Adjuvant treatment of colon cancer: What are the actual recommendations?

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- 25 km east of Brussel: ~ 100,000 inhabitants
- KUL: University founded in 1425: > 55,000 students:
  - Times ranking of innovation: Nr 5 worldwide; Nr 1 in EU
- Largest Beer Brewery in world (>25% of world production)
Outcome of early colon cancer: T4 Stage => Poor Outcome

SEER database 1991-2000 (n = 119,363): 5-yr survival

- Stage II colon cancer +/- adj 5FU : 5-yr risk of death = 17.5% overall
  - 17% had T4 tumors (stage IIB) with 27.8% risk of death
  - 83% had T3 tumors (stage IIA) with 15.3% risk of death (near average risk for all stage II)
- T4 = high risk; T3 = average risk (not necessarily low risk)
Adjuvant Therapy for Stage III Colon Cancer

1990
12 months 5-FU/Levamisole

1996
6 months 5-FU/Folinic Acid

2004
6 months FOLFOX4 is better than LV5FU2
Capecitabine at least as active as IV 5-FU/FA
UFT/LV similar activity compared to IV 5-FU/FA

2005
bolus 5-FU/FA/oxaliplatin better than bolus 5-FU/FA

2008
Capecitabine/oxaliplatin better than bolus 5-FU/FA

2017
3 months as good as 6 months for low risk stage III colon cancer
Adjuvant therapy for stage III colon cancer: Which benefit?

- Surgery alone
- Surgery plus chemotherapy
- No benefit of chemotherapy
- Cured by chemotherapy
- Cured by surgery already

Disease Free Survival

% 100
80
60
40
20
0

0 1 2 3 4 5

exposed to toxicity
LEVAMISOLE AND FLUOROURACIL FOR ADJUVANT THERAPY OF RESECTED COLON CANCER

J. M. Lubsen, M.D.,
P. V. Jemal, M.S.,
S. L. Moore, M.D.,
J. D. Albert, M.D.,
R. de Miranda, M.D.,
W. P. Mar ve d, M.D.*

Abstract

Resected colorectal carcinoma (Stage B) with at least 5-mm tumor-free surgical margins (Stage C) was treated with levamisole and fluorouracil (5-FU). The results of this 12-month trial were compared with a matched population treated with 12 month of adjuvant therapy. The median follow-up time was 30 months. The observed 5-year survival was 81% for levamisole and 75% for the group treated with 5-FU. The results indicate that levamisole and 5-FU are equivalent treatment for Stage C patients. The results imply that levamisole is as effective as 5-FU as a single agent with a better side-effect profile, which may increase patient compliance.

*5th ESO-ESMO Latin American Masterclass in Clinical Oncology

THE NEW ENGLAND JOURNAL OF MEDICINE
Feb. 8, 1990

352
INT 0089:
6 Months of Bolus 5-FU/LV = SOC

- No formal non-inferiority hypothesis
- No appropriate control arm (6 vs 12 m of 5-FU/ LEV)
- No hazard ratios given in paper for comparisons between arms
- We truly do not know if 5-FU/LV over 12 months might be best
- Oncology community was eager to accept a shorter duration

### Table 6. Five- and 10-Year Disease-Free and Overall Survival Treatment Comparisons

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DFS 5 Year</th>
<th>DFS 10 Year</th>
<th>OS 5 Year</th>
<th>OS 10 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment arm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLV</td>
<td>0.60</td>
<td>0.49</td>
<td>0.66</td>
<td>0.52</td>
</tr>
<tr>
<td>HDLV</td>
<td>0.58</td>
<td>0.47</td>
<td>0.66</td>
<td>0.52</td>
</tr>
<tr>
<td>LEV</td>
<td>0.55</td>
<td>0.45</td>
<td>0.64</td>
<td>0.50</td>
</tr>
<tr>
<td>LDLV + LEV</td>
<td>0.49</td>
<td>0.68</td>
<td>0.54</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0.69</td>
<td>0.57</td>
<td>0.76</td>
<td>0.52</td>
</tr>
<tr>
<td>III</td>
<td>0.56</td>
<td>0.45</td>
<td>0.63</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>0.69</td>
<td>0.57</td>
<td>0.76</td>
<td>0.62</td>
</tr>
<tr>
<td>N1</td>
<td>0.61</td>
<td>0.50</td>
<td>0.89</td>
<td>0.55</td>
</tr>
<tr>
<td>N2</td>
<td>0.44</td>
<td>0.35</td>
<td>0.51</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Abbreviations: DFS, disease-free survival; OS, overall survival; LDLV, low-dose leucovorin plus FU; FU, fluorouracil; HDLV, high-dose leucovorin plus FU; LEV, levamisole plus FU.

