Editorial

p53 Prognostication: Paradigm or Paradox?

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Deciphering the genetic Rosetta Stone of cancer holds out a tantalizing promise. Identification of the genetic lesions responsible for carcinogenesis would yield a molecularly based staging system that would dramatically increase our accuracy in predicting prognosis for an individual's cancer. Alas, this promise has yet to be fulfilled. Very few of the oncogenes and tumor suppressor genes that have been identified to date show strong enough correlations with clinical outcomes to be useful on a routine basis. Although this might seem surprising to some, upon reflection, there are good reasons why these markers do not correlate well with prognosis.

One would expect that a gene such as the *p53* tumor suppressor gene, which is so frequently mutated in human cancers, might be a paradigm for a prognostic marker. This gene plays a critical role in the progression from premalignancy to invasive cancer, and its product controls essential cell functions associated with cell cycle control and apoptosis. The study by Tullo *et al.* in this issue (1) suggests that p53 mutations may be associated with a higher metastatic potential for colorectal cancers and a higher likelihood of treatment failure.

This is a provocative study that raises more questions than it answers. A number of the questions revolve around technical and methodological considerations. A retrospective analysis was done, but a prospective analysis would be preferable to avoid selection bias and to improve the accuracy of data collection; however, the authors are to be commended for undertaking this interesting analysis. Only samples showing altered migration on denaturing gradient gel electrophoresis were selected for sequencing. This may have underestimated the frequency of p53 mutations. It is likely that p53 is dysfunctional in many of the specimens, despite the absence of mutations; for example, MDM2 overexpression may functionally inactivate wild-type p53 protein. This is not addressed by the authors, and thus raises the question as to whether some mutations in the *p53* gene or functional alterations are more important prognostically than others. Finally, PCR reactions can, in some instances, introduce mutations. It would have been helpful to have the mutations confirmed independently with separate specimens. This of course raises the issue of tumor heterogeneity. Were the p53 mutations distributed uniformly throughout the tumor, and were they similar to those detected in the primary tumor? The answers to these questions could provide important insights into the genotypic alterations that contribute to the metastatic process.

Many studies have examined the prognostic value of p53 status in all of the common solid malignancies. The overall conclusion from these studies is decidedly mixed. The American Society of Clinical Oncology convened a Tumor Marker Expert Panel that published the results of a comprehensive survey of the literature for markers of breast and colorectal cancer (2). Despite the fact that 7 of the 10 studies reviewed showed decreased overall survival and increased relapse rates in patients with tumors showing abnormal p53 expression, the panel concluded that the data were "insufficient to recommend the use of p53 expression or mutation for . . . staging."

The panel assigned levels from 1 to 5 to the evidence obtained from reviewing studies, with 1 denoting the highest level of evidence from meta-analysis or large concurrently controlled studies. The study by Tullo *et al.* (1) would be considered level 4 evidence, based on the small number of patients and the absence of multivariate analysis. The latter is especially troubling because the association of prognosis with p53 could be explained by other known prognostic factors. For example, the carcinoembryonic antigen levels for the tumors with mutated p53 were twice that of those with wild-type p53, suggesting that those patients may already have higher tumor burdens. A recent study by Tortola *et al.* (3) found a worse prognosis for colorectal cancer patients with p53 tumor mutations; however, in a multivariate analysis looking only at patients having a complete resection, p53 mutations were no longer of prognostic significance.

Indeed it seems paradoxical that we are unable to obtain more accurate prognostic information with more detailed molecular profiles of the tumor. It may well be naïve to think that a single gene mutation, even one as critical as *p53*, can predict prognosis. Carcinogenesis is complex, with multiple genetic lesions and gene product interactions. The p53 gene product is in itself complex, with multiple sites of mutations, inactivation of the wild-type protein by other gene products such as MDM2 and human papilloma virus E6 protein, and regulation of multiple cell cycle and proapoptotic genes. Some studies have suggested more reliable prognostic information from an analysis of multiple genes (4). Thus, if the paradigm of molecular staging is to become a clinical reality, it is clear that we must attain a higher level of understanding of the genes involved in carcinogenesis and the interactions of their products.

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