METASTATIC COLO-RECTAL CANCER.

- 15 to 20% of patients have distant metastatic disease at the time of presentation.
- Spread by lymphatic and hematogenous dissemination, contiguous, transperitoneal routes.
- The most common metastatic sites are the regional lymph nodes, liver, lungs, and peritoneum.
- Because the venous drainage of the intestinal tract is via the portal system, the first site of hematogenous dissemination is usually liver, followed by lungs, bone, and many other sites, including brain.
- Tumors arising in the distal rectum can spread to lungs because the inferior rectal vein drains into the inferior vena cava rather than into the portal venous system.
- The risk of hepatic metastasis increases with tumor size and tumor grade.
- Small tumors may produce distant metastasis.
- Carcinomatosis (diffuse peritoneal metastases) occurs by peritoneal seeding.

Table 28-4 TNM Staging of Colorectal Carcinoma and 5-Year Survival

Stage	TNM	5-Year Survival
I	T1-2, N0, M0	70–95%
II	T3-4, N0, M0	54–65%
III	Tany, N1-3, M0	39–60%
IV	Tany, Nany, M1	0–16%

- Preoperative Evaluation.
  - Colonoscopy/endorectal ultrasound.
  - Chest x-ray. If abnormal CT chest.
  - Abdominal/pelvic CT scan.
  - PET scan.
  - CEA.

Liver Metastasis

- 15% of patients with systemic disease will have metastases limited to the liver.
- Of these, 20% are potentially resectable for cure.
- 5-year survival in these patients is 20 to 40%.
- **A biopsy** is depending upon the clinical picture.
  - The risk of tract seeding from percutaneous fine needle aspiration (FNA) biopsy appears small
  - this complication was described in five of 51 cases of biopsy-proven hepatic colorectal metastases in one series.

Surgical resection.

- The only potentially curative option.
- **Limitation for surgery**: tumor size, location, multifocality, or inadequate hepatic reserve
- **Patient selection** —no radiographic evidence of involvement of the hepatic artery, major bile ducts, or main portal vein, adequate functional hepatic reserve postresection.
    - **Diagnostic laparoscopy** can identify occult intraperitoneal metastases:
    - Lymph node-positive primary tumor
    - Relapse-free interval <12 months
    - Multiple (>1) hepatic tumors on preoperative imaging
    - Serum carcinoembryonic antigen (CEA) level >200 ng/mL within one month of surgery
    - Size of largest hepatic tumor >5 cm by preoperative imaging
    - More then 2 signs → diagnostic laparoscopy
- **The OncoSurge decision model** 2005 ASCO GI cancers symposium
    - Resection is always preferred, if possible, over local ablation strategies (cryosurgery, radiofrequency ablation, laser techniques).
    - Contraindication:
        - unresectable extrahepatic disease
        - extensive liver involvement (> 70 percent, more than 6 segments, or involvement of all three hepatic veins)
        - major liver insufficiency, or other conditions causing the patient to be unfit for surgery.
    - Immediate resection
        - adequate margins could be radiographically defined
        - there is no portal lymph node involvement
        - four or fewer lesions.
        - Resection could be considered for more than four lesions if they were localized to a single lobe.
    - For patients with more than four metastases, or bilobar involvement
        - resection is considered appropriate only after tumor shrinkage using neoadjuvant chemotherapy:
        - 5-FU/leucovorin to be only rarely appropriate
        - whereas 5-FU in combination with either irinotecan or oxaliplatin is generally appropriate.
    - Postoperative chemotherapy is considered appropriate for patients who had received preoperative chemotherapy, although for patients who had a complete resection, benefit was deemed uncertain.
- **Timing of hepatectomy in patients presenting with metastatic disease**
    - One-stage surgery: colectomy & liver resection.
    - Repeat resection for recurrent metastases
        - the liver is the most common site of recurrence
        - Liver is the only site of recurrence in approximately 40%
        - Repeat hepatic resection may be considered in selected patients who have no evidence of extrahepatic disease, and a good performance status.

        - Mortality rates is less than 5%, and relapse-free survival rates ranged from 20 to 43% at two to five years.
        - Patients with a relapse-free interval of longer than one year have a more favorable outcome from reresection .

