Chemotherapy for Colorectal Cancer: What you need to know

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SON Fall Update
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Objectives

- Adjuvant Chemotherapy
  - Benefit, Options, Timing

- Therapy for Advanced CRC – mCRC
  - Benefit, Surgical Implications
Evolution of Adjuvant Therapy

1990  5-FU/Levamisole better than observation.
1994  5-FU/LV better than surgery alone.
1998  5-FU/LV better than 5-FU/Levamisole.
1998  6 months = 12 months.
2003  5-FU/LV plus Oxaliplatin better than 5-FU/LV (FOLFOX)
2012  Is 3 months of FOLFOX enough? 3 vs 6 months

Not Effective
Irinotecan, Bevacizumab (Anti-VEGF), Cetuximab (Anti-EGFR)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Recurrence</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Fluoropyrimidine</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>FOLFOX</td>
<td>55%</td>
</tr>
<tr>
<td>II</td>
<td>Fluoropyrimidine</td>
<td>20%</td>
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<tr>
<td></td>
<td>FOLFOX</td>
<td>Not Proven</td>
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</table>
Standard of Care in Curable CRC

- Adjuvant chemotherapy (AC) is recommended after curative surgical resection of:
  - Stage III colon and rectal cancer
  - Stage II rectal cancer
  - Stage II colon cancer with high-risk features
Clinical Assumptions

1. Chemotherapy should commence as soon as practical after surgical resection

2. Chemotherapy begin ≤ 3 months of surgery, beyond which time the benefit uncertain
Delay to Start Adjuvant Chemotherapy

In general, two factors that result in delays:

- Patient - post-op complications / recovery
- Logistics - institutional delays / inefficiencies
Cochrane $\chi^2$ test showed no evidence of heterogeneity (p-value= 0.2629), justifying fixed-effect model

Biagi et al JAMA 2011
For a 65 year old male, good general health, T3N2 mod/diff. colon cancer treated with 5FU-based chemo.

- ~60% survival at 5 years with AC
- ~45% survival if no chemotherapy

Assuming this estimate depends on TTAC of 4 weeks.

- ~55% survival at 5 years with delay to 8 weeks
- ~50% survival at 5 years with delay to 12 weeks
Message

- Adjuvant chemotherapy for:
  - Node Positive Colon
  - Node Negative and Positive Rectal
  - Some T3/T4 Node Negative Colon – pls. refer

- Begin therapy within 2 months of surgery
- Please refer ASAP
Metastatic Disease

- 1995 – 1 agents
- 2012 – 6 agents
- Much more complex now:

Unresectable

15%

65%

15%

20%

Resectable Liver/Lung Mets

Potentially Resectable
Median OS of mCRC on clinical trials


Best supportive care (BSC)
5-FU

Irinotecan
Capecitabine
Oxaliplatin
Cetuximab
Bevacizumab
Panitumumab

OS (months)

median overall survival

0 5 10 15 20 25 30
What happens to BCCA patients?

Median overall survival

H Lim JOP 2009, D Renouf Clin Colon Cancer 2009, M Ho Submitted to ASCO 2013
% BCCA who received any chemotherapy


5-FU  Irinotecan  Oxaliplatin  Bevacizumab  Anti-EGFR

% Patients Receiving Any Systemic Therapy
Chemo Considerations

* Not observed after $\leq 6$ cycles
Steatosis and Steatohepatitis: Irinotecan
Sinusoidal Obstruction: Oxaliplatin
Potentially Resectable MCRC

- 62-year-old female elementary school teacher presented with increased abdominal girth and malaise for several months
- No change in bowel habit
- Liver enlarged
- ECOG 1
- Mild hypertension
Investigations

- **Labs**
  - CBC: normal
  - LDH: 2000 IU/L
  - AST: 250 U/L
  - ALP: 256 U/L
  - CEA: 550 ng/mL
  - Bilirubin: N
  - ALT: 200 U/L

- **CT Scan** – Cecal mass, bulky liver mets

- **PET Scan** – Liver mets, no extra-hepatic disease
Peri-operative FOLFOX4 chemotherapy and surgery for resectable liver metastases from colorectal cancer

Long-term survival results of the EORTC Intergroup phase III study 40983.


For the EORTC GI Group, CR UK, ALMCAO, AGITG and FFCD
**Aim and design**

Demonstrate that chemotherapy combined with surgery is a better treatment than surgery alone

- **Randomize**
  - Surgery
  - FOLFOX4 (6 cycles, 3 months)
  - Surgery
  - FOLFOX4 (6 cycles, 3 months)

**Main Eligibility criteria**
- Potentially resectable liver metastases of colorectal cancer
- Up to 4 deposits (on CT-scan, at randomization)

**N=364 patients**
Progression-free survival in eligible patients


HR = 0.77; CI: 0.60-1.00, p = 0.041

LV5FU + Oxaliplatin Periop CT

+8.1%
At 3 years

Surgery only

36.2%
28.1%

Number of patients at risk:

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<th>Year</th>
<th>Surgery</th>
<th>Pre&amp;Postop CT</th>
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EORTC
European Organisation for Research and Treatment of Cancer
Overall survival in eligible patients

HR = 0.87; CI: 0.66 - 1.14, p = 0.303

LV5FU + Oxaliplatin
Periop CT

52.4%
48.3%

+8.7 months in median OS
+4.1%
At 5 years

Number of patients at risk:

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
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<td>Pre&amp;Postop CT</td>
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<tr>
<td>12</td>
<td>69,55M</td>
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</table>

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Messages

- Most patients eligible for palliative chemo
- Palliative chemo increases survival
- Patients with “liver or lung only” mCRC should be considered for surgical resection and chemotherapy.