Haller D et al, ASCO 1997; JCO 2005
Adjuvant therapy increases the survival: evidence in 13,793 colon cancer patients

Stage III Colon cancer

Surgery alone
8-year OS rate (95% CI): 42.7%
(39.9% to 45.7%)

Surgery + FU-based chemotherapy
8-year OS rate (95% CI): 53.0%
(50.2% to 55.9%)

p<0.0001

Sargent D et al. JCO 2009
Oxaliplatin + Fluoropyrimididine

**MOSAIC: Study design**

LV5FU2

FOLFOX4: LV5FU2 + oxaliplatin

N=2246
Stage 2 (40%) low-risk 15% high-risk (25%)
Stage 3 (60%) ≤4N (44.5%)≥4N (15.1%)

André, NEJM 2004
J Clin Oncol 2009

**NSABP C07: Study design**

FUFOL Roswell Park

FLOX: FUFOL Roswell Park and oxaliplatin

N=2407
Stage 2: 29%
Stage 3: 71%  N1 (46% ) N2 (20%)

**XELOXA N016968: Study design**

FUFOL Mayo or Roswell Park

XELOX: capecitabine + oxaliplatin

N=1886

**Primary end-point for these 3 studies:**
Disease-free Survival

Yothers G et al, J Clin Oncol 2011
Haller D et al, J Clin Oncol 2011
MOSAIC study
FOLFOX4 vs LV5FU2: DFS by tt arm (ITT)

23% risk reduction in the FOLFOX4 arm

Hazard ratio: 0.77 [0.65 – 0.91]  p =0.002

5 Year Disease-free Survival: Stage II and Stage III

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR [95% CI]</th>
<th>p-value</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>0.84 [0.62–1.14]</td>
<td>0.258</td>
<td>3.8%</td>
</tr>
<tr>
<td>Stage III</td>
<td>0.80 [0.65–0.93]</td>
<td>0.005</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

Data cut-off: June 2006

FOLFOX4 stage II
LV5FU2 stage II
FOLFOX4 stage III
LV5FU2 stage III

Adjuvant treatment of colon cancer: 3 positive phase III trials in favor of oxaliplatin

<table>
<thead>
<tr>
<th></th>
<th>Δ 3y DFS</th>
<th>Δ 5y DFS</th>
<th>Δ 5-6y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mosaic</strong></td>
<td>+ 5.3%</td>
<td>+ 5.9%</td>
<td>+ 2.5%</td>
</tr>
<tr>
<td>LV5FU ± oxaliplatin</td>
<td></td>
<td></td>
<td>HR 0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(median FU: 82 months)</td>
</tr>
<tr>
<td><strong>C-07</strong></td>
<td>+ 4.3%</td>
<td>+ 5.2%</td>
<td>+ 4.2%</td>
</tr>
<tr>
<td>Bolus 5FU/LV ± oxaliplatin</td>
<td></td>
<td></td>
<td>HR 0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(median FU: 67 months)</td>
</tr>
<tr>
<td><strong>XeloxA</strong></td>
<td>+ 4.5%</td>
<td>+ 6.3%</td>
<td>+ 3.4%</td>
</tr>
<tr>
<td>Xelox vs bolus 5FU/FA</td>
<td></td>
<td></td>
<td>HR 0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(median FU: 57 months)</td>
</tr>
</tbody>
</table>
Mosaic long term follow-up in stage III: OS with 10 yr Follow Up : ITT

