Colorectal Cancer Surgery with Stage 4 Disease

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Stage 4 cecal cancer, obstructed ICV
Right colectomy
Chemotherapy
Disease Progression

Stage 4 CRCa, SYMPTOMATIC PRIMARY. Options?

66 M, 2 days nausea, abdominal cramping, vomiting, no flatus or BM for 2 days.
Several months decreased appetite and intermittent nausea and vomiting, 10 pound weight loss, change BM.
Colonoscopy 7 yr ago, benign polyps FMH "stomach cancer", mom, died 43yr.

After initial NGT, IVF, etc, what is the next step?
A. Chemotherapy
B. Stent
C. Urgent surgery
• Two weeks after stent → LAP left hemicolectomy

• Pathology: T4a, N0(0/22), margins (-)
• Chemotherapy declined
• 3 month CT and colonoscopy (-)

Obstructing Colon Cancer: Stent vs. Surgery

• 2014 Meta-analysis, 7 Randomized Controlled Trials (2009-13)
• Stents in 195 and Emergency Surgery in 187
• Successful stenting in 77% (47-100%)
• ↓ Permanent Ostomy with stent, 9% vs. 27% (OR 0.28)
• ↑ Primary Anastomosis with stent: 67% vs. 55% (OR 2.0)
• ↓ Overall complications with stent
• Stenting - Risks of Perforation 4%, Migration 10-12%, re-obst 7-10%

X. Huang, J. Gastrointest Surg 2014
Colon Stent with Stage 4 Disease

- 134 patients obstructive stage 4 CRCA (Right 24%, Left 76%)
- Successful stent: 130 (97%)
- Long-term patency 55%
- Patency duration: 157 days (2-1590)
- Long-term complication: 45%
  - Re-interventions: 46% - Re-obstruction: 33%
  - Stent migration: 10% - Perforation: 8%
- Stoma formation
  - 1 and 2 year: 16% and 24%

Conclusion: a surgical procedure should be considered in those stage 4 incurable patients with >45-month predicted survival

JH Lee, Dis Colon Rectum 2014

Asymptomatic Primary, “Incurable” Stage 4 CRCA

- Median Survival: 16 vs 9 mos
- Actuarial 2yr survival: 25 vs 6%
- Survival dependent on extent of liver involvement
- Need for surgery in initially non-resected sample: 29%

L. Ruo, 2003 (MSKCC, 1995-99)

Stage 4 CRCA with asymptomatic primary tumor (resectability not recorded)

Total cohort (N = 225, 100%)  
No primary tumor complication (N = 207, 91%)  
No intervention (N = 160, 66%)
- Curative resection (N = 47, 28%)
- No resection (N = 8, 4%)
- Preoperative resection (N = 3, 2%)
Primary tumor complication (N = 18, 8%)
- Operative intervention (N = 10, 7%)
- Curative resection (N = 7)
- No resection (N = 8)
- Preoperative resection (N = 3, 2%)
Nonoperative intervention (N = 3, 4%)
- EBRT (N = 2)
- Bypass (N = 1)
- Chemotherapy (N = 1)

GA Pritchard, 2009 MSKCC
Stage 4 CRCA, asymptomatic primary, palliative resection?

- Unresectable Stage 4 CRCA
- N=416, 2000-08
- Propensity Match
- Median survival: 17(R) and 14(NR) months
- Surgery in NR group: 9/113
  - 7 emergent
  - 2 therapeutic
- Palliative resection of the asymptomatic primary tumor is not indicated in patients with unresectable stage 4 disease

MRI is best for characterizing liver lesions
CT is best for detection of extra-hepatic lesions
FDG-PET should be used selectively
"Conversion Chemotherapy" – unresectable to resectable (12-32%*)
"Neoadjuvant Chemotherapy" – prior to surgery for resectable or potentially resectable disease

R. Adam et al, The Oncologist 2012; "R. Adam 2004"
**CRCA with Liver/Lung Mets: NCCN**

- **RESECTABLE:**
  - Start w/resection or neo-adj chemo +/- Bev or other Ab or staged resection with chemo between
  - FOLFI\(I\) or FOLFOX or CapeOx
  - Ab bevacizumab, panitumumab or cetuximab (WT Kras)
  - Staged resection: 2-3mos chemotherapy between operations
  - Total of 6 months neo-adjuvant chemotherapy

