Adjuvant Chemotherapy for Stage III colon Cancer

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Observed survival rates Colon Cancer

Weiser, J Clin Oncol 2011; O’Connor, J Clin Oncol 2011
<table>
<thead>
<tr>
<th>TN Category</th>
<th>Observed 5-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0</td>
<td></td>
</tr>
<tr>
<td>T2N0</td>
<td></td>
</tr>
<tr>
<td>T3N0</td>
<td></td>
</tr>
<tr>
<td>T4aN0</td>
<td></td>
</tr>
<tr>
<td>T4bN0</td>
<td></td>
</tr>
<tr>
<td>T1-2N1</td>
<td></td>
</tr>
<tr>
<td>T1N2a</td>
<td></td>
</tr>
<tr>
<td>T2N2a</td>
<td></td>
</tr>
<tr>
<td>T3N1a</td>
<td></td>
</tr>
<tr>
<td>T4aN1a</td>
<td></td>
</tr>
<tr>
<td>T4bN1a</td>
<td></td>
</tr>
<tr>
<td>T1N1b</td>
<td></td>
</tr>
<tr>
<td>T4aN1b</td>
<td></td>
</tr>
<tr>
<td>T4bN1b</td>
<td></td>
</tr>
<tr>
<td>T1N2b</td>
<td></td>
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<tr>
<td>T2N2b</td>
<td></td>
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<tr>
<td>T3N2a</td>
<td></td>
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<tr>
<td>T4aN2a</td>
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<td>T4bN2a</td>
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<tr>
<td>T2N2b</td>
<td></td>
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<tr>
<td>T3N2b</td>
<td></td>
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<tr>
<td>T4aN2b</td>
<td></td>
</tr>
<tr>
<td>T4bN2b</td>
<td></td>
</tr>
</tbody>
</table>

SEER data base 48,500 stage II colon cancer
Observed 5-year survival by TN category. (TNM VI)

Gunderson L L et al. JCO 2010;28:264-271
Adjuvant treatment: Where are we starting?

- Early colon cancer is a heterogeneous disease
- 5FU/FA is active
Improvement of OS; 5FU versus control

• UICC stage III
  – Several phase III trials: \textbf{+10-12\%}

• UICC Stage II
  – Several meta-analyses
    (e.g. Benson et al., J Clin Oncol 2004): \textbf{+ 3-4\%, n.s.}
  – QUASAR trial (Lancet 2008): \textbf{+ 3.8\%, sign.}
Impact Group: Metaanalysis 1995

Disease free survival: 5-FU vs. no chemotherapy

Event-free survival

Probability of survival

Time from randomisation (years)

Δ 18%
(44 vs 62%)
Adjuvant treatment:
Where are we starting?

- Early colon cancer is a heterogeneous disease
- 5FU/FA is active
- Oxaliplatin improves efficacy?
MOSAIC Trial: Colon Cancer UICC Stage II/III

André T et al., J Clin Oncol 2009; Texeira et al., ASCO 2010
MOSAIC Trial: Benefit of Oxaliplatin

Stage II: HR=0.80

Stage III: HR=0.76

DFS

Andre et al., N Engl J Med 2004
10-y OS Update of the MOSAIC Trial

Stage III

8%/10y.
10-y OS Update of the MOSAIC Trial

Stage IIIA (N1)  Stage IIIB (N2)

Andre et al., J Clin Oncol 2015
ACCENT Database: Factors and treatment effects

Stage II vs. III

Nodal status

Shah et al., J Clin Oncol 2016
Adjuvant treatment: Where are we starting?

- Early colon cancer is a heterogeneous disease
- 5FU/FA is active
- Oxaliplatin improves efficacy
- Any fluoropyrimidine may be used
X-ACT: Superior Relapse-free Survival (ITT)

Estimated probability

Capecitabine (n=1004) 65.5%
5-FU/LV (n=983) 61.9%

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

<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>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.79</td>
<td>0.76</td>
</tr>
<tr>
<td>2</td>
<td>0.63</td>
<td>0.57</td>
</tr>
<tr>
<td>3</td>
<td>0.49</td>
<td>0.45</td>
</tr>
<tr>
<td>4</td>
<td>0.36</td>
<td>0.33</td>
</tr>
<tr>
<td>5</td>
<td>0.24</td>
<td>0.22</td>
</tr>
<tr>
<td>6</td>
<td>0.12</td>
<td>0.10</td>
</tr>
</tbody>
</table>