Hazard ratio = 0.80
95% CI: 0.66 to 0.96  
P = 0.015

André T et al. JCO 2015
Mosaic trial: Overall Survival: Stage III

Stage III N1 (1 to 3 N+)

Stage III N2 (≥ 4N+)

 André T et al et al. JCO 2015
• Higher risk of recurrence over time was associated with higher T and N Stage
• Oxaliplatin demonstrating more benefit in patients with more advanced T and nodal stage
• Addition of oxaliplatin to FU is associated with benefit for T4 and T3, however this benefit exists but is little for T1 and T2
Proportion of patients treated by FOLFOX4 with peripheral sensory neuropathy

At 48 months
Evaluable patients n=811

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>84.3%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>12.0%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2.8%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0.7%</td>
</tr>
</tbody>
</table>
IDEA collaboration: Study Overview

- **Objective:**
  Reduce side-effects of therapy without giving up (too much) anti-cancer efficacy of therapy.

- **Non-inferiority design:**
  As agreed upon by patient advocates and oncologists, shorter duration of therapy should not sacrifice more than 12% of benefit of adjuvant therapy.

- **In statistical terms:**
  Upper 95% confidence interval of Hazard Ratio (HR) of disease free survival (DFS) should not exceed 1.12.

---

**Stage III Colon Cancer**

12,834 patients

R

3 months

FOLFOX* or CAPOX*

6 months

*Investigator’s choice, no randomization
## Patient Characteristics by Study

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>TOSCA (N=2402)</th>
<th>SCOT (N=3983)</th>
<th>IDEA France (N=2010)</th>
<th>C80702 (N=2440)</th>
<th>HORG (N=708)</th>
<th>ACHIEVE (N=1291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years</td>
<td>64</td>
<td>65</td>
<td>64</td>
<td>61</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>ECOG PS*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>95%</td>
<td>74%</td>
<td>71%</td>
<td>82%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5%</td>
<td>25%</td>
<td>28%</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>12%</td>
<td>29%</td>
<td>18%</td>
<td>15%</td>
<td>14%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>12%</td>
<td>29%</td>
<td>18%</td>
<td>15%</td>
<td>14%</td>
<td>28%</td>
</tr>
<tr>
<td>N Stage</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>73%</td>
<td>69%</td>
<td>75%</td>
<td>67%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up time, m</td>
<td>62</td>
<td>37</td>
<td>51</td>
<td>35</td>
<td>48</td>
<td>37</td>
</tr>
</tbody>
</table>

*1% of PS 2 in IDEA France and C80702 trials

Grothey A et al. NEJM 2018
IDEA: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>3m Arm</th>
<th>6m Arm</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
<th>3m Arm</th>
<th>6m Arm</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>G3-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>G2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3-4</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
<td></td>
<td></td>
<td>0.0117</td>
</tr>
<tr>
<td>G2</td>
<td>11%</td>
<td>13%</td>
<td></td>
<td>10%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>G3-4</td>
<td>5%</td>
<td>7%</td>
<td>&lt;.0001</td>
<td>7%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Chi-squared test for trend; Total of 19 grade 5 events; Adverse events only collected on first 617 patients enrolled to SCOT trial

Grothey A et al. NEJM 2018
IDEA:
Primary Outcomes Analysis

**Duration**
- 3 Months
- 6 Months

**3-yr DFS**
- 3m: 74.6%
- 6m: 75.5%

**3-yr DFS diff. = -0.9%**, 95% CI, (-2.4 to 0.6%)

**DFS HR = 1.07**
95% CI, 1.00 to 1.15

N Patients At risk
- 3m: 6424 / 6410
- 6m: 5446 / 5530

**Years from Randomization**
- 0: 4464 / 4477
- 1: 3000 / 3065
- 2: 1609 / 1679
- 3: 826 / 873
- 4: 321
- 5: 334

**Grothey A et al. NEJM 2018**
IDEA:
Primary DFS Analysis (mITT)

Statistical Conclusions

3m TRT better

6m TRT better

Not proven

DFS HR = 1.07
95% CI, 1.00 to 1.15

Hazard Ratio

1.0
1.12

Non-Inferiority Margin

TRT: treatment

Grothey A et al. NEJM 2018
IDEA: DFS Comparison by Risk Groups

mITT all patients independently of the duration of chemotherapy

IDEA, Shi Q et al, personal data

5th ESO-ESMO Latin American Masterclass in Clinical Oncology
### mITT: DFS Comparison by N Groups: N1 vs N2

