhosis
  - 90% of HCC develop on top of cirrhosis
  - 3\(^{rd}\) worldwide cause of mortality from cancer
  - Increasing in incidence
  - Screening programme

Cirrhosis and hepatocellular carcinoma are complications of chronic (1) liver injury.

Notes: (1) In medicine, “chronic” means long term, e.g. over decades
Hepatocellular carcinoma is an extremely challenging cancer to treat

Patients generally have two diseases at the same time

1. Normal liver tissue
2. Chronic viral hepatitis B
   Chronic viral hepatitis C
   Chronic alcohol misuse
3. Cirrhosis = "scarring" of the liver
4. HCC and cirrhosis

- The patient has HCC (a cancer)
- The patient also has cirrhosis (an "injured" liver)
- This makes treatment more challenging

Time (years – decades)
The BCLC staging system allocates patients to a specific treatment based on the stage of their HCC.

- **HCC**
  - **Stage 0**
    - PST 0, Child-Pugh A
      - **Very early stage (0)**
        - Single <2 cm, Carcinoma in situ
        - **Single**
          - Portal pressure/bilirubin
            - Increased
              - Associated diseases
                - No
                - Yes
                  - Resection
                  - Liver transplantation (CLT/LDLT)
                  - RF/PEI
  - **Stage A-C**
    - PST 0-2, Child-Pugh A-B
      - **Early stage (A)**
        - Single or 3 nodules ≤3 cm, PS 0
        - **3 nodules ≤3 cm**
          - Associated diseases
            - No
            - Yes
              - TACE
              - Sorafenib
  - **Stage D**
    - PST >2, Child-Pugh C
      - **Terminal stage (D)**

**Curative treatment (30-40%)**
- Median OS >60 mo; 5-yr survival: 40-70%

**Targeted therapy**
- TACE: Target: 20%
  - OS: 20 mo (45-14)
- Sorafenib: Target: 40%
  - OS: 11 mo (6-14)
- Best supportive care: Target: 10%
  - OS: <3 mo
Each stage has a different prognosis ("life expectancy")

2. Hepatocellular carcinoma – what is it and how is it treated?

- Stage 0:
  - PST 0, Child-Pugh A
  - Single <2 cm, Carcinoma in situ
  - Portal pressure/bilirubin
    - Increased
    - Normal
  - Associated diseases
    - No
    - Yes
  - Resection
  - Liver transplantation (CLT/LDLT)
  - RF/PEI
  - Curative treatment (30-40%)
  - Median OS >60 mo; 5-yr survival: 40-70%

- Stage A-C:
  - PST 0-2, Child-Pugh A-B
  - Early stage (A):
    - Single or 3 nodules ≤3 cm
    - PS 0
  - Intermediate stage (B):
    - Multinodular, PS 0
  - Advanced stage (C):
    - Portal invasion, N1, M1, PS 1-2
  - Terminal stage (D):
    - PST >2, Child-Pugh C

- Treatment Options:
  - TACE
    - Target: 20%
  - Sorafenib
    - Target: 40%
  - Best supportive care
    - Target: 10%
  - OS: <3 mo
Each stage is allocated a different type of treatment

2. Hepatocellular carcinoma – what is it and how is it treated…
In advanced HCC Bayer’s drug sorafenib has been established as the standard of care since 2008

- No treatment available prior to 2008

- Landmark SHARP randomised controlled trial (RCT) presented at ASCO 2008 & published in New England Journal of Medicine

  ➔ 299 patients received sorafenib – median OS = 10.7 mos

  ➔ 303 patients received placebo (sugar pill) – median OS = 7.9 mos

- Sorafenib = first systemic drug to be proven effective

- Sorafenib = reference treatment (control) against which to compare new therapies, e.g. SIRT in future RCTs

While sorafenib is proven to extend survival in advanced HCC...it has some disadvantages

