Advances in treatment options for liver metastases

Merv Rees
Advances in Management of Colorectal Liver Secondaries

Beating Bowel Cancer Day 2016

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Basingstoke
Colorectal Liver Metastases
The Patient Journey

- Diagnosis
- Surgery
- Chemotherapy
- Other modalities
Purpose of Imaging

- Screening for secondaries
-Extent of liver involvement
-Define anatomy
-Extra-hepatic disease
Detection & Assessment

Imaging

Ultrasound
Contrast CT
MRI
CT Chest
Laparoscopy
PET-CT

Fitness for surgery
Liver Biopsy?
Liver Biopsy ?
Needle Track Seeding
Biopsy of resectable colorectal liver metastases & survival

Seeding in 17 / 90 patients (19%) following biopsy

% survival

P=0.008

no biopsy biopsy

No biopsy (n=508)

biopsy (n=90)

Jones et al, Br J Surg 2005
Colorectal Liver Metastases
The Patient Journey

• Diagnosis
• Surgery
• Chemotherapy
• Other modalities
### Outcome of hepatic resection for colorectal metastases

Published single-centre case series (n >100)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Years</th>
<th>n</th>
<th>Study Type</th>
<th>Radical</th>
<th>5 yr surv</th>
<th>Mort</th>
</tr>
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<tbody>
<tr>
<td>Scheele</td>
<td>Germany</td>
<td>1960-1992</td>
<td>469</td>
<td>Retro</td>
<td>84%</td>
<td>33%</td>
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<td>Fong</td>
<td>USA</td>
<td>1985-1991</td>
<td>456</td>
<td>Retro</td>
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<td>1978-1993</td>
<td>301</td>
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<td>Rosen</td>
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<td>280</td>
<td>Retro</td>
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<td>2%</td>
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<td>Gayowski</td>
<td>USA</td>
<td>1981-1991</td>
<td>204</td>
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<td>Fuhrman</td>
<td>USA</td>
<td>1988-1992</td>
<td>151</td>
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<td>44%</td>
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<td>Cady</td>
<td>USA</td>
<td>?-1990</td>
<td>142</td>
<td>Retro</td>
<td>91%</td>
<td>ns</td>
<td>ns</td>
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<td>Jenkins</td>
<td>USA</td>
<td>1975-1993</td>
<td>131</td>
<td>Retro</td>
<td>81%</td>
<td>25%</td>
<td>3.8%</td>
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<tr>
<td>Taylor</td>
<td>Canada</td>
<td>1977-1993</td>
<td>123</td>
<td>Retro</td>
<td>100%</td>
<td>34%</td>
<td>0%</td>
</tr>
<tr>
<td>Schlag</td>
<td>Germany</td>
<td>1981-1989</td>
<td>122</td>
<td>Retro</td>
<td>100%</td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>Ohlsson</td>
<td>Germany</td>
<td>1971-1996</td>
<td>111</td>
<td>Retro</td>
<td>100%</td>
<td>25%</td>
<td>3.6%</td>
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<tr>
<td>Rees</td>
<td>UK</td>
<td>1986-1996</td>
<td>107</td>
<td>Prosp</td>
<td>83%</td>
<td>30%</td>
<td>1%</td>
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<tr>
<td>Doci</td>
<td>Italy</td>
<td>1980-1989</td>
<td>100</td>
<td>Retro</td>
<td>100%</td>
<td>30%</td>
<td>5%</td>
</tr>
</tbody>
</table>
114,155 patients who underwent surgery for CRC between 1998-2004
2.7% subsequently had a liver resection within 3 years
Studied variations in liver resection rates and survival
Liver resection offers the best chance of survival

![Graph showing survival probability over time after resection of colorectal tumour.](image)

