NCCN Increases the Emphasis on Genetic/Familial High-Risk Assessment in Colorectal Cancer

Presented by Heather Hampel, MS

Abstract

NCCN has developed new guidelines for the assessment of high-risk familial/genetic colorectal cancer, and has positioned these recommendations within the guidelines for detection, prevention, and risk reduction. The Panel recommends that all patients with colorectal cancer be screened for Lynch syndrome, which occurs in 1 of every 35 patients and is the most common form of hereditary colorectal cancer. Such screening could be universal so that all tumors are genetically tested, or screening could be restricted to patients under the age of 70 and those aged 70 and older who meet clinical criteria. (J Natl Compr Canc Netw 2014;12:829–831)

NCCN has positioned new recommendations for the assessment of high-risk genetic and familial colorectal cancer (CRC) under Guidelines for Detection, Prevention, and Risk Reduction, paralleling the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian. Before 2014, detection and management of hereditary CRC was discussed within the NCCN Guidelines for Colorectal Cancer Screening.

The repositioning of these recommendations is a reflection of the growing awareness of hereditary CRC syndromes, according to Heather Hampel, MS, Professor and Associate Director, Clinical Cancer Genetics Program, The Ohio State University Comprehensive Cancer Center, Columbus, who presented the update at the NCCN 19th Annual Conference.

“We felt the information about the genetic and familial colorectal cancer syndromes had grown, and this was not where clinicians were looking for it,” Ms. Hampel said.

An important new recommendation by the panel is that all patients with newly diagnosed CRC be screened for Lynch syndrome (previously called hereditary nonpolyposis CRC), which occurs in 1 of 35 of these patients. Surveys have shown that approximately three-fourths of NCCN Member Institutions are already adhering to this new recommendation, but there is room for improvement in the wider cancer community, she suggested.

Four DNA mismatch repair genes can lead to Lynch syndrome: MLH1, MSH2, MSH6, and PMS2. Patients who carry mutations in these genes are at high risk for CRC and select other cancers, and they pass the trait along in an autosomal dominant inheritance pattern. NCCN’s proactive position will greatly help identify individuals and their relatives at high risk for a primary or secondary Lynch syndrome–related cancer, Ms. Hampel predicted.

Differential Diagnosis of CRC Syndromes

The differential diagnosis of hereditary CRC begins with determining the number of polyps. Patients with CRC who have fewer than 10 colon polyps may have Lynch syndrome, familial CRC syndrome type X, or MUTYH-associated polyposis. This group is further differentiated according to 2 genetic pathways: one marked by chromosome instability (85%) and the other by microsatellite instability (MSI) (15%). Of the latter group, 20% have Lynch syndrome, while the remainder have acquired (or somatic) changes to the DNA mismatch repair genes, primarily hypermethylation of the MLH1 promoter.

The determination of MSI positivity or the presence of Lynch syndrome is important because of the implica-
Tumors should be verified whenever possible. “But family histories can be deceiving,” Ms. Hampel cautioned. She noted that family sizes are decreasing, colonoscopy is preventing many cancers, and family members are often unaware when other family members have polyps removed.

“This makes it harder to diagnose Lynch syndrome on the basis of family history. Therefore, we have an interest in screening all colon cancer patients. By doing both (referring patients with a strong family history and screening all newly diagnosed patients with colorectal cancer), we have an opportunity to diagnose as many individuals with Lynch syndrome as possible,” she said.

Routine Tumor Testing

Routine tumor testing is advised for all patients with CRC younger than age 70 years at diagnosis, and those aged 70 and older at diagnosis who meet the Revised Bethesda Guidelines, she said. “Based on the guidelines, you can either test every single colorectal cancer case or the patients under 70 and those 70 and older who meet the Bethesda Guidelines,” she said.

The Revised Bethesda Guidelines include CRC diagnosed younger than age 50; presence of synchronous or metachronous CRC and other Lynch syndrome–related tumors, regardless of age; CRC with MSI-high histology in a person younger than age 60; CRC diagnosed in a patient with 1 or more first-degree relatives with a Lynch syndrome–related cancer, with 1 cancer diagnosed under the age of 50; and CRC diagnosed in a patient with 2 or more first- or second-degree relatives with Lynch syndrome–related cancers, regardless of age.

Tumors can be screened using MSI testing, which is positive in 15% of CRC cases and in up to 89% of Lynch syndrome cases; immunohistochemistry staining, which has a 96% correlation with MSI positivity; and BRAF or methylation testing, which detects acquired methylation that is generally not inherited (20% of MSI-positive cases have Lynch syndrome).

Implications of Screening

Patients with Lynch syndrome need intensive surveillance compared with those with mutation-negative CRC. Their 16% to 30% chance of a second
primary CRC within 10 years mandates more frequent screening: every 1 to 2 years for life, compared with other patients with CRC, who should undergo colonoscopy 1 year after diagnosis, repeated in 1 to 3 years, and then every 3 to 5 years based on the findings. Surveillance for other cancers is also critical (Table 2).

Screening patients with CRC also constitutes a robust cancer prevention strategy among their relatives. “We have found that, on average, 6 relatives are tested per patient with colorectal cancer diagnosed with Lynch syndrome, and 50% of them also have Lynch syndrome and need increased cancer surveillance,” Ms. Hampel said.

The cancer risk of these affected relatives is nearly 6 times higher than the general population, but because their compliance with surveillance is greater than 95%, cancer-related and all-cause mortality are no higher among these affected relatives than among relatives without the mutation.³

### Table 2 Lynch Syndrome Surveillance Options

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Colonoscopy</td>
<td>Every 1–2 y beginning at age 20–25 (MLH1, MSH2, and EPCAM), or at age 25–30 (MSH6 and PMS2); or 2–5 y prior to the earliest colon cancer</td>
</tr>
<tr>
<td>Endometrial sampling</td>
<td>No clear evidence to support but could consider every 1 y</td>
</tr>
<tr>
<td>Transvaginal U/S and CA-125</td>
<td>No clear evidence to support but clinicians could consider at their discretion</td>
</tr>
<tr>
<td>EGD with extended duodenoscopy</td>
<td>No clear evidence to support but clinicians could consider every 3–5 y beginning at age 30–35</td>
</tr>
<tr>
<td>Urinanalysis</td>
<td>Consider every 1 y beginning at age 25–30</td>
</tr>
<tr>
<td>History and examination of systems</td>
<td>Every 1 y beginning at age 25</td>
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</tbody>
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### References