Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

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Adjuvant Chemotherapy of colon cancers

- Adjuvant chemotherapy is a concept with proven efficacy in several human solid tumors including colon cancer.

- Most of the data were generated in the past 20 years.

- Adjuvant chemotherapy benefits to a very limited number of patients, most of them are cured after surgery and numerous patients are over-treated.

- The Risk/benefit ratio has to be considered.

- This is particularly true in stage II colon cancer.

Recommended references:
Early colon cancer ESMO Guidelines Annals of Oncology 24 Suppl 6 2013
ESMO Consensus Guidelines for CRC Annals of Oncology 23; 2479 2012
Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

- What defines a stage II colon cancer?
- Risk factors and outcome of stage II colon cancer
- Adjuvant chemotherapy results from trials
- Could biomarkers help?
- ESMO recommendations and proposed algorithm
TNM staging system
AJCC/UICC 7th edition 2010
Stage II Colon Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Stage (T3, T4a, T4b)</th>
<th>N Stage (N0)</th>
<th>M Stage (M0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

N0: 0 node involved out of at least 12 lymph nodes
TNM staging system
AJCC/UICC 7th edition 2010
Stage II Colon Cancer

\[ T \]

- **TX**: Primary tumour cannot be assessed
- **T0**: No evidence of primary tumour
- **Tis**: Carcinoma *in situ*: intraepithelial or invasion of lamina propria
- **T1**: Tumour invades submucosa
- **T2**: Tumour invades muscularis propria
- **T3**: Tumour invades through the muscularis propria into the pericolorectal tissues
- **T4a**: Tumour penetrates into the surface of the visceral peritoneum
- **T4b**: Tumour directly invades or is adherent to other organs or structures
Colon cancer: stage II subgroups

Stage IIA
- Lymph node
- Blood vessel
- Serosa
- Muscle layers
- Submucosa
- Mucosa

Stage IIB
- Cancer spreads to nearby organs

Stage IIC
- Cancer spreads to nearby organs
TNM staging system AJCC/UICC 7th edition 2010

Stage II Colon Cancer: N stage = N0

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in one to three regional lymph nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis in one regional lymph node</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis in two to three regional lymph nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>Tumour satellite deposits in subsierose or in non peritonealised tissues</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in ≥4 regional lymph nodes (a: 4-6, b: ≥7)</td>
</tr>
</tbody>
</table>

Distant metastases (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastases confined to one organ or site (for example liver, lung, ovary, nonregional node)</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastases in more than one organ/site or the peritoneum</td>
</tr>
</tbody>
</table>
Stage II colon cancer

- The quality of the pathology report is ESSENTIAL
  - T size 3 or 4
  - T4a or T4b
  - Number of lymph nodes retrieved and examined

- Additional features to be described:
  - Perineural invasion
  - Lympho-Vascular invasion
  - Lymphocytic reaction?
  - Stroma reaction?
High risk group according to ASCO NCCN and ESMO

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 primary tumor</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inadequately sampled nodes</td>
<td>+ (&lt;13)</td>
<td>+ (&lt;12)</td>
<td>+ (&lt;12)</td>
</tr>
<tr>
<td>Poorly differentiated tumor</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Perforation</td>
<td>+</td>
<td>+ (localized)</td>
<td>+</td>
</tr>
<tr>
<td>Obstruction</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>LVI</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PNI</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Close/indeterminate or positive margins</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

LVI: lymphovascular invasion; PNI: perineural invasion.
* Ie, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO).
Adjuvant Chemotherapy for Stage II colon Cancer: for which patients?

Risk factors and outcome of stage II colon cancer
Stage II: bad prognostic factors

- **Clinical factors:**
  - Obstruction (subjective)
  - Perforation

- **Histological factors:** (sometime subjective)
  - Differentiation
  - Lymphovascular invasion
  - Neuro invasion

- Depth of invasion
  - pT4a: serosal invasion
    - May be missed
    - May be difficult to recognize (mesothelial hyperplasia, inflammation)
  - pT4b: invasion of adjacent organs
    - May be difficult to differentiate from inflammatory adhesion

Most of the studies published refer to previous TNM Classifications and not to TNM 7 (AJCC 2010)
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
SEER data base 48 500 stage II colon cancer
Observed 5-year survival by T category. (TNM VI)

Revised TN Classification for Colon Cancer Based On National Survival Outcomes Data

