Adjuvant treatment of stage II: Which patients to treat?

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Gunderson et al, JCO 2009
Stage II

Small survival benefit (3%) with 5-FU

No further improvement with FOLFOX

?? Does a Clinically defined high risk group benefit from FOLFOX (PFS) ??
Clinical Data in Stage II Colon Cancer

• Randomized trials: Stage II subsets

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Arms</th>
<th>5y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup 0035</td>
<td>935</td>
<td>5FU/LV vs. Obs.</td>
<td>72% vs. 72%</td>
</tr>
<tr>
<td>QUASAR</td>
<td>3238</td>
<td>FU vs. Obs.</td>
<td>80% vs. 77%</td>
</tr>
<tr>
<td>IMPACT B2</td>
<td>1016</td>
<td>5FU vs. Obs.</td>
<td>82% vs. 80%</td>
</tr>
</tbody>
</table>

• QUASAR-1: superior OS with adjuvant therapy for stage II disease

Gray et al. Lancet 2007
SEER (Medicare) Database
Patients > 65y
Stage II and III
n=43032 1992-2005

Stage II
No risk factor

Stage III

O'Connor et al. JCO 2011
Adjusted* Kaplan Meier Est

NSABP experience: 4 trials

Overall Survival

- 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

Number at-risk
- 5-FU: 1851, 1710, 1571
- 5-FU+Oxali: 893, 339, 247

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

Yothers ASCO 2011
MOSAIK FOLFOX vs. FU/LV
Overall survival all stage II patients

Data cut-off: January 2007

Probability

Overall survival (months)

HR [95% CI]

Stage II 1.00 [0.71–1.42]
Stage III 0.80 [0.66–0.98]

p=0.996

De Gramont et al. ASCO 2007
MOSAIK: disease free survival
High-risk Stage II Patients

Disease-free survival (months)

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX4 n=286</th>
<th>LV5FU2 n=290</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year</td>
<td>85.4%</td>
<td>80.4%</td>
</tr>
<tr>
<td>5-year</td>
<td>82.1%</td>
<td>74.9%</td>
</tr>
</tbody>
</table>

HR [95% CI]: 0.74 [0.52–1.06]

High-risk stage II- defined as at least one of the following:
- T4, tumor perforation, bowel obstruction,
- poorly differentiated tumor, venous invasion,
- <10 lymph nodes examined;

Data cut-off: June 2006

7.2%

De Gramont et al. ASCO 2007
Updated MOSAIK data High Risk Stage II
FOLFOX vs. FU/LV

<table>
<thead>
<tr>
<th>Age</th>
<th>N Pat</th>
<th>5 y DFS</th>
<th>6 y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>high risk</td>
<td>569</td>
<td>0.72</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.51-1.01</td>
<td>0.66-.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.062</td>
<td>.648</td>
</tr>
<tr>
<td>low risk</td>
<td>330</td>
<td>1.36</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.76-2.45</td>
<td>0.67-2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.01</td>
<td>.399</td>
</tr>
</tbody>
</table>

Tournigant et al. JCO 2012
Patient groups in adjuvant Therapy

- No benefit
- Cured
- Cured by surgery already

Graph showing patient groups over time.
Are there subgroups that might benefit from adjuvant chemotherapy?
Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer

Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:
- MMR-D is synonymous with MSI-H
- MMR-P is synonymous with MSI-L/MSS

# MMR-Deficiency (MSI-H) is a Favorable Prognostic Marker

The ~15% of stage II colon cancer patients with MMR-deficient (MSI-H) tumors have been found consistently to have a lower risk of recurrence and/or death.

<table>
<thead>
<tr>
<th>Source</th>
<th>Stage / Treatment</th>
<th>Endpoint</th>
<th>MMR-D vs MMR-P HR (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribic et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>II/III Surgery alone</td>
<td>Overall survival</td>
<td>0.31 (0.14-0.72); p=0.004</td>
</tr>
<tr>
<td>Sargent et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>II/III Surgery alone</td>
<td>Disease-free survival</td>
<td>0.46 (0.22-0.95); p=0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall survival</td>
<td>0.51 (0.24-1.10); p=0.06</td>
</tr>
<tr>
<td>Gray et al&lt;sup&gt;3&lt;/sup&gt; (QUASAR)</td>
<td>II Surgery alone</td>
<td>Recurrence-free interval</td>
<td>0.31 (0.15-0.63); p&lt;0.001</td>
</tr>
<tr>
<td>Roth et al&lt;sup&gt;4&lt;/sup&gt; (PETACC-3)</td>
<td>II 5FU ± irinotecan</td>
<td>Relapse-free survival</td>
<td>0.30 p=0.004</td>
</tr>
</tbody>
</table>

Stage II and III
MSI is prognostic and predictive

DFS by MMR status

Untreated

5Y DFS; p=.009

dMMR  80%
pMMR  56%

Treated

5Y DFS; p=.30

dMMR  70%
pMMR  67%

dMMR: deficient MMR
pMMR: proficient MMR

Sargent D J et al. JCO 2010;28:3219
### Are stage II and Stage III different diseases?