- **Increase in survival**
  - SHARP (Western population) 10.7 vs 7.9 months
  - Asia Pacific (Asian population) 6.2 vs 4.1 months

- **Disadvantages – continuous, expensive, side effects**

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>SHARP Grade ≥3 n (%)</th>
<th>Asia Grade ≥3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Other skin problems</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

3. Overview of key SIRT data in HCC
Clinical studies of SIRT (1) for HCC are a hot topic

All clinical trials (studies) must be listed on a publically searchable registry – the most widely utilised one is [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

- 9 completed studies
- 20 ongoing studies
- 2 unknown status

Notes: (1) Selective internal radiation therapy (SIRT), also known as radioembolization, is performed using yttrium-90 microspheres, e.g. SIR-Spheres microspheres
How may SIRT be used across the 5 stages of HCC?

- Early HCC – “bridging to liver transplantation”
  - Retrospective study
  - French institutional grant (R. Lebtahi) SIRT versus TACE
- Early HCC – “neo-adjuvant treatment” (= pre-surgery)
- Intermediate HCC
  - In lieu of TACE (fewer side effects c.f. TACE)
  - In patients who have failed TACE (or poor candidates for TACE)
- Advanced HCC
  - Instead of sorafenib (requires SARAH and SIRveNIB study results)
  - Combined with sorafenib (requires SORAMIC study results)
Robust evidence of the survival achieved with SIRT in advanced HCC was presented in 2011

Survival After Yttrium-90 Resin Microsphere Radioembolization of Hepatocellular Carcinoma Across Barcelona Clinic Liver Cancer Stages: A European Evaluation

Bruno Sangro,1 Livio Carpanese,2 Roberto Ciani,3 Rita Golfieri,4 Daniele Gasparini,5 Samer Ezzidin,6 Philipp M. Paprottka,7 Francesco Fiore,8 Mark Van Buskirk,9 Jose Ignacio Bilbao,10 Giuseppe Maria Etorre,11 Rita Salvatori,12 Emanuela Giampalma,6 Onelio Geatti,13 Kai Wilhelm,14 Ralf Thorsten Hoffmann,7 Francesco Izzo,15 Mercedes Iñarritaegui,16 Carlo Ludovico Maini,16 Carlo Urgo,6 Alberto Cappelli,17 Alessandro Vi,8 Hojjat Ahmadzadehfar,6 Tobias Franz Jakobs,7 and Secondo Lastoria,18 on behalf of the European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY)

- 8 European sites 2003 – 2009, retrospective
- 325 patients
- Multi-nodular diseases (75.9%)
- Median survival 12.8 months (95% CI, 10.9 – 15.7 months)

Further evidence of the survival achieved with SIRT comes from the glass yttrium-90 MS data

- Survival by BCLC stage is similar for resin and glass yttrium-90 microspheres
- Apparent differences in survival are statistically insignificant

4. The SARAH study – SIRT versus sorafenib (Nexavar®)
4. The SARAH study – SIRT versus sorafenib (Nexavar®)…

**SARAH is a multi-centre randomised controlled trial being conducted in France**

**SARAH study design**

**Eligible Patients:**
- Unresectable HCC
- BCLC stage C or
- BCLC stage A/B:
  - New lesions post-radical therapy and unsuitable for further radical therapy or
  - No objective response after ≤2 TACE sessions
- If cirrhotic, Child-Pugh class A or B ≤7 points
- ECOG performance status (PS) 0–1
- Fit for sorafenib and $^{90}$Y

**Reference:** [www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier NCT01482442
SARAH is a multi-centre randomised controlled trial being conducted in France (cont.)

- **Survival**
  - sorafenib median OS 10.7 months (SHARP study)
  - SIRT mean OS 15 months (pooled analysis of all reported studies of SIRT in advanced HCC)

- SARAH aims to compare SIRT versus sorafenib head-to-head

- **Primary study end-point**
  - Overall survival (OS)

- **Secondary study endpoints**
  - Safety
  - Time to disease progression
  - Quality of life and healthcare costs
What type of patients are being recruited to the SARAH study?

