Liver resection for metastases of colorectal cancer

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Feasible to resect up to 70% of the adult liver based on anatomical principles

A short history of liver surgery

‘Achilles stabbed with his sword at the liver, the liver was torn from its place, and from it the dark blood drenched the fold of his tunic and Troy’s eyes were shrouded in darkness, and the light went out’

Homer, The Iliad, Book XX

Important dates in the history of liver resection

- 1886 first hepatectomy by Luis (patient bled to death 6 hours later)
- 1888 first ‘successful’ hepatectomy by Langenbeck (required further laparotomy for bleeding)
- 1890 McLane-Tiffany resects liver tumour at Johns Hopkins
- 1891 Lucke reports first successful removal of a malignant liver tumour
- 1899 Keen performs first true left lateral segmentectomy

Important dates in the history of liver resection

- 1943 Cattell performs first colorectal hepatic metastasectomy at Lahey Clinic
- 1952 first formal right hepatectomy by Lortat-Jacob and Robert in Paris
- 1953 Quattlebaum describes 3 right hepatectomies using dissection with a scalpel handle
- 1958 Lin describes the finger fracture technique

Advances in the modern era

- Liver dissection technology
- Preoperative imaging (contrast MRI)
- Intraoperative scanning
- Low CVP anaesthesia
- Postoperative high dependency care
Overall survival in advanced colorectal cancer 1989–1999

1943 First hepatectomy for colorectal liver metastasis
1957 Introduction of 5-fluorouracil

Survival (%)

Time (years since diagnosis of colorectal metastases)

Wider acceptance of role of liver surgery


Rees et al 1997

Resection for CRC liver metastases:
traditional definition of resectability in 1999

- Metachronous detection
- Unilobar disease
- <4 metastases
- <5 cm largest metastasis
- >1 cm resection margin
- If we accepted these criteria then less than 10% of patients were eligible for surgery, of whom only 1:3 stood a chance of being cured

Survival after recurrence following apparently curative surgery for primary colorectal cancer recruited into clinical trials


5-year survival improved from 7% to 20%

WHY?

ACCENT study

Historical predictors of poorer outcome after resection of colorectal liver metastases

- Positive resection margin
- Extrahepatic disease
- Node positive (stage 3) primary colorectal cancer
- Disease free interval from primary tumour <1 year
- Largest metastasis >5 cm
- Number of metastases >1
- CEA >200 ng/ml
- Age of patient


7500 liver resections for CRC metastases
45 countries - 130 institutions (1974 – 2008)

7/13/2009
Synchronous vs. Metachronous

Synchronous: 732
Metachronous: 715
91%
60%

Log rank p = 0.49

Survival (%)

Number of metastases resected

> 3 nodules: 398
≤ 3 nodules: 1369
92%
64%

Log rank p < 0.0001

Survival after surgery for pulmonary CRC metastases

313 patients undergoing thoracotomy for CRC pulmonary metastases

Survival after resection of hepatic and extrahepatic disease
Liverpool: 181 liver resections for CRLM in patients over 70 years old

Operative mortality 4.8%


Increasing resectability: Portal vein embolisation

4 weeks later

Possible indications for ablation?

- Difficult distribution bilobar metastases
- Awkward recurrence
- Post-hepatectomy
- Improve resection margin after difficult resection

CLOCC Study (EORTC 40004)

Patients with ≤9 Unresectable liver only Colorectal metastases

N = 105 patients
Primary end point 30 month overall survival

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- FOLFOX4
- RFA

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CLOCC Study: interim analysis

- No difference in morbidity between two arms (ASCO 2008)
- Chemotherapy median PFS 10 mos
- Chemo + RFA median PFS 18 mos ($p = 0.0267$)
- Chemotherapy 1 yr PFS 39%
- Chemo + RFA 1 yr PFS 60%
- Local recurrence at RFA site 9%

*Ruer et al. ASCO 2008
Ruer et al. SSO 2009*

Criteria for resectability in colorectal liver metastases in 2009

- Disease confined to liver
- Resectable with adequate margins
- Adequate future remnant liver (25-30%)
- Preservation of functional liver anatomy

Overall survival after resection of multiple liver metastases according to chemotherapy response

![Graph showing overall survival](image)