**Prognostic Value (RFS)**

*Multivariate Analysis in whole population*

<table>
<thead>
<tr>
<th>Markers</th>
<th>Stage II</th>
<th></th>
<th>Stage III</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR§</td>
<td>p value*</td>
<td>HR§</td>
<td>p value*</td>
</tr>
<tr>
<td>T Stage (T4 vs T3)</td>
<td>2.8</td>
<td>0.0001</td>
<td>1.6</td>
<td>0.0006</td>
</tr>
<tr>
<td>N Stage (N2 vs N1)</td>
<td>N/A</td>
<td>N/A</td>
<td>2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histologic Grade (3-4 vs 1-2)</td>
<td>0.6</td>
<td>0.55</td>
<td>1.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Age (&gt;60 vs ≤60)</td>
<td>1.8</td>
<td>0.026</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>MSI (High vs Stable)</td>
<td>0.3</td>
<td>0.027</td>
<td>0.7</td>
<td>0.12</td>
</tr>
<tr>
<td>p53 (High)</td>
<td>0.7</td>
<td>0.27</td>
<td>1.3</td>
<td>0.015</td>
</tr>
<tr>
<td>SMAD4 (any loss)</td>
<td>1.0</td>
<td>0.9</td>
<td>1.6</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Treatment, Sex, Site, KRAS, BRAF, TS, 18qLOH (Stage II: HR 1.4, p=0.33), hTERT: not significant

* p values from the Wald test in a multiivariate Cox regression

§ HR = hazard ratio
Gene expression signatures

ColoPrint / Agendia
*Fresh frozen tumor tissue*
N=188 stage I-IV CRC

Almac Diagnostics
*Formalin-fixed paraffin-embedded*
N=144 stage II Colon Cancer

Salazar et al. JCO 2011

Kennedy et al. JCO 2011
Prediction of recurrence in Stage II Colon Cancer
Clinical vs. ColoPrint assessment

Clinical assessment

All stage II
N=416

ColoPrint assessment

All stage II
N=416

stage II MSI-S/L
N=301

Kopetz et al. The Oncologist 2015
Prediction of recurrence in Stage II Colon Cancer
Clinical vs. ColoPrint assessment

Multivariate Analysis for risk of recurrence:

<table>
<thead>
<tr>
<th></th>
<th>all pts</th>
<th>untreated pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ColoPrint</td>
<td>2.16</td>
<td>2.65</td>
</tr>
<tr>
<td>MSI vs. MSS</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Other variables:
- Age, Localisation (r/l), grade (1/2 vs. 3), gender, LN, pT (3 vs. 4), Tx (y/n), NCCN clinical factors

Kopetz et al. The Oncologist 2015
Gen-Expression Assay (OncoType Dx)

CRC Stage II

Breast Cancer N- HR +

Gray et al. JCO 2011
Paik et al. NEJM 2004
Recurrence Score® Guideposts for Clinical Decisions: T3, MMR-P Patients with RS ≥ 41

This population of patients with high Recurrence Score disease (~25% of total) has recurrence risk that overlaps with T4 patients and would be expected to have >3% benefit with adjuvant 5FU.
Gen-Expression assay not predictive for adjuvant chemotherapy

Gray et al. JCO 2011
Gene expression platforms in stage II colon cancer all describing prognosis

<table>
<thead>
<tr>
<th>Platform</th>
<th>Oncotype</th>
<th>ColDx</th>
<th>ColoPrint</th>
<th>Preivstage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training set</td>
<td>Stage II/III</td>
<td>Stage II</td>
<td>Stage II/III</td>
<td>Stage II</td>
</tr>
<tr>
<td>Validation set</td>
<td>Stage II</td>
<td>Stage II</td>
<td>Stage II/III</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>n=1436</td>
<td>n=144</td>
<td>n=114</td>
<td></td>
</tr>
<tr>
<td>Tissue source</td>
<td>FFPE</td>
<td>FFPE</td>
<td>Fresh frozen</td>
<td>FFPE LN</td>
</tr>
<tr>
<td>Type of study</td>
<td>Prospective</td>
<td>retrospective</td>
<td>Prospective</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Adj Ctx inclued</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MMR data</td>
<td>Available</td>
<td>Not available</td>
<td>Available</td>
<td>Available</td>
</tr>
<tr>
<td>Technology</td>
<td>RT-PCR</td>
<td>Microarray</td>
<td>Microarray</td>
<td>qRT-PCR</td>
</tr>
<tr>
<td>Type of gene signature</td>
<td>12-gene-signature</td>
<td>634-transcript signature</td>
<td>18-gene classifier</td>
<td>GCC gene expression</td>
</tr>
<tr>
<td>RR high risk group</td>
<td>22%</td>
<td>60%</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>RR reduction to achieve absolute RR of 5%</td>
<td>23%</td>
<td>8%</td>
<td>19%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Chee & Meropol The Oncologist 2014
**Different intentions to use Gen-Expression Assays in Breast or Colon Cancer**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Stage</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>N- (N1-3) HR+</td>
<td>Not to use chemo</td>
</tr>
<tr>
<td>Colon</td>
<td>N- (pMSI?)</td>
<td>To use chemo</td>
</tr>
</tbody>
</table>
Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis

Zhang et al. Lancet Oncol 2013
Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis

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Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis

Zhang et al. Lancet Oncol 2013
Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis

Zhang et al. Lancet Oncol 2013
Adjuvant! Online Prediction: Cancer and non-cancer related 5-year-Mortality

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

Assumption of Gill model
Algorithm for treatment decision in stage II colon cancer

The decision for adjuvant therapy has to balance the risk of cancer and other competing risks.

Stage II colon cancer

- Age < 60y
- Advanced age or comorbidities

**pT4**
- pMMR / MSI-H
- pT3
- dMMR / MSS
- Additional marker? Gen signature / miRNA?

- Consider adj. CTx
- No adj. CTx