Mismatch repair status, inflammation and outcome in patients with primary operable colorectal cancer

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Colorectal cancer

Second most common cause of cancer death in Western Europe and North America

Five-year survival still approximately 50%

Current pathological (TNM) staging inadequate, particularly in patients with node negative disease

Remains a need to identify prognostic factors which may predict survival in (node negative) CRC


Mismatch repair status and microsatellite instability

Approximately 15% of colorectal cancers may exhibit mismatch repair deficiency/microsatellite instability.

Phenotypically characteristic:
- Proximal location
- Poorly differentiated
- Conspicuous inflammatory cell infiltrate
- Good prognosis, but poor response to 5-FU chemotherapy?

Mismatch repair deficiency and the tumour microenvironment

dMMR colorectal cancer associated with the presence of a conspicuous tumour inflammatory cell infiltrate and low tumour stroma percentage

Mismatch repair deficiency and the tumour microenvironment

Relationship with tumour microenvironment may explain increased survival associated with dMMR colorectal cancer?

Not all studies have included measures of the local inflammatory cell infiltrate or venous invasion

Relationship with systemic inflammatory responses, a stage-independent predictor of survival, has not previously been examined

Patients and Methods

Patients undergoing primary, potentially curative resection for stage I-III (TNM 5th ed) colorectal cancer in Glasgow Royal Infirmary 1997-2007

Tissue samples contained in a tissue microarray (TMA) and full sections available for assessment of the tumour microenvironment

Excluded:

  Emergency resection, neoadjuvant therapy, death within 30 days of surgery

MMR status determined on TMA: MLH1, MSH2, MSH6, PMS2
Tumour microenvironment

Immunoscore: CD3+ invasive margin/intraepithelial, CD8+ invasive margin/intraepithelial

Strong Klintrup-Makinen

Weak Klintrup-Makinen

Low tumour stroma percentage

High tumour stroma percentage
Results

• 228 patients included
  – 63% older than 65; 47% male
  – 34% rectal cancer resections; 44% stage III disease

• 29% (66) received adjuvant chemotherapy (50% of stage III patients)

• dMMR colorectal cancer identified in 39 patients (17%)

• 79 cancer deaths, median follow-up of survivors 132 months (74-194)
## MMR status and pathological characteristics

<table>
<thead>
<tr>
<th></th>
<th>MMR competent (N=189) (%)</th>
<th>MMR deficient (N=39) (%)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjuvant chemotherapy (No/yes)</strong></td>
<td>129 (69) / 59 (31)</td>
<td>32 (82) / 7 (18)</td>
<td>0.093</td>
</tr>
<tr>
<td><strong>Tumour site (Right/ left/ rectum)</strong></td>
<td>62 (33) / 55 (29) / 72 (38)</td>
<td>25 (64) / 9 (23) / 5 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>T stage (1-2/ 3/ 4)</strong></td>
<td>21 (11) / 121 (64) / 47 (25)</td>
<td>4 (11) / 20 (51) / 15 (39)</td>
<td>0.197</td>
</tr>
<tr>
<td><strong>N stage (0/ 1/ 2)</strong></td>
<td>101 (53) / 65 (34) / 23 (12)</td>
<td>26 (67) / 12 (31) / 1 (2)</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>Differentiation (Mod-well/ poor)</strong></td>
<td>170 (90) / 19 (10)</td>
<td>30 (77) / 9 (23)</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Venous invasion (Absent/ present)</strong></td>
<td>117 (62) / 72 (38)</td>
<td>31 (80) / 8 (20)</td>
<td>0.037</td>
</tr>
</tbody>
</table>
## MMR status and tumour microenvironment

<table>
<thead>
<tr>
<th></th>
<th>MMR competent (N=189) (%)</th>
<th>MMR deficient (N=39) (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour stroma percentage (Low/ high)</td>
<td>135 (71) / 54 (29)</td>
<td>31 (86) / 5 (14)</td>
<td>0.067</td>
</tr>
<tr>
<td>Klintrup-Makinen grade (Low/ high)</td>
<td>128 (68) / 61 (32)</td>
<td>23 (59) / 16 (41)</td>
<td>0.294</td>
</tr>
<tr>
<td>CD3+ Margin (Low/ high)</td>
<td>101 (56) / 79 (44)</td>
<td>17 (49) / 18 (51)</td>
<td>0.413</td>
</tr>
<tr>
<td>CD3+ Intraepithelial (Low/ high)</td>
<td>130 (70) / 55 (30)</td>
<td>16 (41) / 23 (59)</td>
<td>0.001</td>
</tr>
<tr>
<td>CD8+ Margin (Low/ high)</td>
<td>107 (60) / 72 (40)</td>
<td>20 (54) / 17 (46)</td>
<td>0.521</td>
</tr>
<tr>
<td>CD8+ Intraepithelial (Low/ high)</td>
<td>139 (76) / 44 (24)</td>
<td>22 (56) / 17 (44)</td>
<td>0.013</td>
</tr>
</tbody>
</table>
MMR status and Immunoscore

Score 0: MMR Competent 42.9%
Score 1/2: MMR Competent 33.7%
Score 3: MMR Competent 11.4%
Score 4: MMR Competent 17.6%

Score 0: MMR deficient 23.5%
Score 1/2: MMR deficient 38.2%
Score 3: MMR deficient 20.6%
Score 4: MMR deficient 12%