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Overall</th>
<th>Stage III, no liver resection</th>
<th>Stage IV, no liver resection</th>
<th>Liver resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>114,155</td>
<td>90,868</td>
<td>78,122</td>
<td>69,186</td>
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<tr>
<td>Stage III, no liver resection</td>
<td>34,805</td>
<td>26,846</td>
<td>21,803</td>
<td>18,413</td>
</tr>
<tr>
<td>Stage IV, no liver resection</td>
<td>9,459</td>
<td>4,613</td>
<td>2,297</td>
<td>1,398</td>
</tr>
<tr>
<td>Liver resection</td>
<td>3,116</td>
<td>2,973</td>
<td>2,657</td>
<td>2,169</td>
</tr>
</tbody>
</table>

Survival probability vs. time after resection of colorectal tumour (years)
Colorectal liver metastases
UK resection rates

% patients undergoing liver resection

Year of colorectal resection
Patients undergoing liver resection, by cancer network
Patients undergoing liver resection, by hospital
Management of colorectal liver metastases

Liver resection, if possible
Criteria for Resectability

- Resection with radical margins
- Adequate functioning residual liver volume
- Preservation of portal inflow & hepatic venous drainage
What is a radical margin?

Kaplan-Meier curve of overall disease recurrence for 2715 patients after resection of CRLM stratified by resection margin.

<table>
<thead>
<tr>
<th>Margin</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mm</td>
<td>663 374 190 129 88 73 55 47 37 24 19</td>
</tr>
<tr>
<td>1-4.9 mm</td>
<td>852 570 354 243 191 150 111 87 74 64 57</td>
</tr>
<tr>
<td>5-9.9 mm</td>
<td>439 306 204 145 99 83 68 59 47 40 33</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>761 581 381 271 209 162 136 118 100 93 78</td>
</tr>
</tbody>
</table>
What is adequate functioning residual liver volume?

- 20% if normal liver
- 30% if post chemotherapy
- 40% if cirrhotic
Colorectal liver metastases
Resection rates

- 50% of patients with CRC develop liver metastases
- Resection offers the best survival
- But ~20% of patients are suitable
Improved survival over time

Swan P et al BJS 2011
Improved survival over time

“9x more resections in last 7 years compared to first 7 years, with 16% improved survival”

Swan P et al BJS 2011
Colorectal Liver Metastases
The Patient Journey

• Diagnosis
• Surgery
• Chemotherapy
• Other modalities
Timing in the modern era:
operateable metastases

Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

EPOC Trial – 5 year survival

Overall survival in eligible patients

HR: 0.87; CI: 0.66-1.14, p=0.303

LV5FU + Oxaliplatin Periop CT

52.4%
55 mo
63.7 mo

Surgery only

+8.7 months in median OS
+4.1%
At 5 year

O N
109 171
101 171

Number of patients at risk:

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>109</td>
<td>171</td>
<td>133</td>
</tr>
<tr>
<td>101</td>
<td>171</td>
<td>91</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
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<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Treatment

- Surgery
- Pre & Postop CT

ASCO 2012
Large & Ill-located Metastasis - Pre
Large & Ill-located Metastasis - Post
'Cetuximab – a new team-player.'
Subsequent resection rate vs chemotherapy response rate for inoperable colorectal liver metastases


- Retrospective liver only non-resectable
- Non-selected (all patients)
- Phase III trials
Current challenges
Chemotherapy

Resection rates
Toxicity
Disappearing lesions
Steatosis
Sinusoidal Obstruction Syndrome

Cirrhosis
Can we prevent or reverse chemo-toxicity?

- Timing of surgery
- **Duration of chemotherapy**
- Diet
- Drugs
Effect of timing of cessation of chemotherapy on surgical complications

Welsh F et al, Br J Cancer 2007

*\( p = 0.009, \chi^2 \) test for trend
Can we prevent or reverse chemo-toxicity?

- Timing of surgery
- Duration of chemotherapy
- Diet
- Drugs
Effect of duration of chemotherapy on morbidity & mortality

Welsh F et al, Br J Cancer 2007

Duration of neoadjuvant chemotherapy

- Any Morbidity
- Life-threatening complications
- Surgical complications
- Mortality
Can we prevent or reverse chemo-toxicity?

- Timing of surgery
- Duration of chemotherapy
- Diet
- Drugs
Pre-operative weight loss with a very-low-energy diet: quantification of changes in liver & abdominal fat by serial imaging.