- **UNRESECTABLE**
  - Same chemo as above
  - Re-evaluate for resectability q 2 mos
  - Colon surgery only "if imminent risk of obst. or significant bleeding"

NCCN.org, accessed 10.2014

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**CLM: Neoadjuvant Chemo**

- The EORTC Intergroup trial 40,983 randomized patients with resectable colorectal metastases to six cycles of perioperative chemotherapy with FOLFOX or surgery and found improved 3-year progression free survival (PFS) for neoadjuvant chemotherapy, no difference on overall survival

- Another study, post-hepatectomy chemotherapy but not preoperative chemotherapy increased overall survival


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**CLM: Response to neoadjuvant Rx**

- The disappearance of metastases on CT and MRI scans qualifies as a complete radiographic response but is not an indication of a complete pathological response
- Similarly, the lack of FDG uptake or complete response using PET does not imply complete pathological response.
- Disappearing liver met - residual macroscopic disease is found in about 25-45 per cent of patients at the time of operation

D. Bischoff 2013
Functional Liver Remnant

- ≥20%: A patient without cirrhosis or underlying liver disease, ≥20% of the total liver volume must remain
- ≥30%: In patients with extensive steatosis or chemotherapy a volume of >30% has been proposed
- >40%: Patients with cirrhosis should have a FLR of >40% prior to hepatic resection
- PVE is used to increase FLR.
  - 3 weeks req to reach max liver growth “Atrophy-hypertrophy complex”, up to 30% liver growth, not impaired by concomitant chemotherapy
- PVE contraindicated: PVT, tumor into PV, portal HTN. others


2-Stage Hepatectomy

- Indicated when a single-stage hepatectomy cannot safely remove all CLM
- Systemic chemo before and between surgical stages
- Test of time
- PVE – after 1st stage when FLR <30% or >40% in heavily chemo-treated liver
- First stage may involve resection and ablation, usually of left hemi-liver to obtain PVE of FLR after tumor removal/ablation results in liver regrowth without stim of tumor growth

M. Narita 2011

Simultaneous or staged CLM and CR resection?

- A recent multicenter international analysis compared simultaneous resections to staged (colon first and liver first) in over 1,000 patients and found no significant difference in morbidity, mortality or long-term oncologic outcomes between any of the three sequences.

- The decision to do simultaneous resections is based on the overall complexity of both procedures and the patient's comorbidities. The liver-first sequence is most suited to rectal cancers so that the liver metastases are not left untreated during the radiation portion of treatment to the rectum

SC Mayo JACS 2013, ME Clark 2014, EK Abdalla, 2013
Overall survival probability in relation to response to preoperative chemotherapy in 4,851 patients undergoing a first resection of colorectal liver metastases from the LiverMetSurvey.

Synchronous Mets: Liver First

- 4 single-center studies, 1992-2010, 121 patients (33 C, 88 R)
  - Median Liver Lesions: 2-6 (1-21), >50% bilobar
  - Chemo then liver resection, then colectomy or CRT for rectal cancers with subsequent resection, then adjuvant chemotherapy
  - Neoadjuvant chemo, FOLFOX/IRI +/- Bev 3-6 cycles
  - Liver resection 79%
  - CR resection 75%
  - 19% disease progression during protocol
  - Brouquet et al. (JAAS 2010) compared classic, combined, and reverse approaches and found no diff in OS
    - Reverse strategy is a viable option

Success of CLM Resection

- Age
- Primary stage
- Disease free interval
- Number of hepatic metastases
- Node-positive primary tumors
- Poorly differentiated primary tumors
- Extrahepatic disease
- Tumor diameter
- Carcinoembryonic antigen levels
- Positive resection margins (1cm margin or just a negative margin?)

However, none of these risk factors represents an absolute contraindication to hepatic resection provided that surgery is able to remove all the tumoral disease.