<table>
<thead>
<tr>
<th>NT Category</th>
<th>Number of Patients</th>
<th>5-Yr Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>74,690</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>2,383</td>
<td>95.6%</td>
</tr>
<tr>
<td>T1-2</td>
<td>23,861</td>
<td>97.1%</td>
</tr>
<tr>
<td>T1</td>
<td>10,930</td>
<td>97.4%</td>
</tr>
<tr>
<td>T2</td>
<td>13,931</td>
<td>96.8%</td>
</tr>
<tr>
<td>T3</td>
<td>40,338</td>
<td>87.5%</td>
</tr>
<tr>
<td>T4</td>
<td>8,108</td>
<td>71.5%</td>
</tr>
<tr>
<td>T4a</td>
<td>5,020</td>
<td>79.6%</td>
</tr>
<tr>
<td>T4b</td>
<td>3,088</td>
<td>58.4%</td>
</tr>
</tbody>
</table>

Adapted from Goldberg R, ASCO GI 2014
Documenting the Natural History of Patients With Resected Stage II Adenocarcinoma of the Colon After Random Assignment to Adjuvant Treatment With Edrecolomab or Observation: Results From CALGB 9581


Patients registered (N = 1,738)

Nonrandom treatment assignment (n = 8)

Patients randomly allocated (n = 1,713)

Allocated to MoAb 17-1A (n = 857)

Received allocated intervention (n = 834)

Did not receive allocated intervention (n = 23)

Completed treatment (n = 722)

Lost to follow-up (n = 4)

Discontinued intervention early (n = 108)

Adverse events (n = 54)

Withdrawn (n = 31)

Other disease (n = 3)

Progressed during treatment (n = 2)

Nonprotocol therapy (n = 1)

Other/unknown reason (n = 17)

Analyzed (n = 857)

Excluded from analysis (n = 8)

Allocated to observation (n = 856)

Received allocated intervention (n = 856)

Did not receive allocated intervention (n = 0)

Completed treatment (n = 856)

Lost to follow-up (n = 4)

Refused further follow-up (n = 9)

Analyzed (n = 856)

Excluded from analysis (n = 17)
Smoothing splines of (A) the log hazard for disease-specific disease-free survival by number of nodes examined truncated at 32 nodes, representing 95% of the data, and (B) the log hazard for disease-specific overall survival by age at trial entry.

Niedzwiecki D et al. JCO 2011;29:3146-3152
## Risk factors in CALGB 9581 (Edrecolomab trial)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>0.004</td>
</tr>
<tr>
<td>Age $&gt; 70$</td>
<td>0.03</td>
</tr>
<tr>
<td>Differenciuation</td>
<td>0.004</td>
</tr>
<tr>
<td>Lympho-Vascular Invasion</td>
<td>0.013</td>
</tr>
<tr>
<td>Perineural Invasion</td>
<td>0.001</td>
</tr>
<tr>
<td>Depth of invasion T 3 vs 4</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Stage II colon cancer subgroups

**Low risk**
- T3
- T4a?
- No obstruction (subjective)
- No perforation
- No lymphovascular invasion
- No perineural invasion
- Well differentiated

**High risk**
- T4b
- T4a?
- Obstruction (subjective)
- Perforation
- Lymphovascular invasion
- Perineural invasion
- Poorly differentiated
Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

QUASAR Collaborative Group
7559 patients with complete resection of colon or rectal cancer

4320 patients with clear indication for chemotherapy

3239 patients with uncertain indication for chemotherapy

1617 patients randomly assigned to observation alone
- 6 patients received chemotherapy
- 1611 did not

1622 patients randomly assigned to receive chemotherapy (607 up to 1997, 1015 after 1997*)
- 45 did not receive any chemotherapy
- 1577 start chemotherapy, of whom 13% receive <80%, 19% receive 80–99% and 58% receive 100% of scheduled chemotherapy

47 not flagged or follow-up not received
- 3 lost to follow-up

54 not flagged or follow-up not received
- 7 lost to follow-up

1567 patients with recent follow-up available for analysis

1561 patients with recent follow-up available for analysis
## QUASAR

<table>
<thead>
<tr>
<th></th>
<th>CT* 1622</th>
<th>No CT 1617</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>II</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Rectum or Both</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td><strong>Age &lt;70</strong></td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>&gt;70</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>

*All CT was 5FU/LV 27% with levamisole*

**OS**

- +3.6%
- HR 0.82
- P 0.008

**RECURRENT RATE**

- HR 0.78
- - 4%
- P 0.001
QUASAR CONCLUSION

- Improvement of borderline clinical significance
  - Significant reduction in recurrence rate
    - Mostly early recurrences (2 years)
    - More pronounced in rectum

