The Prognostic Role of MSI Testing in Colorectal Cancer
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Molecular analysis suggests that colorectal carcinoma can be classified into broad groups based on genomic status (microsatellite and chromosomal instability) and epigenomic status (CpG island methylation). These molecular features are more reliable than histopathologic characteristics in establishing the pathogenesis of a particular colon cancer.

Microsatellites are repetitive nucleotide sequences distributed throughout the genome, which are often replicated incorrectly, even in normal cells. Fortunately, a type of DNA repair known as “DNA mismatch repair” normally corrects these replicative errors. Microsatellite instability (MSI) is a phenomenon that occurs in a subset of colorectal cancer (~15-20%) and other tumor types, such as endometrial and gastric cancer, that manifests as expansions or deletions of microsatellite repeats in the patient’s tumor DNA, when compared to patient’s normal DNA. MSI is generally due to defective mismatch repair (MMR). The DNA MMR system includes several proteins, such as MLH1, MSH2, MSH6, and PMS2, which detect and correct these errors. Defective DNA MMR and subsequent MSI result from either a MMR gene germline or somatic mutation, or methylation of a MMR promoter gene (usually MLH1) resulting in loss of protein function.

Polymerase chain reaction (PCR) detects MSI by comparing the length of nucleotide repeats in tumor cells and normal cells. If the length of the repeat sequence between tumor and normal cells differs for a particular microsatellite, then the microsatellite is said to show “microsatellite instability.” If more than 30% of the tested microsatellite regions exhibit MSI, then the tumor is categorized as showing a high-level microsatellite instability (MSI-H) phenotype. Tumors with no instability or instability at <30% of tested loci are categorized as MSS and MSI-L tumor respectively. An MSI-H phenotype indicates that the tumor has defective DNA MMR. Immunohistochemistry (IHC) can be used to assess for MMR protein expression and is another way to assess tumor for evidence of defective MMR. Unlike MSI testing, MMR IHC can help identify the gene that is defective. For example, a tumor showing loss MSH2 and MSH6 expression but normal MLH1 and PMS2 expression is likely to have a germline MSH2 mutation. MMR IHC testing may have legal implications, since it can inadvertently identify patients with HNPCC.

MSI and/or MMR IHC to determine if a tumor exhibits defective DNA MMR is useful in prognostication of colorectal tumors, detection of hereditary nonpolyposis colorectal carcinoma (HNPCC, or Lynch syndrome), and prediction of response to 5-FU and irinotecan therapy. A meta-analysis of 7642 CRC patients, including 1277 MSI-H patients, showed that MSI-H tumors were associated with a better prognosis than microsatellite stable (MSS) tumors (hazard ratio for overall survival 0.65). MSI-H tumors are also less likely to metastasize to lymph nodes or distant sites, compared to MSS tumors (4% vs. 15-17%). Recent data however suggest that the
favorable prognosis conferred by an MSI-H phenotype is muted by concurrent BRAF V600E mutation.\textsuperscript{7} MSI CRC tumors with a BRAF mutation have a prognosis similar to that of MSS CRC.

The role of MSI testing in the diagnosis of HNPCC is well established. Defective MMR is seen in most cases of patients with clinically diagnosed HNPCC and approximately 15-20\% of sporadic CRC.\textsuperscript{1,2} The EGAPP (Evaluation of Genomic Applications in Practice and Prevention) working group reports moderate evidence that universal screening of all CRC patients is the most sensitive method to identify HNPCC patients and kindred.\textsuperscript{8}

While the clinical utility of MSI testing as a predictive marker for response to 5-FU, irinotecan, and other chemotherapeutic agents is still controversial, studies suggest that Stage II MSI-H tumors may respond adversely to 5-FU therapy, and be more responsive than MSS tumors are to irinotecan.\textsuperscript{9,10} Further studies are needed to clarify the role of MSI and IHC testing in therapy decisions for colorectal cancer patients.

In summary, MMR testing offers useful information that guides the clinical management of CRC patients. MSI-H tumors have a better prognosis than MSS tumors, with a lower incidence of lymphatic and systemic metastases. MMR status is especially useful in the identification of patients who have Lynch syndrome, and may also influence selection of therapy for CRC patients.

References
