

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Evaluation and Management of Lynch Syndrome

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H&O What are the distinguishing features of Lynch syndrome?

CB Lynch syndrome is also called hereditary non-polyposis colorectal cancer. It has long been known that there are familial clusters of colon cancer, and in 1991 a group met in Amsterdam to develop criteria designed to identify possible familial colon-cancer associations for genetic study. The Amsterdam group was attempting to isolate families whose colon cancer was not attributable to chance alone. Colon cancer occurs in 5% of the general population, and 10% of people who develop colon cancer have one first-degree family member with the disease. The group focused on families containing three members with colon cancer, one of whom was a first-degree relative of the other two and one of whom was less than 50 years old. This work was very useful in locating the families in whom the genes responsible for Lynch syndrome were isolated. Subsequently, it was discovered that those criteria were too restrictive because some families that truly have Lynch syndrome were not included. Additionally, even among families meeting the criteria, 60% have Lynch syndrome but 40% do not.

Nevertheless, it is possible to analyze the colon cancers from these families and discover whether they have a mutational signature called microsatellite instability. Lynch syndrome is now defined as the subset of hereditary nonpolyposis colon cancer caused by a germline mutation in one of four DNA mismatch repair genes: *MSH2*, *MLH1*, *MSH6*, and *PMS2*. A germline mutation in one of these genes comprises one wild-type gene from the unaffected parent and one mutated gene from the affected parent. A genetic accident occurs and inactivates the wild-

type copy, causing the cell to have no DNA mismatch repair activity and to begin to accumulate mutations at a very high rate. As a result, cancer eventually develops and the DNA in the tumor has microsatellite instability, the characteristic signature of Lynch syndrome.

H&O Is Lynch syndrome more prevalent in specific racial or ethnic groups?

CB It appears that Lynch syndrome is equally distributed across those of European, Asian, and African descent. It has been found in every major group seen in the United States. A Native American family and a Romani family are known to have Lynch syndrome, as well as Ashkenazi Jewish families. There are several founder mutations. For example, there is one particular mutation that accounts for 16% of all Lynch syndromes among Ashkenazi Jews. To the best of my knowledge, Lynch syndrome is not more common in any given race, although in Finland there seems to be a large proportion of colon cancer cases that can be traced to a few specific mutations. This finding does not mean that hereditary colon cancer is necessarily more prevalent in Finland, only that the mutations associated with it are easier to track using available tests.

H&O What is the screening process for Lynch syndrome?

CB The possibility of Lynch syndrome is signaled to a clinician when a young person develops colon cancer or a patient with colon cancer has one or two family members who also have had the disease. Initially, family history should be reviewed to see whether Lynch syndrome is suggested. If so, the colon cancer tissue can be analyzed in two different ways. One analytic method is extraction of the DNA to look for microsatellite instability, which is characterized by a large number of mutations that occur in simple repetitive sequences in DNA. The second analytic method is immunohistochemistry for the four DNA mismatch repair genes; the gene responsible for the disease is not expressed in the tumor. There are exceptions to each method. Occasional patients have Lynch syndrome without microsatellite instability; there are also mutations in the mismatch repair genes that inactivate the

gene, though it is still expressed immunohistochemically, meaning it falsely appears to be functioning normally. Each method is 90–95% sensitive, and some clinicians will use these methods together.

If the screening is positive, blood is sent for DNA analysis to look for a germline mutation in *MSH2*, *MLH1*, or *MSH6*. No test is currently commercially available to look for mutations in *PMS2*, but efforts are ongoing to develop a test for mutations in that gene. The difficulty this gene presents relates to the presence of over 20 additional copies of *PMS2* in the genome in the form of pseudogenes, and DNA sequencing requires differentiation between the authentic gene and the copies.

H&O Once a patient is found to be positive on screening and DNA analysis and Lynch syndrome is diagnosed, what are the next steps?

CB I tell patients who have been definitively diagnosed with Lynch syndrome that men have a 90% lifetime risk of developing some kind of cancer, including just under 70% in the colon, 10% in the stomach, and the remainder in various other sites; women have a 70% lifetime risk of developing a Lynch syndrome–associated cancer, including risks of 40–50% in the colon, 40–50% in the uterus, approximately 12% in the ovaries, and the remainder in various other sites. I focus on the colon and uterus because, in both instances, the disease is highly manageable. If a patient with Lynch syndrome undergoes colonoscopies every 1–2 years and polyps are removed, the mortality from colon cancer can be reduced to nearly zero. Whereas in the general population, colonoscopies are recommended every 5–10 years, in patients with Lynch syndrome, colonoscopies must be undertaken every 1–2 years because polyps become cancerous at a much faster rate.

After high-risk women have given birth to all the children they wish to have, I recommend they have their uterus and ovaries removed. Women should be informed that if they carry one of these genetic mutations, they should be alert to the implications of abnormal uterine bleeding, particularly after menopause.

