Management of Colorectal Liver Metastases

MM Bernon, JEJ Krige

HPB Surgical Unit, Groote Schuur Hospital
Department of Surgery, University of Cape Town
- 50% of patients with colorectal cancer develop liver metastasis.
- 30% present with synchronous liver metastasis.
- In 40% of cases the liver is the only site of metastasis.
- Liver metastasis resectable in 10-20% of cases.
Rationale for surgery in colorectal liver metastasis

- Five year survival after resection of liver metastasis is 30%
- Only chance of long term survival

J Clin Oncol 2009;27:3677
Metastatic colorectal cancer: Survival

Colon Cancer Collaborative Group, BMJ / Tournigand, JCO / Adam, Ann Surg
Resectability

- Complete (R0) resection with a liver remnant consisting of at least two segments with preserved inflow, outflow and biliary drainage.

- Volume of liver remnant should not be less than 20-30% of total liver volume

- Primary and extra hepatic disease should be resectable

Traditional Contraindications
- Bilobar disease
- > 4 liver metastases
- Large tumours (>10cm)
- Extraheptic disease

None are considered an absolute contraindication although they do have **prognostic significance**
When is surgery contraindicated

- Unfit for surgery
- Uncontrolled primary disease
- Untreatable extra-hepatic disease
- Extensive intra-hepatic disease
  - Inadequate residual volume after an R0 resection
  - Caudate lobe involving the IVC
  - Portal vein confluence
  - Hepatic veins and IVC involved

Untreatable extra-hepatic disease includes
  - Widespread pulmonary disease
  - Peritoneal disease
  - Extensive nodal disease (retroperitoneal or portal)
When is surgery appropriate?

- Controllable extrahepatic disease
  - Resectable/ablatable pulmonary disease
  - Resectable isolated extrahepatic sites, spleen adrenal
  - Local direct extension involving diaphragm, adrenal
Preoperative evaluation

- Accurate staging is essential

- Biopsy of a liver lesion is not necessary

- CT
  - Sensitivity 75%

- MRI
  - Sensitivity 81%
  - Contrast MRI is the best modality for detection and characterisation of liver lesions

- FDG-PET
  - Most sensitive means of demonstrating extra hepatic disease
  - May restage up to 28% of patients
  - More likely to change management with increasing disease severity

J Clin Oncol 2010;102:909
Uni- or bilobar mets?
Hepatic veins clear?
Portal vein clear?
Hepatic artery clear?
Bile duct clear?
Residual liver volume?

**Rule of thumb:** ‘2 segments plus caudate’
30% if normal liver
40% if chemotherapy
Chemotherapy

Recurrence = Achilles heel of liver resection

- Recurrent disease develops in 70% of patients who undergo a liver resection

- Chemotherapy has been shown to improve survival

- Timing of the chemotherapy remains controversial

- Conversion chemotherapy - chemotherapy is given to downsize potentially resectable metastasis into resectable disease
Chemotherapy related liver toxicity

- Irinotecan – chemotherapy-associated steatohepatitis (CASH)
- Oxaliplatin – sinusoidal obstruction syndrome
- Bevacizumab – impaired wound healing and liver regeneration
Balance between an adequate resection margin and sufficient residual liver volume

Preserve residual liver volume after chemotherapy

Steatosis and sinusoidal dilatation
Postoperative Chemotherapy

**Study design**

173 patients with R0 resections

- Randomise
  - Surgery
  - Surgery

→ 5FU + FA

6 cycles

AURC 9002 Trial
Portier et al
JCO 2006

173 patients with completely resected liver metastases randomised to either surgery alone (n=87) or surgery (n=86) and systemic chemotherapy with 5 FU + FA
Postoperative Chemotherapy

Study results

173 patients with R0 resections

Randomise

Surgery → 5FU + FA

Significant disease free survival benefit

2yr 5yr
50.4 33.5%
38.1 26.7%

173 patients with completely resected liver metastases randomised to either surgery alone (n=87) or surgery (n=86) and systemic chemotherapy with 5 FU + FA
Preoperative chemotherapy

Perioperative chemotherapy with FOLFOX4 and surgery versus surgery for resectable liver metastases from colorectal cancer

Final efficacy results of the EORTC Intergroup phase III study 40983.


