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?
- Proposed algorithm
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<sup>a</sup>
T1  Tumour invades submucosa
T2  Tumour invades muscularis propria
T3  Tumour invades through the muscularis propria into the pericolic and perirectal tissues
T4a  Tumour penetrates into the surface of the visceral peritoneum<sup>b</sup>
T4b  Tumour directly invades or is adherent to other organs or structures<sup>b,c</sup>
TNM staging system AJCC/UICC 7th edition 2010
Stage II Colon Cancer: N stage

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in one to three regional lymph nodes
  - **N1a** Metastasis in one regional lymph node
  - **N1b** Metastasis in two to three regional lymph nodes
  - **N1c** Tumour satellite deposits in subsierose or in non peritonealised tissues
- **N2** Metastases in ≥4 regional lymph nodes (a: 4–6, b: ≥7)
- **M0** No distant metastases
- **M1** Distant metastases
  - **M1a** Metastases confined to one organ or site (for example liver, lung, ovary, nonregional node)
  - **M1b** Metastases in more than one organ/site or the peritoneum
TNM staging system
AJCC/UICC 7th edition 2010
Stage II Colon Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T Stage</th>
<th>N Stage</th>
<th>M Stage</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

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
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>
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<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.
* I.e., 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 factors

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

**Histological factors:** (sometimes 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>95.6%</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>

Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart AK, J Clin Oncol, 28 264-71, 2009

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

Niedzwiecki D et al. JCO 2011;29:3146-3152
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

<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 $\geq 70$</td>
<td>0.03</td>
</tr>
<tr>
<td>Differenciartion</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

<table>
<thead>
<tr>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>T4b</td>
</tr>
<tr>
<td>T4a?</td>
<td>T4a?</td>
</tr>
<tr>
<td>No obstruction (subjective)</td>
<td>Obstruction (subjective)</td>
</tr>
<tr>
<td>No perforation</td>
<td>Perforation</td>
</tr>
<tr>
<td>No lymphovascular invasion</td>
<td>Lymphovascular invasion</td>
</tr>
<tr>
<td>No perineural invasion</td>
<td>Perineural invasion</td>
</tr>
<tr>
<td>Well differenciated</td>
<td>Poorly differenciated</td>
</tr>
</tbody>
</table>
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

1567 patients with recent follow-up available for analysis

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

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 &gt;70</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

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

#### OS

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

#### RECURRENCE RATE

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>
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
OS (A) by treatment arm and (B) by treatment arm and by stage.

MOSAÏC
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>0.72</td>
<td>0.51 to 1.01</td>
<td>.062</td>
</tr>
<tr>
<td>Low risk</td>
<td>330</td>
<td>1.36</td>
<td>0.76 to 2.45</td>
<td>.306</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.

Tournigand C et al. JCO 2012;30:3353-3360
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

Yothers ASCO 2011
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+ oxaliplatin

<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 3 years</th>
<th>DFS 4 years</th>
<th>DFS 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>XELOX</td>
<td>71,0%</td>
<td>HR 0,80</td>
<td>68,4%</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>67,0%</td>
<td>P=0,004</td>
<td>62,3%</td>
</tr>
</tbody>
</table>

Analysis according to age

- <70 ans: HR 0,79 (95% CI 0,66-0,94)
- > 70 ans: HR 0,87 (95% CI 0,63-1,18)

- **Mosaic**

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX</th>
<th>LV5FU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=315</td>
<td>155</td>
<td>160</td>
</tr>
<tr>
<td>DFS</td>
<td>HR 0,91 (95% IC 0,62-1,34)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>HR 1,10 (95% IC 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**
## Cross-trial comparison: Age

<table>
<thead>
<tr>
<th></th>
<th>NSABP C-07&lt;sup&gt;1&lt;/sup&gt;</th>
<th>MOSAIC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NO16968</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLOX*</td>
<td>FOLFOX*</td>
<td>XELOX*</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>0.76</td>
<td>na</td>
<td>0.80</td>
</tr>
<tr>
<td>≥70</td>
<td>1.03</td>
<td>na</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>DFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>(0.66–0.88)</td>
<td>(0.62–1.34)</td>
<td>(0.67–0.94)</td>
</tr>
<tr>
<td></td>
<td>(0.77–1.36)</td>
<td>(0.64–1.16)</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.80</td>
<td>na</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>(0.68–0.95)</td>
<td>(0.67–1.65)</td>
<td>(0.66–1.26)</td>
</tr>
<tr>
<td></td>
<td>1.18</td>
<td>na</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>(0.86–1.62)</td>
<td>(0.73–1.65)</td>
<td>(0.66–1.26)</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)

Schmol H.J. ASCO GI 2012
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)

- Considering the absence of clear benefit of adjuvant chemotherapy in stage II, elderly patients > 70 years of age should not be treated
Adjuvant chemotherapy for stage II colon cancer

Can we get help from biomarkers?
Microsatellite instability

Colorectal Cancer: Genomics

15%
MIN (MSI+)
(Microsatellite Instability)

85%
CIN
(Chromosome 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

<1% / 85%
FAP
Germline Mutation
APC
Sporadic
Acquired
APC, p53, DCC, kras, LOH,...
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 al(^1)</td>
<td>II/III Surgery alone</td>
<td>Overall survival</td>
<td>0.31, 0.004</td>
</tr>
<tr>
<td>Sargent et al(^2)</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 al(^3) (QUASAR)</td>
<td>II Surgery alone</td>
<td>Recurrence-free interval</td>
<td>0.31, 0.001</td>
</tr>
<tr>
<td>Roth et al(^4) (PETACC-3)</td>
<td>II 5FU ± irinotecan</td>
<td>Relapse-free survival</td>
<td>0.30, 0.004</td>
</tr>
</tbody>
</table>

QUASAR

Recurrence by mismatch repair (MMR) status: (A) all patients, (B) colon stage II only.

Hutchins G et al. JCO 2011;29:1261-1270
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
MSI as an indicator for adjuvant CT in stage II

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
Gene signature in colon cancer

- Oncotype Dx (Genomic Health)
- ColIDx (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)
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 (Quick and Simple and Reliable) Oncotype DX

Low risk - 3.1%

Intermediate risk - 4.7%

High risk - 5.7%
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>
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<tr>
<td>Age</td>
<td>1.01</td>
<td>0.97-1.05</td>
<td>0.59</td>
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<tr>
<td>Localization</td>
<td>1.34</td>
<td>0.59-3.06</td>
<td>0.48</td>
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<tr>
<td>Grade</td>
<td>0.71</td>
<td>0.22-2.26</td>
<td>0.27</td>
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<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>

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

ColoPrint + NCCN clinical factors

All patients

3-year RFS

93 %  Low Risk ColoPrint, low risk NCCN
88 %  Low Risk ColoPrint, high risk NCCN
76 %  High Risk ColoPrint, low risk NCCN
71 %  High Risk ColoPrint, high risk NCCN

Tabernerio J et al ASCO GI 2012
Adjuvant chemotherapy for stage II colon cancer

ESMO recommendations (Annals of Oncology 2010)

Standard treatment options: (i) wide surgical resection and anastomosis; (ii) following surgery, in high-risk patients (who present at least one of the previously mentioned features) adjuvant therapy could be considered in clinical practice [II, B]. Even better, all patients should be considered for entry into randomized clinical trials evaluating new options for adjuvant treatment.

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?