Practical approach to Colorectal Liver Metastases

Maja Segedi
HepatoPancreatoBiliary and Liver Transplant Surgery, VGH
Oct 22 2016
Disclosure

- Ipsen Biopharmaceuticals Canada
- advisory board honorarium
Disclosure

- Managing conflict of interest
- Not applicable here
Outline

- Improvements in treatment of CRLM
- Extended criteria for resection
- What should/can be done before referral
- When to refer to HPB center
- Outcomes of liver resection
- Common postop complications after liver resection
Colorectal Liver Metastases (CRLM)

- The liver is the most common site for hematogenous metastasis
- 25% of patients with primary CRC present with synchronous hepatic metastasis
- Nearly 50% of patients will eventually develop metachronous liver metastases
Dramatic improvements in prognosis

Dramatic improvement from the seminal study by Foster (1978)

- 5-year survival was 20%.

With newer multimodal treatments and careful patient selection 5-year survival approaching 70% can be achieved after resection (Nikfarjam et al, 2009).

**TABLE III** Liver Resection for Metastatic Colorectal Cancer: Operation versus Survival

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy</th>
<th>Segmental Resection</th>
<th>Wedge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>46</td>
<td>25</td>
<td>97</td>
</tr>
<tr>
<td>Operative deaths</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>5 year survivors</td>
<td>6/45 (13%)</td>
<td>5/24 (21%)</td>
<td>22/93 (24%)</td>
</tr>
</tbody>
</table>
Resection makes a difference

Wood and colleagues (1976)

* Very few patients had resectable disease;

* 1-, 3-, and 5-year survival of these untreated patients were 77%, 23%, and 8%, respectively, compared with 15%, 0%, and 0% for the unresectable group.

Similarly, Wagner and colleagues (1984)

- 3- and 5-year survivals for untreated resectable disease of 14% and 2%, respectively, compared with 4% and 0% for patients with unresectable disease.

Patients who survive 10 years appear to be cured of their disease.

In well-selected patients, 1 in 6 chance of cure after hepatectomy for CLM. The presence of poor prognostic factors does not preclude the possibility of long-term survival and cure.
Better Patient Selection

General Health
• Identification and management of co-morbidities
  • Cardiac disease
  • Pulmonary disease
  • Renal disease

Liver Health
• Understanding and management of primary liver disease or dysfunction
  • Cirrhosis/NASH/Chemo induced liver injury
  • Portal HTN
  • Synthetic dysfunction
  • Cholestatic disease

Tumor Factors
• Better preoperative imaging
• Better preoperative planning
• Laparoscopic staging
Stratifying patients with CRLM

Four large studies with robust design of useful predictive models for favorable survival after metastasectomy

1. Nordlinger and colleagues (1996): multicenter series of more than 1500 patients.

2. Fong and colleagues (1999): single institutional series of 1001 patients


<table>
<thead>
<tr>
<th>Clinical Indicators</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Node-positive primary tumor</td>
<td>Poultatsides 2012[36]</td>
</tr>
<tr>
<td>a Disease-free interval less than 12 mo from primary</td>
<td></td>
</tr>
<tr>
<td>a Size of largest lesion &gt; 5 cm</td>
<td></td>
</tr>
<tr>
<td>a More than one tumor</td>
<td></td>
</tr>
<tr>
<td>a Carcinoembryonic antigen level &gt; 200 ng/dL</td>
<td></td>
</tr>
<tr>
<td>Extrahepatic disease</td>
<td></td>
</tr>
<tr>
<td>Response to chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Fibrotic response to chemotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Pathologic Indicators</strong></td>
<td><strong>Author</strong></td>
</tr>
<tr>
<td>Margin-positive resection</td>
<td>Turcotte 2014[37]</td>
</tr>
<tr>
<td>High TIL cells</td>
<td></td>
</tr>
<tr>
<td><strong>Molecular Indicators</strong></td>
<td><strong>Author</strong></td>
</tr>
<tr>
<td>CXCR4</td>
<td>Yopp 2012[38]</td>
</tr>
<tr>
<td>HumanHT-12 gene chip/MRS panel</td>
<td>Ito 2013[40]</td>
</tr>
<tr>
<td>KRAS</td>
<td>Kemeny 2014[13]</td>
</tr>
</tbody>
</table>
The “Fong Score” - CRS