Statistical analysis L. Collette

For the EORTC GI Group, CR UK, ALMCAO, AGITG and FFCD

Lancet 2008; 371:1007-1016
364 patients with up to 4 liver metastases randomised to either chemotherapy and surgery (n=182) or surgery alone (n=182)
## Complications of surgery

<table>
<thead>
<tr>
<th></th>
<th>Peri-op CTx</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-operative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complications*</td>
<td>40 / 159</td>
<td>27 / 170</td>
</tr>
<tr>
<td></td>
<td><strong>(25.2%)</strong></td>
<td><strong>(15.9%)</strong></td>
</tr>
<tr>
<td>Cardio-pulmonary failure</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Biliary fistula</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>(output &gt;100ml/d, &gt;10d)</td>
<td>(9)</td>
<td>(2)</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>(bilirubin&gt;10mg/dl, &gt;3d)</td>
<td>(10)</td>
<td>(5)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Intra-abdominal infection</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Need for reoperation</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td><strong>Post-operative death</strong></td>
<td>1 patient</td>
<td>2 patients</td>
</tr>
</tbody>
</table>

*P=0.04
Results

**Surgery only**
- 84% had successful resections
- 11% non-therapeutic laparotomy rate
- 5y progression free survival 28%
- 5y overall survival 48%

**Perioperative chemotherapy**
- 83% had successful resections
  - 67/182 had an objective response (4 complete)
  - 11/182 progressed on chemo
- 5% non-therapeutic laparotomy rate
- 5y progression free survival 35%
- 5y overall survival 52%
Conversion Chemotherapy

- Conversion of initially irresectable hepatic metastasis into resectable disease (Conversion Chemo)

- Definition of initially unresectable is subjective

- Conversion rates of 5-40%
Colorectal liver metastases
Paul Brousse Hospital - 1400 patients (1988 - 2000)

CHEMO: 1105 (79%)
- Non resectable: 139 (13%)
- Initially non resectable: 966 (87%)
- Resectable: 139 (32%)
- Generally resectable: 295 (68%)

RESECTION: 434

Complete Radiological Response

66 metastases showing complete response on imaging

- Macroscopic residual disease: 20 metastases
  - Intra-op exploration (liver exam + US)

- No macroscopic residual disease: 46 metastases
  - Resection of site of initial met: 15 metastases
    - Viable tumour cells: 12 sites
    - No cancer deposit: 3 sites
  - 31 sites of initial met left in place 1 year of follow-up
    - No recurrence in situ: 8/31 met
    - Recurrence in situ: 23/31 met

11/66 (17%) metastases: no evidence of disease
55/66 (83%) metastases: persistent microscopic or macroscopic disease or early recurrence

Strategies to prevent postoperative liver failure

- Risk of postoperative liver failure is greatest with extensive liver resections – functional residual volume < 30%

- **Portal Vein Embolisation**
  - Ipsilateral atrophy, contralateral hypertrophy
  - Gelfoam, lipiodol, cyanoacrylate, fibrin
  - Increase in volume 15% of total liver volume
  - Maximum effect 3-9 weeks

- **Staged resection**
  - Multiple bilobar disease
  - Clearance of one hemiliver followed by embolisation of the contralateral side
  - Resection of the contralateral side
Timing of Resection

- Patients with synchronous liver metastasis have traditionally had staged surgery

- Synchronous resection can be safely performed

- Usually reserved for simple resections
  - E.g. Right hemicolecotomy/ segment 2/3 resection
Ablative Therapy

Thermo-ablative

- Cryotherapy
- Radiofrequency ablation (RFA)
- Microwave Ablation

Chemo-ablative

- Acetic acid
- Ethanol
Ablative Therapy

Radiofrequency Ablation
- Alternating current with frequency of 350-480KHz
- Oscillation of tissue ions causes frictional heat – coagulative necrosis

Microwave Ablation
- Microwaves with a frequency of 900MHz
- Agitate water molecules causing frictional heat and coagulative necrosis
- Quicker than RFA
- Not limited by tissue desiccation
Ablative Therapy

- Open, laparoscopic or percutaneous
- Lack of good evidence. No randomised trial comparing ablation to resection
- Higher local recurrence rate, inferior disease free survival
- Liver metastasis not amenable to curative resection
  - Location
  - Multifocality
  - Inadequate hepatic reserve
Complications

