Management of Liver Metastasis from Colorectal Carcinoma

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Management of Colorectal Liver Metastasis
Epidemiology

- 25% of patients diagnosed with colorectal carcinoma will have liver metastasis at presentation.
- Another 50% of patients will have recurrent disease develop within the liver.
- 85% of tumor recurrences are detected within 2.5 years after resection of the primary colorectal CA and the remaining 15% are detected within the next 2.5 years.
History

- The earliest hepatic procedures were performed almost exclusively for trauma.
- The earliest resection for tumor was by Langenbuch in 1888.
- By the 1940s a more aggressive operative approach was being taken in the treatment of patients with colorectal carcinoma metastatic to the liver.
Hematogenous metastases from primary colorectal cancer develop in a step-wise fashion. In most patients, the primary tumor disseminates to local lymph nodes, to the liver, or to peritoneal surfaces. This is considered a metachronous or step-wise progression of the malignant process. Only in a minority of patients is there synchronous spread of the malignancy from the primary site to systemic sites.
Natural History of Colorectal Liver Metastasis

- Death of colorectal cancer is often a result of liver metastasis.
- Surgical resection of distant metastasis can produce long-term survival and cure in some patients.
A retrospective study by Wilson et al. (Arch Surg 1976; 111: 330-334) looking at the survival of patients with potentially resectable colorectal liver mets left untreated reported a 0% 5-year survival for patients untreated compared with a 28% 5-year survival for patients whose liver mets were resected.
A retrospective study by Wanebo et al. (Am J Surg 1978; 135: 81-85) found that patients with an untreated single liver metastasis had a median survival of 19 months, with no patient surviving 5 years, while patients with a resected single liver metastasis had a median survival of 36 months with 25% of patients surviving 5 years.
Diagnosis of Liver Metastasis

- The most common symptoms of hepatic metastatic disease are pain, ascites, jaundice, palpable mass, weight loss, anorexia, fever, and vague GI complaints.
- Many patients are diagnosed through routine radiologic studies or elevations in the CEA level, which prompt further investigation.
Prognostic Variables for Liver Metastasis

- Age >70
- Primary tumor stage
- Primary tumor location (colon > rectum)
- Clinical presentation of metastasis (signs/symptoms, lab abnormalities)
- Synchronous metastasis
- Size of metastatic lesion(s)
- Extent of liver involvement
Prognostic Variables for Liver Metastasis continued...

- Interval between primary diagnosis and appearance of metachronous metastasis (diagnostic interval ≤ 1 year)
- Multiple metastases
- Presence of satellite lesions
- Presence of extrahepatic disease
Pre-op Work-up for Candidates for Resection of Metastasis

- Detailed history and physical
- Labs including CBC and LFTs
- CXR
- CT or MRI of abdomen/pelvis
- Colonoscopy (if none within 6 months)
- PET scan
Liver Anatomy- Morphological

The liver is divided by the umbilical fissure and falciform ligament into two lobes- the right lobe (which is larger) and the left lobe.

The right lobe is comprised of two accessory lobes which are individualized by well-defined fissures.
Liver Anatomy- Functional

This description was initiated by Cantlie in 1898. It was later followed by the works of McIndoe & Counseller (1927), Hjörstjö (1931), Ton That Tung (1939), Goldsmith & Woodburne (1957), and Couinaud (1957).

This description of hepatic segmentation is based upon the distribution of the portal pedicles and the location of the hepatic veins.
LOBECTOMY

right
C

left
D

Gall bladder

principal plane

portal triad

A
right

B
left

HEPATECTOMY

ligamentum teres

umbilical fissure
Hepatic Resections

There are 3 types of hepatic resection:

1. Anatomic Resections
   a. R Hepatectomy
   b. L Hepatectomy
   c. R Lobectomy (R Trisegmentectomy)
   d. L Lobectomy (L Lateral Segmentectomy)
   e. Extended L Hepatectomy (L Trisegmentectomy)
   f. Transverse Hepatectomy
Hepatic Resections continued...

