Current adjuvant treatment options for colon cancer

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Conclusions: For every day practice

Adjuvante Chemotherapy is indicated in stage III (N+)

- Capecitabine or (inf.) FU/LV are options for all patients
- FOLFOX / CapeOx is an option for patients < 70y

Biologicals are no therapeutic option

The decision for adjuvant therapy has to balances the risk of cancer and other competing risks
Conclusions: Good to know

• Correlation between 3y DFS on 5Y OS for 5-FU and Oxaliplation/Irinotecan based adjuvant chemotherapy
• FOLFIRI was not negative but not as positive as FOLFOX in stage III colon cancer
• No real stage migration in UICC stage III colon cancer over decades
• Younger patients (<40y or <50y) also benefit from adjuvant chemotherapy
• Most relapses occur within 2 years after adjuvant therapy
• Long term neuropathy after oxaliplation, seldom fully reversible
Primary tumor (T)

- **T₂** Tumor invades muscularis propria
- **T₃** Tumor invades through muscularis propria or subserosa
- **T₄** Tumor directly invades other organs or structures

**T₄a** = Tumor penetrates to the surface of the visceral peritoneum.

**T₄b** = Tumor directly invades or is adherent to other organs or structures.

Regional lymph nodes (N)

- **N₀** No regional lymph node metastases
- **N₁** Metastases in 1–3 regional lymph nodes
  - **N₁a** = Metastases in 1 regional lymph node
  - **N₁c** = Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N₂** Metastases in 4 or more regional lymph nodes
  - **N₂a** = Metastases in 4–6 regional lymph nodes.
  - **N₂b** = Metastases in ≥7 regional lymph nodes.

Distant metastases (M)

- **M₀** No distant metastases
- **M₁** Distant metastases

**M₁a** = Metastasis confined to 1 organ or site (e.g., liver, lung, ovary, nonregional node).

**M₁b** = Metastases in >1 organ/site or the peritoneum.
AJCC v7

Stage II

Stage III

T3N0  T4aN0  T4bN0  T1-2N1a  T1-2N1b  T3N1a  T3N1b  T3N2a  T3N2b  T4aN2a  T4bN1a  T4bN1b  T4bN2a  T4aN2b  T4bN2b

Gunderson et al, JCO 2009
5FU Increases OS and Cure in Stage III colon cancer patients
Evidence in 13,793 Patients with Stage III

Moertel et al. NEJM 1990

Sargent D, J Clin Oncol 2009
X-ACT: Superior Relapse-free Survival (ITT)

Estimated probability

<table>
<thead>
<tr>
<th>Years</th>
<th>Capecitabine (n=1004)</th>
<th>5-FU/LV (n=983)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>6</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

HR = 0.86 (95% CI: 0.74–0.99)
p = 0.0407

Cassidy ASCO 2004
Stage III  
X-ACT: Overall Survival  
Capecitabine vs. 5-FU/FA

Estimated probability

Years

HR = 0.84 (95% CI: 0.69–1.01)  
p=0.07

3-year

Capecitabine (n=1004) 81.3%

5-FU/LV (n=983) 77.6%

Cape 2500mg/m² d1-14
Dose modifications in ~60% of patients

Twelves et al. NEJM 2005
3 Year DFS vs 5 Year OS
Individual patient data from 20,898 patients on 18 randomized trials

Regression equation:
5 yr OS = -0.05 + 1.07 * 3 yr DFS
Coefficients not significantly different from 0 and 1
Correlation 0.94, R^2 = 0.88

Sargent et al. JCO 2005
Predicted vs. Actual overall survival

Sargent et al. JCO 2005
Correlation PFS and OS for metastatic CRC

**PFS and OS**

Surrogate End Points for Median Overall Survival in Metastatic Colorectal Cancer: Literature-Based Analysis From 39 Randomized Controlled Trials of First-Line Chemotherapy

Patricia A. Tang, Soren M. Bentzen, Eric X. Chen, and Lillian L. Siu

**Fig 1.** Correlation between median progression-free survival and median overall survival. FU, fluorouracil; LV, leucovorin.
MOSAIK Study   Survival: Stage III
infusional 5-FU/FA vs. FOLFOX

Data cut-off: January 2007

Overall survival (months)

Probability

HR [95% CI]
Stage III 0.80 [0.66–0.98]

