Oncotype DX® Colon Cancer Assay Symposium

Ready for Use in Adjuvant Therapy Decision?
• Which one of these patients should receive treatment?
  • Patient 1 or 2 or Both or Neither

• Would you order any additional molecular tests ie. Oncotype DX?
  • Yes or No

• What chemotherapy would you use?
  • 5FU/cape or FOLFOX?
## NCCN Guidelines Version 2.2014
### Colon Cancer

<table>
<thead>
<tr>
<th>Pathologic Stage</th>
<th>Adjuvant Therapy</th>
<th>Surveillance</th>
</tr>
</thead>
</table>
| T3, N0, M0 (no high risk features) | Clinical trial or Observation or Consider capcitabine or 5-FU/leucovorin | • History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y  
• CEA every 3-6 mo for 2 y, then every 6 mo for a total of 5 y  
• Chest/abdominal/pelvic CT annually for up to 5 y for patients at high risk for recurrence  
• Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo:  
  ➢ If advanced adenoma, repeat in 1 y  
  ➢ If no advanced adenoma, repeat in 3 y, then every 5 y  
• PET-CT scan is not routinely recommended  
• See Principles of Survivorship (COL-G) |
| T3, N0, M0 at high risk for systemic recurrence or T4, N0, M0 | Capecitabine or 5-FU/leucovorin or FOLFOX or CapeOx or FLOX or Clinical trial or Observation | |
PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE

- Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.

- When determining if adjuvant therapy should be administered, the following should be taken into consideration:
  - Number of lymph nodes analyzed after surgery (<12)
  - Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; perineural invasion; localized perforation; close, indeterminate, or positive margins)
  - Assessment of other comorbidities and anticipated life expectancy.

- The benefit of adjuvant chemotherapy does not improve survival by more than 5%.

- MSI Testing - See NCCN Guidelines for Colorectal Cancer Screening
  The panel recommends that MMR protein testing be performed for all patients younger than 50 years with colon cancer, based on an increased likelihood of Lynch syndrome in this population. MMR testing should also be considered for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.
The Stage II Colon Cancer Controversies/Dilemmas

- Complicated discussion with patients
  - Patient perceptions of risk (and MD’s)
  - Cannot predict absolute risk for individual
  - Cannot link risk and treatment benefit
  - Cannot define which factors are most important
QUASAR: 5FU/LV Chemotherapy Benefit in the 1,436 Evaluable Stage II Colon Cancer Patients

RFI (recurrence-free interval)

DFS (disease-free survival)

OS (Overall Survival)

Kerr et al., ASCO 2009, #4000
MOSAIC: Kaplan-Meier estimates of disease-free survival by treatment arm and by stage (B)

André T et al. JCO 2009;27:3109-3116
MOSAIC: Kaplan-Meier estimates of overall survival by treatment arm and by stage (B)
80% of Recurrences occur by 2 years

Risk of recurrence by 6-month interval

Sargent D et al. JCO 2009;27:872-877
Existing Tools for Selecting Stage II Patients for Treatment Are Inadequate

<table>
<thead>
<tr>
<th>Recurrence Risk</th>
<th>Treatment Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T-Stage</td>
<td>• MMR?</td>
</tr>
<tr>
<td>• Bowel obstruction or perforation</td>
<td></td>
</tr>
<tr>
<td>• Mismatch Repair (MMR)</td>
<td></td>
</tr>
<tr>
<td>• Margin status</td>
<td></td>
</tr>
<tr>
<td>• # of lymph nodes assessed</td>
<td></td>
</tr>
<tr>
<td>• Tumor grade</td>
<td></td>
</tr>
<tr>
<td>• Lymphatic/vascular invasion</td>
<td></td>
</tr>
<tr>
<td>• Perineural invasion</td>
<td></td>
</tr>
</tbody>
</table>

According to Current Guidelines\(^1,2\)

• Only one molecular marker, MMR status, recommended.
• Treatment decisions are based on the expectation that higher risk stage II patients derive larger absolute benefit with adjuvant chemotherapy