H&O Is genetic testing of family members recommended after one is diagnosed with Lynch syndrome?

CB When I encounter a family with Lynch syndrome, I identify the member most likely to be the gene carrier. Here is a hypothetical illustration: a patient at age 25 comes to the clinic to be tested because her mother died from colon cancer; her aunt is alive but had uterine cancer removed recently at age 42; and her grandfather is

alive but survived prostate cancer. I would judge that the prostate cancer is not part of the Lynch syndrome phenotype, but the other familial cancers are, and the aunt with uterine cancer should be tested first because she is most likely to be the gene carrier. Next, first-degree relatives, with whom 50% of one's DNA is shared, should be tested. In this illustration, if the mutation is found in the aunt, the 25-year-old patient should be tested next because her mother has died from colon cancer. The patient should be tested only for the mutation found in the aunt. In 20–30% of Lynch syndrome families, it is not currently possible to find the germline mutation. We know it exists, but we cannot find it. Thus, with routine genetic testing, the test will be negative in 20–30% of cases even though the patient has Lynch syndrome. If an asymptomatic young person is tested blindly, a positive result generally indicates presence of the disease, but a negative result does not definitively prove the patient does not have Lynch syndrome. There may be a gene present in the family which the patient does not carry or is undetectable with current technology. It is recommended that reference laboratories test *MSH2* and *MLH1* genes and also look for deletions, which are not found by routine sequencing. This process is labor-intensive and expensive. Once the mutation is found, the other family members are tested for that specific mutation, which is a very sensitive and specific test. Once the mutation has been identified in a particular family, third-degree relatives, for example, can be tested with accuracy. I believe it is very important to test many members of the family.

H&O What is the management of cancer in a patient with Lynch syndrome?

CB A patient with Lynch syndrome who presents with colon cancer is very likely to develop another colon cancer later in life. Thus, if a tumor is found in the cecum or the ascending colon, a subtotal colectomy is indicated. In women, a hysterectomy should also be considered at the same time, if feasible. In addition, the natural history of colon cancer with microsatellite instability is different from that of sporadic microsatellite-stable tumors; it is less virulent. For both stage I and II colon cancers in patients with Lynch syndrome, the 5-year survival is 92%, as opposed to 95% for stage I and 80–85% for stage II sporadic cancers. Moreover, 5-year survivals are over 70% for stage III colorectal cancers with microsatellite instability versus approximately 40% for sporadic tumors.

There is some controversy regarding the benefit of adjuvant 5-fluorouracil (5-FU)-based chemotherapy in this population. Several researchers have suggested that no benefit is conferred by adjuvant 5-FU-based chemotherapy for stage II or III colon cancer in patients

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with microsatellite instability (including Lynch syndrome), unlike in patients with sporadic cancers. One key article suggested that there might be an increased risk of mortality for patients with stage II or III disease with microsatellite instability, given 5-FU–based adjuvant chemotherapy. Other researchers have reported different results, but they used historical datasets in which patients were selected to receive chemotherapy or rejected by the clinician due to age or comorbidities—and thus inadvertently included patients with Lynch syndrome who tended to be young, otherwise healthy, and with a better natural history—and analyzed to determine which patients had better outcomes. These researchers erroneously concluded that giving adjuvant chemotherapy was life-saving for patients with microsatellite instability or Lynch syndrome tumors. In other subsequent research in which this design flaw was avoided and patients were randomized to receive or not receive chemotherapy initially, regardless of age or comorbidities, no benefit or harm was seen in patients with microsatellite instability who received chemotherapy. Until more is known, it seems that adjuvant chemotherapy should not be given to patients with microsatellite instability. In the future, I believe microsatellite instability must always be taken into account when assessing response to chemotherapy.

H&O Could you discuss further research in this setting?

CB There are ongoing studies looking at chemoprevention that might reduce the risk of a patient getting cancer in the future. Finally, as stated above, a good test for *PMS2* Lynch syndrome is needed, as are improved diagnostic tests for Lynch syndrome. Much recent progress has been made in the technical area of finding deletions, particularly of the *MSH2* gene, which is highly prone to deletions because of its many Alu sequences.

Suggested Readings

Boland CR. Clinical uses of microsatellite instability testing in colorectal cancer: an ongoing challenge. *J Clin Oncol*. 2007;25:754-756.

Boland CR, Koi M, Chang DK, Carethers JM. The biochemical basis of microsatellite instability and abnormal immunohistochemistry and clinical behavior in Lynch Syndrome: from bench to bedside. *Fam Cancer*. 2007 Jul 17; [Epub ahead of print]

Lynch HT, Boland CR, Rodriguez-Bigas MA, Amos C, Lynch JF, Lynch PM. Who should be sent for genetic testing in hereditary colorectal cancer syndromes? *J Clin Oncol*. 2007;25:3534-3542.

Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med*. 2003;349:247-257.