Fong and colleagues (1999):

- Node-Positive Primary Tumor
- Disease free interval <12 months between colon resection and appearance of metastases
- Size of largest lesion >5 cm
- >1 Tumor
- CEA >200 ng/dL

- Validated by a group in Norway (Mala et al, 2002)
Better surgery for CRLM

- Modern Liver Surgery has Markedly Improved
  - Better operative tools >> Less blood loss and trauma
  - Lower morbidity and mortality
  - Anesthesia care improved

- Better Understanding of Treatable Liver Disease
  - Many lesions → staged or combination procedures (PVE, ablation)
  - It’s not what you take out, it is what you leave behind
Surgical Tools: Parenchymal Transections

- All techniques aimed at minimizing blood loss and transfusion need
- Finger crushing
- Crush-clamp technique
- Staplers
- Hydrojet and CUSA
- Aquamantis
- Ligasure, harmonic
A Retrospective Comparison of Microwave Ablation vs. Radiofrequency Ablation for Colorectal Cancer Hepatic Metastases

Camilo Correa-Gallego, Yuman Fong, Mithat Gonenc, Michael I. D'Angelica, Peter J. Allen, Ronald P. DeMatteo, William R. Jarnagin, T. Peter Kingham

* Combined procedures
* Ablation with resection
Laparoscopic vs. open resections

The morbidity of an open abdomen has been recognized

- Trauma – incisions, exposure, manipulation
- Pain / Narcotics / Ileus / Prolonged recovery
- Fluid shifts / higher transfusion rates
- Immunosuppression
- Physiologic changes associated with an open abdomen

Long term: incisional hernias and bowel obstructions

Select patients in high volume centers to undergo major hepatectomy with equivalent results
Laparoscopic resection for left sided CRLM
Intraoperative ultrasound
Liver resection techniques
Resectability Criteria

2 Contiguous Segments

Vascularity and Biliary Flow
* Arterial Inflow
* Portal Venous Inflow
* Biliary Outflow
* Hepatic Venous Outflow

Required Remnant Liver
* Normal Liver: > 20%
* Chemo Injury: > 30%
* Cirrhotic Liver: > 40%

No Portal HTN
* Plt > 100
* PV gradient < 10
Liver resection techniques

Table 1 Brisbane consensus nomenclature 2000 for describing hepatic resectional surgery based on liver segmental and sectorial anatomy

<table>
<thead>
<tr>
<th>Anatomical term</th>
<th>Couinaud segments</th>
<th>Term for HRS</th>
<th>Major or minor resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hemi liver</td>
<td>5, 6, 7, 8</td>
<td>Right hemihepatectomy or right hemihepatectomy</td>
<td>Major</td>
</tr>
<tr>
<td>Left hemi liver</td>
<td>2, 3, 4 (&quot;-&quot; 1)</td>
<td>Left hemihepatectomy or left hemihepatectomy</td>
<td>Major</td>
</tr>
<tr>
<td>Right anterior section</td>
<td>5, 8</td>
<td>Right anterior sectionectomy</td>
<td>Minor</td>
</tr>
<tr>
<td>Right posterior section</td>
<td>6, 7</td>
<td>Right posterior sectionectomy</td>
<td>Minor</td>
</tr>
<tr>
<td>Left medial section</td>
<td>4</td>
<td>Left medial sectionectomy or resection segment 4 or segmentectomy 4</td>
<td>Minor</td>
</tr>
<tr>
<td>Left lateral section</td>
<td>2, 3</td>
<td>Left lateral sectionectomy or bisectionectomy 2, 3</td>
<td>Minor</td>
</tr>
<tr>
<td>-</td>
<td>4, 5, 6, 7, 8 (&quot;-&quot; 1)</td>
<td>Right trisectionectomy or extended right hemihepatectomy or extended right hepatectomy</td>
<td>Major</td>
</tr>
<tr>
<td>-</td>
<td>2, 3, 4, 5, 8 (&quot;-&quot; 1)</td>
<td>Left trisectionectomy or extended left hemihepatectomy or extended left hepatectomy</td>
<td>Major</td>
</tr>
</tbody>
</table>