FOLFOX4 stage III
LV5FU2 stage III

p=0.029

4.4%

De Gramont et al. ASCO 2007
## Fluoropyrimidines ± Oxaliplatin Stage III

<table>
<thead>
<tr>
<th></th>
<th>HR for DFS</th>
<th>P value</th>
<th>DFS ∆ (%)</th>
<th>HR for OS</th>
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<th>OS ∆ (%)</th>
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<tbody>
<tr>
<td><strong>MOSAIC (FOLFOX)</strong></td>
<td>0.78</td>
<td>0.005</td>
<td>∆ 7.5%</td>
<td>0.80</td>
<td>0.023</td>
<td>∆ 4.2%</td>
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<tr>
<td></td>
<td>Cl, 0.65-0.93 @ 5 year</td>
<td></td>
<td>58.9% vs 66.4% @ 5 year</td>
<td>Cl, 0.65-0.97 @ 6 year</td>
<td></td>
<td>68.7% vs 72.9% @ 6 year</td>
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<td><strong>NSABP C-07 (FLOX)</strong></td>
<td>0.78</td>
<td>0.0007</td>
<td>∆ 6.6%</td>
<td>0.85</td>
<td>0.052</td>
<td>∆ 2.7%</td>
</tr>
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<td>Cl, 0.68-0.90 @ 5 year</td>
<td></td>
<td>57.8% vs 64.4% @ 5 year</td>
<td>Cl, 0.72-1.00 @ 5 year</td>
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<td>73.8% vs 76.5% @ 5 year</td>
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<td><strong>XELOXA (XELOX)</strong></td>
<td>0.80</td>
<td>0.0045</td>
<td>∆ 4.4%</td>
<td>0.87</td>
<td>0.1486</td>
<td>∆ 3.4%</td>
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<td>Cl, 0.69-0.93 @ 3 year</td>
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<td>66.5% vs 70.9% @ 3 year</td>
<td>Cl, 0.72-1.05 @ 5 year</td>
<td></td>
<td>ND (57 months FU)</td>
</tr>
</tbody>
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1 André T, J Clin Oncol 2009
2 Yothers G, J Clin Oncol 2011
3 Haller D, J Clin Oncol 2011
### Fluoropyrimidines ± Oxaliplatin Stage III

<table>
<thead>
<tr>
<th>Study</th>
<th>HR for DFS</th>
<th>P value</th>
<th>DFS $\Delta$ (%)</th>
<th>HR for OS</th>
<th>P value</th>
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<td>0.1486</td>
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<td><strong>X-ACT FU/FA bolus vs. Capecitabine</strong></td>
<td>0.87</td>
<td>0.0528</td>
<td>$\Delta$ 3.6% 60.6% vs 64.2% @ 3y</td>
<td>0.84</td>
<td>p=0.07</td>
<td>$\Delta$ 3.7% 77.6% vs 81.3% @3y</td>
</tr>
</tbody>
</table>

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1 André T, J Clin Oncol. 2009  
2 Yothers G, J Clin Oncol 2011  
3 Haller D, J Clin Oncol 2011
**Adjuvant treatment with irinotecan**

- **Negative experience (?) -**

<table>
<thead>
<tr>
<th>Author</th>
<th>Saltz et al.</th>
<th>Van Cutsem et al.</th>
<th>Ychou et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>CALGB</td>
<td>PETACC 3</td>
<td>FNCLCC/FFCD</td>
</tr>
<tr>
<td>Regimen</td>
<td>FU/FA vs. IFL</td>
<td>LV5FU2 vs. FOLFIRI</td>
<td>LV5FU2 vs. FOLFIRI</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Survival</td>
<td>DFS</td>
<td>DFS</td>
</tr>
<tr>
<td>Toxicity</td>
<td>&gt; IFL</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
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**Graphs and figures**

1. **Overall Survival by Arm**
   - Overall survival for all patients.
   - Comparison between 5-FU/LV and CPT-11/5-FU/LV.
   - Significance level: *p* = 0.01.

2. **DFS - Stage III**
   - Disease-free survival for Stage III patients.
   - Comparison between IFL vs. others.
   - Significance level: *p* = 0.22.

