Chemotherapy of colon cancers
Stage distribution

Stage I: 15% T1, 2 NO

Stage II: 20–30% T3, 4 NO

Stage III N+: 30–40%

Stage IV: 20–25% M+
clinical stages I, II, or III colon cancer are at risk for having occult stage IV disease.

The goal of chemotherapy in colorectal cancer is eradication of any residual micro metastatic disease.
Indications of CTX in colon cancer

- **Stage I**: No indicated
- **Stage II**: Only in high risk patients
- **Stage III**: All patients
- **Stage IV**: Palliation, Salvage
Stage II High risk patients

- 18q deletion
- Poorly differentiated histology
- High levels microsatellite instability
- Obstruction and perforation
- ↑ SPF
- ↑ CEA
Common chemotherapy regimens for adjuvant setting in colorectal cancers
Levamisole is an antihelminthic that is widely used in veterinary medicine.
Levamisole was extensively investigated as an anticancer agent. The results of the majority of these trials were negative.
LV is a modulator of 5FU.

The NSABP C-03 trial randomized 1,081 Dukes B and C patients to 1 year of treatment with either the MOF regimen or 5-FU plus LV.

<table>
<thead>
<tr>
<th></th>
<th>3year OS</th>
<th>3 year DFS</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU</td>
<td>84%</td>
<td>73%</td>
<td>↓</td>
</tr>
<tr>
<td>MOF</td>
<td>77%</td>
<td>64%</td>
<td>↑</td>
</tr>
</tbody>
</table>
**Myo clinic schedule:**
5FU : 425 mg / m2 on days 1-5
LV : 20 mg / m2 on days 1-5 before administration of 5FU
Repeat cycle every 4-5 weeks for a total of 6 cycle

**Weekly schedule (high dose)**
5FU : 500 mg / m2 weekly for 6 week
LV : 500 mg / m2 on 2 hour weekly for 6 week before administration of 5FU
Repeat cycle every 8 weeks for a total of 4-6 cycle

**Weekly schedule (low dose)**
5FU : 500 mg / m2 weekly for 6 week
LV : 20 mg / m2 on 2 hour weekly for 6 week before administration of 5FU
Repeat cycle every 8 weeks for a total of 4-6 cycle

**Different Schedules Of 5FU + LV regimens**
Outcome
Daily = weekly

Toxicity
Daily > weekly
Fluorouracil Plus Alfa Interferon

the NSABP C-05 trial randomized 2,176 Dukes B and C patients to receive 5-FU/leucovorin with or without al IFN

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>DFS</th>
<th>TOXICITY</th>
</tr>
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<tbody>
<tr>
<td>5FU + LV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU +LV + αIFN</td>
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Thus, there is no role for the use of alfaIFN in the adjuvant treatment of colon cancer.
Oral administration of 5-FU proved to be problematic secondary to erratic bioavailability. Dihydro pyrimidine dehydrogenase (DPD) have important role in this problem. Two oral 5-FU prodrugs, capecitabine and uracil / tegafur (UFT), have demonstrated efficacy in metastatic disease that is comparable to the Mayo clinic schedule of parenteral 5-FU/leucovorin. Both of these agents have now been studied in the adjuvant setting in comparison to Mayo Clinic 5-FU.
Twelves et al randomly assigned 1,987 resected stage III colon cancer patients to receive either oral capecitabine or Mayo Clinic bolus 5-FU plus leucovorin. This trial demonstrates that capecitabine is a reasonable alternative to intravenous 5-FU plus leucovorin in the adjuvant treatment of colon cancer.

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>RFS</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYO clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>xeloda</td>
<td></td>
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</tbody>
</table>

- this trial demonstrates that capecitabine is a reasonable alternative to intravenous 5-FU plus leucovorin in the adjuvant treatment of colon cancer.
• The NSABP C-06 trial randomly assigned to receive either oral UFT plus leucovorin or intravenous 5-FU plus leucovorin.

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>OS</th>
<th>TOXICITY &amp; QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFT+ LV</td>
<td>![Arrows]</td>
<td>![Arrows]</td>
<td>![Arrows]</td>
</tr>
<tr>
<td>5FU+LV</td>
<td>![Arrows]</td>
<td>![Arrows]</td>
<td>![Arrows]</td>
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</tbody>
</table>

• **Oral UFT+LV is an acceptable alternative to parenteral 5-FU/ leucovorin**

• **use of oral fluoropyrimidine plus leucovorin alone is no longer routine standard practice**
Capecitabine:
- 1250 mg/m² PO bid on days 1-14
- Repeat cycle every 21 days for total 8 cycle
- Dose may be decreased to 850-1000 mg/m² for reduced toxicity
Oxaliplatin Combination Therapies
Clinical trials evaluated (5FU + LV) VERSUS (Oxaliplatin + 5FU + LV)

