COLORECTAL CANCER WITH SYNCHRONOUS LIVER METASTASES
Case presentation

- 46 yo male without significant PMH/PSH
- Presented in LICH ER with c/o mid/lower abdominal pain
- Pain was described as intermittent, dull, cramping for 2-3 weeks
- Associated symptoms – abdominal bloating and constipation
- Denied any constitutional symptoms or rectal bleeding
Case presentation

- PE - unremarkable beside mild abdominal tenderness and mild distention.
- Labs – WNL
- FOB positive
Case presentation
Case presentation
Case presentation
Case presentation

- Colonoscopy – non obstructive, friable, fungating, irregular, ulcerative mass at 13-18 cm from anal verge
- Biopsy – moderate to poorly differentiated adenoCa.
- CT-PET scan:
  - Rectosigmoid mass with robust metabolic activity and max SUV 15.9
  - Presacral LNs, max size 1.4 cm, max SUV 6.7
  - Liver – Rt and Lt lobe mets, cluster of mets in Lt. lobe, max SUV 16.7
Case presentation
Case presentation

- Patient underwent course of neoadjuvant chemotherapy – FOLFOX with Bevacizumab
- CT-PET scan at 4/2010
  - Decreased in size and metabolic activity of rectal mass
  - Decreased in size and number presacral LNs, no previous metabolic activity of LNs.
  - Liver
    - rt lobe no previous metabolic activity
    - lt lobe decreased metabolic activity
  - Chest – new metastatic lymphadenopathy in the left internal mammary chain
Case presentation
Case presentation

- Patient underwent Chamberlain procedure with removal in Lt Int mammary mass
- Pathology – metastatic colon ca
- Patient continued chemotherapy FOLFIRI plus Bevacizumeb.
- Restaging CT-PET scan at Nov 2010:
  - No abnormal metabolism in the rectosigmoid
  - No abnormal metabolism in LNs
  - Liver – decreased in size mets with no significant changes in metabolic activity
  - Chest – no metabolic activity
- Colonoscopy Nov 2010- erythematous mucosa at 15 cm, tattoo performed, biopsy showed no malignant tissue.
On Dec 6, 2010 patient underwent

- Diagnostic laparoscopy – no evidence of carcinomatosis, known liver mets.
- Left total hepatectomy (segments 1/2/3/4) and wedge resection of segment 8.
- Low anterior resection of rectosigmoid colon with colorectal stapled (EEA) anastomosis

Postoperative course was uncomplicated
Case presentation

Pathology:

- Rectum – moderately differentiated mucin producing adeno ca, T2, N2 (5 out of 18), M1. Distal (2.4 cm) and radial margin are negative.

- Liver
  - Left lobe, metastatic mucin producing ca, margins are negative.
  - Rt lobe wedge resection – metastatic ca, the closest margin 1 mm.
Case presentation
Colorectal cancer

- 3rd most common site of new cancer
- 3rd most common cause of cancer related death
- Lifetime risk for colorectal Ca in US:
  - 5.79% for men
  - 5.37% for women
- 150,000 new cases / year
- 40,000 deaths / year in US
15-20% patients with colorectal ca have synchronous liver metastases

Only 25% of liver mets are resectable

Median overall survival is 12 months without treatment

The only potential curative treatment is removal of primary tumor and liver metastases, reported 5y survival 35-58%
Treatment of colorectal Ca has changed significantly during past 20 years

It is multimodal:

- Surgery – is the only treatment for cure
- Radiation – local control and local downstaging
- Chemotherapy- systemic disease(+LN/mets)
  - 5FU/Leucovorin/Irinotecan – FOLFIRI
  - 5FU/Leucovorin/Oxaliplatin - FOLFOX
- Targeted therapy
  - VEGF monoclonal Ab (Bevacizumab)
  - EGFR monoclonal Ab (Cetuximab)
WHAT IS IDEAL TIME OF EACH MODALITY WITH RELATION TO THE OTHER
Colorectal ca with synchronous liver metastases