Colles SL, Dixon JB, Marks P, O’Brien PE. 
Can we prevent or reverse chemo-toxicity?
The milk diet
Can we prevent or reverse chemo-toxicity?

The milk diet

<table>
<thead>
<tr>
<th></th>
<th>In phase</th>
<th>Out of phase</th>
<th>Steatosis score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td><img src="pre_in_phase.png" alt="Image" /></td>
<td><img src="pre_out_of_phase.png" alt="Image" /></td>
<td>5.7</td>
</tr>
<tr>
<td>Post</td>
<td><img src="post_in_phase.png" alt="Image" /></td>
<td><img src="post_out_of_phase.png" alt="Image" /></td>
<td>1.8</td>
</tr>
</tbody>
</table>
Chemotherapy-associated hepatic injury

Implications for clinical practice

- Taylor drug regimen to patient
- Limited duration
- Parenchymal-sparing approach
Colorectal Liver Metastases
The Patient Journey

• Diagnosis
• Surgery
• Chemotherapy
• Other modalities
Techniques for Improving Resectability

• Neoadjuvant Chemotherapy
• Portal Vein Embolisation (PVE)
• Staged Liver Resection
• Ablation – RFA/ microwave
• Sir-spheres
Portal vein embolisation

Pre Right PVE Post
Techniques for Improving Resectability

• Neoadjuvant Chemotherapy
• Portal Vein Embolisation (PVE)
• Staged Liver Resection
• Ablation – RFA/ microwave
• Sir-Spheres
Techniques for Improving Resectability

- Neoadjuvant Chemotherapy
- Portal Vein Embolisation (PVE)
- Staged Liver Resection
- Ablation – RFA/ microwave
- Sir-Spheres
Radiofrequency Ablation

- Combined resection & RFA / MWA can extend resectability

- Is it good palliation?

- Is it an alternative to surgery?
MD Anderson RFA Data


• Review of solitary CLM – resection vs RFA

• RFA used when liver resection not feasible
  • Inadequate remnant
  • Significant comorbidity

• Otherwise similar groups with regard to potential prognostic indicators
Results – Local recurrence rates

Figure 1. Local recurrence after hepatic resection (HR) or radiofrequency ablation (RFA) for all of the patients with solitary colorectal liver metastasis ($P<.001$) (A) and for those patients with tumors 3 cm or smaller ($P=.001$) (B).
## Results – Survival at 5 years

<table>
<thead>
<tr>
<th></th>
<th>Overall Survival</th>
<th>Disease-free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR</strong></td>
<td>71%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>RFA</strong></td>
<td>27%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Radiofrequency ablation (RFA) combined with chemotherapy for unresectable CRLM: The CLOCCC Trial

- ≤ 9 CRLM
- No EHD
- n=119, randomised to CT vs CT + RFA
- 1° end point = overall survival at 30 months

The CLOCC Trial
Improved progression-free survival with RFA

Overall Logrank test: p=0.025
Case History- Operable or not?

- 36 male
- Dec 2008 Inoperable on Imaging
- 12 cycles Folfiri and Avastin
Case History

Prechemo MRI
Case History - Operable or not?

- 36 male
- Dec 2008 Inoperable on Imaging
- 12 cycles Folfiri and Avastin
- Sept 2009 Extended left hepatectomy
Case History - Operable or not?

- 36 male
- Dec 2008 Inoperable on Imaging
- 12 cycles Folfiri and Avastin
- Sept 2009 Extended left hepatectomy
- Feb 2010 MWA for 3 recurrences
- May 2010 Left Hemicolecetomy T3N2
- Adjuvant Xelox and Avastin
Techniques for Improving Resectability

• Neoadjuvant Chemotherapy
• Portal Vein Embolisation (PVE)
• Staged Liver Resection
• Ablation – RFA/ microwave
• Sir-Spheres
Unresectable CRLM

Palliative chemotherapy +/- SIRT

Selective Internal Radiotherapy (SIRT)
- Yttrium-90 microspheres
- Unresectable CRLM
- Liver-only disease
Liver is sensitive to radiation