- In colon cancer stage II:
  - 18% reduction in the risk of death (absolute benefit + 3.6%)
  - No benefit > 70 years of age

- No data on benefit in high-risk patients (T4, vascular invasion, < 8 LN)
QUASAR vs. older trials

- **5FU/Levamisol (MOERTEL 1990)**
  - Stage II: 3.5y Recurrence-free survival:
    - 84 vs. 77% (ns)

- **IMPACT B2 (1999)**
  - Stage II: 5y Relapse-free survival:
    - 76 vs. 73% (ns)

- **Meta-analysis (Figueroedo JCO 2004)**
  - 37 trials, 11 meta-analysis
    - HR for recurrence: 0.87 (ns)
SEER (Medicare) Database
24,847 Patients > 65y Stage II

O'Connor E S et al. JCO 2011;29:3381-3388
Adjuvant chemotherapy for stage II

- The issue of Oxaliplatin
DFS (A) by treatment arm and (B) by treatment arm and by stage

MOSAÏC

+3.8%

©2009 by American Society of Clinical Oncology

André T et al. JCO 2009;27:3109-3116
OS (A) by treatment arm and (B) by treatment arm and by stage.
**MOSAÏC outcome according to subgroup stage II TNM VII + clinical factors**

<table>
<thead>
<tr>
<th>FOLFOX4 v FL by Subgroup</th>
<th>No. of Patients</th>
<th>Five-Year DFS</th>
<th>Five-Year TTR</th>
<th>Six-Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Stage II</td>
<td>899</td>
<td>0.84</td>
<td>0.62 to 1.14</td>
<td>.258</td>
</tr>
<tr>
<td>High risk</td>
<td>569</td>
<td><strong>0.72</strong></td>
<td><strong>0.51 to 1.01</strong></td>
<td>.062</td>
</tr>
<tr>
<td>Low risk</td>
<td>330</td>
<td><strong>1.36</strong></td>
<td><strong>0.76 to 2.45</strong></td>
<td>.305</td>
</tr>
</tbody>
</table>

Tournigand C et al. JCO 2012;30:3353-3360
Rates of (A) disease-free, (B) relapse-free, (C) overall, and (D) post–disease-free survival in high-risk stage II colon cancer treated with LV5FU2 or FOLFOX4.
Adjusted* Kaplan Meier Estimate of OS in Stage II

NSABP experience: 4 trials

- 5-FU: 2009 Pts, 483 Deaths
- 5-FU+Oxali: 991 Pts, 100 Deaths

HR = 0.95, 95% CI 0.75 - 1.21
P = 0.67

*Adjusted for age, gender, race, nodes examined, and T-stage

*Adjusted for age, gender, race, nodes examined, and T-stage
Adjuvant colon cancer: stade II
NSABP  C05-06-07-08

➔ 3000 patients stage II high (HR) and low risk (LR)
treated in NSABP studies

➔ 2009 pts treated with 5-FU and 901 with 5-FU+ oxaliplatine

<table>
<thead>
<tr>
<th>At 5 years</th>
<th>oxaliplatin</th>
<th>No oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS HR</td>
<td>81%</td>
<td>76%</td>
</tr>
<tr>
<td>DFS LR</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>OS HR</td>
<td>90%</td>
<td>87%</td>
</tr>
<tr>
<td>OS LR</td>
<td>91%</td>
<td>89%</td>
</tr>
</tbody>
</table>

➔ Minimal benefit, Risk/benefit questionable, no consensus…

GA Yothers et al., ASCO 2011, A#3507
Adjuvant treatment of colon cancer stage II

- The issue of age
Adjuvant chemotherapy of stage II colon cancer issues in the elderly

• Recent analysis showed that elderly (>70 years-old) may not benefit from adjuvant chemotherapy
  • Already seen in the Quasar trial (stage II)
  • Already seen in the Mosaïc trial (stage II and III)
  • Recently reported in NO 16968 (stage III, Xelox vs. 5FU/LV)
**Adjuvant chemotherapy in the elderly with colon cancer**

**• XELOX versus 5FU/LV (NO16968)**

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>XELOX</td>
<td>71.0%</td>
<td>HR 0.80</td>
<td>68.4%</td>
<td>66.1%</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>67.0%</td>
<td>P=0.004</td>
<td>62.3%</td>
<td>59.8%</td>
</tr>
</tbody>
</table>

Analysis according to age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>DFS (HR and CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 yrs</td>
<td>HR 0.79 (0.66-0.94)</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>HR 0.87 (0.63-1.18)</td>
</tr>
</tbody>
</table>