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Evaluating Genomic Assays

Analytical Validity

Fit for purpose

Clinical Validity

Clinical Utility

Development and Validation of the Onco
type DX® Colon Cancer Assay for Use in Stage II/III Colon Cancer

Development Studies – Stage II & III (n=1851, 761 genes)
NSABP C-01/C-02 (n = 270)  NSABP C-04 (n = 308)
Cleveland Clinic (n = 765)  NSABP C-06 (n = 508)

Clinical Validation – Stage II Colon Cancer
QUASAR (N = 1436)
CALGB 9581 (N = 690)

Clinical Validation Study – Stage II/III Colon Cancer
5FU vs 5FU+Oxaliplatin
NSABP C-07 (N = 892)

Prospective Decision Impact Study
Mayo Clinic Network (N = 141)
The 12-Gene OncoType DX® Colon Cancer Recurrence Score® Result

Recurrence Score Genes and Algorithm

**STROMAL**
- FAP
- INHBA
- BGN

**CELL CYCLE**
- Ki-67
- C-MYC
- MYBL2

**REFERENCE**
- ATP5E
- GPX1
- PGK1
- UBB
- VDAC2

Recurrence Score Result = 0.15 x Stromal Group
- 0.30 x Cell Cycle Group
+ 0.15 x GADD45B

Validation Study of a Quantitative Multigene Reverse Transcriptase–Polymerase Chain Reaction Assay for Assessment of Recurrence Risk in Patients With Stage II Colon Cancer

Richard G. Gray, Philip Quirke, Kelly Handley, Margarita Lopatin, Laura Magill, Frederick L. Baehner, Claire Beaumont, Kim M. Clark-Langone, Carl N. Yoshizawa, Mark Lee, Drew Watson, Steven Shak, and David Kerr

Clinical Validation of the Pre-specified Colon Cancer Assay: Stage II Colon Cancer Patients from QUASAR

- Enrolled 1994-2003, primarily from UK
- Parent study demonstrated 3-4% absolute benefit of adjuvant 5FU/LV for stage II disease (approximate 20% relative risk reduction)

QUASAR:
Evaluable Stage II Colon Cancer Patients

Parent QUASAR Trial
n = 3239

Patients with collected blocks
n = 2197 (68%)

Confirmed stage II colon cancer
n = 1490 (69%)

Final evaluable populations
n = 1436

707 cases of stage III and rectal cancer

54 excluded (3.6%):
- 29 synchronous tumors
- 8 insufficient tissue
- 7 identifier queries
- 6 RNA quality/quantity
- 4 ineligible histology

QUASAR Results: Colon Cancer Recurrence Score® Predicts Recurrence Following Surgery

Prospectively-defined Primary Analysis in Stage II Colon Cancer (n = 711)

## QUASAR Results: Clinical/Pathological Covariates and Recurrence

### Pre-specified Multivariable Analysis, Surgery Alone Patients (n = 605)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence Score®</td>
<td>Continuous per 25 units</td>
<td>1.61</td>
<td>(1.13, 2.29)</td>
<td>0.008</td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td>13% deficient vs. 87% proficient</td>
<td>0.32</td>
<td>(0.15, 0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T stage</td>
<td>15% T4 vs. 85% T3</td>
<td>1.83</td>
<td>(1.23, 2.75)</td>
<td>0.005</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>29% high vs. 71% low</td>
<td>0.62</td>
<td>(0.40, 0.96)</td>
<td>0.026</td>
</tr>
<tr>
<td># of nodes examined</td>
<td>62% &lt;12 vs. 38% ≥ 12</td>
<td>1.47</td>
<td>(1.01, 2.14)</td>
<td>0.040</td>
</tr>
<tr>
<td>LVI</td>
<td>13% present vs. 87% absent</td>
<td>1.40</td>
<td>(0.88, 2.23)</td>
<td>0.175</td>
</tr>
</tbody>
</table>

In these multivariable analyses, the Recurrence Score result, MMR status, and T stage were found to be the most significant independent predictors of recurrence risk.

