**BACKGROUND**

- High tumor grade is included in practice guidelines as a marker of higher recurrence risk in stage II colon cancer.
- Published studies of the prognostic power of tumor grade in colon cancer have reported variable findings.

**OBJECTIVES**

- Essential association of grade with recurrence in the context of:
  - Clinicopathological covariates such as mismatch-repair (MMR), mucinous histology and tumor location.
  - Known association of grade with pathological markers such as MMR, tumor histology and tumor location.
  - Standardized, reproducible assays are needed for decision-making in clinical practice.

**METHODS**

- From their colon cancer clinical practice, 413 patients with stage II colon cancer were graded independently by two academic GI pathologists (P1, P2) using the grading methods used for clinical practice.

**RESULTS**

- Differences in the distribution of grade were significant by either of two pathologists using the grading methods used for clinical practice.

**CONCLUSIONS**

- Importantly, accounting for MMR status did not affect this conclusion – the known association of grade with pathological markers such as MMR, tumor location and mucinous histology is not affected by accounting for MMR status.

- The 12-gene colon cancer Recurrence Score, as an example, is a standardized, clinically validated assay that has been extensively validated for accuracy and reproducibility.

**REFERENCES**

- Quah, et al.3, MSKCC. RFI — recurrence free interval; DSS — disease specific survival; RFS — recurrence free survival.

**STRENGTHS AND LIMITATIONS**

**STRENGTHS**

- Larger database of stage II colon cancer patients treated with surgery alone.
- Central grade assessment by two academic pathologists with specialization in GI cancer.
- Pathological Recurrence Score benefit in stage II colon cancer.
- Analysis of survival data in conjunction with pathological markers.
- Higher tumor grade was associated with higher recurrence risk.
- Analysis of survival data in conjunction with pathological markers.

**LIMITATIONS**

- Only two academic pathologists with specialization in GI cancer.
- Recurrence Score benefit in stage II colon cancer.
- Only two academic pathologists with specialization in GI cancer.
- Higher tumor grade was associated with higher recurrence risk.

**Table 1. High Tumor Grade is Not a Marker of Higher Recurrence Risk**

<table>
<thead>
<tr>
<th>Grade</th>
<th>RFS (P1)</th>
<th>RFS (P2)</th>
<th>RFS (P1-P2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.68</td>
<td>0.72</td>
<td>0.06</td>
</tr>
<tr>
<td>High</td>
<td>0.59</td>
<td>0.63</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Table 2. Tumor Grading Methods**

<table>
<thead>
<tr>
<th>Method</th>
<th>Pathologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical grade assessment</td>
<td>P1</td>
</tr>
<tr>
<td>Pathological grade assessment</td>
<td>P2</td>
</tr>
</tbody>
</table>

**Table 3. Grade Distribution**

- Grade assessed by P1 and P2.

**Table 4. Association of Grade with Recurrence Risk in the Context of Pathological Markers**

<table>
<thead>
<tr>
<th>Grade</th>
<th>MMR-D vs MMR-P</th>
<th>Location N</th>
<th>Location M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.76 (0.32,1.76)</td>
<td>0.50</td>
<td>0.74</td>
</tr>
<tr>
<td>High</td>
<td>0.88 (0.42,1.86)</td>
<td>0.74</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**Table 5. Association of Grade with Recurrence Risk in Conjunction with RS and Pathological Markers**

- RS: Recurrence Score.

<table>
<thead>
<tr>
<th>Grade</th>
<th>MMR-D vs MMR-P</th>
<th>Location N</th>
<th>Location M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.76 (0.32,1.76)</td>
<td>0.50</td>
<td>0.74</td>
</tr>
<tr>
<td>High</td>
<td>0.88 (0.42,1.86)</td>
<td>0.74</td>
<td>0.74</td>
</tr>
</tbody>
</table>

**Table 6. Agreement Between Two Pathologists**

<table>
<thead>
<tr>
<th>Grade</th>
<th>P1 Grade</th>
<th>P2 Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.68</td>
<td>0.72</td>
</tr>
<tr>
<td>High</td>
<td>0.59</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**Figure 1. Colon Carcinomas**

- Chart showing the distribution of grade.

**Figure 2. Distribution of Pathological Markers**

- High vs Low.

**Figure 3. Distribution of Pathological Markers**

- High vs Low.

**Figure 4. Distribution of RS Values by Tumor Grade**

- High vs Low.

**Figure 5. Association of Grade with Recurrence Risk**

- In colorectal cancers, grade was not associated with risk of recurrence.

**Figure 6. Analysis of Survival Data**

- Kaplan-Meier estimates for high and low grade.

**Figure 7. Table 6. Agreement Between Two Pathologists**

- Agreement between P1 and P2.

**Figure 8. High Grade Tumors Were More Likely to Be MMR Deficient and Right-Sided Compared to Low Grade**

- Table showing the distribution of grade.

**Figure 9. Table 3. Grade Distribution**

- Grade assessed by P1 and P2.

**Figure 10. Table 4. Association of Grade with Recurrence Risk in the Context of Pathological Markers**

- Grade assessed by P1 and P2.

**Figure 11. Table 5. Association of Grade with Recurrence Risk in Conjunction with RS and Pathological Markers**

- Grade assessed by P1 and P2.

**Figure 12. Table 6. Agreement Between Two Pathologists**

- Agreement between P1 and P2.