3. **Disease-Free Survival**
   - 3-year DFS: 60% vs. 51%.
   - HR = 1.19, 95% CI [0.90-1.59].
The achievements: 
Adjuvant chemotherapy for stage III colon cancer

FOLFOX + 4%
(Cape ? + 3%)
FU/FA +15%
Total ~ 20%
Bevacizumab for adjuvant therapy in Colon Cancer
- negative data -

NSABP C-08
2673 pts. stage II and III

AVANT
3451 pts. stage II and III

Allegra et al. JCO 2013
De Gramont et al. Lancet Oncol 2012
FOLFOX +/- Cetuximab in stage III colon cancer

Albers et al. JAMA 2012
FOLFOX +/- Cetuximab in stage III colon cancer - Subgroups -

Albers et al. JAMA 2012
Cetuximab for adjuvant therapy in Colon Cancer

FOLFIRI +/- Cetuximab a missed opportunity?

Huang et al. Clinical Colorectal Cancer 2013
Age specific death rate
Colorectal Cancer - Germany 1999

% Patients receiving adjuvant CTx

<table>
<thead>
<tr>
<th>Age Group</th>
<th>% Male</th>
<th>% Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>70-74</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>75-79</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>80-84</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>85-89</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>&gt;=90</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Adjuvant FU/Lev or FU/LV offered or received by colon cancer patients by age at diagnosis

Potosky et al.  
JCO 2002
Pooled Analysis of 7 Studies

3351 Patients, 506 Patients > 70 years

Colon Cancer Stage II – III

Sargent et al. NEJM 2001
## Elderly patients and Oxaliplatin
### ACCENT analysis and NO16968 data

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td><strong>ACCENT analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years (n=3877)</td>
<td>0.77 (0.68–0.86)</td>
<td>0.81 (0.71–0.93)</td>
</tr>
<tr>
<td>≥70 years (n=703) 18%</td>
<td>1.04 (0.80–1.35)</td>
<td>1.18 (0.90–1.57)</td>
</tr>
<tr>
<td>Interaction of age by treatment</td>
<td>p=0.016</td>
<td>p=0.037</td>
</tr>
<tr>
<td><strong>NO16968 (XELOXA) n= 1886</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years (n=1477)</td>
<td>0.79 (0.66–0.94)</td>
<td>0.86 (0.69–1.08)</td>
</tr>
<tr>
<td>≥70 years (n=409) 28%</td>
<td>0.87 (0.63–1.18)</td>
<td>0.94 (0.66–1.34)</td>
</tr>
<tr>
<td>Interaction of age by treatment</td>
<td>p=0.6222</td>
<td>p=0.7065</td>
</tr>
</tbody>
</table>

†CO7 + MOASAIK
Pooled analysis of individual patient data (NSABP C-08, XELOXA, X-ACT, and AVANT) survival for age groups

Recurrence Rate by time from randomization (all pts)

After 5 years, recurrence rates < 1.5% / year

After 8 years, recurrence rates < 0.5% / year
Peripheral Sensory Neuropathy

- % of treated patients
  - Grade 1: 48.1%
  - Grade 2: 30.9%
  - Grade 3: 22.2%
- During Tx: 27.6%
- 6 months: 17.4%
- 1 year: 14.2%
- 2 years: 11.4%
- 3 years: 8.8%
- 4 years: 2.1%

Grade 1
Grade 2
Grade 3
Neuropathy during oxaliplatin Tx: 96%

Oxaliplatin dose reduction due to neuropathy: 30%

Case of oxaliplatin prior completion of oxaliplatin Tx: 33%

Worsening of neuropathy after completion of oxaliplatin Tx: 25%

Persistent neuropathy at 29±4 mo: 79%
  - upper limbs 46%
  - lower limbs 79%

At follow-up no improvement of neuropathy: 33%
  persistent functional difficulties with fine motor skills or walking balance. 42%

*Park et al. The Oncologist 2011*
Patient groups in adjuvant Therapy

No benefit

cured

Cured by surgery already

TOXICITY
## Conclusions

### Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt; 70y</th>
<th>&gt; 70y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td>5FU/LV or Cape</td>
<td>FOLFOX</td>
</tr>
<tr>
<td>Stage II</td>
<td>5FU/LV or Cape?</td>
<td>5-FU/LV or Cape?</td>
</tr>
<tr>
<td>- Low risk</td>
<td>No adj CTx</td>
<td></td>
</tr>
<tr>
<td>- High risk</td>
<td>5FU/LV or Cape?</td>
<td></td>
</tr>
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**Biologicals currently no therapeutic option**

**Gen signatures are prognostic, but predictive?**

**The decision for adjuvant therapy has to balances the risk of cancer and other competing risks**