HR = 0.84 (95% CI: 0.69–1.01)  p=0.07

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

Twelves et al. NEJM 2005
### Fluoropyrimidines ± Oxaliplatin Stage III

<table>
<thead>
<tr>
<th>Study</th>
<th>HR for DFS</th>
<th>P value</th>
<th>DFS Δ (%)</th>
<th>HR for OS</th>
<th>P value</th>
<th>Δ OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOSAIC (FOLFOX)</strong></td>
<td>0.78 CI, 0.65-0.93 @ 5 year</td>
<td>0.005</td>
<td>Δ 7.5% 58.9% vs 66.4% @ 5 year</td>
<td>0.80 CI, 0.65-0.97 @ 6 year</td>
<td>0.023</td>
<td>Δ 4.2% 68.7% vs 72.9% @ 6 year</td>
</tr>
<tr>
<td><strong>NSABP C-07 (FLOX)</strong></td>
<td>0.78 CI, 0.68-0.90 @ 5 year</td>
<td>0.0007</td>
<td>Δ 6.6% 57.8% vs 64.4% @ 5 year</td>
<td>0.85 CI, 0.72-1.00 @ 5 year</td>
<td>0.052</td>
<td>Δ 2.7% 73.8% vs 76.5% @ 5 year</td>
</tr>
<tr>
<td><strong>XELOXA (Xelox)</strong></td>
<td>0.80 CI, 0.69-0.93 @ 3 year</td>
<td>0.0045</td>
<td>Δ 4.4% 66.5% vs 70.9% @ 3 year</td>
<td>0.87 CI, 0.72-1.05 @ 5 year</td>
<td>0.1486</td>
<td>Δ 3.4% ND (57 months FU)</td>
</tr>
<tr>
<td><strong>X-ACT FU/FA bolus vs. Capecitabine</strong></td>
<td>0.87 CI, 0.75-1.00 @ 3y</td>
<td>0.0528</td>
<td>Δ 3.6% 60.6% vs. 64.2% @ 3y</td>
<td>0.84 CI: 0.69–1.01 @3y</td>
<td>p=0.07</td>
<td>Δ 3.7% 77.6% vs. 81.3% @3y</td>
</tr>
</tbody>
</table>

1 André T, J Clin Oncol. 2009  
2 Yothers G, J Clin Oncol 2011  
3 Haller D, J Clin Oncol  2011
The achievements: Adjuvant chemotherapy for stage III colon cancer

- FOLFOX + 4%
  - (Cape ? + 3%)
- FU/FA +15%
- Total ~ 20%

[Graph showing survival rates over years with FOLFOX, Cape ?, and FU/FA treatments compared to the total benefit.]
Early colon cancer is a heterogeneous disease

5FU/FA is active

Oxaliplatin improves efficacy

Any fluoropyrimidine may be used

But: further intensification has not improved outcome
  - 4 trials with targeted agents – all without any improvement in DFS!
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

Wild-type KRAS

Disease-Free Survival, %

0 20 40 60 80 100

Years

No. at risk

mFOLFOX6 909 659 413 163 48
mFOLFOX6 + cetuximab 954 667 417 154 39

HR, 1.21; 95% CI, 0.98-1.49; P = .08; Log-rank P = .18

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

Wild-type KRAS + Age ≥70 y

- mFOLFOX6
- mFOLFOX6 + cetuximab

Mutated KRAS

- mFOLFOX6
- mFOLFOX6 + cetuximab

Disease-Free Survival, %

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type KRAS + Age ≥70 y</td>
<td>112</td>
<td>90</td>
<td>64</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Mutated KRAS</td>
<td>374</td>
<td>329</td>
<td>233</td>
<td>86</td>
<td>19</td>
</tr>
</tbody>
</table>

HR, 1.59; 95% CI, 0.93-2.70; P = .09; Log-rank P = .06
HR, 1.12; 95% CI, 0.86-1.46; P = .38; Log-rank P = .32

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

FOLFIRI +/- Cetuximab a missed opportunity?

Abbreviations: DFS = disease-free survival; FOLFIRI = irinotecan, 5-fluorouracil, and leucovorin; HR = hazard ratio; mut Braf = mutated v-Raf murine sarcoma viral oncogene homolog B1; mut Kras = mutated Kirsten rat sarcoma viral oncogene homolog; wt Braf = wild type v-Raf murine sarcoma viral oncogene homolog B1; wt Kras = wild type Kirsten rat sarcoma viral oncogene homolog.
Adjuvant treatment of colon cancer stage III

The issue of age
Elderly patients and Oxaliplatin
ACCENT analysis and NO16968 data

<table>
<thead>
<tr>
<th>Hazard ratio (95% CIs)*</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCENT analysis(^4)†</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NO16968 (XELOXA) n= 1886</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 years (n=1477)</td>
</tr>
<tr>
<td>≥70 years (n=409) 28%</td>
</tr>
<tr>
<td>Interaction of age by treatment</td>
</tr>
</tbody>
</table>

\(^{†}CO7 + MOASAIK\)
ACCENT Database: Effect of „newer“ drugs

DFS

OS

NO benefit from combinations, if > 70y?

