

## **Molecular Diagnostics in GI Neoplasia**

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The molecular genetics and genomics of GI cancers have been studied extensively, but clinical applications are currently meager. Determining prognosis of patients is important for management and for patient life-planning. At present, prognosis is based predominantly upon the pathological stage of the disease. Three examples of clinical settings with potential for improvement of the management of colorectal cancer patients are evident. Patients with Stage I (Dukes' A) colorectal cancers have excellent prognosis whereas those with Stage IV (Dukes' "D") cancers have poor prognosis. However, patients with Stages II and III (Dukes' B and C) colorectal cancers have intermediate 5-year survival rates of 50-75%, and it is currently difficult to define accurately within these stage categories individual patients who are at exceptionally high risk or low risk of metastasis and death. These considerations are particularly important with the advent of effective adjuvant chemotherapy regimens. Secondly, in patients with rectal carcinoma surgical decisions regarding local versus radical excision and adjuvant chemo-irradiation would be impacted by better prognostic markers. Thirdly, patients who undergo colonoscopic polypectomy with the specimen found to contain infiltrating adenocarcinoma require decisions regarding resection.

Prognosis is determined by the presence or absence of metastatic disease that is often microscopic. Molecular staging strategies have applied molecular biology techniques to identify the presence of tumor cells in anatomic sites of clinical metastasis (e.g. lymph nodes, liver) and/or surrogate sites (e.g. blood, bone marrow). Molecular characterization of the metastatic phenotype, i.e. the characteristics of tumor cells that result in their metastatic capability, is another strategy that has been employed to attempt to identify prognostic markers.

A wide range of prognostic features has been reported in the literature. Pathologic features are most easily assessed, and those with ascribed prognostic value include TNM classification, tumor grade, pattern of infiltration at the tumor border, extramural venous invasion, and peritumoral and intra-tumoral host lymphoid response. Application of methods to determine total DNA content have resulted in contradictory results, as have methods to evaluate tumor cell proliferation, including S-phase fraction by flow cytometry, argyrophilic nucleolar organizing regions, and proliferation-associated antigens detected by immunohistochemistry. A wide variety of other prognostic markers has been proposed.

Various molecular genetic alterations have also been proposed to be of prognostic value, including allelic deletion of the DCC/Smad4/Smad2 gene region on chromosome 18q, allelic deletion of the region of the p53 gene on chromosome 17p, and loss of chromosome 8p; p53 gene product over-expression and p53 gene mutations; ras gene mutation; and loss of the nm23 gene. All of these alterations reportedly indicate patients at higher risk. Microsatellite instability (MSI) has been reported as a marker of better prognosis. Genomic profiles are under investigation as prognostic markers.

Individualizing therapy by use of predictive markers for response or resistance to therapy is important in patients with advanced disease as well as those in the adjuvant therapy setting. Markers for response or resistance to chemotherapy or radiotherapy (i.e. predictive markers) have been investigated. These include expression of genes responsible for 5-fluorouracil metabolism (thymidylate synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase), status of the p53 gene and other genes involved in agent-induced apoptosis, and microsatellite instability status. Large-scale clinical evaluations of predictive markers, including genomic profiles are currently in progress, including determination of their ability to predict response of patients to therapy for advanced disease and for adjuvant treatment.