MMR-D and Disease Free Survival in Stage II Colon Cancer: Utility of Adjuvant 5FU Therapy

Pooled Analysis of Stage II MMR-D patients from randomized trials (surgery alone vs. 5-FU)

Whether 5-FU is harmful in MMR-D patients remains controversial, but at best, 5-FU appears to yield little, if any, absolute benefit for MMR-D patients.

• Gene expression profiling of known MSI-H stage II pt resulted in 64-gene signature
  • Similar mutation frequency and clinico-pathologic features
• Doubled the number of MSI-H with similar favorable prognosis
• J Pathol 2012; 228: 586–595
Recurrence Score® Guideposts for Clinical Decision-Making: T3, MMR-P Patients With Recurrence Score Result ≥41

- T4 and MMR proficient (13%)
- T3 and MMR proficient (74%)
- T3 and MMR deficient (11%)

Recurrence Score results for T3 MMR-P patients ≥41 (~25% of total) has recurrence risk (>18%) that overlaps with T4 MMR-P patients and would be expected to have a higher absolute benefit with adjuvant 5FU.

Recurrence Score® Guideposts for Clinical Decision-Making: T3N0 MMR-P Patients With Recurrence Score Results <30

Patients with Recurrence Score results for T3 MMR-P patients <30 (~45% of total) have recurrence risks ≤15% and would be expected to have <3% absolute benefit with adjuvant 5FU.

Relationship of 5FU/LV Absolute Benefit and Recurrence Score® Result

- Proportional reductions in risk of recurrence with 5FU were similar across Recurrence Score groups (Recurrence Score result by treatment interaction p = 0.76).
- The absolute improvements in 3-year recurrence with adjuvant 5FU/LV treatment will increase with increasing Recurrence Score result from approximately 3% in the low-risk group to approximately 6% in the high-risk group.

QUASAR Validation Summary:
The Recurrence Score result predicts the recurrence risk for Stage II colon cancer patients

The continuous Recurrence Score® result:

• Independently, quantitatively predicts individual recurrence risk
• Provides additional clinical value beyond available measures
• Has the greatest clinical utility for T3, MMR-P patients, who constitute the majority of stage II colon cancer patients (~70%).

These results support a new paradigm for quantitative assessment of recurrence risk in stage II colon cancer, emphasizing the role of three measures: Recurrence Score result, MMR, and T stage.

Biologic Determinants of Tumor Recurrence in Stage II Colon Cancer: Validation Study of the 12-Gene Recurrence Score in Cancer and Leukemia Group B (CALGB) 9581

Alan P. Venook, Donna Niedzwiecki, Margarita Lopatin, Xing Ye, Mark Lee, Paula N. Friedman, Wendy Frankel, Kim Clark-Langone, Carl Millward, Steven Shak, Richard M. Goldberg, Najjia N. Mahmoud, Robert S. Warren, Richard L. Schilsky, and Monica M. Bertagnolli

CALGB 9581 Parent Trial
Randomized Phase III Clinical Trial in Stage II Colon Cancer

Low/standard-risk, resected Stage II colon cancer

- 1738 patients enrolled 1997-2002
- Negative results for MAb 17-1A
- Targeted and enrolled primarily low-risk stage II patients (excluded pT4b, obstruction/perforation, positive margins)

Comparison of CALGB 9581 and QUASAR Study Populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CALGB 9581 % of cohort</th>
<th>QUASAR % of cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>MMR deficient</td>
<td>22%</td>
<td>14%</td>
</tr>
<tr>
<td>Age ≥70 yrs</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td>&lt;12 Nodes examined</td>
<td>47%</td>
<td>62%</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>High tumor grade</td>
<td>32%</td>
<td>31%</td>
</tr>
<tr>
<td>Recurrence risk (5 yr)</td>
<td>14.6%</td>
<td>21.7%</td>
</tr>
</tbody>
</table>

