Surgical Management of Advanced Stage Colon Cancer

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6/11/14
Colon Cancer Overview

• Approximately 50,000 attributable deaths per year
• Colorectal cancer is the 3rd most common cause of cancer-related death in the US
• The liver is the most common site for metastasis

Topics

1. Management of obstructing colon cancer
2. Synchronous metastasis
3. Resection of primary colon tumor in unresectable metastatic disease
Other Goals

• Temper fatalism about metastatic colon cancer
• Avoid a rush to surgery
• Glimpse into the future
1) **Obstructing colon cancer**  
(No Known Metastasis)

- NCCN Col-2
- Options
  - Resection with or without colostomy
  - Diversion
  - Colonic Stent
Colon Cancer

CLINICAL PRESENTATION
- Colon cancer appropriate for resection (non metastatic)

WORKUP
- Pathology review
- Colonoscopy
- CBC, platelets, chemistry profile, CEA
- Chest/abdominal/pelvic CT
- PET-CT scan is not routinely indicated

FINDINGS
- Resectable, nonobstructing
- Resectable, obstructing
- Locally unresectable or medically inoperable

SURGERY
- Colectomy with en bloc removal of regional lymph nodes
- One-stage colectomy with en bloc removal of regional lymph nodes or Resection with diversion or Stent or Diversion
- Colectomy with en bloc removal of regional lymph nodes

Suspected or proven metastatic adenocarcinoma

See Management of suspected or proven metastases (COL-5)

See Pathologic Stage, Adjuvant Therapy, and Surveillance (COL-3)

See Chemotherapy for Advanced or Metastatic Disease (COL-C)
Comparison of one-stage resection and anastomosis of acute complete obstruction of left and right colon

• 214 cases of acute colonic obstruction were managed with one-stage resection and anastomosis by a single surgeon (1986 to 2003)

• 80 right side
  – operative mortality was 10% (8/80);
  – 2 cases (2.5%) of anastomotic leakage.

• 134 left side
  – operative mortality was 1.5% (2/134)
  – 3 cases (2.3%) of anastomotic leakage.

Objective: To date, this is the largest prospective series in patients with malignant colorectal obstruction to evaluate the effectiveness and safety of colonic self-expanding metal stents (SEMSs) as an alternative to emergency surgery. SEMSs allow restoration of bowel transit and careful tumor staging in preparation for elective surgery, hence avoiding the high morbidity and mortality associated with emergency surgery and stoma creation.

Methods: This report is on the SEMS bridge-to-surgery subset enrolled in two multicenter international registries. Patients were treated per standard of practice, with documentation of clinical and procedural success, safety, and surgical outcomes.

Results: A total of 182 patients were enrolled with obstructive tumor in the left colon (85%), rectum (11%), or splenic flexure (4%). Of these patients, 86% had localized colorectal cancer without metastasis. Procedural success was 98% (177/181). Clinical success was 94% (141/150). Elective surgery was performed in 150 patients (9 stomas) and emergency surgery in 7 patients for treatment of a complication (3 stomas). The overall complication rate was 7.8% (13/167), including perforation in 3% (5/167), stent migration in 1.2% (2/167), bleeding in 0.6% (1/167), persistent colonic obstruction in 1.8% (3/167), and stent occlusion due to fecal impaction in 1.2% (2/167). One patient died from complications related to surgical management of a perforation.

Conclusions: SEMSs provide an effective bridge to surgery treatment with an acceptable complication rate in patients with acute malignant colonic obstruction, restoring luminal patency and allowing elective surgery with primary anastomosis in most patients.
Stents

• Roughly half of emergency colon surgery pts require a stoma
  – 40% become permanent
• Colon stents allowed elective surgery in majority of patients (90%)
• Median time to surgery after stenting = 14 days
Stent Safety

- Overall complication rate 8%

<table>
<thead>
<tr>
<th>Complication category</th>
<th>Time of occurrence</th>
<th>Management</th>
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<tbody>
<tr>
<td></td>
<td>Procedural</td>
<td>Post-procedural</td>
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<tr>
<td>Perforation</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Stent migration</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
<td>—</td>
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<tr>
<td>Persistent obstruction</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Stent occlusion*</td>
<td>—</td>
<td>2</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>6</strong></td>
<td><strong>7</strong></td>
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*Due to fecal impaction.
2) Synchronous Metastasis

• Isolated Liver and/or Lung
  – NCCN Col-5, Col-6 and Col-B

• Abdominal / Peritoneal
  – NCCN Col-8
Suspected or proven metastatic synchronous adenocarcinoma (Any T, any N, M1)

- Colonoscopy
- Chest/abdominal/pelvic CT
- CBC, platelets, chemistry profile
- CEA
- Determination of tumor KRAS gene status (if KRAS non-mutated, consider BRAF testing)
- Needle biopsy, if clinically indicated
- PET-CT scan only if potentially surgically curable M1 disease
- Multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary and lung metastases