"Non-anatomical" resections are also performed either as the main index procedure or in combination with the above anatomical hepatic resectional surgery. A non-anatomical resection refers to a situation in which there is a small tumour that is excised with a negative margin but leaving a remnant segment – a so-called "chip-shot" or metastectomy.
Big surgery: Patients with extensive disease can be treated.
Staged Liver Resection

- Extensive bilobar metastases
- Initial resection of lesions in FLR
- PVE to contralateral (more diseased) segment
- Subsequent resection of this embolized segment

Contraindications to PVE:
- Ipsilateral thrombus
- Portal hypertension

Figure 1. Right portal vein embolization is performed to allow for left liver hypertrophy prior to second-stage right hepatectomy.
Staged liver resection - tools

- Need for adequate liver remnant (FLR)
  - TELV = -794.41 + 1267.28 (BSA)

- Cross sectional imaging with CT or MRI

- Quantitative assessment with indocyanine green clearance test (ICG) in Far East

- Volumetrics (Pathfinder, Myrian)
Liver resection techniques
Portal vein embolization

**Figure: The Use of Preoperative Portal Vein Embolization to Increase Future Liver Remnant Volume**—Although the liver metastasis (arrow) is small, its location adjacent to the vena cava and the right and middle hepatic veins mandates formal right hepatectomy. Volumetry studies are utilized to estimate future liver remnant volume (outlined in orange). Estimated volumes (“Before”) were considered inadequate, given prior treatment with chemotherapy; portal vein embolization was performed, successfully increasing future liver remnant volume (“After”).
Response to PVE

Normal livers

* regenerate 12 to 21 cm$^3$/day
* sufficient hypertrophy typically occurs within 2 to 4 weeks

Cirrhotic patients:

* 9 cm$^3$/day
* Sufficient hypertrophy in 4-6 wks
PVE complications

- General: subscapular hematoma, hemobilia, hemoperitoneum, vascular injuries, pneumothorax, and cholangitis.

- Specific to PVE: nontarget embolization, recanalization of embolized segments, and complete PVT
ALPPS Procedure

- Associating Liver Partition and Portal vein Ligation for Staged hepatectomy
- controversial
Simultaneous resection of primary and CRLM

- Still controversial, no trials

Considerations:
- Similar or decreased complication rate (several series) with simultaneous
- Patients who underwent simultaneous resection maybe would have progressed to unresectability during the interval between removal of the primary and metastasectomy.
- 2/3 patients can be spared unnecessary hepatic resection by using a delayed-resection approach
Simultaneous resection

**Perform** a simultaneous resection:
- in patients with low-volume disease in the liver
- when the risk of early and rapid progressive disease is relatively low.

**Avoid** simultaneous resection:
- in patients who appear frail
- When liver disease is best addressed in a delayed fashion
  - such as with obstruction or bleeding.
Work up prior to referral
Basic work up of a suspected liver metastasis

HP

- Patient’s fitness for surgery

Biochemical tests:
  - CBC, CEA level, liver panel

Imaging:
  - CT chest/abdo/pelvis
  - CT liver to be 3 phasic

Staging laparoscopy:
  - Reserve for patients with high CRS (poor prognostic profile)
Metachronous CRLM NCCN 2016

Documented metachronous metastases by CT, MRI, and/or biopsy

- Resectable
  - Consider PET-CT scan
    - Resectable
      - See Primary Treatment (COL-10)
    - Unresectable
      - See Primary Treatment (COL-11)
  - Unresectable (potentially convertible or unconvertible)