**General treatment strategy influenced by:**

- Symptoms pattern of primary tumor
  - Obstructive
  - Bleeding
  - Perforation
  - Locally advanced

- Potential resectability of liver metastases
  - Ready resectable metastatic disease
  - Non resectable but potentially resectable after chemo
  - Unlikely resectable after chemo
Current treatment practice

- Resectable liver mets –
  - Surgery for primary source with simultaneous or staged liver resection
  - Adjuvant CTx

- Unresectable liver mets
  - Neoadjuvant CTx
  - Surgery for primary source if patient responded well
  - Hepatectomy - simultaneous or staged
  - Adjuvant CTx
Respectability criteria

- Varies in different centers and surgical groups

Traditional factors of unresectability:

- 4 or > metastases
- Bilobar metastases
- Extrahepatic metastatic disease
- Large size of hepatic disease, > 5 cm
- Inability to achieve margin a resection at least 1 cm
New paradigm of Resectability \(^{(10)}\)

1. An R0 resection of both the intra- and extra hepatic disease sites must be feasible.

2. At least two adjacent liver segments need to be spared.

3. Vascular inflow and outflow, as well as biliary drainage to the remaining segments, must be preserved.

4. The volume of the future liver remnant must be adequate
   - At least 20% of the total estimated liver volume for normal parenchyma,
   - 30%–60% if the liver is injured by chemotherapy- steatosis, or hepatitis
   - 40%–70% in the presence of cirrhosis, depending on the degree of underlying hepatic dysfunction.
New paradigm of Resectability

<table>
<thead>
<tr>
<th>OLD</th>
<th>NEW</th>
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<tbody>
<tr>
<td>By what is REMOVED</td>
<td>By what REMAINS</td>
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<tr>
<td>Number of metastases</td>
<td>• R0 resection</td>
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<tr>
<td>Size of metastases</td>
<td>• Adequate remnant liver</td>
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<td>Extrahepatic disease</td>
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Liver resection appropriate whenever feasible and potentially curative irrespective to prognostic factors
Neoadjuvant RTx/CTx for Locally Advanced Rectal Ca

- Recommended for stage >II rectal Ca (T3-4), or +LN

- Preoperative RTx combined with CTx is superior to postoperative, improve local control (local failure 8% vs 13%), decreased toxicity, increase rate of sphincter preserving surgery but no impact on survival \(^{(1)}\) \(^{(3)}\)

- USA: Long course of 40-50 Gy during 5 weeks combine with chemo by 5FU/leucovorin (chemo usually given during first and last week of RTx)

- Europe/Canada – Short course 25 Gy in 1 week without chemo to any stage \(^{(4)}\)
Potential advantage of neoadjuval CTx:

- Increase complete resection rate
- Downstaging of primary and metastatic process
  - Liver mets downstatging 50-70%
  - Primary Tu – complete pathological response 15-20%
- Convert unresectable liver meta to resectable
- Facilitate limited liver resection
- Treat micrometastases
- Test of chemoresponsiveness
- Identify aggressive diseases
Colorectal ca with synchronous liver metastases

- Potential disadvantage of neoadjuval CTX:
  - Oxaliplatin based CTX – vascular lesions:
    - Sinusoidal lesions – M&M are not increased
    - Hemorrhagic centrilobular necrosis and regenerative nodular hyperplasia - increased morbidity (intraop bleeding, transfusion requirement, infection rate) but not mortality
Potential disadvantage of neoadjuval CTx

- **Irinotecan** based CTx- non alcoholic steatohepatitis – NASH
  - ?Increase 90 days mortality due to liver failure (5)

- **Bevacizumab**
  - May increase vascular lesions
  - Decrease regenerative ability of liver (antiangiogenic effect)
Colorectal ca with synchronous liver metastases

- CTx related morbidity depended on # of CTx cycles.