**• Mosaic**

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX</th>
<th>LV5FU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>155</td>
<td>160</td>
</tr>
<tr>
<td>DFS</td>
<td>HR 0.91 (0.62-1.34)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>HR 1.10 (0.73-1.65)</td>
<td></td>
</tr>
</tbody>
</table>

**→ Relapse in FOLFOX in Elderly:**
- fewer patients resected (p=0.01)
- fewer patients treated with combined therapy (p=0.01)

**→ More 2nd cancer in FOLFOX**

D.G. Haller et al. ASCO 2010. Abstract 3521
C. Tournigand et al. ASCO 2010. Abstract 3522
## Cross-trial comparison: Age

<table>
<thead>
<tr>
<th></th>
<th>NSABP C-07(^1)</th>
<th>MOSAIC(^2)</th>
<th>NO16968</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLOX(^*)</td>
<td>FOLFOX(^*)</td>
<td>XELOX(^*)</td>
</tr>
<tr>
<td>Age, years</td>
<td>&lt;70</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>DFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.66–0.88)</td>
<td>1.03 (0.77–1.36)</td>
<td>na</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.80 (0.68–0.95)</td>
<td>1.18 (0.86–1.62)</td>
<td>na</td>
</tr>
</tbody>
</table>

*Comparison vs 5-FU/LV

na: not available

1. Yothers et al. JCO 2011;28:3768–74
2. Tournigand et al. JCO 2010;28:15s (abstr 3522)
Adjuvant chemotherapy of stage II colon cancer: issues in the elderly

• Recent analysis showed that elderly (>70 years-old) may not benefit from adjuvant chemotherapy
  • Already seen in the Quasar trial (stage II)
  • Already seen in the Mosaïc trial (stage II and III)
  • Also reported in NO 16968 (stage III, Xelox vs. 5FU/LV)

• Considering the absence of clear benefit of adjuvant chemotherapy in stage II, elderly patients > 70 years of age should not be treated
Impact of Age on the Efficacy of Newer Adjuvant Therapies in Patients With Stage II/III Colon Cancer: Findings From the ACCENT Database


Conclusion

Patients age ≥ 70 years seemed to experience reduced benefit from adding oxaliplatin to fluoropyrimidines in the adjuvant setting, although statistically, there was not a significant effect modification by age, whereas oral fluoropyrimidines retained their efficacy.
Adjuvant chemotherapy for stage II colon cancer

Can we get help from biomarkers?
Microsatellite instability

Colorectal Cancer: Genomics

15% MIN (MSI+) (Microsatellite Instability)

2-3% Lynch Sx
- Germline Mutation
  MMR genes
  MLH1, MSH2, MSH6 & PMS2

13% Sporadic MSI(+)
- Epigenetic silencing of MLH1 by hypermethylation of its promoter region

85% CIN (Chromosome Instability)
  <1% FAP
  - Germline Mutation
  - APC
  Acquired
  APC, p53, DCC, kras, LOH,...

85% Sporadic
MSI-H as a consistent favorable prognostic marker

<table>
<thead>
<tr>
<th>Source</th>
<th>Stage / Treatment</th>
<th>Endpoint</th>
<th>MMR-D vs MMR-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribic et al¹</td>
<td>II/III Surgery alone</td>
<td>Overall survival</td>
<td>0.31 0.004</td>
</tr>
<tr>
<td>Sargent et al²</td>
<td>II/III Surgery alone</td>
<td>Disease-free survival Overall survival</td>
<td>0.46 0.03 0.51 0.06</td>
</tr>
<tr>
<td>Gray et al³ (QUASAR)</td>
<td>II Surgery alone</td>
<td>Recurrence-free interval</td>
<td>0.31 0.001</td>
</tr>
<tr>
<td>Roth et al⁴ (PETACC-3)</td>
<td>II 5FU ± irinotecan</td>
<td>Relapse-free survival</td>
<td>0.30 0.004</td>
</tr>
</tbody>
</table>

Recurrence by mismatch repair (MMR) status: (A) all patients, (B) colon stage II only.
A. DFS in untreated patients by DNA mismatch repair (MMR) status
B. DFS in treated patients by DNA mismatch repair (MMR) status

Sargent D J et al. JCO 2010;28:3219-3226
Predictive value of MMR status in stage II colon cancer

Sargent D J et al. JCO 2010;28:3219-3226
Conclusions

- dMMR is a prognostic marker in untreated patients
- No suggestion of benefit from 5-FU based treatment in dMMR patients
- Significant OS decrement to 5-FU based treatment in stage II patients
Braf as a prognostic biomarker