Synchronous liver only and/or lung only metastases

Resectable

Unresectable (potentially convertible or unconvertible)

Synchronous abdominal/peritoneal metastases

See Treatment and Adjuvant Therapy (COL-6)

See Treatment and Adjuvant Therapy (COL-7)

See Primary Treatment and Adjuvant Therapy (COL-8)
<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>ADJUVANT THERAPY</th>
<th>SURVEILLANCE</th>
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<tbody>
<tr>
<td>Resectable synchronous liver and/or lung metastases only</td>
<td>(resected metastatic disease) (6 MO PERIOPERATIVE TREATMENT PREFERRED)</td>
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<tr>
<td>Colectomy, with synchronous or staged liver or lung resection</td>
<td>Consider observation or shortened course of chemotherapy</td>
<td>If patient stage IV, NED:</td>
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<tr>
<td>Neoadjuvant therapy (for 2-3 months) FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS wild-type [WT] gene only) followed by synchronous or staged colectomy and resection of metastatic disease</td>
<td></td>
<td>• History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y</td>
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<td>Colectomy, followed by chemotherapy (for 2-3 months) FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS WT gene only) and staged resection of metastatic disease</td>
<td>Consider observation or shortened course of chemotherapy</td>
<td>• CEA every 3-6 mo x 2 y, then every 6 mo x 3-5 y</td>
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<td></td>
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<td>• Chest/abdominal/pelvic CT scan every 3-6 mo x 2 y, then every 6-12 mo up to a total of 5 y</td>
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<td>• Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo</td>
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<td>► If advanced adenoma, repeat in 1 y</td>
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<td>If Recurrence, See Workup (COL-9)</td>
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Liver Metastasis

• Approximately 25% of CRC patients have liver metastasis at time of diagnosis

• Clinical risk score (0-5) from MSKCC database predicts recurrence free survival after hepatectomy
  – positive nodal status of the primary
  – disease-free interval <12 months
  – number of liver metastases >1 on preop imaging,
  – size of the largest metastases >5 cm on preop imaging
  – preoperative CEA >200 ng/mL

Surgical Management of Patients with Synchronous Colorectal Liver Metastasis: A Multicenter International Analysis

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Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD (Mayo, Wolfgang, Choti, Pawlik); the Department of Surgery, Liver Unit, Scientific Institute San Raffaele, Milan, Italy (Pulitano, Aldrighetti); the Unit of Hepato-Biliary-Pancreatic Surgery, Lisbon, Portugal (Marques, Lamelas, Gindrat, Barroso); and the Department of Visceral Surgery, University Hospitals of Geneva, Switzerland (de Saussure, Mentha)
Surgical Management of Patients with Synchronous Colorectal Liver Metastasis: A Multicenter International Analysis

The goal of this study was to investigate the surgical management and outcomes of patients with primary colorectal cancer and synchronous liver metastasis.

**STUDY DESIGN—**

- multi-institutional database
- 1,004 patients treated between 1982 and 2011.
- Clinical, pathologic and outcomes data
Surgical Management of Patients with Synchronous Colorectal Liver Metastasis: A Multicenter International Analysis

RESULTS—
• Simultaneous CRC and liver operation in 329 (33%)
• Staged 675 (67%)
  – “classic” staged approach, n = 647;
  – liver-first strategy, n = 28.
• Liver therapy included hepatectomy (90%) or combined resection + ablation (10%).
• No difference in morbidity between staged and simultaneous groups or major vs minor hepatectomies (p > 0.05).
• Ninety-day postoperative mortality was 3.0%, with no difference between simultaneous and staged approaches (p = 0.94).
• The overall median and 5-year survivals were 50.9 months and 44%, respectively; long-term survival was the same regardless of the operative approach (p > 0.05).

CONCLUSIONS—
Simultaneous and staged resections for sCRLM can be performed with comparable morbidity, mortality, and long-term oncologic outcomes.
Liver

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.6
- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.7
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.8-11 Plan for a debulking resection (less than an R0 resection) is not recommended.7
- Patients with resectable metastatic disease and primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the heptectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.12
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization13 or staged liver resection14 can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Some institutions use arterially-directed embolic therapy in highly select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases (category 3).
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3).
- Re-resection can be considered in selected patients.15

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.16-19
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.20-23
- Re-resection can be considered in selected patients.24
- Ablative techniques can be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3).

