

## MSI testing in Stage II colon cancer: are we ready for prime time?

Amil Shah, MDCM, FRCPC, FACP

For Stage II colon cancer, in which the majority of patients are cured by surgical resection, the role of adjuvant chemotherapy is uncertain. Some subgroups of Stage II patients are recognized to be at high risk for recurrence and may be potential candidates for adjuvant therapy. High-risk factors include tumour characteristics (adherence to adjacent tissues, perforation or complete obstruction), biologic characteristics (aneuploidy or deletion of 18q) and treatment-related characteristics (inadequate lymph node sampling). In 2004 the Gastrointestinal Cancer Disease Site group of Cancer Care Ontario's Program in Evidence-Based Care published a meta-analysis of randomized studies of adjuvant chemotherapy compared with observation for Stage II colon cancer.<sup>1</sup> With a mortality risk ratio of 0.87 (95% CI 0.75 to 1.01;  $p = 0.07$ ), the analysis did not support the routine use of adjuvant therapy. Another meta-analysis of pooled individual data of patients with Stage II and III colon cancer from 7 trials showed a benefit in 5-year disease-free survival (76% vs 72%) for those with node-negative disease receiving adjuvant chemotherapy compared with surgery alone, but no overall survival advantage (81% vs 76%).<sup>2</sup>

Interest in molecular prognostic and predictive factors has been kindled by a report at the 2008 American Society of Clinical Oncology Annual Meeting from Sargent et al<sup>3</sup> of the impact of deficient mismatch repair on the outcomes of patients with Stages II and III colon cancer, the details of which were reviewed by Dr. Sharlene Gill in the November, 2008 issue of *Oncology Exchange*.<sup>4</sup> Microsatellite instability (MSI) refers to the insertion or deletion of nucleotide units in segments of DNA with short runs of repeated nucleotide sequences. The presence of MSI suggests a defect in one of the DNA mismatch repair genes, and it is present in up to 15% of tumours from patients with sporadic colorectal cancers. High microsatellite instability (MSI-H) is associated with improved survival for Stage II colon cancer patients, while chromosomal instability, a different pathway of tumorigenesis characterized by loss of heterozygosity on chromosomes 5q, 17p and 18q, carries a poorer prognosis. While ongoing studies will add to our understanding of this issue, is the evidence about MSI robust enough for us to advocate adjuvant chemotherapy now for certain subgroups of patients with Stage II colon cancer? I think we can answer this in the affirmative.

The Western Canadian Colorectal Cancer Consensus Conference in September 2008 (see page 28 of this issue of *Oncology Exchange*)<sup>5</sup> endorsed the use of MSI testing to guide the selection of patients with Stage II colon cancer under consideration for adjuvant fluoropyrimidine monotherapy. This requires that cancer centres gear up to offer this test in a timely manner. At present, MSI testing is not routine, but it is used in some jurisdictions as an initial screening test in individuals suspected of having hereditary nonpolyposis

colon cancer (HNPCC) syndrome. MSI molecular testing to detect the possible presence of a defective MMR gene in colorectal cancer is favoured over other methods, such as immunohistochemical testing (IHC). Although easier to conduct, IHC testing may be more difficult to interpret and subject to more false positives or false negatives, and the expression of up to 4 genes would need to be assessed — possibly affecting quality control and increasing costs.

MSI testing is not expensive — about \$200 per test. Successful implementation for Stage II colon cancer will require communication among surgeons, pathologists and oncologists. Pathologists may be in the best position to coordinate testing by referring appropriate cases to certified provincial (or central referral) molecular pathology laboratories, which do not currently exist in all provinces. In BC, one laboratory currently conducts MSI testing, although it is publicly funded only for suspected cases of HNPCC. The methodology of MSI testing is well defined and testing can be done quickly, but laboratories will likely do it in batches; even so, the results should be available within 2 weeks — fast enough for clinical decisions about adjuvant therapy. When more laboratories are doing the test, better inter-laboratory collaboration will be possible within and between provinces to conduct quality assurance, including the ability to exchange samples on a regular basis to validate each other's results.

The additional expense of MSI testing is justified by the important treatment information it provides. The advances of tumour biology are taking us in a new direction, and healthcare providers must now step up to the plate. This is a promise we made to our patients yesterday and is a duty we owe them today.

**Amil Shah, MDCM, FRCPC, FACP** is a Medical Oncologist at the BC Cancer Agency, Vancouver Cancer Centre and Clinical Professor, University of British Columbia, Vancouver, BC

### References

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