![Graph showing DFS comparison between N1 and N2 groups over different durations](image)

<table>
<thead>
<tr>
<th>N-Stage</th>
<th>Duration</th>
<th>Event Rate</th>
<th>3 Year Est (95% CI)</th>
<th>HR (95% CI)</th>
<th>Sup p</th>
<th>NI p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>3 Months</td>
<td>953</td>
<td>79.7 (78.5-81.0%)</td>
<td>1.07 (0.97-1.17)</td>
<td>0.1684</td>
<td>0.1427</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>910</td>
<td>80.8 (79.7-82.1%)</td>
<td>Reference</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>N2</td>
<td>3 Months</td>
<td>716</td>
<td>61.6 (59.3-64.1%)</td>
<td>1.07 (0.96-1.19)</td>
<td>0.1965</td>
<td>0.2093</td>
</tr>
<tr>
<td></td>
<td>6 Months</td>
<td>662</td>
<td>61.8 (59.5-64.3%)</td>
<td>Reference</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**Years from Randomization**

<table>
<thead>
<tr>
<th>N1</th>
<th>4583</th>
<th>4006</th>
<th>3334</th>
<th>2262</th>
<th>1212</th>
<th>600</th>
<th>234</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2</td>
<td>1790</td>
<td>1409</td>
<td>1108</td>
<td>721</td>
<td>387</td>
<td>222</td>
<td>85</td>
</tr>
</tbody>
</table>

IDEA, Shi Q et al, personal data
mITT: DFS Comparison by N Groups: T1-T3 vs T4

IDEA, Shi Q et al, personal data
Analysis by Risk Groups and Regimens

• Large difference in overall prognosis observed between (T1-3 N1) and (T4 and/or N2) cancers
  – 3-year DFS ∆ 20% (~80% vs 60%)
  – Preplanned subgroup analysis for T and N
    ➢ Analysis of 3m vs 6m adjuvant therapy by risk groups

• Two different adjuvant regimens used, FOLFOX (N=7763) and CAPOX (N=5071)
  – Preplanned analysis of 3m vs 6m based on regimen
IDEA: DFS Comparison by Regimen

**FOLFOX**

- **3m TRT better**
- **6m TRT better**
- DFS HR = 1.16
- 95% CI, 1.06 to 1.26
- **Inferiority**

**CAPOX**

- **3m TRT better**
- **6m TRT better**
- DFS HR = 0.95
- 95% CI, 0.85 to 1.06
- **Non-Inferiority**

**HR**

- 1.0
- 1.12

**NI Margin**

**Interaction p-value = 0.0051**

TRT: treatment

Grothey A et al. NEJM 2018
3 yr DFS in trial of 3 v 6 months CAPOX in 5071 stage 3 patients proves non inferiority for 3 month regimen!

**CAPOX**

Duration 3-yr DFS
3m 75.9 %
6m 74.8 %
3-yr DFS diff. = 1.1%
95% CI, (-1.3 to 3.5%)

DFS HR = 0.95
95% CI, 0.85 to 1.06
Non-Inferiority

Grothey A et al. NEJM 2018
3 yr DFS in trial of 3 v 6 months FOLFOX in 7763 stage 3 patients shows inferiority of 3 month regimen!