---

9 See Principles of Surgery (COL-B 2 of 3).
10 Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

*Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.*
Suspected or proven metastatic synchronous adenocarcinoma (Any T, any N, M1)

- Colonoscopy
- Chest/abdominal/pelvic CT
- CBC, chemistry profile
- CEA
- Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF
- Determination of tumor MMR or MSI status (if not previously done)
- Needle biopsy, if clinically indicated
- Consider PET-CT scan if potentially surgically curable M1 disease in selected cases
- Multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary and lung metastases

**Workup**

**Clinical Presentation**

**Findings**

Synchronous liver only and/or lung only metastases

- Resectable
- Unresectable (potentially convertible or unconvertible)

Synchronous abdominal/peritoneal metastases

Synchronous unresectable metastases of other sites

See Treatment and Adjuvant Therapy (COL-6)

See Treatment and Adjuvant Therapy (COL-7)

See Primary Treatment (COL-8)

See Chemotherapy for Advanced or Metastatic Disease (COL-C 1 of 9)

---

*aSee Principles of Pathologic Review (COL-A 4 of 5)* - KRAS, NRAS and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

*See Principles of Surgery (COL-B 2 of 3).*

CT should be with IV contrast. Consider MRI with IV contrast if CT is inadequate.


Consider colon resection only if imminent risk of obstruction or significant bleeding.
CT scan chest/abdo/pelvis

- Standard CT should be 3 phasic with arterial, portal venous, and delayed phases.
- Portal venous phase is important, because the lesions are not typically well vascularized.
- Arterial phase - CRLM vs. hemangiomas, or to better define the arterial anatomy of the liver.
MRI

* MRI is most useful to evaluate indeterminate hepatic lesions
* To define the relationship of tumors to the hepatic vasculature and biliary tree using MRC P
* Not used routinely
Consider PET-CT scan if potentially surgically curable M1 disease in selected cases (Moulton et al 2014)

- Uses IV radioactive tracer, which in most cases is $^{18}$F-FDG.
  - Tracer cannot proceed down the glycolytic pathway → accumulates within glucose-avid cancer cells.

- Limitations:
  - Poor sensitivity for lesions < 1 cm
  - Larger lesions are not FDG avid
  - Anatomic detail low
  - FPs:
    - Inflammation
    - Infection
  - FNs: Recent chemotherapy
Role of liver biopsy

- Only indicated to confirm the diagnosis when the clinical picture is unclear. (after CT and MRI unclear)
- Differentiation between metastatic tumors and benign hepatic lesions can usually be done with imaging
- If done → core biopsy preferable
- The risk of tract seeding low
  - with only a few case reports in the literature.
Staging laparoscopy
Staging laparoscopy

Select cases:
- Preexisting liver disease
- Ascites, suspicion of carcinomatosis
- High CRS score
  - Advanced primary
  - LN involved
  - High burden disease
  - Synchronous
Management of post hepatectomy complications
Post hepatectomy outcomes

The mortality due to resection CRLM decreased significantly over the past 3 decades

- less than 10% across major series

Morbidity:

- largely due to metabolic and immunologic derangements
- in most series is over 20%
- Liver insufficiency and liver failure
  - most dangerous liver-related complication
  - in 3% to 8% of major hepatic resections
117 patients underwent major liver surgery at a Dutch tertiary referral center 2000-2015