CALGB 9581 Primary Analysis: Association of Continuous Recurrence Score® Result with Recurrence Risk

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS per 25 units</td>
<td>1.52</td>
<td>(1.09, 2.12)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

- The continuous Recurrence Score® result was significantly associated with the risk of recurrence
- Strength of association consistent with QUASAR

CALGB 9851: Discriminating High vs. Low Risk of Recurrence in Standard Risk Stage IIA Colon Cancer

<table>
<thead>
<tr>
<th>Recurrence Score® Group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% of MMR Proficient Patients&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Average 5-Year Recurrence Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>44</td>
<td>13% (10%, 16%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>33</td>
<td>16% (13%, 19%)</td>
</tr>
<tr>
<td>High</td>
<td>22</td>
<td>21% (16%, 26%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Groups based on pre-specified percentile cutpoints (cutpoint equivalents for Recurrence Score: <29, 29-39, and >39)

<sup>b</sup>Weighted based on cohort sampling design

In the T3 MMR-proficient population Recurrence Score result identified 22% of patients with an average risk of recurrence at 5 years >20%

Venook et al. J Clin Oncol. 2013
Development and Validation of the Oncotype DX® Colon Cancer Assay for Use in Stage II/III Colon Cancer

Development Studies – Stage II & III (n=1851, 761 genes)
- NSABP C-01/C-02 (n = 270)
- Cleveland Clinic (n = 765)
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Clinical Validation – Stage II Colon Cancer
- QUASAR (N = 1436)
- CALGB 9581 (N = 690)

Clinical Validation Study – Stage II/III Colon Cancer
- 5FU vs 5FU+Oxaliplatin
- NSABP C-07 (N = 892)

Prospective Decision Impact Study
- Mayo Clinic Network (N = 141)
The Clinical Question in Stage III Colon Cancer: Which Patients Should Receive Oxaliplatin?

- Current practice guidelines\(^1\) recommend 5-FU/LV + oxaliplatin for adjuvant therapy.

- Oxaliplatin likely benefits only a fraction of treated patients (6-7\%)\(^2,3\) and comes with significant toxicity, including the prospect of long-term peripheral neuropathy.\(^2-6\)

- Conventional clinical and pathologic risk factors do not adequately discriminate risk and expected absolute benefit of oxaliplatin to guide decision-making.

Validation of the 12-gene Colon Cancer Recurrence Score® Result in NSABP C-07 as a Predictor of Recurrence in Stage II and III Colon Cancer Patients Treated with 5FU/LV (5FU) and 5FU/LV + Oxaliplatin (5FU+Ox)

O’Connell MJ,1 Lee M,2 Lopatin M,2 Yothers G,1 Clark-Langone K,2 Millward C,2 Paik S,1 Sharif S,1 Shak S,2 Wolmark N1

NSABP C-07 Validation Study: CONSORT Diagram

Parent C-07 study
n=2,409

Eligible patients with available tumor tissue
n=1,860 (77%)

Randomly selected 50% of patients with available tissue
with stratification on recurrence status and stage

Study Cohort (n=929)
37 excluded (4%):
9 insufficient tissue
19 ineligible histology
9 RNA quality/quantity

Final evaluable population (n=892)

Study Objectives and Methods

Prospectively designed study in patient specimens from NSABP C-07 with pre-specified endpoints, analytical methods and analysis plan.

- **Primary Objective:**
  - Determine whether there is a significant relationship between the continuous 12-gene Recurrence Score® value and recurrence risk in stage II/III patients treated with 5FU or 5FU+oxaliplatin