Overall Survival of Microsatellite Stable Colon Cancer Cases by BRAF V600E Status (BRAF V600E Mut or Wt)

Proportion Surviving

Survival Time (Months)

Samowitz, Can Res, 2005
Association of race with BRAF and KRAS mutation status in stage III colon cancer patients. * Reference is BRAF or KRAS mutated. † Reference is wild-type for both BRAF and KRAS. Chi-square or Fisher's exact test was used.
Gene signature in colon cancer

- Oncotype Dx (Genomic Health)
- ColDx (Almac)
- ColonPRS (Signal Genetics LLC)
- ColoPrint (Agendia NV)
- GeneFx Colon (Precision Therapeutics)
- Onco-Defender-CRC (Everist Genomics)

- Still under investigation, Not approved
- Not routinely available
- Costly
Kaplan-Meier estimates of 3-year recurrence in surgery-alone patients by risk group. (Oncotype DX)

Gray R G et al. JCO 2011;29:4611-4619
Estimated absolute risk of recurrence at 3 years with and without FUFA chemotherapy, assuming the overall treatment effect for all stage II colon cancer patients in QUASAR Oncotype DX

Low risk
- 3.1%

Intermediate risk
- 4.7%

High risk
- 5.7%

Gray R G et al. JCO 2011;29:4611-4619
ColoPrint identifies patients at risk of distant and local-regional relapse (RFS)

Local, Regional and Distant Relapse

ColoPrint risk assessment

3-year RFS
Low Risk = 91% (86-95%)
High Risk = 74% (64-83%)

5-year RFS
Low Risk = 88% (83-93%)
High Risk = 71% (62-80.5%)

Tabernero J et al ASCO GI 2012
Subgroup analysis in T3-MSS patients (n=227)

Univariate Analysis of 3-year RFS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ColoPrint</td>
<td>3.04</td>
<td>1.45-6.34</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.97-1.05</td>
<td>0.59</td>
</tr>
<tr>
<td>Localization</td>
<td>1.34</td>
<td>0.59-3.06</td>
<td>0.48</td>
</tr>
<tr>
<td>Grade</td>
<td>0.71</td>
<td>0.22-2.26</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender</td>
<td>0.46</td>
<td>0.19-1.061</td>
<td>0.07</td>
</tr>
<tr>
<td>LN &gt; 12</td>
<td>0.83</td>
<td>0.37-1.85</td>
<td>0.65</td>
</tr>
</tbody>
</table>

3-year RFS
Low Risk = 91% (86-96%)
High Risk = 73% (63-83%)

Tabernero J et al ASCO GI 2012
ColoPrint in combination with clinical factors might give best risk stratification

According to that study, for stage II ColoPrint is a better predictor than the clinico-pathologic HR and LR

3-year RFS

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk ColoPrint, low risk NCCN</td>
<td>93 %</td>
</tr>
<tr>
<td>Low Risk ColoPrint, high risk NCCN</td>
<td>88 %</td>
</tr>
<tr>
<td>High Risk ColoPrint, low risk NCCN</td>
<td>76 %</td>
</tr>
<tr>
<td>High Risk ColoPrint, high risk NCCN</td>
<td>71 %</td>
</tr>
</tbody>
</table>

Tabernero J et al ASCO GI 2012
Adjuvant chemotherapy for stage II colon cancer
ESMO recommendations (Annals of Oncology 2013)

1: wide surgical resection and anastomosis.
2: Adjuvant therapy
   -should not be routinely recommended for unselected patients.
   - In HR patients, adjuvant therapy could be considered [II, B].

ASCO recommendation
Direct evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer.
Features associated with an increased risk of recurrence include inadequate lymph node sampling, T4 disease, perforation and a poorly differentiated histology.
Possible algorithm for stage II colon cancer

Resected colon cancer

Stage II

Low risk
Stage II A
➢ >12 lymph nodes examined
➢ No vascular/neural invasion
➢ No perforation or obstruction
➢ Well differentiated

NO ADJUVANT CT

High risk
Stage IIA / IIB / IIC
➢ < 12 lymph nodes examined
➢ Vascular/neural invasion
➢ Perforation, obstruction
➢ Poorly differentiated

MMR

MSI H
No Adjuvant CT

MSI L or MSS
Discuss adjuvant CT:
➢ 5FU/LV?
➢ FOLFOX?
Integrated Centres of Oncology
ICO R Gauducheau Nantes France