Evaluation for conversion to resectable disease

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.25-28
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.29
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.30
Isolated Lung Metastasis

MSKCC
• 144 pts CRC mets
  – 5 yr survival 40%
  – 10 year survival 30%
  – Chemotherapy alone (0% beyond 24 months)

International Registry of Lung Metastases
• 645 CRC mets
  – 5 yr survival – 37%
  – 10 yr survival 22%


Size of metastatic deposits affects prognosis in patients undergoing pulmonary metastectomy for colorectal cancer

- 66 patients (2004-2010) at a single center
- 30 day hospital mortality rate 0%
- 63 R0 resections
- Median survival 45 months
- Cumulative 3 year survival 61%
- Size >2 cm was statistically significant prognostic factor (p=0.047)

Figure 2  Kaplan–Meier curves showing overall survival after curative resection of pulmonary metastasis. Patients grouped according to size of pulmonary deposit

Figure 3  Kaplan–Meier curves showing overall survival after curative resection of pulmonary metastasis. Patients grouped according to presence or absence of concurrent hepatic metastasis
Abdominal / Peritoneal Mets

• 17% of Stage IV have peritoneal met
  – 2% isolated

• Verwall et al
  – Randomized 105 patients
    • 5FU/LV +/- palliative surgery
    • Mitomycin C HIPEC 33/47 also had post op 5-FU/LV
    • OS 12.6 vs 22.3 months
FINDINGS

Synchronous abdominal/peritoneal metastases

Nonobstructing

Obstructed or imminent obstruction

PRIMARY TREATMENT

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

Colon resection
or Diverting colostomy
or Bypass of impending obstruction
or Stenting

See Chemotherapy for Advanced or Metastatic Disease (COL-C)
HIPEC NCCN Comments

- HIPEC treatment mortality 8% (bowel leak)
- No irinotecan, oxaliplatin
- Included appendiceal origin tumors (skewing survival data)
- Conclusion – HIPEC should be investigational of colon cancer with peritoneal metastasis (clinical trial)
3) Management of primary colon cancer in unresectable metastatic disease

- NCCN Col-7
- Recent pooled analysis of 4 clinical trials
- NSABP C10
TREATMENT
Unresectable\textsuperscript{g} synchronous liver
and/or lung metastases only

- Systemic therapy
  (FOLFIRI or FOLFOX
  or CapeOX\textsuperscript{aa} ±
  bevacizumab\textsuperscript{bb}
  or FOLFIRI or FOLFOX ±
  panitumumab
  or FOLFIRI ± cetuximab
  (KRAS WT gene only)\textsuperscript{c,c,2}
  or FOLFOXIRI
  [category 2B])
- Consider colon
  resection\textsuperscript{g} only if
  imminent risk of
  obstruction or
  significant bleeding

Re-evaluate for
conversion to
resectable\textsuperscript{g} every
2 mo if conversion
to resectability is
a reasonable goal

Converted to
resectable

Synchronized
or staged
resection\textsuperscript{g} of
colon and
metastatic
cancer

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

ADJUVANT THERAPY\textsuperscript{w}
(6 MO PERIOPERATIVE
TREATMENT PREFERRED)

- Active chemotherapy
  regimen for advanced
disease (See COL-C)\textsuperscript{cc}
  (category 2B)
  or
  If patient received
  neoadjuvant therapy,
  consider observation
  or shortened course
  of chemotherapy

SURVEILLANCE

If patient stage IV, NED:
- History and physical every 3-6
  mo for 2 y, then every 6 mo for a
  total of 5 y
- CEA every 3-6 mo x 2 y, then
  every 6 mo x 3-5 y
- Chest/abdominal/pelvic CT scan
  every 3-6 mo x 2 y, then every 6-
  12 mo up to a total of 5 y
- Colonoscopy\textsuperscript{b} in 1 y except if no
  preoperative colonoscopy due to
  obstructing lesion, colonoscopy
  in 3-6 mo
  - If advanced adenoma, repeat
    in 1 y
  - If no advanced adenoma,\textsuperscript{u}
    repeat in 3 y, then every 5 y\textsuperscript{v}
Impact on survival of primary tumor resection in patients with colorectal cancer and unresectable metastasis: Pooled analysis of individual patients’ data from four randomized trials.

**Goal:** estimate the effect of primary tumor resection on survival,

**Methods:**
- Retrospective review of records of 1,155 patients with metastatic CRC included in 4 first-line chemotherapy trials (FFCD 9601, FFCD 2000-05, ACCORD 13 and ML 16987)
- 810 patients beginning first-line chemotherapy with either fluoropyrimidine alone, oxaliplatin, irinotecan and/or bevacizumab were eligible.

**Results:**
- Patients with a history of resection (n = 478 (59%)), as compared to those without (n = 332 (41%)), were more likely to:
  - Have colonic primary (p < 0.0001)
  - Lower carcino embryonic antigen (CEA) (p < 0.0001)
  - Lower alkaline phosphatase (ALP) level (p=0.04)
  - Normal white blood cell count (WBC) (p < 0.0001).
- In the univariate analysis, stratified on the trial, primary tumor resection was associated with
  - a better OS (Hazard Ratio HR: 0.73 [0.63-0.84]; p < 0.0001)
  - PFS (HR : 0.73 [0.63-0.84]; p < 0.0001).