- **Secondary Objectives**
  - Determine whether the Recurrence Score result provides significant information beyond number of nodes examined, pathologic T-stage, tumor grade and MMR status
  - Compare recurrence risk between high and low Recurrence Score groups defined using pre-specified cut-points
Pre-Specified Primary Analysis:
Recurrence Score® Result Predicts Recurrence Risk in Stage II & III Colon Cancer Patients in NSABP C-07 (n=892)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>HR</th>
<th>HR 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(by nodal status)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III A/B vs II</td>
<td>2.53</td>
<td>(1.70, 3.78)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stage III C vs. II</td>
<td>5.29</td>
<td>(3.54, 7.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU+Ox vs. 5FU</td>
<td>0.76</td>
<td>(0.59, 0.98)</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Recurrence Score result</td>
<td>per 25 units</td>
<td>1.96</td>
<td>(1.50, 2.55)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Continuous Recurrence Score result is significantly associated with risk of recurrence, controlling for effects of treatment and stage (by nodal status)
  - Interaction of Recurrence Score result and nodal status, treatment, and age were not significant (p=0.90, 0.48, and 0.76, respectively)

Primary Analysis: Recurrence Score® Result Predicts Recurrence Risk in Stage II & III Colon Cancer Patients in NSABP C-07 (n=892)

Recurrence Score® Groups and Treatment in Stage III A/B

Kaplan-Meier Analysis

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>N events</th>
<th>N Pts</th>
<th>5FU</th>
<th>5FU + Ox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low RS Group</td>
<td>31</td>
<td>169</td>
<td>19% (12%,28%)</td>
<td>17% (10%,27%)</td>
</tr>
<tr>
<td>Int RS Group</td>
<td>38</td>
<td>138</td>
<td>30% (20%,42%)</td>
<td>19% (11%,30%)</td>
</tr>
<tr>
<td>High RS Group</td>
<td>40</td>
<td>102</td>
<td>43% (31%,57%)</td>
<td>31% (20%,46%)</td>
</tr>
</tbody>
</table>

KM Estimates (95% CI) of 5-year Recurrence Risk

The Recurrence Score® Result Provides Value Beyond Clinical and Pathologic Covariates

*Pre-specified Multivariable Analysis (n=892)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>HR</th>
<th>HR 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage (by nodal status)</td>
<td>Stage III A/B vs. II</td>
<td>0.97</td>
<td>(0.55, 1.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Stage III C vs. II</td>
<td>2.07</td>
<td>(1.16, 3.68)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>5FU+Ox vs. 5FU</td>
<td>0.82</td>
<td>(0.64, 1.06)</td>
<td>0.12</td>
</tr>
<tr>
<td>MMR</td>
<td>MMR-D vs. MMR-P</td>
<td>0.27</td>
<td>(0.12, 0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-stage</td>
<td>T4 st II &amp; T3-T4 st III vs.</td>
<td>3.04</td>
<td>(1.84, 5.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>T3 st II &amp; T1-T2 st III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodes examined</td>
<td>&lt;12 vs. ≥12</td>
<td>1.51</td>
<td>(1.17, 1.95)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>High vs. Low</td>
<td>1.36</td>
<td>(1.02, 1.82)</td>
<td>0.041</td>
</tr>
<tr>
<td>RS</td>
<td>per 25 units</td>
<td>1.57</td>
<td>(1.19, 2.08)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

O’Connell et al. ASCO 2012. Abstract 3512
The Recurrence Score® Result Enables Better Discrimination of Absolute Treatment Benefit as a Function of Risk

For RS ≤ 30, 5 yr recurrence risk = 14-25% (41% of stage IIIA/IIIB patients)
Absolute benefit from adding oxaliplatin to 5FU = 3-4%

The Recurrence Score® Result Enables Better Discrimination of Absolute Treatment Benefit as a Function of Risk

For RS ≥ 41, 5 yr recurrence risk ≥ 32% (25% of stage III A/B patients)
Absolute benefit from adding oxaliplatin to 5FU is 7-10%

NSABP C-07 Validation Study: The Recurrence Score® result predicts the recurrence risk for Stage II and III colon cancer patients

- The Recurrence Score result predicts recurrence risk in stage II and III colon cancer patients treated with 5FU or 5FU+oxaliplatin.

- A similar relative risk reduction was observed in oxaliplatin-treated patients across the range of Recurrence Score values.