<table>
<thead>
<tr>
<th>Patient Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key inclusion criteria</strong></td>
</tr>
<tr>
<td>• Advanced HCC with or without PVT not eligible for surgical resection, transplantation nor RFA, or</td>
</tr>
<tr>
<td>• Recurrence of HCC after surgical or loco-regional treatment not eligible for surgical resection, liver transplantation nor RFA, or</td>
</tr>
<tr>
<td>• No objective response after ≤ 2 TACE</td>
</tr>
<tr>
<td>• <strong>Child A or B ≤ 7</strong></td>
</tr>
<tr>
<td>• Life expectancy ≥ 3 months</td>
</tr>
<tr>
<td><strong>Key exclusion criteria</strong></td>
</tr>
<tr>
<td>• Extrahepatic metastases (pulmonary nodules &lt;1 cm and lymph nodes &lt;2 cm are permitted)</td>
</tr>
<tr>
<td>• HCC previously treated with systemic therapy</td>
</tr>
</tbody>
</table>
What type of patients are being recruited to the SARAH study? (cont.)
SARAH is currently enrolling patients at 23 hospitals in France

- Study start: December 2011
- 67% recruited by December 2013 (44% by June 2013)
- Estimated study end: Q4 2015
- France is uniquely placed to run such a trial
  - SIR-Spheres have regulatory approval but no reimbursement in France which limits routine access to SIRT
Why is the SARAH study of SIRT in advanced HCC an important study?

- Sorafenib a major advance, but...
  - Limited efficacy (2.8 month survival benefit c.f. placebo Rx)
  - Disadvantages – continuous, expensive, side effects

- SIRveNIB: SIRT versus sorafenib
  - Asia Pacific study by Prof. Pierce KH Chow (Singapore)
  - 360 patients

- Eastern / Western differences
  - Patient population (Hep B in East / Hep C & alcohol in West)
  - Differences in overall survival can be expected as there were for sorafenib in (SHARP and Asian RCTs)

Reference: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) identifier NCT01135056
The SARAH and SIRveNIB studies represent an important opportunity in advanced HCC

- A total of 800 patients
- Few differences in the study protocols
  - Complete portal venous obstruction
  - Number of SIRT sessions (1 versus up to 2 x 2 for each liver lobe)
- Meta-analysis on raw data
Conclusions

- We need to do (much) better for our patients with advanced HCC
- SARAH is a large multi-centre RCT
- Aims to possibly change management in advanced HCC
- Results will confirm / refute survival benefit of SIRT
- Study will also give information on
  - Procedure costs, quality of life...
- Results are highly awaited!
Merci!

Questions?
Metastatic Colorectal Cancer (mCRC):

An Emerging Role for Selective Internal Radiation Therapy (SIRT)?

A/Prof Peter Gibbs
MBBS, FRACP, MD
Consultant Medical Oncologist
The Royal Melbourne Hospital

Melbourne, 25th February 2014
Sydney, 26th February 2014
Overview of today’s talk

1. Introduction

2. Colorectal cancer – a basic primer

3. Overview of key SIRT data in mCRC

4. The SIRFLOX study – the future of SIRT will be data driven…
1. Introduction
Who am I?

- **Medical Oncologist** = “cancer specialist”
  - We typically treat cancer with chemotherapy, biologic therapies, hormonal therapy
  - Specialise in bowel cancer

- **My research interests**
  - Global Lead Investigator
    - SIRFLOX study of SIR-Spheres in mCRC
    - Alchemia’s HA-irinotecan phase III study (NCT01290783)
  - Laboratory Head, Walter and Eliza Hall Institute, Parkville
    - Translational research – “personalised medicine”
What do Medical Oncologists do?