**Conclusions:** This study confirmed the independent prognostic value on survival of primary tumor resection in patients with unresectable metastases of CRC.
Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10.

PURPOSE:
• Major concerns surround combining chemotherapy with bevacizumab in patients with colon cancer presenting with an asymptomatic intact primary tumor and synchronous but unresectable metastatic disease.

PATIENTS AND METHODS:
• Eligibility for this prospective, multicenter phase II trial included:
  – Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1
  – asymptomatic primary tumor
  – unresectable metastases.
• All received infusion fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) combined with bevacizumab.
• Primary end point was major morbidity events, defined as surgical resection because of symptoms or death related to IPT. A 25% major morbidity rate was considered acceptable.
• Secondary end points included overall survival (OS) and minor morbidity related to chemo requiring hospitalization, transfusion, or nonsurgical intervention.

NSABP C10 outcomes

RESULTS:
• Ninety patients registered between March 2006 and June 2009:
  • 86 were eligible with follow-up, median age was 58 years, Median follow-up was 20.7 months.
  • There were 12 patients (14%) with major morbidity related to IPT:
    – 10 required surgery (8 obstruction; 1 perforation; 1 abdominal pain)
    – two patients died.
• The 24-month cumulative incidence of major morbidity was 16.3%
  – 11 IPTs were resected without a morbidity event:
    – 8 for attempted cure and three for other reasons.
• Median OS was 19.9 months

CONCLUSION:
• This trial met its primary end point. Combining mFOLFOX6 with bevacizumab did not result in an unacceptable rate of obstruction, perforation, bleeding, or death related to IPT. Survival was not compromised.
• These patients can be spared initial non-curative resection of their asymptomatic IPT.
A look to the future
Neoadjuvant FOLFOX-bev, without radiation, for locally advanced rectal cancer.

- **Background:** Pilot feasibility trial of pre-op FOLFOX-bevacizumab (bev) without RT for good-risk RC.
- **Methods:** Pts with clinical stage II-III RC (but not T4 tumors) who were candidates for sphincter-sparing surgery, were treated with 6 cycles of FOLFOX. Bev was included for cycles 1-4. Pts then were re-imaged and had repeat sigmoidoscopy with endorectal ultrasound (ERUS) performed by their surgeon to assess the primary tumor response.
  - Those with stable/progressive disease were to be referred for pre-op 5FU plus RT, followed by surgery
  - Those with clinical regression were to have surgery without pre-op RT.
  - Post-op 5FU plus RT was planned for any pts who did not have an R0 resection.
  - Post-op chemo was left to investigator discretion, however 6 cycles of FOLFOX were recommended.
  - The primary outcome was the R0 resection rate. Secondary outcomes were the pathologic CR rate, the 3-year disease free survival and local recurrence (LR) rate.

Neoadjuvant FOLFOX-bev, without radiation, for locally advanced rectal cancer.

Results:

- 31 pts accrued since March 2007
  - 2 withdrawn from the study for cardiovascular toxicity (1 angina, 1 arrhythmia) after 1-2 cycles of FOLFOX-bev. Both had R0 resections.
  - 29 who have completed pre-op chemo, all 29 had clinical regression and proceeded to surgery without pre-op RT.
  - All 29 had R0 resections.
  - 8/29 (27%) had a path CR.
  - 1 pt with 14+ nodes and a close deep margin received post-op RT, and has since developed pulmonary mets.
  - One pt with pathologic yT1N0 disease had high output ileostomy post-op but was discharged home in stable condition on day 10. He died suddenly 3 days later. Autopsy did not identify a cause.
  - No LRs and 3 distant recurrences, all pulmonary
  - 26 patients remain alive and disease-free

Conclusions: Preliminary results of this pilot trial indicate that preoperative FOLFOX-bev chemo without RT achieves a high rate of R0 resections and path CRs in good risk RC.
OBJECTIVES

• To assure that neoadjuvant oxaliplatin, leucovorin calcium, and fluorouracil (FOLFOX)...maintains the current high rate of pelvic R0 resection and is consistent with non-inferiority for time to local recurrence (TLR). (Phase II)

• To compare neoadjuvant FOLFOX to standard 5FUCMT with respect to the proportion of patients who achieve a pathologic complete response (pCR) at the time of surgical resection. (Phase III)

• To compare bowel function in patients randomized to the neoadjuvant FOLFOX vs standard 5FUCMT at approximately 1 and 2 years postoperatively.

• Phase II 300, Phase III 1000
Questions?