<table>
<thead>
<tr>
<th></th>
<th>3 year DFS</th>
<th>OS</th>
<th>toxicity</th>
<th>Mortality In 60 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU + LV</td>
<td>66%</td>
<td>No published</td>
<td>lesser</td>
<td>Same</td>
</tr>
<tr>
<td>5FU + LV + Oxaliplatin</td>
<td>72%</td>
<td>No published</td>
<td>Greater but manageable</td>
<td>same</td>
</tr>
</tbody>
</table>

**Oxaliplatin combined therapies is an important regimen in metastatic and adjuvant setting**
Different schedules of combination of (Oxali + LV + 5FU)

**FOLFOX4:**
- **Oxaliplatin:** 85 mg/m² IV on day 1
- 5FU: 400 mg/m² IV bolus + 600 mg/m² continuous inf. For 22 hour on days 1-2
- LV: 200 mg/m² IV on days 1, 2 two hour before 5FU infusion.
- Repeat cycle every 2 weeks for total 12 cycle

**mfolfox7:**
- **Oxaliplatin:** 100 mg/m² IV on day 1
- 5FU: 3000 mg/m² IV continuous infusion on days 1, 2 for 46 hour
- LV: 200 mg/m² IV on days 1 two hour before 5FU infusion.
- Repeat cycle every 2 weeks
Common chemotherapy regimens for metastatic setting in colorectal cancers
This agent has important role in the metastatic disease.

In the adjuvant setting this agent has elevation of early mortality rate.
Different schedules of **Irinotecan** combination

**IFL saltz regimen:**
Irinotecan: 125 mg/m² IV over 90 min weekly for 4 week
5FU: 500 mg/m² IV weekly for 4 week
LV: 20 mg/m² IV weekly for 4 week
Repeat weekly every 6 weeks

**IFL saltz regimen + bevacizumab:**
Irinotecan: 125 mg/m² IV over 90 min weekly for 4 week
5FU: 500 mg/m² IV weekly for 4 week
LV: 20 mg/m² IV weekly for 4 week
Bevacizumab: 5mg/kg IV every 2 weeks
Repeat weekly every 6 weeks
Modofide IFL saltz regimen:
Irinotecan: 125 mg/m² IV over 90 min weekly for 2 week
5FU: 500 mg/m² IV weekly for 2 week
LV: 20 mg/m² IV weekly for 2 week
Repeat weekly every 3 weeks

Douillard regimen:
Irinotecan: 180 mg/m² IV on day 1
5FU: 400 mg/m² IV bolus + 600 mg/m² continuous inf. For 22 hour on days 1-2
LV: 200 mg/m² IV on days 1,2 two hour before 5FU infusion.
Repeat cycle every 2 weeks

FOLFIRI regimen:
Irinotecan: 180 mg/m² IV on day 1
5FU: 400 mg/m² IV bolus on day 1 + 2400 mg/m² continuous inf. For 46 hour on days 1-2
LV: 200 mg/m² IV on days 1 two hour before 5FU infusion.
Repeat cycle every 2 weeks
Other regimens used for metastatic disease

- FOLFOX4 +/- bevacizumab
- FOLFOX6
- FOLFOX7
- Mfolfox7
- FOLFOXIRI
- Cetuximab + Irinotecan
- XELOX +/- bevacizumab
- XELIRI
- IROX
- Myo clinic schedule
- 5FU + LV + bevacizumab
**Bevacizumab (Avestin)**

- Bevacizumab (bev) is a humanized **monoclonal antibody** that binds to **Vascular Endothelial Growth Factor**, 
- The first trial of bev in colorectal cancer was a modest-sized, three-arm, randomized phase II trial

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>TTP</th>
<th>OS</th>
<th>TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU +LV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU+LV+</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5mg/kg bev</td>
<td><img src="up.png" alt="up" /></td>
<td><img src="up.png" alt="up" /></td>
<td><img src="up.png" alt="up" /></td>
<td></td>
</tr>
<tr>
<td>5FU+LV+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10mg/kg bev</td>
<td><img src="up.png" alt="up" /></td>
<td><img src="up.png" alt="up" /></td>
<td><img src="up.png" alt="up" /></td>
<td>thrombosis</td>
</tr>
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- RR: Response Rate  
- TTP: Time to Progression  
- OS: Overall Survival  
- TOXICITY: Adverse Effects
• ECOG also performed a trial (ECOG 3200) to evaluate the use of bevacizumab in the second-line setting:

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>toxicity</th>
<th>PFS</th>
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</thead>
<tbody>
<tr>
<td>Bevacizumab+ FOLFOX</td>
<td>![arrow up]</td>
<td>![arrow unchanged]</td>
<td></td>
</tr>
<tr>
<td>FOLFOX4</td>
<td></td>
<td>![arrow unchanged]</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
<td>![arrow unchanged]</td>
<td>![arrow down]</td>
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</tbody>
</table>
• Several other studies have now been reported that demonstrate the activity of bev in conjunction with chemotherapy in colorectal cancer.