Log Rank: $p < 0.0001$


Conversion chemotherapy and resection of colorectal liver metastases

*FOLFIRI*

July 2001  CEA 997  Jan 2002  CEA 3

Correlation of outcome after hepatectomy to histologic response to neoadjuvant chemotherapy

*Blaer et al. JAMA 2008* 26: 5344-51

Complete response

Major response

Minor response
Resection rate of metastases and tumour response

Studies including selected patients (liver metastases only, no extrahepatic disease) 
(r=0.96; p=0.002)

Studies including non-selected patients with mCRC (solid line) 
(r=0.74; p=0.001)

Phase III studies including non-selected patients with mCRC (dashed line) 
(r=0.67; p=0.024)


LiverMetSurvey.org
Survival after liver resection of colorectal metastases: Initially resectable vs. initially unresectable

Study design EORTC 40983 (EPOC)

FOLFOX4 
Surgery 
FOLFOX4

N=364 patients

Peri-operative FOLFOX4 chemotherapy and surgery for resectable liver metastases from colorectal cancer

The EPOC Intergroup Phase III Study (EORTC 40863)


Lancet 2008; 371: 1007-16


<table>
<thead>
<tr>
<th>Post-operative complications</th>
<th>Peri-op CT</th>
<th>Surgery</th>
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<tbody>
<tr>
<td>Cardio-pulmonary failure</td>
<td>3 / 159</td>
<td>2 / 170</td>
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<tr>
<td>Bleeding</td>
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<td>3</td>
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<tr>
<td>Biliary Fistula (Incl. Output &gt;100ml/d, &gt;10d)</td>
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<td>5 / (2)</td>
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<tr>
<td>Hepatic Failure (Incl. Bilirubin&gt;10mg/dl, &gt;3d)</td>
<td>11 / (10)</td>
<td>8 / (5)</td>
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<tr>
<td>Wound infection</td>
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<td>4</td>
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<tr>
<td>Intra-abdominal infection</td>
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<tr>
<td>Need for reoperation</td>
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<td>3</td>
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<tr>
<td>Other</td>
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<td>16</td>
</tr>
<tr>
<td>Incl. post-operative death</td>
<td>1 patient</td>
<td>2 patients</td>
</tr>
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Progression-free survival in resected patients Nordlinger et al. Lancet 2008

HR= 0.73; CI: 0.55-0.97, p=0.025

+9.2% 
At 3 years
Liver after prolonged chemotherapy (not observed after ≤6 cycles)

We used to call this ‘chemotherapy associated steato-hepatosis’ (CASH)


Steatosis and steatohepatitis: seen with irinotecan

Steatohepatitis causes increased post-operative liver failure and death within 90 days


Sinusoidal Obstruction Syndrome
Seen with oxaliplatin but not irinotecan

Causes increased peri-operative bleeding

Courtesy of Professor Gilles Mentha, University of Geneva

CT- based evaluation
66 metastases disappeared on imaging after CT

Macroscopic residual disease: 20 LM
30%

Surgical exploration
No macroscopic residual disease: 46 LM

15 initial sites resected
31 initial sites left in liver

Viable tumor cells in 12 sites
80%

In situ recurrence: 23
74%

55/66 (83%) LM non-cured

Benoist et al. JCO 2006;24:3939-45

Macroscopic CR after chemotherapy: ~20% of cells in periphery are viable

Too much pre-surgery chemotherapy:

- The liver surgeons nightmare
  - Excessive oxaliplatin causes sinusoidal congestion and thrombosis:
    - excessive bleeding at surgery
  - Excessive irinotecan causes steatosis and steatohepatitis:
    - increased risk of post-operative liver failure and 90 day death
- Disappearing tumours!
Why are we getting better?

- Multi-modal therapy
- No one medical specialty is dominant
- All are required:
  - hepatobiliary surgery
  - medical oncology
  - radiology
  - anesthesiology
  - gastroenterology
- **MULTI-DISCIPLINARY TEAM WORKING**

The impact of multidisciplinary management

![Graph showing survival rates over years after diagnosis](https://example.com/graph.png)

| Year | Survival Rate
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1999</td>
<td>20%</td>
</tr>
<tr>
<td>2000</td>
<td>9%</td>
</tr>
<tr>
<td>2009</td>
<td>2009 chemotherapy Median survival: 5 year survival = &gt;24 months, 9%</td>
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<tr>
<td>2019</td>
<td>3%</td>
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