Can We Refine The Selection Of Adjuvant Therapy For Stage II Colon Cancer?

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USA
Prognosis of Stage II and III CC - AJCC v7

Gunderson et al, JCO 2009
QUASAR: OS in patients with “no clear indication for chemo” (mostly stage II)
5-FU/LV vs surgery alone

5-year OS, Observation = 77.4% vs Chemotherapy = 80.3%
Relative risk = 0.83 (95% CI, 0.71-0.97)

5-yr OS difference: 2.9%

P = .02
QUASAR group, Lancet 2007
In 2004, Standard Adjuvant Therapy in Stage III Colon Cancer Defined by MOSAIC

**n=2246**
- **Enrollment:** Oct 1998–Jan 2001 (146 centers; 20 countries)
  - Completely resected colon cancer
  - **Stage II, 40%; Stage III, 60%**
  - Age 18–75 years
  - KPS ≥60
  - No prior chemotherapy

- **Primary end-point:** disease-free survival
- **Secondary end-points:** safety, overall survival

LV5FU2, Leucovorin 200 mg/m² iv over 2 hours followed by 5-fluorouracil 400 mg/m² bolus and 5-fluorouracil 600 mg/m² iv over 22 hours on Days 1 and 2, every 14 days; FOLFOX4, LV5FU2 + oxaliplatin 85 mg/m² iv over 2 hours on Day 1

Stage III: 1347 pts

Andre NEJM 2004
“High-risk” Stage II Colon Cancer

• Clinical-pathological parameters
  • T4 tumors
  • Less than 10 (12) LNs examined
  • Obstruction/perforation
  • Lymphatic or vascular invasion
  • Undifferentiated histology
## MOSAIC: Disease-free Survival

<table>
<thead>
<tr>
<th></th>
<th>5-year DFS %</th>
<th>HR [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX4</td>
<td>LV5FU2</td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>73.3</td>
<td>67.4</td>
<td>0.80 [0.68–0.93]</td>
</tr>
<tr>
<td>Stage III</td>
<td>66.4</td>
<td>58.9</td>
<td>0.78 [0.65–0.93]</td>
</tr>
<tr>
<td>Stage II</td>
<td>83.7</td>
<td>79.9</td>
<td>0.84 [0.62–1.14]</td>
</tr>
<tr>
<td>High-risk stage II</td>
<td>82.1</td>
<td>74.9</td>
<td>0.74 [0.52–1.06]</td>
</tr>
<tr>
<td>Low-risk stage II</td>
<td>86.3</td>
<td>89.1</td>
<td>1.22 [0.66–2.26]</td>
</tr>
</tbody>
</table>

Andre et al., JCO 2009
MOSAIC 6 yr OS: Stage II and Stage III

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**Probability of survival at 6 years (%)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>FL</th>
<th>FL + oxaliplatin</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>86.8</td>
<td>86.9</td>
<td>1.00 (0.70 to 1.41)</td>
<td>.986</td>
</tr>
<tr>
<td>Stage III</td>
<td>68.7</td>
<td>72.9</td>
<td>0.80 (0.65 to 0.97)</td>
<td>.023</td>
</tr>
</tbody>
</table>

Andre et al., JCO 2009
Who benefits from adjuvant therapy in stage II colon cancer?

Cured because they got adjuvant therapy after surgery

Only ones that benefit from chemo (as measured by cure)

FOLFOX/CAPEX

Modified from Meyerhardt, ASCO 2017
“High-risk” Stage II Colon Cancer

- Clinical-pathological parameters
  - T4 tumors
  - Less than 10 (12) LNs examined
  - Obstruction/perforation
  - Lymphatic or vascular invasion
  - Undifferentiated histology

- Molecular parameters
  - Single marker vs signature
DFS/OS in Stage II MMR-D Patients (N=102)

5-yr DFS

- Untreated: 87%
- Treated: 72%
- HR: 2.80 (0.98-8.97)
- p=0.05

N = 47

5-yr OS

- Untreated: 93%
- Treated: 75%
- HR: 3.15 (1.07-9.29)
- p=0.03

Sargent JCO 2010
### PETACC 3: Multivariate Analysis Prognostic Factors Stage II

<table>
<thead>
<tr>
<th>Markers</th>
<th>HR [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 v. T3</td>
<td>2.58 [1.56 - 4.28]</td>
<td>0.00024</td>
</tr>
<tr>
<td>MSI-H v. MSS</td>
<td>0.28 [0.10 - 0.72]</td>
<td>0.0089</td>
</tr>
<tr>
<td>18qLOH</td>
<td>1.37 [0.67 - 2.77]</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Decision Algorithm in Adjuvant Therapy - 2010

Resected Colon Ca

Stage II
- T4 and/or <12 LNs
  - yes: High-Risk
  - no: MMR-D
    - yes: Intermed. Risk
      - yes: FOLFOX XELOX
      - no: 5-FU/LV or Capecitabine
    - no: Marker signature?
      - yes: No therapy!
      - no: *pts not considered candidates for oxaliplatin

Stage III
- yes: FOLFOX XELOX
- no: 5-FU/LV or Capecitabine

Grothey, Oncology 2010
QUASAR: Recurrence Score, T Stage, and MMR Deficiency Independent Predictors of Recurrence in Stage II Colon Cancer

Kerr et al., ASCO 2009, abstr. 4000
QUASAR Results: Recurrence Risk in Pre-specified Recurrence Risk Groups (n=711)