**FOLFOX**

<table>
<thead>
<tr>
<th>Duration</th>
<th>3-yr DFS</th>
<th>3-yr DFS diff.</th>
<th>95% CI, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3m</td>
<td>73.6%</td>
<td>-2.4%</td>
<td>(-4.3 to -0.5%)</td>
</tr>
<tr>
<td>6m</td>
<td>76.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DFS HR = 1.16**
95% CI, 1.06 to 1.26

Inferiority

**NI Margin**

N Pts  
At risk

3870  
3227  
2561  
1822  
1121  
633   
291   
3893  
3308  
2633  
1859  
1150  
666   
309   

Grothey A et al. NEJM 2018
mITT: DFS Comparison by Regimen, N, T and Low versus High risk

Grothey A et al. NEJM 2018
# IDEA Recommendations

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Regimen</th>
<th>CAPOX</th>
<th>FOLFOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (T1-3 N1) ~60%</td>
<td>3 months</td>
<td>(3-)6 months</td>
<td></td>
</tr>
<tr>
<td>High-risk (T4 and/or N2) ~40%</td>
<td>3(-6) months</td>
<td>6 months</td>
<td></td>
</tr>
</tbody>
</table>

**Non-inferior**

**Not proven**

**Inferior**
Adjuvant chemotherapy for Stage II colon cancer: What is the benefit?

Overall Survival

Years

Surgery alone

Surgery plus chemotherapy

Chemotherapy without benefit

already cured by surgery

80%

15%

5%

3-5%

0 1 2 3 4 5

0 20 40 60 80 100
QUASAR 1: survival in patients with uncertain indication for adjuvant chemotherapy

Survival (% patients)

5-FU + AF (Mayo or Roswell Park 6 mth) ± levamisole
Observation

Chemo
No chemo

Years of follow-up

Survival (% patients)

n         Deaths    5y survival     p
Chemo   1622     281           80.3               0.02
No          1617     328           77.4

HR 0.83 (95% CI: 0.71-0.97)

Adjuvant therapy increases the survival: evidence in 7,105 colon cancer (stage II) patients

Stage II colon cancer

<table>
<thead>
<tr>
<th>Follow-up time (years)</th>
<th>OS estimate</th>
<th>p=0.026</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
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</tr>
<tr>
<td>5</td>
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<td>8</td>
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</tbody>
</table>

Surgery alone
8-year OS rate (95% CI): 66.8% (63.7% to 70.0%)

Surgery + FU-based chemotherapy
8-year OS rate (95% CI): 72.2% (69.3% to 75.2%)
Table: Kaplan-Meier analysis of 5-year disease-free survival for stage II and stage III colon cancer patients treated with FOLFOX4 and LV5FU2.

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>0.84 [0.62–1.14]</td>
<td>0.258</td>
</tr>
<tr>
<td>Stage III</td>
<td>0.80 [0.65–0.93]</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Data cut-off: June 2006

Improvement of cancer specific survival by 1.7% (FU) and 2.3% (FOLFOX).

Adjuvant! Online Prediction:
Cancer and non-cancer related 5-year-Mortality

Death other cause

T3 NO MO

T4 NO MO
Proposed Stage II Algorithm - 2010

Deficient = MSI

MMR

Intact = MSS

No Adjuvant

Clinical Risk

High

Not High

Adjuvant

No Adjuvant Or Adjuvant

*all decisions require discussion with patient

Meropol N, Ed. Session ASCO 2010
Defective mismatch repair as predictive marker for adjuvant therapy (Accent meta-analysis)

Sargent D J et al. JCO 2010;28:3219-3226
Factors influencing prognosis in stage II
Concept of high risk stage II

- Tumor invasion (T4)
- Perforation Occlusion
- Age
- No. of nodes examined
- Less to 8-12
- MSS-MSI
- Molecular markers or signatures
- Lymphatic invasion
- Venous invasion
- Perineural invasion
- Poor Differentiation

T3N0 without favorable prognostic factors and or MSI: prognosis close to Stage I

T 3-4 N0 with unfavorable prognostic factors: prognosis close to Stage III

- CEA increase
What is the future?
What we need for optimal selection in adjuvant treatment?

