Utility of Universal Colorectal Cancer Screening for Lynch Syndrome in Advanced Age

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Disclosures

• The authors have no relevant disclosures.
Universal Screening

• Routine screening of CRCs has been advocated to identify more patients and family members with Lynch syndrome

• Benefit: Make diagnosis and offer intensive surveillance in asymptomatic patients

• Debate: should all patients or just selected ones based on age and clinical criteria?

• EGAPP: recommended all patients regardless of age or family history
NCCN Guidelines

• The National Comprehensive Cancer Network (NCCN) recommends routine CRC tumor testing for Lynch syndrome for the following:

“All CRC patients diagnosed <70 years, and also those ≥ 70 who meet Bethesda Guidelines”
Study Goal

• To review our experience with colorectal cancer universal screening by tumor testing, with specific analysis of results by age
Methods

- Universal screening of CRC for Lynch syndrome has been routinely performed at our institution since April 2009
- DNA MSI and/or IHC for expression of the mismatch repair proteins MLH1, MSH2, MSH6, and PMS2
- MSI-H tumors with loss of MLH1 were reflexed into testing for *BRAF V600E* mutation and/or *MLH1* methylation
CCF Tumor Algorithm

Colorectal Cancer

Adequate for MSI (≈50% tumor)?

YES

 MSI

MSI-H

MLH1, MSH2 IHC

MSH2 Loss

MLH1, MSH2 IHC

MLH1 Loss

PMS2, MSH6 IHC

BRAF/MLH1 methyl

NO

IHC

PMS2

LOST

INTACT

MSH6

LOST

MSH2

MLH1

Check dotting (≈50% tumor)

Review by genetic counselor

STOP
Methods

- Patients with genetic or molecular suggestion of Lynch syndrome were offered genetic counseling and testing
- Patient demographics, family history, tumor characteristics, and genetic test results were prospectively collected
- Maintained in RedCap database since Nov. 2012; data through June 2014
- Tumors that were MSI-H and/or had loss of MMR protein expression were defined as MMR deficient (MMRd)
Results: Total Population

- 882 patient tumors were studied
- Median Age: 64 years (range 23-99 years)
- 44% female, 56% male
- 57% proximal colon tumors
- 760 (86.2%) MMR proficient
- 122 (13.8%) were MMR deficient (MMRd)
Results: MMRd

- 122 MMRd tumors
  - IHC done on all tumors
  - MSI testing on 97
- Median Age: 73 years (range 23-95 years)
- 58% female, 42% male
- 79% proximal colon tumors
Sorting out Lynch

- If IHC loss MSH2, MSH6, PMS2 ➔ GC
- IHC loss of MLH1 ➔ tumor testing
MMRd: MLH1 loss

• 99 with MLH1 loss on IHC
  – 97 had *BRAF V600E* mutation testing
  • 34 samples were WT
  • *MLH1* promoter methylation testing
    – 17 had *MLH1* methylated (sporadic)
    – 14 *MLH1* not methylated, suggesting Lynch syndrome
    – 3 not tested
Patients with Tumor or Genetic Lynch

- 34 of 122 (28%) of all MMRd patients

<table>
<thead>
<tr>
<th>Gene/Proteins</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>14</td>
</tr>
<tr>
<td>MSH2</td>
<td>11</td>
</tr>
<tr>
<td>MSH6</td>
<td>6</td>
</tr>
<tr>
<td>PMS2</td>
<td>3</td>
</tr>
</tbody>
</table>
Detected Lynch Cases

Number of Cases Detected

Age Groups

- < 50
- 50-59
- 60-69
- 70-79
- 80-89
- > 90

Putative Lynch
## Results by Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>MMRd, N</th>
<th>Putative Lynch , N</th>
<th>% of MMRd with Lynch</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>125</td>
<td>12 (10%)</td>
<td>11</td>
<td>92%</td>
</tr>
<tr>
<td>50-59</td>
<td>209</td>
<td>15 (7%)</td>
<td>9</td>
<td>60%</td>
</tr>
<tr>
<td>60-69</td>
<td>228</td>
<td>23 (10%)</td>
<td>8</td>
<td>35%</td>
</tr>
<tr>
<td>70-79</td>
<td>181</td>
<td>33 (18%)</td>
<td>4</td>
<td>12%</td>
</tr>
<tr>
<td>80-89</td>
<td>118</td>
<td>32 (27%)</td>
<td>2</td>
<td>6%</td>
</tr>
<tr>
<td>≥ 90</td>
<td>21</td>
<td>7 (33%)</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

6 of 34 (17.6%) cases > 70 years old
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Bethesda?</th>
<th>Tumor Results</th>
<th>Genetic Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>No</td>
<td>PMS2 loss</td>
<td>mutation</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>M</td>
<td>No</td>
<td>PMS2 loss</td>
<td>Refused counseling</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>M</td>
<td>No</td>
<td>BRAF WT, MLH1 not meth</td>
<td>Not done</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>Yes, (Am)</td>
<td>MSH2 loss</td>
<td>germline MSH2 methylation*</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>F</td>
<td>Yes (LS)</td>
<td>MSH6 loss</td>
<td>mutation</td>
</tr>
<tr>
<td>6</td>
<td>83</td>
<td>M</td>
<td>No</td>
<td>MSH2 loss</td>
<td>Counseled, not tested</td>
</tr>
</tbody>
</table>

*Negative MSH2 and EpCAM
Limitations

- Not all patients with putative Lynch syndrome had confirmatory genetic testing
Summary

• The yield of diagnosing Lynch by universal screening of CRC decreases with advancing age
• Clinically significant percentage of Lynch patients are incidentally diagnosed over age 70
Conclusions

- Universal screening of colorectal cancers identifies Lynch syndrome patients who would have been missed by following NCCN guidelines.
- This has significant implications for the proband and their family.
- We advocate universal testing, regardless of age.