• use of greater than a 5 mg/kg dose of bev in first-line colorectal cancer treatment at this time.

• single-agent bev does not have meaningful activity in colorectal cancer and should not be used
Cetuximab (Erbitux)

- Cetuximab is a chimeric monoclonal immunoglobulin G1 antibody that recognizes and binds to the extracellular EGFR.

- EGFR regulates cell proliferation, migration, adhesion, differentiation, and survival.

- Preclinical models of cetuximab, or its murine precursor, have demonstrated only modest in vitro and in vivo single-agent activity against a variety of malignancies, but have shown substantial activity when given in combination with cytotoxic chemotherapy.

- The role of cetuximab in first-line therapy remains investigational at the time of this writing.
Investigational Adjuvant Approaches
Portal Vein Infusion

- Liver is the most common extra regional site of metastases.
- Large, established hepatic metastases derive their blood supply primarily from the hepatic artery. However, tumors less than 5 mm in diameter obtain substantial portions of their blood supply from both the hepatic and portal circulations.
- Higher doses of 5-FU can be safely given by intraportal than by intravenous infusion.
- The NSABP C-02 trial randomized 1,158 patients with Dukes A, B, or C colon cancers to either a 7-day portal vein infusion of 5-FU (600 mg/m²/day) or to surgery alone.

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>Hepatic recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal vein inf. Of 5FU + Surgery</td>
<td>74%</td>
<td>Same</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>64%</td>
<td>same</td>
</tr>
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</table>
Intraperitoneal Chemotherapy

- The peritoneal cavity is drained by portal lymphatics into the **portal vein**

- Intraperitoneal chemotherapy therefore delivers **high concentrations** of drug to the portal circulation, without the need for portal vein canalization.

- The high first-pass hepatic clearances of floxuridine ([FUDR](#)) and **5-FU** make these drugs good agents for intraperitoneal administration.
Edrecolomab

- a murine monoclonal IgG2a antibody directed against the cell surface glycoprotein 17-1A.

- Show to inhibit growth of human colon cancer.

- Total of 166 patients were randomized to edrecolomab at a dose of 500 mg by 1-hour infusion 2 weeks after surgery, and then 100 mg during 1 hour given every 4 weeks for four doses, or to surgery only.

- This small trial showed a 32% reduction in mortality for the edrecolomab arm at a median follow-up of 7 years.

- This encouraging preliminary finding, however, was not supported by a larger confirmatory trial, in which 2,761 patients with stage III colon cancer were randomized to 5-FU/leucovorin (Mayo Clinic schedule) plus edrecolomab, 5-FU/leucovorin alone.
Vaccines

• anti-idiotypic monoclonal antibody vaccine that mimics CEA

• canarypox virus (ALVAC)
Complications of chemotherapy
5FU

- B.M. suppression
- Mucositis
- Diarrhea
- Hand foot syndrome
- Neurotoxicity
- Photosensitivity
- Nausea
- Vomiting
Xeloda

- Diarrhea
- Hand foot syndrome
Irinotecan

• Neutropenia
• Delayed onset diarrhea
• Cholinergic syndrome (early onset diarrhea)
Oxaliplatinine

- Neurotoxicity
- Paresthesia
- Dysesthesia of pharynolaryngeal
BEVACIZUMAB

- Hypertension
- Thromboembolic events
- Proteinuria
- GI perforations (1.4-2%; Mortality 0.4-1%)
- Arterial thrombotic events
Cetuximab

- Acne like rash (75% to 100%)
- Hypomagnesemia
Main objectives of neoadjuvant chemoradiation in rectal cancer

- 1) To convert unresectable tumor to resectable
- 2) Sphincter preservation
Indications

• Patients who potentially need adjuvant therapy
• Locally advanced and unresectable (T4), N+, T3N0(?). (RT or Chemo are not sufficient salvages for R+)
• Low lying tumors
• Unable to undergo a local full thickness excision
• Surgeon office assessment is accurate
Advantages

• Increase resectability (R0 Surgery)
• Potentially increase sphincter preservation
• Increase local control
• Facilitate subsequent surgery
• No increase in overall morbidity and mortality of surgery
• Equivalent and even increased overall survival
• Assessment of response to CT and RT
• CT+RT is widely accepted
Advantages of CT+RT

. Higher downstaging

. Higher pathological complete response

. An improvement in OS (American trials)
Technical aspects

- Conventional dose and techniques of radiotherapy 45-50Gy/25-28f
- 5FU based +/- Platinum based concurrent chemotherapy
- Intense short course RT (25Gy/5f) and surgery 1 week later, is unacceptable