- Multi-disciplinary treatment of cancer

- Different disciplines have a lead role at different times
  - **Surgical oncologists**
    - Primarily at diagnosis, remove primary tumour
  - **Medical oncologists**
    - Additional treatment after initial surgery (adjuvant Rx)
    - Treatment of patients with advanced cancer
    - Care for the patient long-term and tend to be the “gatekeeper”
  - **Radiation oncologists**
  - **Interventional radiologists**

Service provision as required
A little bit about The Royal Melbourne Hospital

• Tertiary referral and academic teaching hospital, affiliated with the University of Melbourne

• Part of the Parkville Precinct
  – Walter and Eliza Hall Institute
  – University of Melbourne
  – Royal Women’s Hospital
  – (2015 - Peter McCallum Cancer Centre – Victorian CCC)
What initiated my interest in SIRT?

- First SIRT patient treated in 2002
  - Spectacular response, remains alive and in remission today
  - (Second patient didn’t do so well….)
  - Experience now of over 100 patients
  - Learning curve +++

- We started to combine SIRT with modern first-line chemotherapy in 2002

Conclusions

- “The present findings confirm the effectiveness of SIRT plus systemic chemotherapy for mCRC”
- “Patients with liver-confined disease derived the greatest benefit, with median survival times beyond 36 months”
- “Larger datasets from ongoing phase III trials are needed to further define the safety and efficacy of SIRT in the first-line setting”

2. Colorectal cancer – a basic primer
2. Colorectal cancer – a basic primer...

**Colorectal cancer = bowel cancer**

- **Obesity**
- High fat diet
- Red meat

- **Age & lifestyle**
- Excessive alcohol
- Lack of exercise

- **Worldwide incidence**
  - 1.36 million cases per year
  - 690,000 deaths per year

Metastatic colorectal cancer = bowel cancer that has spread

- Liver is the “first port of call”
  - Blood from the gut drains into the liver
- Liver = commonest site of metastatic disease
- Also may spread to lungs, lymph glands
- But liver is often the main problem
  - ~90% of patients eventually die due to overwhelming disease in the liver (i.e. their liver “fails”)

Metastatic colorectal cancer = bowel cancer that has spread

- Multiple treatment options
  - Surgery
    - aim is to cure
  - Traditional chemotherapy
    - aim is to palliate (extend survival)
  - Newer biologic therapies (e.g. Avastin® Roche; Erbitux® Merck; Stivarga®, Bayer)
    - aim is to palliate (extend survival)
  - More recently SIRT (= liver directed radiotherapy)
    - aim is to palliate (extend survival) and/or increase % of patients suitable for curative surgery

2. Colorectal cancer – a basic primer…

Metastatic colorectal cancer = bowel cancer that has spread

CT scan of patient’s liver
- Not suitable for surgery (curative Rx not possible)
- Chemotherapy + biologic therapy (palliative Rx)
- Liver tumours are the life-limiting problem
- Liver directed radiotherapy with SIRT “makes sense”
- Strategy is to target tumour control in the liver
3. Overview of key SIRT data in mCRC
Six previous clinical studies of SIRT in mCRC have been reported – all positive (but very small) studies

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray (1)</td>
<td>First RCT</td>
<td>2001</td>
<td>70</td>
<td>mCRC</td>
</tr>
<tr>
<td>van Hazel (2)</td>
<td>Second RCT</td>
<td>2004</td>
<td>21</td>
<td>mCRC</td>
</tr>
<tr>
<td>Sharma (3)</td>
<td>Prelude to SIRFLOX</td>
<td>2007</td>
<td>20</td>
<td>mCRC</td>
</tr>
<tr>
<td>van Hazel (4)</td>
<td>Phase II</td>
<td>2009</td>
<td>25</td>
<td>mCRC</td>
</tr>
<tr>
<td>Hendlisz (5)</td>
<td>Third RCT</td>
<td>2010</td>
<td>44</td>
<td>mCRC</td>
</tr>
<tr>
<td>Cosimelli (6)</td>
<td>Phase II</td>
<td>2010</td>
<td>50</td>
<td>mCRC</td>
</tr>
</tbody>
</table>