McCleary, J Clin Oncol 2013
Other analyses – no clear picture

MOSAIC (FOLFOX vs 5-FU)

NSABP-C07 (FLOX vs 5-FU)

Yothers, J Clin Oncol 2011; Andre, J Clin Oncol 2009
Age and comorbidities: A pooled analysis

NSABP C-08, XELOXA, X-ACT and AVANT trials (chemo-only arms)

Overall population

Comorbidities CCI

Relative benefit of oxaliplatin – also in patients > 70y and in relation to comorbidity

Age > and < 70y

Comorbidities NCI
Oxaliplatin in adjuvant setting

Long term neurotoxicity
Peripheral Sensory Neuropathy

<table>
<thead>
<tr>
<th>Time</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>During Tx</td>
<td>48.1</td>
<td>31.4</td>
<td>12.5</td>
</tr>
<tr>
<td>6 months</td>
<td>30.9</td>
<td>7.2</td>
<td>1.4</td>
</tr>
<tr>
<td>1 year</td>
<td>22.2</td>
<td>4.2</td>
<td>1.2</td>
</tr>
<tr>
<td>2 years</td>
<td>14</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>3 years</td>
<td>12</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>4 years</td>
<td>8.8</td>
<td>2.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

% of treated patients
### Outcome (median 25 mo) of oxaliplatin induced neurotoxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy during oxaliplatin</td>
<td>96%</td>
</tr>
<tr>
<td>Oxaliplatin dose reduction due to neuropathy:</td>
<td>30%</td>
</tr>
<tr>
<td>Caese of oxaliplation prior completion of oxaliplation</td>
<td>33%</td>
</tr>
<tr>
<td>Worsening of neuropathy after completion of oxaliplatin</td>
<td>25%</td>
</tr>
<tr>
<td>Persistent neuropathy at 29±4 mo:</td>
<td>79%</td>
</tr>
<tr>
<td>- upper limbs</td>
<td>46%</td>
</tr>
<tr>
<td>- lower limbs</td>
<td>79%</td>
</tr>
<tr>
<td>At follow-up no improvement of neuroneuropathy:</td>
<td>33%</td>
</tr>
<tr>
<td>persistent functional difficulties with fine motor skills or walking balance.</td>
<td>42%</td>
</tr>
</tbody>
</table>

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

No benefit

cured

Cured by surgery already

TOXICITY

Years

0 1 2 3 4 5

0 20 40 60 80 100
Decision making – on which basis?

- Are there strong prognostic factors available?
- ....or even *predictive* markers?
Known prognostic factors in CRC

• pTNM
• Microsatellite instability
• methylation status (CIMP)
• BRAF (metastatic CRC)
• Multi gene testings
• Conflicting data: p53, loss of 18q, 17p, gain of 20q13, KRAS, etc.
# MSI as Prognostic factor in stage II and III

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribic et al</td>
<td>II/III OP</td>
<td>OS</td>
<td>0.31 (0.14-0.72)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sargent et al</td>
<td>II/III OP</td>
<td>DFS</td>
<td>0.46 (0.22-0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Gray et al</td>
<td>II OP</td>
<td>RFS</td>
<td>0.31 (0.15-0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Roth et al</td>
<td>II 5FU +/- Irinotecan</td>
<td>RFS</td>
<td>0.30</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Ribic, N Engl J Med 2003; Sargent, JCO 2009; Gray, JCO 2011; Roth, JNCI 2009
Subgroups and OS with UICC III: NO147 Study

Stage III Colon Cancer Subtypes (N=2720)

Proficient DNA Mismatch Repair (pMMR)

Deficient DNA Mismatch Repair (dMMR)

![Graph showing event-free survival by molecular subtype](image_url)

- Non mutated BRAF & KRAS, pMMR
- Mutant KRAS pMMR
- Mutant BRAF pMMR
- Sporadic dMMR
- Familial dMMR

Sinicrope, Gastroenterology 2015
Pooled analysis: PETACC-8 and NO147 – Stage III, MSS

**OS: KRAS exon 2 and BRAF mutational status**

<table>
<thead>
<tr>
<th>Mutational Status</th>
<th>HR for OS [95% CI]</th>
<th>p-value (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>1.72 [1.33; 2.22]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KRAS exon 2</td>
<td>1.52 [1.29; 1.79]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

KRAS Exon2 and BRAF: prognostic biomarkers
Sporadic MSI-Patients: prognostic biomarker
Adjuvant chemotherapy of colon cancer
BRAF-Mutation impact depends on localization

HR (BRAFmut vs WT2) = 6.4 (3.6-11.5)

HR (BRAFmut vs WT2) = 1.5 (0.8-2.7)