2. Nonanatomic Resections

3. Enucleation Procedures
Extended right lobectomy
Right lobectomy
Right Trisegmentectomy

Right lobectomy
Right hepatectomy

Principal plane
Portal triad
Ligamentum teres
Umbilical fissure

Left lobectomy
Left hepatectomy

Extended left lobectomy
Extended left hepatectomy
Left Trisegmentectomy
Contraindications to Major Resection for Metastases

- Total hepatic involvement
- Advanced cirrhosis
- Jaundice (except from extrinsic hepatic ductal obstruction)
- Vena Cava or main Portal Vein invasion
- Extrahepatic tumor involvement (except lung)
Complications of Surgery

- Operative Mortality ranges from 0-7%
  - Hemorrhage
  - Sepsis
  - Liver Failure
- Morbidity ranges from 22-39%
  - Hemorrhage (1-3%)
  - Biliary leak or fistula (4%)
  - Liver failure (3-8%)
Complications of Surgery continued…

- Perihepatic abscess (2-10%)
- Pneumonia (5-22%)
- Symptomatic pleural effusion (5-10%)
- Pulmonary embolism (1%)
Prehepatectomy Predictors of Survival and Nonrecurrence
Retrospective Study of 144 patients between 1992-2000 who underwent potentially curative hepatic resection for colorectal liver metastases.

The study looked at identifying factors that influence overall survival and recurrence in the remnant liver.

The study sought to demonstrate that metastatic tumor doubling time is the most important prehepatectomy predictor of survival and nonrecurrence of hepatic colorectal metastasis.
Tanaka et al. continued…

Univariate Analysis of Influence of Tumor-Related Variables on Survival After Hepatectomy

<table>
<thead>
<tr>
<th></th>
<th>Overall Survival (%)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>3Y</td>
<td>5Y</td>
</tr>
<tr>
<td><strong>Concomitant extrahepatic disease</strong></td>
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<tr>
<td>present</td>
<td>32.8</td>
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<tr>
<td>absent</td>
<td>66.6</td>
<td>57.5</td>
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<tr>
<td><strong>Distribution</strong></td>
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<tr>
<td>unilobar</td>
<td>69.4</td>
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<tr>
<td>bilobar</td>
<td>46.2</td>
<td>38.5</td>
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<tr>
<td><strong>Size (mm)</strong></td>
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<tr>
<td>&lt;20</td>
<td>75.5</td>
<td>70.1</td>
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<tr>
<td>20-50</td>
<td>62.6</td>
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<tr>
<td>&gt;50</td>
<td>30.4</td>
<td>24.4</td>
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</table>
Tanaka et al continued…

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<tr>
<td>Doubling time</td>
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<tr>
<td>≤45 days</td>
<td>47.6</td>
<td>29.7</td>
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<td>&gt;45 days</td>
<td>74.3</td>
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<td>48.7</td>
<td>4.4</td>
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<tr>
<td>negative</td>
<td>63.3</td>
<td>60.6</td>
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Tanaka et al continued…
Multivariate Analysis of Prognostic Factors

<table>
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<tr>
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<th>p value</th>
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<tr>
<td><strong>Maximum size (mm)</strong></td>
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<tr>
<td>20</td>
<td>0.132</td>
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<td>20-50</td>
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<td><strong>Doubling time</strong></td>
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<tr>
<td>&gt;45 days</td>
<td>0.247</td>
<td>0.013</td>
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<tr>
<td><strong>p53 expression</strong></td>
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<tr>
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<td>0.250</td>
<td>0.011</td>
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Tanaka et al continued…
Univariate Analysis of Risk Factors for Remnant Liver Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Disease-Free Survival (%)</th>
<th>p value</th>
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<tbody>
<tr>
<td></td>
<td>1Y</td>
<td>3Y</td>
</tr>
<tr>
<td><strong>Primary lesion site</strong></td>
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<tr>
<td>colon</td>
<td>70.4</td>
<td>38.4</td>
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<tr>
<td>rectum</td>
<td>79.2</td>
<td>67.1</td>
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<td><strong>Lymph node mets</strong></td>
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<td></td>
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<tr>
<td>present</td>
<td>66.8</td>
<td>46.6</td>
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<tr>
<td>absent</td>
<td>90.4</td>
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<td><strong>Vascular permeation</strong></td>
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<td>absent</td>
<td>82.0</td>
<td>66.0</td>
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<td><strong>Liver metastases</strong></td>
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<td>synchronous</td>
<td>65.2</td>
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<td>metachronous</td>
<td>81.8</td>
<td>58.5</td>
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</table>
Tanaka et al continued…
Univariate Analysis of Risk Factors for Remnant Liver Recurrence