- The Recurrence Score result enables better discrimination of absolute oxaliplatin benefit as a function of risk.

Development and Validation of the Oncotype DX® Colon Cancer Assay for Use in Stage II/III Colon Cancer

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Prospective Decision Impact Study
- Mayo Clinic Network (N = 141)
Prospective evaluation of Oncotype DX Colon Cancer 12-gene assay on treatment recommendations in stage II colon cancer patients

Prospective Decision Impact Study in Stage II

- A prospective study of 221 patients with stage IIA (T3N0) colon cancer across 17 academic/community sites by 105 oncologists within the Mayo Clinic Cancer Research Network.

Study Schema

**Primary objective:** Does the Oncotype DX® Colon Cancer Assay results affect recommendations regarding adjuvant chemotherapy for Stage II patients

Srivastava et al. ASCO GI 2013.
Changes in Treatment Recommendations for Stage IIA T3N0 MMR-P Patients

- **55% Unchanged**
- **33.3% Changed**
- **11.3% Changed**

- 47 (33.3%) patients were recommended LESS Treatment
- 16 (11.3%) patients were recommended MORE Treatment

Srivastava et al. ASCO GI 2013.
Changes in Treatment Recommendations for T3N0 MMR-P Patients

<table>
<thead>
<tr>
<th>Pre-Assay</th>
<th>Observation</th>
<th>5-FU monotherapy</th>
<th>5-FU + oxaliplatin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>54 (38.3%)</td>
<td>8 (5.7%)</td>
<td>6 (4.3%)</td>
<td>68 (48.2%)</td>
</tr>
<tr>
<td>5-FU monotherapy</td>
<td>24 (17.0%)</td>
<td>8 (5.7%)</td>
<td>2 (1.4%)</td>
<td>34 (24.1%)</td>
</tr>
<tr>
<td>5-FU + oxaliplatin</td>
<td>21 (14.9%)</td>
<td>2 (1.4%)</td>
<td>16 (11.3%)</td>
<td>39 (27.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>99 (70.2%)</td>
<td>18 (12.7%)</td>
<td>24 (17.0%)</td>
<td>141 (100%)</td>
</tr>
</tbody>
</table>

- 63 (44.7%) of 141 recommendations changed:
  - Treatment decreased for 47 (33.3%) patients
  - Treatment increased for 16 (11.3%) patients
- Recommendations for any chemotherapy decreased 22%: from 73 (52%) patients to 42 (30%) after the Recurrence Score® result

Srivastava et al. ASCO GI 2013.
Mayo Clinical Utility Study: Overall change in Treatment Recommendations in T3N0 MMR-P Patients

Overall recommendations for chemotherapy reduced by 22%
Recommendations for FOLFOX (5-FU+oxaliplatin) reduced by 11%

Srivastava et al. ASCO GI 2013
Mayo Clinical Utility Study: The Recurrence Score® result changed treatment recommendations for Stage IIA MMR-P patients

- First prospective study to assess the role of the quantitative Recurrence Score® result in clinical decision-making for Stage IIA MMR proficient colon cancer.

- Treatment recommendations changed for 45% of Stage IIA MMR proficient patients.

- Direction of changes concordant with the Recurrence Score results.

Srivastava et al. ASCO GI 2013.
Mutation Profiling of NSABP C-07 and C-08

NSABP C-07
Randomly assigned
N = 2,492

- Group 1
  5-FU + leucovorin
  Ineligible or no consent no follow up n = 122
  Clinically eligible with follow-up (n = 2,370)
  NO block or unsuccessful DNA preparation n = 534
  With tumor blocks and DNA isolation n = 1,836
  Mutation profiling with OncoCarta n = 235 with ColoCarta n = 1,601

NSABP C-08
Randomly assigned
N = 2,710

- Group 1
  mFOLFOX6
  Ineligible or no consent no follow up n = 278
  Clinically eligible with follow-up (n = 2,432)
  Defined representative cohort n = 500
  Missing blocks or unsuccessful DNA isolation n = 47
  Mutation profiling with ColoCarta n = 463


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Overlap of mutations in the BRAF, KRAS, NRAS, and PIK3CA


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Kaplan–Meier plots of BRAF and MMR status cases.
Survival plots for colorectal cancer according to combined MSI/BRAF subgroup.