M. Rees 2006, A Taylor 2010, ME Clark 2014

CLM: Unresectable

- RFA – thermal destruction of cells (60 celcius)
  - Most effective for lesions <3cm
  - RFA + Resection: 43% 5 yr OS
  - RPT: Chemotherapy + RFA is better than chemo alone
- MWA – Microwave Ablation, coagulative necrosis
  - “Less “heat sink”, better applicability to larger tumors?
- Cryoslation – liquid N or Argon gas
  - Too much complication potential, out of favor
- HAI – HAI-systemic chemo, converts to resectable CLM in up to 50% **
- TACE – trans-arterial chemoembolization
- RE – Radio Embolization (Yttrium 90)
- SBRE – stereotactic body radiotherapy

T. Ruers 2012, S. Evrard 2012, ** NE Kemeny 2009

Extra-Hepatic Metastatic CRCA

- Review, 22 studies, 1142 patients
- Resection of CLM and EHD
  - Mostly simultaneous for LN and PD
  - Simultaneous or staged for lung
- 53% neo-adjuvant chemotherapy
- Morb/mortal: median 28 and 1%
- 5 yr OS for IO resection: 25% (10-36%)
  - Lung: Median 41 months, 5yr 27%
  - PCLN: Med 25, 5yr 17%
  - PD: Med 25, 5yr 8%

TC Chua, Eur J Cancer 2012
**CRCA Peritoneal Metastases ("carcinomatosis")**

- Occurs synchronously in 4.7% and metachronously in 4%
- No extraperitoneal mets: chemotherapy → cyto reduction surgery + HIPEC → more chemotherapy
- HIPEC: cisplatin, mitomycin-c, 42.5°C, 60 min
- Cytoreduction surgery: CCR0-2
    - 101 cases: 67 pre-HIPEC systemic chemo, 34 no pre-HIPEC chemo
    - Major complications: 24%
    - Resections: 10%
    - Overall survival: Median 32 mos, 5 yr 43%
    - 5 yr DFS of 52% in no complications group and 14% in complications group
    - Other RF for ↓DFS: CCR>0, PCI>19, metachronous peritoneal mets
- Systematic Reviews: med surv 13-29 mos, 5yr 11-19%
  - CCR 0: med surv 28±60 mos, 5yr 22-49%
  - NCCN: Use in trial setting recommended be/ ad/ sennadv/ syst chem

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**Case 2: 52 M, minimally symptomatic sigmoid colon cancer, bilobar liver metastases**

June 2013: After 4 doses of FOLFOX + Bevacizumab. There are numerous liver metastases, most of which have decreased in size. The largest lesion in the posterior right hepatic lobe measures 5.9 x 5.7 cm (image 37); previously 6.7 x 6.7 cm. The caudate lobe lesion now measures 2.5 x 1.7 cm, previously 3.6 x 2.6 cm. PLAN: 4 more doses of FOLFOX + BEV
11/2013: After 12 doses FOLFOX + Bevacizumab; CT-PET (-) ex-hepatic mets

CT read: No change in size or number of multiple hepatic metastases. No new lesions
DR: Sigmoid colectomy, RFA (I) and 3 lesions (II-IV) resected. Right liver tumors not treated
Pathology: Sigmoid (-) CA, Liver – met CA: largest 2.7cm, nearly entirely necrotic, margin (-)

- 5FU per OPTIMOX Re-started on 1/7/14 (2 months after partial resection)
- CT 4/21/14: No progression of right liver disease
- 4/21/14: Right hepatectomy, seg IV resection
- Pathology: focal residual met adenoca in seg IV, minimal residual CA in right hepatectomy
- Post-op chemo: 5-FU (per OPTIMOX), CEA 1.0

- July 2014, 15 months since diagnosis, 8 months from surgery #1, 3 months from surgery #2.
- CEA 1.0
- Chemotherapy plan: Watch and wait
Stage 4 CRCA Surgery

• Is the disease resectable?
• If incurable, how to palliate?
• The asymptomatic primary can often be left alone
• Non-surgical interventional procedures are helpful
• Liver and Extra-hepatic mets may be curable
• Even carcinomatosis can benefit from aggressive approach
• It’s often complicated. The multi-d approach is an asset