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<tr>
<th>Distribution</th>
<th>Disease-Free Survival (%)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>unilobar</td>
<td>84.1 58.7 58.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>bilobar</td>
<td>60.1 41.9 37.3</td>
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<table>
<thead>
<tr>
<th>Vascular invasion</th>
<th>Disease-Free Survival (%)</th>
<th>p value</th>
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<tr>
<td>present</td>
<td>70.2 40.8 40.8</td>
<td>&lt;0.05</td>
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<tr>
<td>absent</td>
<td>80.1 69.7 64.7</td>
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<thead>
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<th>Doubling time</th>
<th>Disease-Free Survival (%)</th>
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<tbody>
<tr>
<td>≤45 days</td>
<td>55.7 41.8 41.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>&gt;45 days</td>
<td>88.5 61.6 56.5</td>
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<tr>
<th>p53 expression</th>
<th>Disease-Free Survival (%)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>positive</td>
<td>76.1 40.4 36.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>negative</td>
<td>84.3 64.5 64.5</td>
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Multivariate Analysis of Risk Factors for Remnant Liver Recurrence

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Conclusions

- Patients with doubling times >45 days had relatively few liver recurrences. Moreover, when there was a recurrence, the patient was a candidate for repeat hepatectomy.

- Prophylactic chemotherapy and highly sensitive follow-up testing might improve the prognosis for patients with a short doubling time.
Timing of Hepatectomy-
Simultaneous vs. Delayed
Retrospective study of 39 consecutive patients with synchronous colorectal liver metastases who underwent curative simultaneous “1-stage” hepatectomy and resection of colorectal primary.

91 patients with colorectal CA and synchronous liver mets were evaluated as candidates for simultaneous resection. Simultaneous resections were performed in patients with a relatively small number of liver neoplasms considered to be completely removed by a relatively simple hepatectomy procedure.
Liver resection was contraindicated at the time of primary operation in 50 patients for the following reasons: poor performance status (4), massive neoplasm (2), unfavorably located neoplasm (2), multicentricity (6), and multiple, bilobar metastases (36).

Intraoperatively, the following criteria for simultaneous liver resection were applied:

- Primary colorectal neoplasm resectable with a negative margin
- Absence of uncontrollable extrahepatic disease
- Ability to resect all liver neoplasms with negative margins
Tanaka et al continued…
*Surgery* 2004; 136(3):650-659

- **Overall cumulative survival rates**

<table>
<thead>
<tr>
<th></th>
<th>1Y</th>
<th>3Y</th>
<th>5Y</th>
</tr>
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<tbody>
<tr>
<td>simultaneous resection</td>
<td>86%</td>
<td>68%</td>
<td>53%</td>
</tr>
<tr>
<td>metachronous resection</td>
<td>83%</td>
<td>47%</td>
<td>47%</td>
</tr>
</tbody>
</table>

- **Disease-free survival rates**

<table>
<thead>
<tr>
<th></th>
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<th>3Y</th>
<th>5Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>simultaneous resection</td>
<td>64%</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>metachronous resection</td>
<td>51%</td>
<td>35%</td>
<td>28%</td>
</tr>
</tbody>
</table>
Variables influencing survival after simultaneous resection of colon & liver lesions (univariate analysis):
- Histologic features of primary (well to mod diff) $p<0.01$
- Age ($<70$) $p<0.05$

No variables affected survival after metachronous resection
Potential disadvantages of synchronous resection:

- Intraoperative contamination of the cut liver surface may be more likely
- Postoperative anastomotic leakage may be favored by impairment of liver function
- Occult micrometastatic lesions may remain unresected, leading to higher recurrence rates
Conclusion- Simultaneous colorectal and hepatic resections are not recommended for the following:

- Patients who require resection of more than 1 hepatic section to remove liver metastases
- Patients 70 years of age or older
- Patients with poorly differentiated or mucinous adenocarcinoma as the primary lesion
Role of Rescue Surgery for Unresectable Liver Metastases
Prospective study of 1439 patients with colorectal liver metastases managed between 1988 and 1999. 1104 (77%), initially unresectable, were treated by chemotherapy and 335 (23%), resectable, were treated by primary liver resection.