- Surgery should be considered after 4-6 cycles of CTx based on restaging imaging

- Bevacizumab break 5-6 weeks before surgery
Locally Advanced Rectal Ca with synchronous liver metastases

Low volume Liver mets:
1. Neoadjuvant chemoRTx
2. Staged or simultaneous resection of primary and liver mets
3. Adjuvant CTx

Low volume Liver mets:
1. Liver directed neoadjuvant CTx
2. Staged or simultaneous resection of primary and liver mets
3. Adjuvant CTx with or without RTx
Synchronous resectable liver metastases

- Special subgroup which probably has favorable tumor biology
- EORTC 40983 study compared pre- and post-operative chemotherapy
  - Progress Free Survival at 3 years increased by 8.1 %
- Expert panel recommends Neoadjuvant chemotherapy (Annals of Oncology June 2009) (2)
Colorectal ca with synchronous liver metastases

**Staged vs Simultaneous surgery**

- Simultaneous surgery recommended for minimal liver resections – less then lobectomy
- Simultaneous major liver resection (lobectomy or more) increases postop M&M
- Staged surgery – primary lesion then liver resection in 4-6 weeks if major liver resection needed
- Experienced selected surgical groups report similar M&M for simultaneous vs staged surgery (9)

[www.downstatesurgery.org](http://www.downstatesurgery.org)
Colorectal ca with synchronous liver metastases

Adjuvant CTx after liver resection

- Ro resection + observation vs Ro resection + 5FU/LV (6)
  - 5 y disease free survival 27% vs 34%
  - Statistically not significant difference
  - Multivariate analysis showed positive effect of CTx with trend to increased overall survival and progression free survival
Colorectal ca with synchronous liver metastases

Adjuvant CTx after liver resection

- Ro resection+postop 5FU/LV vs Ro resection +postop FOLFIRI (8)
  - 1 y survival 51% and 77%
  - 2 y survival 46% and 63%
  - Median disease free survival 21.6 vs 24.7 months
Colorectal ca with synchronous liver metastases

- Current data about CTx effectiveness
  - FOLFIRI or FOLFOX in combination of Bevacizumab or Cetuximab or both is equally effective
  - Cetuximab is effective for tumor bearing Wild type of K-ras gene (7)

- Ongoing studies - triple chemotoxic agents
  - FOLFOXIRI + Bevacizumab or Cetuximab
    - Response rate 85%, resection rate 75%
Colorectal ca with synchronous liver metastases

- Ongoing studies
  - New targeted agents
    - Sunitimab (Gleevec) – oral multitargeted Tyrosine kinase inhibitor, targets:
      - VEGF receptors
      - PDGFR receptors (platelets-derived growth factor receptors)
Colorectal ca with synchronous liver metastases

Liver metastases

Resectable

- Neoad. Comb. chemo
- Liver resection

Not optimally resectable

- Oncological (> 1 factor)
- >4 Metastases
- Size >5cm
- Synchronous CRCLM
- Primary LN-positive
- Positive tumor marker

- Technically difficult:
  - Close to all hepatic veins
  - Close to both portal branches

Neoadjuvant chemotherapy +/- biologics

Liver resection if sufficient response

Unresectable and never likely to be resectable

Palliative chemotherapy +/- biologics
Summary

- Presence of liver mets at initial Dx of Rectal Ca is difficult dilemma
- Patients are extremely heterogeneous
- Each patient must be highly individualized
- Treatment must be directed for POTENTIAL CURE
- Multidisciplinary team
- Neoadjuvant CTx recommended even in case of resectable liver mets
  - Exclusion could be isolated solitary mets < 2cm with favorable location
- Simultaneous surgery for liver metastases and primary tumor may have place in experienced hands
- Most patient should receive postop adjuvant CTx
8. Randomized phase III trial comparing infused 5-fluorouracil/folinic acid (LF5FU) versus LV5FU + irinotecan (LV5FU + iri) as adjuvant treatment after complete resection of liver metastases from colorectal cancer (LMCRC). (CPT-GMA-301). J Clin Oncol 2008; 26