- Biloma
- Abscess
- Thermal injury to surrounding structures
- Haemorrhage
- Haemobilia
53 y old female
T3 Rectal adenocarcinoma 7cm above anal verge
Synchronous liver met
Pre-operative radiotherapy
Synchronous anterior resection and microwave ablation of liver lesion
Developed a liver abscess 14 days after the procedure.
Managed with percutaneous drainage
Hepatic anatomy and nomenclature of resections
<table>
<thead>
<tr>
<th>Anatomical Term</th>
<th>Couinaud segments referred to</th>
<th>Term for surgical resection</th>
<th>Diagram (pertinent area is shaded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Hemiliver OR Right Liver</td>
<td>Sg 5-8 (+/- Sg 1)</td>
<td>Right Hepatectomy OR Right Hemihepatectomy (stipulate +/-segment 1)</td>
<td>![Diagram of liver segments]</td>
</tr>
<tr>
<td>Left Hemiliver OR Left Liver</td>
<td>Sg 2-4 (+/- Sg 1)</td>
<td>Left Hepatectomy OR Left Hemihepatectomy (stipulate +/-segment 1)</td>
<td>![Diagram of liver segments]</td>
</tr>
<tr>
<td>Anatomical Term</td>
<td>Couinaud segments referred to</td>
<td>Term for surgical resection</td>
<td>Diagram</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------</td>
<td>----------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Right Anterior Section</td>
<td>Sg 5,8</td>
<td>Add (-ectomy) to any of the anatomical terms as in Right anterior sectionectomy</td>
<td>![Diagram of liver segment 5, 6, 7, 8, 4, 2, 3 shaded]</td>
</tr>
<tr>
<td>Right Posterior Section</td>
<td>Sg 6,7</td>
<td>Right posterior sectionectomy</td>
<td>![Diagram of liver segment 6, 7, 8, 4, 2, 3 shaded]</td>
</tr>
<tr>
<td>Left Medial Section</td>
<td>Sg 4</td>
<td>Left medial sectionectomy OR Resection segment 4 (also see Third order) OR Segmentectomy 4 (also see Third order)</td>
<td>![Diagram of liver segment 6, 7, 8, 4, 2, 3 shaded]</td>
</tr>
<tr>
<td>Left Lateral Section</td>
<td>Sg 2,3</td>
<td>Left lateral sectionectomy OR Bisegmentectomy 2, 3 (also see Third order)</td>
<td>![Diagram of liver segment 6, 7, 8, 4, 2, 3 shaded]</td>
</tr>
</tbody>
</table>
Border or watershed: The borders or watersheds of the sections are planes referred to as the right and left intersectional planes. The left intersectional plane passes through the umbilical fissure and the attachment of the falciform ligament. There is no surface marking of the right intersectional plane.
<table>
<thead>
<tr>
<th>Anatomical Term</th>
<th>Couinaud segments referred to</th>
<th>Term for surgical resection</th>
<th>Diagram (pertinent area is shaded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segments 1-9</td>
<td>Any one of Sg 1 to 9</td>
<td>Segmentectomy</td>
<td><img src="image1" alt="Diagram" /></td>
</tr>
<tr>
<td></td>
<td>(e.g. segmentectomy 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 contiguous</td>
<td>Any two of Sg 1 to Sg 9 in</td>
<td>Bisegmentectomy</td>
<td><img src="image2" alt="Diagram" /></td>
</tr>
<tr>
<td>segments</td>
<td>continuity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(e.g. bisegmentectomy 5,6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For clarity Sg. 1 and 9 are not shown. It is also acceptable to refer to ANY resection by its third-order segments, e.g. right hemihepatectomy can also be called resection sg 5-8.

Border or watersheds: The borders or watersheds of the segments are planes referred to as intersegmental planes.
Technique

Basic steps in liver resection

- Exposure/Mobilise liver
- Intra-operative assessment (including intra-operative ultrasound)
- Vascular control
- Parenchymal transection
- Seal cut surface/haemostasis
How to stay out of trouble

- Minimise blood loss
- Avoid prolonged ischaemia
- Resect tumour with adequate margin
- Preserve sufficient functional residual liver
LIVER RESECTION ACCORDING TO PATHOLOGY
\[ n = 356 \]

THE BIG THREE
\[ n = 240 \]

GSH + UCT PAH - HPB unit
All liver resections entered on a prospective data base which includes 1º and 2º pathology, operative details, blood loss, transfusion requirements, complications, survival, etc

Accurate audit and assessment of performance

Bar chart showing:
- Colon Sec: 173
- HCC: 35
- Cholangio: 32
- IH Stones: 26
- Hemangioma: 19
- Cystadenoma: 15
- FNH: 13
Complications

- Series of 173 patients at Groote Schuur

- Peri-operative mortality – 2.9%

- Major Morbidity -19%
  - Bile leak
  - Subphrenic/perihepatic collection
  - Bleeding requiring re-laparotomy
  - Liver failure – all patients had extended resections
Complications

Major vs. Minor Resections (%)

Major Resections
122/173 (70.9)

- 93 (76.2) - Hepatic
- 10 (8.2) - Non-hepatic
- 5 (4.1) - No complication
- 14 (11.5) - Liver failure

Minor Resections 51/173 (29.5)

- 47 (92.2) - No complications
- 4 (7.8) - Non-hepatic complications
Conclusion

- Liver resection for colorectal liver metastasis prolongs survival and is the only treatment associated with long term survival.

- A multimodality approach offers the best results and patients should be discussed in multidisciplinary team meeting.

- Complex procedures best carried out in high volume centers with the appropriate expertise.