P=0.032
MMR status and systemic inflammatory responses

**C-reactive protein**

- Preoperative CRP (mg/L)
  - MMR competent: 8 (6-18) mg/L
  - MMR deficient: 20 (5-40) mg/L; \( P = 0.021 \)

**Albumin**

- Preoperative albumin (g/L)
  - MMR competent: 40 g/L (37-42)
  - MMR deficient: 37 g/L (34-42); \( P = 0.006 \)

**NLR**

- Preoperative neutrophil/lymphocyte ratio
  - MMR competent: 3.2 (2.2-4.6)
  - MMR deficient: 4.2 (3.2-5.4); \( P = 0.002 \)

**Haemoglobin**

- Preoperative haemoglobin (g/L)
  - MMR competent: 12.4 g/L (10.9-13.9)
  - MMR deficient: 10.6 g/L (9.3-13.0); \( P = 0.003 \)

**Mann-Whitney U-Test**
MMR status and systemic inflammatory responses

- **mGPS=0**: CRP $\leq$ 10mg/L
- **mGPS=1**: CRP $>$ 10mg/L and Albumin $\geq$ 35g/L
- **mGPS=2**: CRP $>$ 10mg/L and Albumin $<$ 35g/L

$P=0.011$
Mismatch repair and cancer-specific survival

<table>
<thead>
<tr>
<th></th>
<th>Number at risk</th>
<th>Mean survival in months (95% CI)</th>
<th>P</th>
<th>5-yr survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR competent</td>
<td>189</td>
<td>136 (125-148)</td>
<td>-</td>
<td>73</td>
</tr>
<tr>
<td>MMR deficient</td>
<td>39</td>
<td>152 (131-173)</td>
<td>0.177</td>
<td>81</td>
</tr>
</tbody>
</table>
# Cancer-specific survival

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>P</th>
<th>Multivariate analysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T stage</strong> (1/ 2/ 3/ 4)</td>
<td>1.62 (1.13-2.33)</td>
<td>0.009</td>
<td>-</td>
<td>0.859</td>
</tr>
<tr>
<td><strong>N stage</strong> (0/ 1/ 2)</td>
<td>1.82 (1.35-2.45)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>0.133</td>
</tr>
<tr>
<td>Differentiation (mod-well/ poor)</td>
<td>1.75 (0.95-3.25)</td>
<td>0.073</td>
<td>2.22 (1.11-4.44)</td>
<td>0.024</td>
</tr>
<tr>
<td>Venous invasion (no/ yes)</td>
<td>2.53 (1.62-3.95)</td>
<td>&lt;0.001</td>
<td>2.26 (1.38-3.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Margin involvement (no/ yes)</td>
<td>2.44 (1.12-5.31)</td>
<td>0.025</td>
<td>-</td>
<td>0.446</td>
</tr>
<tr>
<td>Peritoneal involvement (no/ yes)</td>
<td>2.11 (1.34-3.30)</td>
<td>0.001</td>
<td>-</td>
<td>0.158</td>
</tr>
<tr>
<td>Tumour perforation (no/yes)</td>
<td>7.79 (2.78-21.85)</td>
<td>&lt;0.001</td>
<td>4.12 (1.34-12.64)</td>
<td>0.013</td>
</tr>
<tr>
<td>Invasive margin (expanding/ infiltrative)</td>
<td>1.84 (1.18-2.87)</td>
<td>0.007</td>
<td>-</td>
<td>0.605</td>
</tr>
<tr>
<td>Necrosis (low/ high)</td>
<td>1.49 (0.96-2.33)</td>
<td>0.078</td>
<td>-</td>
<td>0.771</td>
</tr>
<tr>
<td>mGPS (0/ 1/ 2)</td>
<td>1.68 (1.25-2.26)</td>
<td>0.001</td>
<td>1.79 (1.28-2.50)</td>
<td>0.001</td>
</tr>
<tr>
<td>Tumour stroma percentage (low/ high)</td>
<td>2.11 (1.33-3.36)</td>
<td>0.002</td>
<td>1.89 (1.15-3.10)</td>
<td>0.012</td>
</tr>
<tr>
<td>Klintrup-Makinan grade (high/ low)</td>
<td>2.36 (1.34-4.14)</td>
<td>0.003</td>
<td>2.07 (1.12-3.82)</td>
<td>0.021</td>
</tr>
<tr>
<td>Mismatch repair status (competent/ deficient)</td>
<td>0.622 (0.31-1.25)</td>
<td>0.182</td>
<td>0.42 (0.17-1.04)</td>
<td>0.059</td>
</tr>
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Mismatch repair status, systemic inflammation and survival

<table>
<thead>
<tr>
<th>mGPS=0</th>
<th>Number at risk</th>
<th>Mean survival in months (95% CI)</th>
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<tr>
<td>mGPS=0</td>
<td>131</td>
<td>151 (138-163)</td>
<td>-</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>mGPS≥1 and MMR competent</td>
<td>75</td>
<td>113 (93-132)</td>
<td>0.001</td>
<td>-</td>
<td>60</td>
</tr>
<tr>
<td>mGPS≥1 and MMR deficient</td>
<td>22</td>
<td>138 (114-163)</td>
<td>0.795</td>
<td>0.052</td>
<td>81</td>
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Conclusion

• Assessment of the tumour microenvironment of greater prognostic value than mismatch repair status alone in patients with stage I-III colorectal cancer

• Mismatch repair status associated with systemic inflammatory responses, however may abrogate adverse effects on survival