Ninety-day mortality 8%

Major postoperative complications in 27% of patients

DFS 11mos

Median OS 44mos
### Post CRLM resection mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Operative Mortality (%)</th>
<th>SURVIVAL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1-Year</td>
<td>3-Year</td>
</tr>
<tr>
<td>Schlag, 1992</td>
<td>122</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Doci et al, 1991</td>
<td>100</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Younes et al, 1991</td>
<td>133</td>
<td>—</td>
<td>91</td>
</tr>
<tr>
<td>Rosen et al, 1992</td>
<td>280</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>Scheele et al, 1995</td>
<td>434</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Nordlinger et al, 1996</td>
<td>1568</td>
<td>2.3</td>
<td>88</td>
</tr>
<tr>
<td>Jamison et al, 1997</td>
<td>280</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>Fong et al, 1999</td>
<td>1001</td>
<td>2.8</td>
<td>89</td>
</tr>
<tr>
<td>Minagawa et al, 2000</td>
<td>235</td>
<td>0.85</td>
<td>—</td>
</tr>
<tr>
<td>Choti et al, 2002</td>
<td>226</td>
<td>1</td>
<td>93</td>
</tr>
<tr>
<td>Belli et al, 2002</td>
<td>181</td>
<td>—</td>
<td>91.2</td>
</tr>
</tbody>
</table>
### Post-op morbidity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total resections</strong></td>
<td>219</td>
<td>122</td>
<td>100</td>
<td>75</td>
<td>80</td>
<td>83</td>
<td>146</td>
<td>1803</td>
<td>244</td>
</tr>
<tr>
<td><strong>Liver related</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>7 (3)</td>
<td>3</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>4 (3)</td>
<td>18</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile fistula</td>
<td>8 (4)</td>
<td>5 (4)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perihepatic abscess</td>
<td>4 (2)</td>
<td>11 (9)</td>
<td>5</td>
<td>5 (7)</td>
<td>2 (3)</td>
<td></td>
<td></td>
<td>110</td>
<td>1</td>
</tr>
<tr>
<td>Liver failure</td>
<td>17 (8)</td>
<td>3</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>6</td>
<td></td>
<td></td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3 (1)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (1)</td>
<td>1</td>
<td>1 (&lt;1)</td>
<td>9</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI bleed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>2 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4 (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cardiac/MI</td>
<td>2 (1)</td>
<td>6 (5)</td>
<td>1</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td>1 (&lt;1)</td>
<td>21</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 (8)</td>
<td>22</td>
<td>3 (4)</td>
<td>7</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>154</td>
<td>2</td>
</tr>
</tbody>
</table>

**Note:** The numbers in parentheses indicate percentages of the total resections.
High complication rate does not always translate into a prolonged hospital stay.

If recognized and treated promptly, most complications do not result in a poor outcome.
Post Operative Care

- Drains – no studies, plan for care and removal needed

- Electrolytes – in setting of cirrhosis, colloids or albumin are preferred to crystalloids
  - Na restriction, judicious diuresis also important

- Hypo/hyperglycemia, hypocalcemia, hypophosphatemia

- Thromboprophylaxis: more hypercoagulable despite high INR/PTT
Normal post op changes in liver enzymes
Post operative hepatic failure

- Impaired ability of the liver to maintain synthetic, excretory, and detoxifying functions, >POD4
- **Prolonged** elevated INR, bili, ascites, encephalopathy

- Risk factors: bleeding, PVT, poorly functioning liver remnant, previous chemo, steatosis, sepsis
Post operative liver failure management

Largely supportive:

- Support synthetic function with FFP
- Administer colloids – albumin
- Avoid Na administration
- Lactulose for encephalopathy
- Prophylactic antibiotics
- Judicial use of diuretics
- Anticipate and manage HRS
- Image liver (other causes of jaundice?)
Bile leaks

- 4.8-7.6% in large series
- ISGLS definition = drain fluid bilirubin >3 times serum after POD 3
- Treat associated infection
- Define location and extent
- Drain, ERCP/PTC and consider reconstructive surgery later
Conclusion

- Surgery for CRLM has better outcomes and can cure a small portion of patients
- More extended resections are routine
- Work up should include staging CTabdo/chest and 3-phases, tumor markers
- Prior to referral if possible:
  - Staging CT chest/abdo/pelvis, multiphasic CTT l l e r
  - Laparoscopy, MRI/PET in select patients
- Biopsy for lesions that are indeterminate on at least 2 imaging modalities
- Refer to HPB center early
What?
I thought we had nine livers.

Thank you
Questions?
References