Comparison of High vs. Low Recurrence Risk Groups using Cox Model: HR = 1.47 (p=0.046)

<table>
<thead>
<tr>
<th>Recurrence Risk Group</th>
<th>Range of RS</th>
<th>Proportion of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;30</td>
<td>43.7%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30-40</td>
<td>30.7%</td>
</tr>
<tr>
<td>High</td>
<td>≥41</td>
<td>25.6%</td>
</tr>
</tbody>
</table>

Kerr et al., ASCO 2009, abstr. 4000
Circulating Tumor DNA (ctDNA)

**Biology of ctDNA**
- Tumors release small **cell-free DNA** fragments
- ctDNA ≠ CTC (circulating tumor cells)
- Identify point mutations (or other genetic changes) in tumor → examine blood for matching mutation

**ctDNA in Solid Tumors**
- Frequently detected in metastatic solid malignancies
- ? Useful marker of minimal residual disease after early-stage cancer surgery (lung, breast, pancreas)

250 Subjects with Stage II Colon Cancer

July 2011 – Sept 2014

Excluded (n = 19): ineligible (n = 8), withdrew consent (n = 4), insufficient blood (n = 7)

Tumor Tissue (n = 231)
- Targeted Sequencing of 15 Genes

Mutated Identified (n = 230)

Blood Collection
- 4 – 10 weeks post-op (n = 231)
- 3-monthly follow-up blood collection (n = 167)

Blood Biomarker Analysis
- Circulating tumor DNA
- Serum CEA

Standard Follow-Up
- +/- Adjuvant Chemotherapy*
- Surveillance
  - 3-monthly review + CEA
  - 6-monthly CT for 2 years

Evaluable Population (n = 230)
- Median follow-up 27 mths
- Recurrences (n = 34, 15%)

*Adjuvant chemotherapy at clinician discretion [Chemo = 52 (23%); No chemo = 178 (77%)]

Tie et al. Sci Transl Med 2016
Recurrence-Free Survival
(Patients \textit{not} treated with chemotherapy)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>3-yr RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctDNA Negative</td>
<td>164</td>
<td>16</td>
<td>90%</td>
</tr>
<tr>
<td>ctDNA Positive</td>
<td>14</td>
<td>11</td>
<td>0%</td>
</tr>
</tbody>
</table>

HR: 18 (95% CI: 7.9–40), \( p < 0.001 \)

Tie et al. Sci Transl Med 2016
Clinical Low-Risk
(dMMR or pMMR + no poor prognostic features)

Clinical High-Risk
(pMMR + at least one poor prognostic feature)

Recurrence-Free Survival

Tie et al. Sci Transl Med 2016
### RFS: Univariate and Multivariate Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
<td>HR</td>
</tr>
<tr>
<td>T stage, T3 vs T4</td>
<td>4.0</td>
<td>0.002</td>
<td>8.1</td>
</tr>
<tr>
<td>Lymph node yield, ≥12 vs &lt;12</td>
<td>3.1</td>
<td>0.009</td>
<td>--</td>
</tr>
<tr>
<td>Lymphovascular invasion, no vs yes</td>
<td>2.4</td>
<td>0.03</td>
<td>--</td>
</tr>
<tr>
<td>MMR status, deficient vs proficient</td>
<td>3.6</td>
<td>0.08</td>
<td>--</td>
</tr>
<tr>
<td>Clinical Risk Group, low vs high</td>
<td>3.2</td>
<td>0.002</td>
<td>--</td>
</tr>
<tr>
<td>Post-op ctDNA status, negative vs positive</td>
<td>18</td>
<td>&lt;0.001</td>
<td>28</td>
</tr>
</tbody>
</table>

*Multivariate analysis performed with manual backwards step-wise cox regression modelling adjusting for T stage, LN yield, LVI, MMR and post-op ctDNA.

Tie et al. Sci Transl Med 2016
ctDNA and 3-year Recurrence Prediction Accuracy

Post-op ctDNA Positive

Yes

8%

PPV = 100%

No Recurrence

92%

0%

9%

NPV = 91%

No Recurrence

Post-op ctDNA Positive

Yes

8%

PPV = 100%

No Recurrence

92%

0%

9%

NPV = 91%

No Recurrence

Tie et al. Sci Transl Med 2016
Markers of Minimal Residual Disease - Consequences for adjuvant therapy

1. Treat where we would normally NOT treat (stage II)
   • Identify patient population at high risk for recurrence

2. NOT treat where we would normally treat (stage III)
   • Identify patient population with very low risk of recurrence

Each of these settings has unique ethical challenges
NRG CR 1643: ctDNA as a predictive marker for response to adjuvant chemotherapy in Stage II colon cancer

Endpoints:
Phase II: Clearing rate of ctDNA
Phase III: DFS

PI V. Morris
DYNAMIC Study

Stage II Colon Cancer (N=450)

ctDNA testing

Biomarker Driven Group (N=300)

ctDNA

Pos
Adjuvant Tx

Neg
No adjuvant Tx

Standard Group* (N=150)

*blinded to ctDNA results
Conclusions

After more than a decade of stagnation, we now see new developments in adjuvant colon cancer

• Shorter duration of therapy and focus on CAPOX constitutes appropriate adjuvant therapy for most patients with stage III colon (and rectal) cancer
  • Analysis of stage II population ongoing

• Molecularly defined patient subgroups are specifically targeted with immunotherapy and biologics (MSI-H, BRAF)

• Innovations in molecular techniques allow to investigate concept of minimal residual disease in CRC