References
First randomised controlled trial of liver directed chemotherapy *versus* liver directed chemotherapy + SIRT

First RCT: 70 “first-line” patients (Australia)

<table>
<thead>
<tr>
<th></th>
<th>Time to liver progression</th>
<th>Proportion surviving</th>
<th>Delta in primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUDR chemotherapy</td>
<td>9.7 months</td>
<td>68% 29% 6%</td>
<td></td>
</tr>
<tr>
<td>FUDR chemotherapy +</td>
<td>15.9 months</td>
<td>72% 39% 17%</td>
<td>6.2 months</td>
</tr>
<tr>
<td>SIRT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ P = 0.001 \]

Results led to SIR-Spheres FDA & EU regulatory approval (2002)

Second randomised controlled trial of systemic chemotherapy *versus* systemic chemotherapy + SIRT

**Second RCT: 21 “first-line” patients (Australia)**

<table>
<thead>
<tr>
<th></th>
<th>Time to progression</th>
<th>Survival duration</th>
<th>Delta in primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU/LV chemotherapy</td>
<td>3.6 months</td>
<td>12.8 months</td>
<td></td>
</tr>
<tr>
<td>5FU/LV chemotherapy + SIRT</td>
<td>18.6 months</td>
<td>29.4 months</td>
<td>16.6 months</td>
</tr>
</tbody>
</table>

\[ P < 0.005 \quad P = 0.02 \]

### Third randomised controlled trial of systemic chemotherapy *versus* systemic chemotherapy + SIRT

**Third RCT: 44 “last-line” patients (Belgium)**

<table>
<thead>
<tr>
<th></th>
<th>Time to liver progression</th>
<th>Survival duration</th>
<th>Delta in primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU chemotherapy</td>
<td>2.1 months</td>
<td>7.3 months (¹)</td>
<td>3.4 months</td>
</tr>
<tr>
<td>5FU chemotherapy + SIRT</td>
<td>5.5 months</td>
<td>10.0 months</td>
<td></td>
</tr>
</tbody>
</table>

³ 10 patients in the 5FU alone arm received SIR-Spheres as salvage therapy after disease progression

What do medical oncologists base their treatment decisions on?

- We believe data from large randomized controlled trials (Level 1 data)
- We begin to believe single arm, prospective data (Level 2b data)
- We do not believe retrospective reports, case series, etc. (Level 3 data)
- We practice evidence based medicine, typically based on large RCTs
- We have biases…we like biologics and chemotherapy
- We are typically very conservative…we need data!
- Patients and their families have a reasonable expectation that their cancer therapy has been proven effective and safe
Medical oncologists require Level 1 evidence from randomised controlled trials

### Chemotherapy RCTs
- Many RCTs completed (10s – 100s)
- Usually **big trials**, recruiting 500+ patients
- Compare new chemotherapy drugs **versus current “gold standard”** chemotherapy regimen
- Usually **international, multi-centre** RCTs
- Usually set out to demonstrate overall survival (**OS**) advantage
- **Level 1 evidence currently available**

### SIRT RCTs
- Three RCTs completed
- Small trials - recruited 70, 21 & 44 patients
- Compare SIRT **versus old chemotherapy** regimens, no longer clinically relevant
- Two RCTs performed in Perth, only one RCT international, multi-centre
- Three RCTs primarily demonstrated time to progression (**TTP**) advantage, a surrogate of OS
- **True Level 1 evidence not currently available**
4. The SIRFLOX study – the future of SIRT will be data driven…
Returning to our early results with SIRT at The Royal Melbourne, they were of considerable interest...