- It has dual blood supply (hepatic artery and portal vein)
- With liver cancer, tumour blood supply is almost exclusively from hepatic artery

**Rationale**

- Conformal Beam, IMRT Radiation
- SIRT

Radiation from the “Inside-Out”
- Majority of liver tissue spared
- Minimizes non-target irradiation
SIRT - Mechanism of Action

- Targeted internal radiation due to tumour hypervascularity & parasitization of blood flow
- Minimizes exposure to normal parenchyma
- Administered via hepatic artery
- Radiolabelled beads are trapped in the tumour
  - well tolerated
  - toxicity
  - long-term outcomes awaited
Does SIRT improve overall (OS) or progression-free survival (PFS)?

Clinical Trial in Colorectal Cancer
Currently Enrolling Patients

The SIRFLOX Trial
SIR-Spheres® + FOLFOX versus FOLFOX Alone
(with or without bevacizumab) in Patients with Unresectable Liver Metastases from Colorectal Cancer

The FOXFIRE Trial
Can Selective Internal Radiotherapy to Liver Metastases Improve Overall Survival for Patients Treated with OxMdG Chemotherapy as First-Line Treatment of Metastatic Colorectal Cancer?

Randomised controlled trial evaluating SIR-Spheres microspheres in combination with OxMdG chemotherapy vs. OxMdG chemotherapy alone for the first-line treatment of unresectable liver-only or liver-predominant colorectal cancer metastases.
Colorectal Liver Metastases
The Patient Journey

- Diagnosis
- Surgery
- Chemotherapy
- Other modalities
- Latest Tactics
Timing in the modern era: liver first approach

When delay (sepsis) puts liver at risk of becoming inoperable: patients initially inoperable downsized with chemotherapy.
- vital structures initially involved
- initially extensive spread
Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary

G. Mentha¹, P. E. Majno¹, A. Andres¹, L. Rubbia-Brandt², P. Morel¹ and A. D. Roth¹

Departments of ¹Visceral and Transplantation Surgery and ²Clinical Pathology, University Hospitals of Geneva, 1211 Geneva 14, Switzerland

Correspondence to: Professor G. Mentha (e-mail: gilles.mentha@hcuge.ch)

Small series 20 patients

All had non-obstructing C/R Ca

Good response to chemo….

Similar survival to ‘traditional approach’
Propensity score-matched outcomes analysis of the liver-first approach for synchronous colorectal liver metastases

F. K. S. Welsh, K. Chandrakumaran, T. G. John, A. B. Cresswell and M. Rees

Hepatobiliary Unit, Hampshire Hospitals NHS Foundation Trust, Aldermaston Road, Basingstoke RG24 9NA, UK

Correspondence to: Miss F. K. S. Welsh (fenella.welsh@hhft.nhs.uk)
Disease-free survival

Unmatched vs. Matched

Fig. 1 Disease-free survival (DFS) after diagnosis of synchronous colorectal liver metastases according to surgical strategy: a in all patients and b in patients matched for preoperative Basingstoke Predictive Index. a $P = 0.001$, b $P = 0.083$ (log rank test)
Patient reported outcomes – quality of life short-term
Fig 1. Mean patient-reported outcome (PRO) scores assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 regarding (A) global health-related quality of life and (B) role function. Error bars mark 95% CIs for each of the scores. A higher score reflects better function.
Patient-reported outcomes in long-term survivors of metastatic colorectal cancer needing liver resection

J. R. Rees\textsuperscript{1,2}, J. M. Blazeby\textsuperscript{1,2}, S. T. Brookes\textsuperscript{1}, T. John\textsuperscript{3}, F. K. Welsh\textsuperscript{3} and M. Rees\textsuperscript{3}

\textsuperscript{1}Centre for Surgical Research, School of Social and Community Medicine, University of Bristol, and \textsuperscript{2}Division of Surgery, Head and Neck, University Hospitals Bristol NHS Foundation Trust, Bristol, and \textsuperscript{3}Department of Hepatobiliary Surgery, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK

\textit{Correspondence to:} Professor J. M. Blazeby, School of Social and Community Medicine, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK
(e-mail: j.m.blazeby@bristol.ac.uk)
Patient-reported outcomes in long-term survivors of metastatic colorectal cancer needing liver resection

*Original article*

**Table 4** Proportion and change in proportion of patients reporting severe symptoms at baseline and long-term follow-up after liver resection for colorectal liver metastases, assessed using the EORTC QLQ-LMC21

<table>
<thead>
<tr>
<th>EORTC QLQ-LMC21 scales and items</th>
<th>Long-term survivors reporting severe symptoms before surgery (%)</th>
<th>Severe symptoms at long-term follow-up (%)</th>
<th>Change from baseline to long-term follow-up (%)</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>3 (1, 14)</td>
<td>5 (2, 17)</td>
<td>2 (−5, 11)</td>
<td>1.000</td>
</tr>
<tr>
<td>Activity/vigour problems</td>
<td>14 (6, 29)</td>
<td>8 (3, 21)</td>
<td>−6 (−22, 10)</td>
<td>0.690</td>
</tr>
<tr>
<td>Eating problems</td>
<td>0 (0, 10)</td>
<td>0 (0, 9)</td>
<td>0 (−3, 3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Taste problems</td>
<td>0 (0, 10)</td>
<td>3 (1, 14)</td>
<td>3 (−5, 11)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0, 10)</td>
<td>3 (1, 15)</td>
<td>3 (−6, 13)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sore mouth/tongue</td>
<td>3 (1, 14)</td>
<td>0 (0, 9)</td>
<td>−3 (−11, 5)</td>
<td>1.000</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>9 (3, 22)</td>
<td>11 (4, 25)</td>
<td>2 (−12, 17)</td>
<td>1.000</td>
</tr>
<tr>
<td>Jaundice</td>
<td>3 (1, 14)</td>
<td>3 (1, 14)</td>
<td>0 (−11, 10)</td>
<td>1.000</td>
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<tr>
<td>Anxiety problems</td>
<td>28 (16, 44)</td>
<td>3 (1, 14)</td>
<td>−25 (−42, −8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sexual function</td>
<td>29 (16, 45)</td>
<td>30 (17, 47)</td>
<td>2 (−24, 27)</td>
<td>1.000</td>
</tr>
<tr>
<td>Nutritional issues</td>
<td>3 (1, 14)</td>
<td>5 (2, 17)</td>
<td>2 (−5, 11)</td>
<td>1.000</td>
</tr>
<tr>
<td>Contact with friends</td>
<td>8 (3, 22)</td>
<td>3 (1, 14)</td>
<td>−6 (−20, 8)</td>
<td>0.630</td>
</tr>
<tr>
<td>Talking about feelings</td>
<td>8 (3, 22)</td>
<td>0 (0, 9)</td>
<td>−8 (−21, 4)</td>
<td>0.250</td>
</tr>
</tbody>
</table>

Values in parentheses are 95 per cent ci. †A higher score represents a greater proportion of individuals with severe symptoms (‘quite a bit’ or ‘very much’ – more problems). EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.
Management of colorectal liver metastases

Summary

• Hepatic resection offers the best chance of long-term survival
• Get your best liver imaging upfront
• Neoadjuvant therapies
  – ↑ resectability
  – ↑ recruitment of patients
  – Not for everyone
Management of colorectal liver metastases

Summary

• Hepatic resection offers the best chance of long-term survival
• Get your best liver imaging upfront
• Neoadjuvant therapies
  – ↑ resectability
  – ↑ recruitment of patients
  – Not for everyone - YET
Detection & treatment of colorectal liver metastases

Summary

1986 → 2016

Hepatectomy if

- ≤ 3 lesions
- ≥10mm margin
- No EHD

No limits.

- Multiple, bilobar metastases
- Using neoadjuvant therapy, staged resection, PVE, ablation
- Treatable EHD
“better to travel hopefully than to arrive”