Stage II CRC Treatment Summary

• Discuss risks and benefits with patients
• Understand that all recommended risk factors are prognostic and not predictive of treatment benefit
• MSI testing for all stage II patients
  – MSI-H, T3 – no treatment, MSI-like being investigated
• Oxaliplatin-based chemo in T4, mut BRAF-MSS
• 5FU alone in elderly

• Era of Personalized Medicine..... Oncotype DX Colon Cancer only test presently available; which stage II to treat and optimize oxaliplatin use
OncoType DX® Colon Cancer Assay
Incorporating the Recurrence Score® Result to Better Inform Treatment Decisions

Resected Colon Cancer

• Stage II
  • T-Stage MMR Status
    • T3 & MMR-D Low Risk
    • T3 & MMR-P Standard Risk
    • T4 & MMR-P High Risk

• Stage III
  • IIIA/B
  • IIIC
    • Oxaliplatin-containing Chemotherapy; 5FU/LV or Capecitabine*

The Recurrence Score Result

- Predicts recurrence risk in stage II and III colon cancer
- Enables better discrimination of absolute treatment benefit as a function of risk

MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient
*Patients not considered candidates for oxaliplatin
# Case Studies Stage IIA

<table>
<thead>
<tr>
<th>PATIENT CASE #1 – Stage IIA</th>
<th>PATIENT CASE #2 – Stage IIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>63 year old male with generally good health.</td>
<td>56 year old female with 6.5-cm tumor</td>
</tr>
<tr>
<td><strong>Tumor Type:</strong> Moderately differentiated adenocarcinoma in ascending colon</td>
<td><strong>Tumor Type:</strong> Adenocarcinoma of the Colon</td>
</tr>
<tr>
<td><strong>Tumor Size:</strong> 5.0 x 5.0 x 1.0 cm</td>
<td><strong>Tumor Size:</strong> 6.5 cm</td>
</tr>
<tr>
<td><strong>T Stage:</strong> pT3</td>
<td><strong>T Stage:</strong> pT3</td>
</tr>
<tr>
<td><strong>Histologic Grade:</strong> Low Grade</td>
<td><strong>Histologic Grade:</strong> Low Grade</td>
</tr>
<tr>
<td><strong>Lymph Node Status:</strong> Negative</td>
<td><strong>Lymph Node Status:</strong> Negative</td>
</tr>
<tr>
<td><strong>Number of Lymph Nodes Assessed:</strong> 26</td>
<td><strong>Number of Lymph Nodes Assessed:</strong> 13</td>
</tr>
<tr>
<td><strong>Mismatch Repair (MMR) Status:</strong> MMR-P</td>
<td><strong>Mismatch Repair (MMR) Status:</strong> MSS (PCR)</td>
</tr>
<tr>
<td><strong>Lymphovascular Invasion:</strong> Not identified</td>
<td><strong>Lymphovascular Invasion:</strong> No</td>
</tr>
<tr>
<td><strong>Perforation:</strong> No</td>
<td><strong>Perforation:</strong> N/A</td>
</tr>
<tr>
<td><strong>Obstruction:</strong> No</td>
<td><strong>Obstruction:</strong> No</td>
</tr>
<tr>
<td><strong>Patient History:</strong> Generally good health; no prior tobacco or family history</td>
<td></td>
</tr>
</tbody>
</table>

CASE SUBMITTED BY:
Colorectal Surgeon, Akron, OH

CASE SUBMITTED BY:
M. V. Karamouzis, MD, PhD
• Which one of these patients should receive treatment?
  • Patient 1 or 2 or Both or Neither

• What chemotherapy would you use?
  • 5FU/cape or FOLFOX?