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

Results: Overall response rate according to the Response Evaluation Criteria in Solid Tumors was 84% (two complete responses and 14 partial responses). Median progression-free survival (PFS) time was 10.4 months and median overall survival (OS) time was 29.4 months. For patients with disease confined to the liver, PFS improved (10.7 mo vs 3.6 mo; P = .09), with significant prolongation of OS (median, 37.8 mo vs 13.4 mo; P = .03) compared with those who had EHD. Nine patients, including three long-term (> 3 y) survivors, remained alive after a median follow-up of 18.6 months. Serious treatment-related toxicities included febrile neutropenia with concurrent FOLFOX treatment, a perforated duodenal ulcer, and one death from hepatic toxicity.

Conclusions: The present findings confirm the effectiveness of RE plus systemic chemotherapy for metastatic CRC. Patients with liver-confined disease derived the greatest benefit, with median survival times beyond 36 months. Larger datasets from ongoing phase III trials are needed to further define the safety and efficacy of RE in the first-line setting.

- 85% response rate Typically ~ 60% with chemotherapy
- Median PFS 10.4 months Typically ~ 8 – 9 months with chemotherapy
- Median OS 29.4 months Typically ~ 24 months with chemotherapy
- Median OS 37.8 months for patients with liver only disease
- Three long-term (> 3 years) survivors

Conclusion: Large datasets from ongoing RCTs (e.g. SIRFLOX) are needed to further define safety and efficacy of SIRT in the first-line setting

4. The SIRFLOX study – the future of SIRT will be data driven…

…but our group concluded that the early results should be further defined in a large randomised controlled trial

SIRFLOX study design

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 = 532
- FOLFOX6m* ± bevacizumab
- SIR-Spheres microspheres

1 SIR-Spheres microspheres implanted day 3–4 of Cycle 1
2 oxaliplatin administered at 60 mg/m² for Cycles 1–3 in the SIR-Spheres microspheres + FOLFOX arm
3 at the investigator’s discretion, bevacizumab may commence at Cycle 4 in the test arm and at Cycle 1 (or per institutional protocol) in the control arm
SIRFLOX is an international multi-centre randomised controlled trial in ANZ, USA, Europe, Israel

- Radiation therapy – proven role in CRC (& other cancers)

- SIRFLOX aims to compare chemo-radiotherapy (liver targeted) against chemotherapy alone

- Primary study end-point
  - Progression-free survival (PFS)

- Secondary study end-points
  - Overall survival (OS)
  - Tumour response rate (liver and any site)
  - Quality of life
  - Surgical resection rate
SIRFLOX has completed enrolment and treatment of all patients – we are now waiting for the data to “mature”

- Expect results in early 2015
  - Data needs to mature and is somewhat dependent on patients’ disease behaviour
In respect of the SIRFLOX results what would it take to see increased use of SIRT in first-line treatment?

- **“First-line use warranted”**
  1. SIRFLOX demonstrates an improvement in progression free survival of ≥ 3 months

- **“First-line use mandated”**
  1. SIRFLOX demonstrates an increased rate of hepatic resection
    - Increased use in borderline resectable cases only
  2. SIRFLOX demonstrates an overall survival advantage
If SIRFLOX results are positive more patients may benefit from SIRT if used at an earlier “line” of therapy
e.g. 100 patients with unresectable mCRC

1\textsuperscript{st}-line chemo

\begin{align*}
85\% & \rightarrow 85 \\
75\% & \rightarrow 64 \\
25\% & \rightarrow 16 \\
\sim25\% & \rightarrow \sim75\% 
\end{align*}

2\textsuperscript{nd}-line chemo

\begin{align*}
85\% & \rightarrow 15\% \\
75\% & \rightarrow 25\% \\
\sim75\% & \rightarrow \text{no further Rx} 
\end{align*}

3\textsuperscript{rd}-line chemo

Acknowledgement:
I would like to thank those patients at The Royal Melbourne Hospital and The Western Hospital who participated on the SIRFLOX study
Thank you

Questions?