Cryotherapy

- for lesions that are less than 5 cm since the zone of necrosis that is formed is 3 to 5 cm in size.
- Requires laparotomy.
- Experience with laparoscopic or percutaneous application is accumulating.
- In one of the largest series of 116 patients with hepatic metastases from CRC, who were followed after cryotherapy for an average of 21 months,
    - the actuarial one, three, and five-year survival rates were 82%, 32%, and 13% percent, respectively.
- Following cryotherapy, most failures occur in the liver but at new sites.
- Cryosite failures are reported in from 10 to 44% of cases.
- Cryosurgery is often applied following incomplete resection in patients with isolated liver metastases.
- There are no randomized trials evaluating this approach compared to cryosurgery alone.
- The suggestion is that the same effect as complete resection.

Radiofrequency ablation

- Radiofrequency ablation (RFA) using cooled-tip electrodes produces larger volumes of coagulation necrosis with fewer electrode insertions than with other RFA techniques.
- Local recurrence is 0 – 39%, average less than 10%
- Follow-up of 20 months or less.
- The median survival for all patients after RFA was 29 months
- Median survival is better with
    - a preoperative CEA level <200 ng/mL (median 34 versus 16 months)
    - small tumor size :median survival is 38 months-
        - for Tu < 3 cm - 34 months
        - for Tu 3 to 5 cm - 21 months
        - for Tu >5 cm. - 1 to 3 versus 29 months
    - less than 3 tumors - 22 months.
    - No significant impact of extrahepatic disease on median survival.
- Complications:
    - fatal- liver failure
    - colon perforation
    - portal vein thrombosis
    - Liver abscess
    - Pleural effusion and skin burns
    - Hypoxemia during treatment
    - Pneumothorax
    - Subcapsular hematoma
    - Acute renal insufficiency
    - hemoperitoneum

HEPATIC INTRAARTERIAL CHEMOTHERAPY

- For liver tumors that are not amenable to surgical resection or local ablation
- Regional administration of drugs that are rapidly metabolized in the liver by a first pass effect leads to higher levels of drug exposure and minimizes systemic side effects.
- Macrometastases in the liver that are larger than 0.5 cm derive more than 80 percent of their blood supply from the hepatic arterial circulation, while normal hepatocytes are supplied primarily by the portal circulation .
- As a result, the administration of chemotherapy into the hepatic artery allows the selective delivery of drug to the tumor with relative sparing of normal hepatocytes.
- At least five major prospective trials, enrolling over 400 previously untreated patients with metastatic CRC, randomly assigned patients to systemic fluoropyrimidine chemotherapy or to HIA FUDR (floxuridine) delivered via an implanted pump .
    - In each study, the response rate to HIA chemotherapy was superior to systemic treatment.
    - However, this did not translate into a survival improvement in any study.
- **Technique of HIA pump placement**
    - The goal of intrahepatic artery catheter placement is to enable bilobar hepatic perfusion with chemotherapy and to prevent administration of chemotherapy to the stomach or duodenum (misperfusion).
    - Angiogram to define the arterial supply of the liver.
        - Conventional anatomy - 61 percent of patients
    - Exploratory laparotomy,
        - to exclude unresectable extrahepatic tumor
        - evaluate the lymph nodes in the porta hepatis, along the common hepatic artery, and at the celiac axis.
        - Cholecystectomy
        - Total devascularization of the distal stomach and proximal duodenum.
    - Postoperatively, before initiating HIA chemotherapy, a Tc-99m macro-aggregated albumin (TcMAA) scan is necessary to ensure the absence of misperfusion and to assess the adequacy of whole liver perfusion.
- **Complications of pump placement**
    - hepatic artery thrombosis
    - incomplete perfusion of the entire liver due to missed recognition of an accessory hepatic artery
    - misperfusion to the stomach or duodenum
    - pump pocket hematoma.
    - In fewer than 5 percent of patients.
    - Operative mortality should approach that of an open cholecystectomy.
    - Late complications
        - inflammation or ulceration of the stomach or duodenum
        - pump pocket infection
        - catheter thrombosis
        - antral or duodenal ulceration

Summary: hepatic intraarterial chemotherapy.

- The relative benefit of hepatic intraarterial chemotherapy - unclear.

- At present, the standard approach for newly diagnosed metastatic colorectal cancer is the combination of intravenous irinotecan or oxaliplatin plus 5-FU and leucovorin, with or without bevacizumab.
- These regimens have been shown to improve survival compared to 5-FU and leucovorin alone in randomized trials.
- With these newer approaches to therapy, objective response rates as high as 45 to 50% have been achieved, with median survival durations of up to 20 months which is significantly better than the 12 to 15 month average survivals reported for 5-FU and leucovorin alone.
- It is unknown whether any HIA approach will improve upon or even match these results.

Nikolay Bugaev, M.D.
December 19, 2005