- **Recurrence Risk**
  - Low
  - High

- **Life Expectancy**
  - Low
  - High

- **DON’T TREAT**
  - Low High

- **TREAT**
  - Low High

?
PETACC-3 in stage II patients overall survival

Roth A, ..... Van Cutsem E JNCI 2012
Multigene platforms in Colon Cancer

✓ Genomic Health
✓ Agendia
✓ Almac
✓ Veridex

Are prognostic, but are not proven to be predictive (info on benefit of treatment)
ColoPrint®: an independent prognostic factor

RFS 5 y (all stages, n=206):
Low risk 87.6%
High risk 67.2%
(HR) 2.5 (95% CI: 1.33 – 4.73; p<0.005)

RFS 5 y (stage II, n=114):
Low risk 90.9%
High risk 73.9%
(95% CI: 59.2% – 88.6%; p=0.017)

RFS 5 y (stage III, n=62):
Low risk 78.2%
High risk 47.2%

Salazar R. et al. JCO 2011
Conclusions—Lack of CDX2 expression identified a subgroup of patients with high-risk stage II colon cancer who appeared to benefit from adjuvant chemotherapy. (Funded by the National Comprehensive Cancer Network, the National Institutes of Health, and others.)

Figure 2. Relationship between CDX2 Expression and Disease-free Survival in the NCBI-GEO Discovery Data Set
Analysis of CDX2 messenger RNA (mRNA) expression in the NCBI-GEO discovery data set revealed the presence of a minority subgroup of CDX2-negative colon cancers that were characterized by high ALCAM mRNA expression levels (Panel A) and that were associated with a lower rate of 5-year disease-free survival than CDX2-positive colon cancers (Panel B). In Panel A, each circle in the scatter plot represents one patient sample. The association between CDX2-negative cancers and a lower rate of disease-free survival remained significant in a multivariate analysis that excluded tumor stage, tumor grade, age, and sex as confounding variables (Panel C).
Alternative assessment of recurrence risk

Traditional Approach

Alternative Approach
Circulating tumor DNA (ctDNA)

- Large amounts of fragmented cell free DNA are present in the circulation

- **Normal DNA** – BM, GI tract, skin,….
- ↑ with inflammation, trauma, etc.,

- **Tumor DNA** - small DNA fragments released via necrosis or apoptosis.
- ↑ with tumor burden, 0.01 – 60 % of total cell free DNA
- Markers: point mutations, translocations, deletions, amplifications, methylation
- Half-life ~ 2hrs, renal clearance
Colon Cancer Stage III: tumoral circulating DNA

- 95 patients with colon cancer stage III
- Fluoropyrimidine alone: 23% and Fluoropyrimidine + oxaliplatin: 77%

Tie J et al., abstr. 3516 ASCO 2018
ctDNA to guide treatment intensity?

N = 159

At diagnosis
- ctDNA positive (77%)”

After chemoradiation
- ctDNA positive (8%)

Post-operatively
- ctDNA positive (12%)
<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Lymph Node</th>
<th>Metastasis</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1</strong></td>
<td>N0</td>
<td>M0</td>
<td>B0</td>
</tr>
<tr>
<td>Tumor size/local invasion</td>
<td>Local nodes</td>
<td>No regional lymph node invasion</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>N1</td>
<td>M1</td>
<td>B1</td>
</tr>
<tr>
<td>Tumor size/local invasion</td>
<td>Local nodes</td>
<td>Tumor spread to closest or small number of regional lymph nodes</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>N2</td>
<td>M2</td>
<td>B2</td>
</tr>
<tr>
<td>Tumor size/local invasion</td>
<td>Local nodes</td>
<td>Tumor spread to an extent between N1 and N3</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>N3</td>
<td>M3</td>
<td>B3</td>
</tr>
<tr>
<td>Tumor of any size that invades to other organs</td>
<td>Local nodes</td>
<td>Tumor spread to more distant or regional numerous lymph nodes</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Yang et al. (2018)
Optimal surgery and adequate staging are mandatory in patients with colon cancer.

Multidisciplinary approach is important.
- Expert teams

Benefit of adjuvant chemotherapy in stage II colon cancer has been demonstrated, but is limited. In stage III the benefit is much larger.
- Selection of patients is important.

New data of molecular markers and of circulating DNA are emerging and hopefully impactful in the future.
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BARCELONA