Among 1104 unresectable patients, 138 “good responders” (12.5%) underwent secondary hepatic resection after an average of 10 courses of chemotherapy. (95 patients had a 50% or more decrease in total tumor size.)
René et al. continued…


- Combined techniques to achieve resectability
  - Preop portal embolization in 12 patients (9%)
  - RFA or cryosurgery in 20 patients (14%)
  - Two-stage hepatectomy in 15 patients (11%)
- Most liver resections were nonanatomic or mixed (anatomic & nonanatomic) procedures (69%)
- The majority of resections were potentially curative (93%)
Conclusions

- Modern chemotherapy allows 12.5% of patients with unresectable colorectal liver metastases to be rescued by liver surgery.
- Despite a high recurrence rate, 5 year survival is 33%.
Options for Palliation
Radiofrequency Ablation (RFA)

RF thermal ablation works by converting RF waves into heat. A high-frequency alternating current (100-500 kHz) passes from an uninsulated electrode tip into the surrounding tissues and causes ionic vibration. The ionic vibration causes frictional heating of the tissues surrounding the electrode. The goal of RFA is to achieve local temperatures that make tissue destruction occur. Tissue heating also drives
extra- and intracellular water out of the tissue and results in further destruction due to coagulative necrosis.

Studies have shown that hyperthermia can also cause accelerated emigration of peripheral blood mononuclear cells, activation of effect cells, secretion of cytokines, and increased induction of apoptosis.
The abundant portal venous blood flow present in normal hepatic parenchyma acts as a heat pump, which makes the creation of thermal injury in normal liver more difficult than in liver tumors.

RFA has been found to be safer and better tolerated than other ablative techniques, such as cryotherapy, lasar ablation, and microwave ablation, and is described as having a 0% mortality rate. It is also associated with fewer local recurrence.
Complications of RFA

- Symptomatic pleural effusion
- Fever
- Pain
- Hemorrhage
- Subcutaneous hematoma
- Subcapsular liver hematoma
- Ventricular fibrillation
- Skin burn (in percutaneous procedures)
Complications of RFA continued...

- Diaphragmatic necrosis
- Hepatic abscess
- Hepatic artery injuries
- Bile duct injuries
- Renal failure
- Liver failure
- Coagulopathy
Cryotherapy

Hepatic cryotherapy involves the freezing and thawing of liver tumors by means of a cryoprobe inserted into the tumors. During freeze/thaw cycles, intracellular and extracellular ice formation occurs in an area termed the “iceball”, leading to tumor destruction.

This procedure is done through an abdominal incision and cannot be done percutaneously like RFA.
Complications of Cryotherapy

- Hemorrhage of cracking frozen liver
- Bile collection
- Biliary fistula
- Pleural effusion
- Liver abscess
- Thrombocytopenia
- Myoglobinuria
Complications of Cryotherapy continued...

- Arrhythmia
- Acute renal failure
- Cryoshock due to multi-organ failure with DIC
- Mortality rates range from 0-8% (overall mortality rate of 1.6%)
Hepatic Artery Chemotherapy

The rationale for hepatic artery catheter chemotherapy is based on the fact that liver metastases over 1 cm derive most of their blood supply from the hepatic artery. The other rationale is the high first pass hepatic extraction of the drug used for this approach. Both factors cause high local drug concentrations with reduced systemic toxicity and allow higher dosages compared with intravenous treatment.
5-FU and fluorodeoxyuride (FUDR) are the chemotherapy agents usually used for this route of administration.

One British study reported a response rate of 43% in the intra-arterial group compared with 9% in the systemic chemotherapy group. Another study reported longer survival in the intra-arterial group compared with the systemic group (405 days vs. 226 days).
Immunotherapy

Immunotherapy is mainly used in advanced diseases which have failed to respond to conventional therapy. Levamisole, a non-specific immune stimulant, has been used in adjunctive treatment with 5-FU as an immune modulator. Some clinical trials have also shown that monoclonal antibody 17-1A is effective in increasing survival following resection of Dukes C primary colorectal tumors.
Radiotherapy

Traditional external beam irradiation has found little place in the management of liver tumors because of the particularly radiosensitive nature of normal liver tissue, which limits the total dosage to 30-50 Gy.

Selective internal radiation therapy (SIRT) is a new modality that may be valuable in colorectal liver metastases that are not suitable to resection, RFA, or cryotherapy.
Selective Internal Radiation Therapy (SIRT)

SIRT is a technique that allows high average doses of radiation (200-300 Gy) to liver tumors with minimal serious effects on the non-tumorous liver. The treatment entails delivery of usually a single dose of Yttrium microspheres into the hepatic artery which, by virtue of almost exclusive arterial supply to liver tumors compared with the predominant portal supply to normal liver, results in selective tumor uptake and irradiation.
Conclusions

- Indications for resection of colorectal liver metastasis continue to broaden.
- Minimally invasive surgical techniques allow resection and palliation to be available to more patients.
- New technologies for palliation continue to emerge and become refined.