Popovici, BMC Cancer 2013
Recurrence rate lower in MSI+ cancers ($p < 0.001$)
Recurrence rate higher in k-ras mutant cancers ($p = 0.02$)

Hutchins et al. (2011) J Clin Oncol 29: 1261-1270
MOSAIC Study 10 years later

MSS - Tumor

MSI - Tumor

Andre et al., J Clin Oncol 2015
Adjuvant chemotherapy of colon cancer
Oxaliplatin and BRAF Mutation

MOSAIC Study 10 y later

BRAF - Wildtype

BRAF - Mutant

Andre et al., J Clin Oncol 2015
Between UICC stages: Oncotype DX

12 gene recurrence score – continuous scale

Risk reduction with 5-FU 18%

Kerr, ASCO 2009, #4000; O’Connell, J Clin Oncol 2010
Oncotype DX: Effect of oxaliplatin in the NSABP database

Some more benefit with oxaliplatin @ higher risk population
Relationship between CDX2 Expression and Benefit from Adjuvant Chemotherapy.

A  Patients with Stage II Disease

All Tumors

CDX2-Negative

CDX2-Positive

Disease-free Survival (%)

Years

P=0.07

P=0.006

P=0.40

No. at Risk

Chemotherapy

No chemotherapy

P=0.02 for interaction

412 388 365 344 326 310

23 22 21 21 20 20

389 366 344 323 306 290

25 18 14 8 7 6

232 212 185 142 107 78

B  Patients with Stage III Disease

All Tumors

CDX2-Negative

CDX2-Positive

Disease-free Survival (%)

Years

P<0.001

P<0.001

P=0.002

No. at Risk

Chemotherapy

No chemotherapy

P=0.005 for interaction

1063 935 796 721 654 607

60 53 47 43 40 37

1003 882 749 678 614 570

165 128 96 83 70 55

27 13 9 8 7 7

138 115 87 75 63 48

The consensus molecular subtypes of colorectal cancer

Justin Guinney¹,²,21, Rodrigo Dienstmann¹,²,21, Xin Wang³,4,21, Aurélien de Reyniès⁵,21, Andreas Schlicker⁶,21, Charlotte Soneson⁷,21, Laetitia Marisa⁵,21, Paul Roepman⁸,21, Gift Nyamundanda⁹,21, Paolo Angelino⁷, Brian M Bot¹, Jeffrey S Morris¹⁰, Iris M Simon⁸, Sarah Gerster⁷, Evelyn Fessler³, Felipe De Sousa E Melo³, Edoardo Missiaglia⁷, Hena Ramay⁷, David Barras⁷, Krisztian Homicsko¹¹, Dipen Maru¹⁰, Ganiraju C Manyam¹⁰, Bradley Broom¹⁰, Valerie Boige¹², Beatriz Perez-Villamil¹³, Ted Laderas¹, Ramon Salazar¹⁴, Joe W Gray¹⁵, Douglas Hanahan¹¹, Josep Taberner², Rene Bernards⁶, Stephen H Friend¹, Pierre Laurent-Puig¹⁶,¹⁷,²², Jan Paul Medema³,²², Anguraj Sadanandam⁹,²², Lodewyk Wessels⁶,²², Mauro Delorenzi⁷,¹⁸,¹⁹,²², Scott Kopetz¹⁰,²², Louis Vermeulen³,²² & Sabine Tejpar²⁰,²²
Subtypes and consequences

Guinney, Nature Medicine, online first October 2015
Molecular subtypes are prognostically relevant

Guinney, Nature Medicine, online first October 2015
Discussion for an algorithm for adjuvant tx in CRC

- Low risk (5y OS > 85%)
  no treatment?
- Intermediate risk (5y OS 75-85%)
  5FU / Capecitabine single agent?
- High risk (5y OS < 75%)
  5FU plus Oxaliplatin?*

Risk assessment:
Prognostic biomarker +/- prognostic clinical factor
Prognostic clinical factors +/- prognostic biomarker
Adjuvant treatment in CRC: What needs to be done?

- Do not expect further improvement of CTX
  - FOLFIRI-Cet´mab and FOLFOXIRI: large scale benefits are unlikely

- Prospective validation of prognostic clinical markers and biomarkers
  - Algorithms for calculating risk factors essential
  - Not necessarily gene based assays

- Evaluation of predictive value in randomized trials
  - difficult, if not prospectively validated
7.3.2.2 Stage III disease. Adjuvant chemotherapy should be offered to all eligible patients with stage III disease [I, A]. FU and oxaliplatin combinations (FLOX, FOLFOX, XELOX) are superior to single-agent 5-FU in terms of DFS and OS [97–99]. Therefore, stage III patients should receive adjuvant chemotherapy with FU and oxaliplatin [I, A], with a clear preference for infused (FOLFOX) or oral FU (XELOX) combinations over the bolus FLOX regimen (see...